

Arthritis Care & Research

Aims and Scope

Arthritis Care & Research is an official journal of the American College of Rheumatology and the Association of Rheumatology Professionals, a division of the College. *Arthritis Care & Research* is a peer-reviewed journal that publishes both original research and review articles that promote excellence in the clinical practice of rheumatology. Relevant to the care of individuals with arthritis and related disorders, major topics are evidence-based practice studies, clinical problems, practice guidelines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

Arthritis Care & Research

An Official Journal of the American College of Rheumatology
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Cover design: Sandra Pulmano

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Arthritis Care & Research

An Official Journal of the American College of Rheumatology
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Cover image: The image on the cover (Day-Lewis et al; page 1358–1370) shows a timeline of therapeutic advances in the field of pediatric rheumatology and FDA approval of medications frequently used to treat immune dysregulation. This image was made with assistance from OpenAI.

EDITORIAL

Fifty Years of Advocacy With Connections and Collaborations in Pediatric Rheumatology

Patience White, MD, MA, MACR, MACP, FAAP

Advocacy is the act of supporting a cause to raise awareness, influence decisions, and create positive change locally or nationally. It is standing up for something you are passionate about, helping others understand its importance, and including the action to move forward. The definition describes the many champions who have grown the pediatric rheumatology (PR) field to become what it is today, a vibrant pediatric subspecialty caring for youth, young adults with rheumatic diseases, and their families through innovative care and research. This author admittedly will not be able to mention all who labored to help children with arthritis or the field of PR nor will this be a global history of the advocacy for the PR field but will mention some landmark events focusing mainly on the US events and some of the key players in the US, Canada and Europe through the decades from the 1940s to the early 2020s. Each decade starts with context of federal laws that assisted the PR community. In addition, each decade will review many of the major PR community champions through positions held, major awards won, or actions taken to move the PR field forward. Throughout the 50-year history of PR, there are several key entities that collectively offered major support for the growing PR field: March of Dimes (MOD), Shriners Hospitals, Maternal and Child Health Bureau (MCHB), Department of Health and Human Services, the Arthritis Foundation (AF) and American Juvenile Arthritis Organization (AJAO), CureJM, the American Academy of Pediatrics (AAP) and the American College of Rheumatology (ACR), the US Food and Drug Administration (FDA), and the National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS) of the NIH. Connections and collaborations are a key feature of the PR field as exemplified by these important supporting organizations and the outlined advocacy presented in this chapter.

1940s-1950s

There is no specific date one can look to for the start of PR. Appreciation for pediatric rheumatic diseases started back

to the late 19th century,¹ and PR emerged as an area of clinical care and research with the establishment of a unit at the Canadian Red Cross War Memorial Hospital at Taplow in England directed by Professor Eric Bywaters in 1947. In the 1950s, Drs Barbara Ansell and Eric Bywaters collaborated on developing an international center using a multidisciplinary model of care.² Several American rheumatologists imbued by the enthusiasm of Dr Ansell trained at Taplow over the years: Drs John Baum, James Cassidy, Chester Fink, Virgil Hanson, Ross Petty, Jane Schaller, and Patience White. In the US, the AF was founded in 1948 with a goal to act on the challenges of arthritis through a national program to fund better care and medical research. The first issue of the journal *Arthritis and Rheumatism*, a major journal about rheumatic disease, was published in 1958.

Dr Earl Brewer, who many identify as the founding networker and driver of PR in the US, said he learned about children with arthritis in his residency. In 1959, he returned to Texas Children's Hospital and established a clinic where physical therapy rather than putting children with arthritis to bed rest was established as an approach to therapy in the US. Other early leaders in the PR field were Drs Jim Cassidy (Ann Arbor, Michigan), Joseph Levinson (Cincinnati, Ohio), Chester Fink (Dallas, Texas), Virgil Hanson (Children's Hospital, Los Angeles, California), J. Sidney Stillman (Boston, Massachusetts), and Jerry Jacobs (Columbia, New York City).³ All established outstanding PR programs that flourish today and train many pediatric rheumatologists.

In 1958, Dr William Clark took over MOD when they were looking for a new disease to tackle after polio. At a pivotal meeting with Dr Brewer and other rheumatologists in Nashville, Tennessee, in 1959, Dr Clark quickly moved to establish Special Treatment Centers for juvenile rheumatoid arthritis (JRA) under the auspices of MOD. The first three centers were awarded to Drs Earl Brewer at Texas Children's Hospital, Joe Levinson in Cincinnati, and John Calabro in New Jersey. In 1959, Nelson's

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80091>.

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Submitted for publication April 7, 2026; accepted in revised form April 15, 2026.

Textbook of Pediatrics, seventh edition, first included a dedicated chapter on childhood rheumatic diseases by Ralph Wedgwood.

1960s

The 1960s saw the passage of Medicaid in 1965 that represented a major shift in the insurance of health care for maternal and child populations. Although Medicaid focused on payment, Title V filled an important gap by assuring that systems of care were in place to support maternal and child health.

In 1964, the American Rheumatism Association (ARA) appointed the JRA Subcommittee of the Classification Committee. Dr Marian Ropes, then President of the ARA, appointed Dr J. Sydney Stillman from Boston to be chairman of the first JRA Criteria Subcommittee to study classification. Dr Earl Brewer was the next chairman followed by Dr Jim Cassidy. The other members of the committee were Drs Chester Fink (Dallas), William Gibson (Columbus), Jack Bass (Columbus), Jerry Jacobs (New York City), Milton Markowitz (Baltimore and Hartford), William Reynolds (New York City), Jane Schaller (Seattle), and Stanley L. Wallace (Brooklyn). The resulting data collected allowed preparation of “JRA Criteria” published in 1972.⁴

The American Rheumatology Health Profession (ARHP) organization that today is the Association of Rheumatology Professionals (ARP) was created at the time the ARA and the AF merged in 1965. The ARHP remained with the AF when the ARA left to create an independent organization, the ACR, in 1986. Dr Joe Levinson led the committee to organize the AF’s Paramedical Section. Seven charter members were Joyce Corderoy, OTR, Judith Klinger, OTR, MA, Edith Shear MSW, Marlin Shields, RPT, David Wayne Smith, DEd, Addie Thomas, ASCW, and Berthold Wolf, PhD.

1970s

The National Arthritis Act of 1974 established the National Commission on Arthritis and Related Musculoskeletal Diseases to create a long-range, comprehensive national plan for combating arthritis that resulted in a long-term federal approach including the creation of the National Institute for Arthritis and Musculoskeletal diseases in 1986. In 1975, the MCHB took the lead in funding the first Regional Arthritis grant for three PR centers (Houston, Philadelphia, and Los Angeles).

In 1972, many advocates pushed Congress to designate May as National Arthritis Month, which has occurred every May since. In 1970, Dr Brewer published the first book on JRA.⁵ In 1973, Dr Brewer created The Pediatric Rheumatology Collaborative Study Group (PRCSG). At the time, Dr Brewer observed, “With the criteria as a stepping-stone, it became clear that we needed drugs to treat children with JRA. We developed a methodology to study medicines for children with JRA.”⁶ The first members were a group of PRs, Drs Earl Brewer, chair, Houston;

John Baum, Rochester; Virgil Hanson, Los Angeles; Chester Fink, Dallas; Jerry Jacobs, New York City; Joseph Levinson, Cincinnati; and Jane Schaller, Seattle; along with Dr John Harter, from the FDA; and Dr Stan Gottlieb of McNeil Laboratories. The PRCSG has changed the landscape of drug therapy for juvenile arthritis (JA), and its chairs were Drs Earl Brewer (1973–1991), Dan Lovell (1991–2021), and Hermine Brunner (2021–current). Dr Ed Gianini started as PRCSG Scientific Director in 1976, and the acting Scientific Directors have been Drs Pamela Weiss (2020–2022) and Michael Shishov (2023–2024).

In 1975, another pivotal event driven by advocacy and collaboration started in 1972 when President Richard Nixon and Secretary Leonid Brezhnev of the USSR signed an agreement of scientific cooperation. The advocacy of Dr John Decker from the NIH with Dr Brewer led to collaboration of the PRCSG, the FDA, and the NIH into a partnership that resulted in three trials with their Russian collaborator, Professor Valentina Nassonova, the last of which was a key article on a methotrexate versus placebo published in the *New England Journal of Medicine* in 1992.^{7–9}

In 1975, the ARA that is today the ACR established the Council of Pediatric Rheumatology that organized the first meeting of clinicians interested in PR in 1976. Today, the Council of Pediatric Rheumatology exists as the Committee on Pediatric Rheumatology and continues to advocate for the PR community. The AF, ARA, and the Shriners of North America sponsored the first meeting in Park City, Utah, in 1976.¹⁰ The initial group of attendees were 27 pediatric rheumatologists and 156 attendees. Some of the original pediatric rheumatologists who continued to be dedicated advocates for many years were Drs Bram Bernstein, Audrey Nelson, Jim Cassidy, Jane Schaller, Sydney Sillman, Helen Emery, Earl Brewer, Balu Athreya, Carol Lindsley, and Virgil Hanson. There were international colleagues from England, Drs Barbara Ansell and Eric Bywaters, and from Canada, Ross Petty (see Figure 1).

In 1976, Dr Ross Petty established the first formal program in University of Manitoba in Canada. In 1977, the collaboration between American and European PR gathered in Oslo and began discussing the classification of juvenile arthritis that was resolved when in 1994 the International League of Associations of Rheumatology proposed global criteria for Juvenile Idiopathic Arthritis that became in 2001 the universally recognized classification.

1980s

Two federal events brought PR into the forefront through funding and acknowledgment. First, the Omnibus Budget Reconciliation Act of 1981 authorized “special projects of regional and national significance (SPRANS)” that funded research and training for maternal and child health and children with disabilities within what is now called the MCHB.

SPRANS funding provides grants for projects that aim to address national or regional needs, priorities, or emerging MCH issues. Attention was needed to develop centers to give



Figure 1. Photo of first Pediatric Rheumatology Meeting in 1976 and listing of attendees. Upper row left to right: Barbara Conove, Lynn Bonfiglio, Evelyn Hess, Gerson Bernhard, George Baltz, Betty Bywaters, Bram Bernstein, Berne Singsen, Deborah Kredich, George Lockie, Audrey Nelson, James Cassidy, Gilbert Omen, John Baum, Barbara Ansell, Milton Markowitz, Gerold Rodnan, Elia Ayoub, Jane Schaller, Peter Schur, Virgil Hanson, Jane Fowler, Helen Emery, Lawrence (Larry) Schulman, Jack Hutto, Eric Bywaters, Anthony Russell, Sidney Stillman, Robert Hill, Lauren Pachman, James Boone, John Calabro, John Miller, Bill Donovan. Lower row left to right: Aram Hanissian, Peter Vance, Chester Fink, Ralph Wedgewood, Alfonse Masi, Naomi Rothfield, Jerry Jacobs, Joseph Levenson, Karen Koster King, Carol Larsen, Linda Gorin, Helen Kornreich, Carol Lindsley, Betty Lowe, Donita Sullivan, Raquel Hicks, Earl Brewer, Balu Athreya, Carol Ragsdale, Richard Stiehm, Ross Petty, Dan Magilevy, Jack Zuckner, Roger Hollister, Paul Phillips.

coordinated care for children with arthritis. Dr Merle McPherson, who served in MCHB Habilitative Services Branch (now the Division of Services for Children with Special Health Needs) as its director from 1987 to 2007, partnered with Dr Earl Brewer and selected PR for development. Five regional PR centers were funded through SPRANS grants and were a landmark for improved care through access to PR multidisciplinary, family-centered, community-based team care.¹¹ The MCHB sponsored a pivotal meeting in Houston in 1984, *New Horizons in Pediatric Rheumatology*. In addition, the allied health partners of the five SPRANS centers gathered with other rheumatology centers and created standards of Practice in Pediatric Nursing led by Sandra Amundson-Jacobowitz, RN, MS, and Diane Erlandson, RN, MS, MPH. Second, the Surgeon General's Report on Children with Special Health Care Need in 1987 made specific recommendations that included recognition of youth with arthritis and the lack of pediatric rheumatologists and shined a light on transitions to adult systems issues. The first MCHB conference on Family Centered Community Based Care was held in June, 1987. Drs Merle McPherson and Earl Brewer authored a paper of the proceedings published in *Pediatrics* in 1989.¹² The concepts outlined in this article were adopted into Federal Legislation (the Omnibus Budget Reconciliation Act of 1989) on how care should be offered to children. The NIAMS was established in 1986.

The AAP formed a PR section of the AAP in 1980 to improve the education of general pediatricians in arthritis. Dr Betty Lowe was on the AAP board and helped initiate the section. The original committee members were Drs Earl Brewer, Balu Athreya, Jack Bass, Virgil Hanson, Jerry Jacobs, and Carol Lindsley.

The first textbooks devoted to PR were published and further legitimized the field. *Rheumatic Disorders in Childhood* by Dr Barbara Ansell in 1980 served as a major early resource in the UK and Europe, and in 1982, *Textbook of Pediatric Rheumatology* by Drs James T. Cassidy and Ross E. Petty, *Pediatric Rheumatology for the Practitioner* by Dr Jerry Jacobs, and *Juvenile Rheumatoid Arthritis* by Drs Earl Brewer, Edward Giannini, and Donald Person were published.

The eighth edition of *Primer on Rheumatic Disease* marked the first time this educational publication formally recognized PR with a dedicated chapter by Dr Jane Schaller. *Primer on Rheumatic Disease* was a foundational medical text published by the AF that has served as a standard teaching tool in medical schools for rheumatology since the early 20th century (last edition was 13th edition in 2007).

In 1987 Dr David Glass became chair of PR at Cincinnati Children's until 2006. He built a program studying childhood musculoskeletal diseases and researching the complex genetics of JA.

The Canadian PR community met for the first time at the second Park City Pediatric Rheumatology meeting in 1986 formalizing the Canadian Pediatric Rheumatology Association. Below is a list of Pediatric Rheumatology meetings and their organizers when known over the past 50 years.

- 1976 ARA Conference on the Rheumatic Diseases of Childhood—"Park City I" Jane Schaller and Virgil Hansen
- 1986 Park City II—Balu Athreya, Jim Cassidy, Virgil Hansen, and Brenard Singen
- 1991 Park City III
- 1998 Park City IV
- 2003 "Pediatric Rheumatology 2003: Park City and Beyond"—Snowmass
- 2008 Pediatric Rheumatology Symposium (PRSYM)—Keystone—Bob Colbert and Ciaran Duffy
- 2011 PRSYM, Miami—Rob Fuhlbrigge, Yuki Kimura
- 2014 PRSYM, Orlando—Brian Feldman, Rob Fuhlbrigge
- 2017 PRSYM, Houston—Peter Nigrovic
- 2020 PRSYM, Virtual—Stacy Ardoin
- 2023 PRSYM, New Orleans—Bryce Binstadt
- 2026 PRSYM, Minneapolis—Andrea Knight and Dan Horton

Although health care professionals often provide the initial stimulus, families who affiliate with organizations and individuals with arthritis play an essential role in supporting each other and creating the needed services for those youth with rheumatic diseases. Their focused, organized work for children with arthritis started in the 1980s. The AJAO, which became the Juvenile Arthritis Alliance in 2006, was founded in 1981 with the founding leaders: Arlene Johnson (President, Ohio), Richard Weaver (Vice President, California), Janna Zeltwanger (Secretary, Indiana), Barbara Barrett (Member, Washington), Dr Jim Cassidy (Member), Dawn Hafeli (Member, Michigan), Dr Joseph Levinson (Member, Ohio), Art Choate (Member, Ohio), and Al Moske (Member, Virginia). In 1984, the first AJAO meeting was held in Keystone, Colorado, under the auspices of the AF.

The AF has several awards for members of the pediatric community who have made a difference for children with arthritis. The first winners of the awards are as follows: Earl Brewer Award for Physician Leadership (1989)—Dr Merle McPherson; Patty Rettig Health Care Professional Award (2000)—Patricia Rettig, RN CRNP; Dawn Hafeli Award for Youth Leadership (1989)—Sean Barrett; Steve and Liz Smith Legacy Award (2018)—Steve and Liz Smith. The Charles B. Harding award is the AF's highest national volunteer honor, established in 1976, and continues today to recognize individuals demonstrating exceptional commitment to the arthritis community. Eight winners are from the pediatric arthritis community: Julia McClanahan, Linda Wilson, Dr Helen Emery, Steve Smith, Amye Leong, Ann Kunkel, Janalee Taylor, MSN, RN, CNC, CNP, and Coleen Ryan.

In 1984, Dawn Hafeli, Kathy Angel, and Barbara Basset, who are often called "the mothers of PR," planned the first National Juvenile Arthritis Conference (now JA Family Summit) in Keystone, Colorado, and brought together children with JA and their families to learn, exchange tips, make new friends, and have fun. This landmark conference continues every year bringing together young people and their families, along with health professionals and dedicated volunteers (Table 1).

In 1985, Dr Peter Dent developed the PR Listserv that brought the clinical community caring for children with rheumatic disease together to share ideas about patient care and research. This listserv, renamed in 2021 the Dr Peter Dent Pediatric Rheumatology Bulletin Board, today has 2,293 emails subscribed to the board.

In 1988, Norma Liburd, RN, MSN, part of the multidisciplinary teams funded by the SPRANS grants, started a newsletter edited by Melanie Bacon, RN, and Pat Vondran, RN, that was published until 1996. In 1998, she founded PRNet, a listserv for allied health professionals in PR with seven nurses. It has operated continuously, connecting pediatric allied health clinicians, and today there are 180 nurses on the listserv.

1990s

On July 26, 1990, the Americans with Disabilities Act—the world's first comprehensive civil rights law for people with disabilities—was passed. Also in 1990, the Education for All Handicapped Children Act of 1975, which required that children from ages 6 to 21 years with disabilities received a free and appropriate public education based on individual needs, was amended and renamed the Individuals with Disabilities Education Act. In 1992, Family Voices was established and has evolved into a national grassroots organization whose mission is to achieve family-centered care for all children and youth with special health care needs and/or disabilities. Family involvement has always been an integral part of PR organizations with families and youth with rheumatic diseases being at the forefront of designing care approaches and research directions.

In 1994, the final rule—Revisions to the Pediatric Labeling Rule—was passed. The extrapolation of efficacy concept was first described. The FDA proposed use of extrapolation of efficacy findings from adults to pediatric populations to maximize use of adult data and other data when designing pediatric drug development programs.

In 1996, the Health Insurance Portability and Accountability Act attempted to make health insurance more portable for people and ensured their coverage would not be subject to pre-existing conditions. In addition, in 1997, the State Children's Health Insurance Program provided health coverage to more children and families, thus increasing insurance coverage of children with pediatric rheumatic disease. In 1998, the FDA Pediatric Rule required

Table 1. Juvenile Arthritis Family Summit history with organizers as provided by the Arthritis Foundation

Year	Location: City, State	Chair(s)
1984	Keystone, CO	Dawn Hafeli, Kathy Angel, and Barbara Basset
1985	St. Louis, MO	Organizers not listed
1986	Philadelphia, PA	Organizers not listed
1987	Long Beach, CA	Organizers not listed
1988	Lincolnshire, IL	Organizers not listed
1989	Orlando, FL	Organizers not listed
1990	Salt Lake City, UT	Organizers not listed
1991	Providence, RI	Linda Wilson, Larry Zemel, MD
1992	Columbus, OH	Beverly Reiner, Karla Jones, RN, PNP
1993	Denver, CO	J. Roger Hollister, MD, Monique Miller
1994	Philadelphia, PA	Balu Athreya, MD, Ronnie McCall, Kathy Ott
1995	Kansas City, MO	Carol Lindsley, MD, Ann Kunkel
1996	San Francisco, CA	Helen Emery, MD, Lynne Mangan
1997	Cincinnati, OH Los Angeles, CA Philadelphia, PA	Carol Henderson, RD, LD, Patty Rettig, RN
1998	Washington, DC	Patty Ellis, Patience White, MD
1999	Tucson, AZ Chattanooga, TN Chicago, IL	Pam Harrell, OTR, LHT, Julia McClanahan, Linda Wilson
2000	Orlando, FL	Tina Dorries, Rhonwyn Ullman
2001	Houston, TX Boston, MA Seattle, WA	Ann Christiano, Marcia Imbrescia
2002	Minneapolis, MN	Ed and Peggy Bonach, Ann Reed, MD
2003	Phoenix, AZ Williamsburg, VA Omaha, NE	Carol Dewey, Eric Peters, MD
2004	San Diego, CA	Mindy Ripley, Ilona Szer, MD
2005	Providence, RI	Thomas W. Connelly, Jr, PhD, RN, Peter and Cynthia Vican
2006	Atlanta, GA	Amanda Vinson, PT
2007	Hershey, PA	Barbara Ostrov, MD
2008	Los Angeles, CA	Jennifer Horonjeff, Mindy Ripley
2009	Houston, TX	Laura Bellomy, Stacy Shivers
2010	Philadelphia, PA	Donna Trigone, RN
2011	Washington, DC	Steve and Liz Smith
2012	St. Louis, MO	Kellea Wright
2013	Anaheim, CA	Mindy Ripley, Colleen Ryan
2014	Keystone, CO	Julie Butscher
2015	Orlando, FL	Rochelle Lentini, Liz Smith, Andrea Jones
2016	Phoenix, AZ Philadelphia, PA	Colleen Ryan
2017	Houston, TX, Indianapolis, IN	Katy Carter
2018	Seattle (Bellevue), WA Washington, DC	Kate Kuhns
2019	Houston, TX Minneapolis, MN	Bob and Jenn Tanning
2020	Virtual	Adam Vigil
2021	Virtual	Jen and Shane Cox
2022	Orlando, FL and Virtual	Adam Vigil
2023	Atlanta, GA	Corrine Pinter
2024	St. Louis, MO	Abby Brown
2025	Salt Lake City, UT	Anie Cooper, Samantha Tuazon
2026	Indianapolis, IN	Dr Gina, David Schell

pharmaceutical companies to study the safety and efficacy of new drugs in children. Although invalidated in 2002, its principles were codified by the Pediatric Research Equity Act (PREA; 2003) and the Best Pharmaceuticals for Children Act (BPCA), which mandate pediatric assessments for many new drugs. These laws, made permanent in 2012, significantly increased the number of

pediatric studies and improved labeling for children. This catapulted PCRSF's ability to study many medications for pediatric rheumatic diseases.

Drs Earl Brewer, Debbie Kredich, and Jim Cassidy petitioned for a board of PR in 1988, and in 1990, the American Board of Pediatrics and the American Board of Medical Specialties formally

approved formation of the sub-Board of PR. The first committee included Drs Debbie Kredich (chair), Balu Athreya, Peter Dent, Helen Emery, Carol Lindsley, and Jim Cassidy.

In 1995, the first formal examinations were offered in PR and were conducted by the Royal College of Physicians (UK). Dr Abe Shore was the first Ped Rheum fellow of the Royal College of Physicians and Surgeons in Canada in 1980, with Dr Alan Rosenberg qualifying next in 1982. In the UK, specialist training was approved by the Royal College of Physicians that subsequently became the Royal College of Paediatrics and Child Health in 1996. With the foundation of the first and only international professional society for PR in 1997, the Pediatric Rheumatology European Society (PReS) gained recognition within the European Union (EU).²

The Blue-Ribbon Committee for Academic Pediatric Rheumatology met in 1997. The members were James T. Cassidy, MD (chair), Balu H. Athreya, MD, Janet S. Austin, PhD, Suzanne L. Bowyer, MD, James Whitcomb, Robert A. Colbert, David N. Glass, MD, Norman T. Ilowite, MD, Ildy M. Katona, Deborah W. Kredich, MD, Carol B. Lindsley, MD, Audrey M. Nelson, MD, Barbara S. Nepom, MD, Christy I. Sandborg, and Patience H. White, MD.¹³ It recommended increasing the numbers of PR trainees and medical school PR programs across the country.

Paediatric Rheumatology International Trials Organization was founded in Europe in 1996 by Alberto Martini, Anne-Marie Prieur, and Patricia Woo with the first EU-funded clinical trial. Subsequent leaders have been Drs Nicola Ruperto, Alberto Martini, Angelo Ravelli, and Fabrizio De Benedetti.

In 1991, with funding from the AF, the Partnership Training Program was launched with three components with major PR involvement and provided training for 400+ parent/professional teams across the country in Partners in Care Coordination (co-authors, Dan Lovell and Diane Erlandsen), Partners in Education (co-authors, Janalee Taylor and Peggy Richey), and Partners in Family Support (co-authors, James May and Dawn Hafell).

In 1991, Patti Rettig, RN, and Balu Athreya, MD, published the first article in PR on health care transition entitled, "Adolescents with chronic disease. Transition to adult health care in arthritis and rheumatism." This was the beginning of interest in health care transition in the PR community that is a continuing interest today.

The ARHP first published one of its signature educational products, *Clinical Care in the Rheumatic Diseases*, after joining the ACR in 1994. In 1998, Liz Smith, a mother of a child with arthritis, first went to a JA Conference where she became a passionate advocate along with her husband, Steve Smith. This couple's energy and engagement gave children's issues a key place in the AF. Liz went on to receive the Kathy Angel Award in 2004, and the AF named the Liz and Steve Legacy Award after them in 2020. Steve received the 2020 Charles B. Harding award.¹⁴ Their physician, Dr Harry Gewanter, also has served as another tireless advocate and leader of the rheumatology community in Virginia, as well as nationally with the AF.

2000s

In 2000, new regulations to the Health Insurance Portability and Accountability Act of 1996 expanded patients' authority over personal health information. The Children's Health Act of 2000 provided for intensified research into JA and began closing the gap in the PR shortage. In 2000, [To Err Is Human: Building a Safer Health System](#) was released by the Institute of Medicine. The landmark report highlighted high rates of medical errors in US hospitals. This report offered a clear prescription for raising the level of patient safety in American health care and the field of quality improvement grew dramatically. In 2001, HRSA's MCHB launched the National Survey of Children with Special Health Care Needs (NS-CSHCN). In 2016, the NS-CSHCN was combined with the National Survey of Children's Health (NSCH). The redesigned survey is fielded annually and covers the content previously covered in the NS-CSHCN. NSCH was (and remains) the only source of both state- and national-level data on multiple key indicators of child health and well-being.

The American Recovery and Reinvestment Act of 2009 invested in the lives of children and families by creating new jobs and enhancing safety net services like community health centers and unemployment benefits. This funded the NIH to offer investigator-initiated research for groups like the Childhood Arthritis and Rheumatology Research Alliance (CARRA).

In 2009, Dr Lynne P. Yao, Director of Division of Pediatric and Maternal Health, FDA, and Drs Carolyn Yancey, Jeffrey Siegal, and Yeruk Mulugeta convened the FDA Public Workshop Meeting: Development of a Consolidated Pediatric Rheumatology Observational Registry. This public gathering brought together the PR community to discuss extrapolation, dose selection, and clinical trial design including postmarketing safety studies.

In 2000, the first major conference on health care transition, Chronic Illness and Disability Conference: Transition From Pediatric to Adult-Based Care, was held at Baylor College of Medicine in Texas; Dr Albert Hergenroeder has continued to host this annual conference that brings together experts nationally and worldwide to share developments and innovations in health care transition practice, education, and health policy.

The Health Care Transition Research Consortium (HCTRC) began their annual research meeting in 2007 at the University of North Carolina at Chapel Hill, founded by Dr Maria Ferris. The HCTRC today has over 700 members. In 2012, this meeting partnered with the Baylor College of Medicine transition conference and continues to be a major venue to present health care transition research and is guided by Drs David Wood, Maria Ferris, and Cecily Betz.

In 2001, Dr Deborah Kredich was awarded the first Rheumatology James T. Cassidy Award from the AAP. This award recognizes members for outstanding achievement, education, and contributions to the field of PR. In 2001, the ACR expanded its meeting offerings to include dedicated tracks like the Pediatric

Rheumatology Residents Program, established to encourage medical residents to enter the field.

In 2002, CARRA was formed to conduct collaborative, investigator-initiated research. CARRA began with Drs Christy Sandborg and Betsy Mellins at Stanford who realized the potential of the new treatments for children with rheumatic disease, and Dr Sandborg, hearing the rumor that the American Board of Pediatrics might stop offering boards because there were so few trainees, thought they needed to develop a pediatric rheumatology research group to emphasize the innovations and attract trainees.¹⁵ Along with the two founders, Drs Brian Feldman, Norm Ilowite, Laura Schanberg, Yukiko Kimura, Carol Wallace, Bob Fuhlbrigge, and Emily von Scheven joined in founding CARRA. In 2002, the first scientific meeting brought together partners such as the NIH, PRCSSG, and other research groups. Dr Susanna Serrate-Sztejn from the NIH attended and facilitated the first funded CARRA grants, APPLE and TREAT. The year 2005 saw the first convening of CARRA's annual meeting, and it continues today. In 2009, with NIH ARRA funds, grants started Consensus Treatment Plans, the first of which was led by Brian Feldman on dermatomyositis. In addition, CARRAnet was initiated. During the 2000s, CARRA was led by consecutive chairs Drs Elizabeth Mellins, Christy Sandborg, and Carol Wallace. Family volunteers were invited to an early annual scientific CARRA meeting to meet the membership and witness how research was developed in CARRA. During the meeting, the researchers formed relationships with family volunteers and began to ask questions about their opinions of the studies being planned such as "Is this study important to families?" This was an important step in the initiation of patient engagement in PR.¹⁶

In 2002, Ann Kunkel, RN, served as the AF Volunteer Representative for the Bone and Joint Decade and is an avid advocate for PR having served as chair of AJAO. The ARP Ann Kunkel Advocacy Award is named after her, which honors her service in advocating for patients with arthritis.

In 2000, Drs Frederick Miller and Lisa Rider at the NIH created the International Myositis Assessment and Clinical Studies (IMACS) Group that has brought together many centers to focus on both adult and pediatric myositis, to achieve consensus in areas of clinical research and therapeutic trials. In 2003, the CureJM Foundation was founded by advocates Tom and Sherry Hume and Harriet Bollard and strives to ensure no family has to navigate this rare disease alone and to fund juvenile myositis (JM) research toward a cure for the disease. Drs Lauren Pachman, Lisa Rider, and Ann Reed subsequently led the early centers of excellence in JM clinical care and research, funded in part by CureJM, and were the foundation's first medical advisers. In 2007, the key handbook *Myositis and You* was published with editors Drs Lisa Rider, Lauren Pachman, and Frederick Miller, and Harriet Bollard, which is still a major text used nearly 20 years later.

Pediatric Rheumatology, the specialized open-access journal, was launched in 2003 (originally as *Pediatric Rheumatology*

Online Journal) with editors-in-chief Drs Charles H. Spencer and Alberto Martini and later published by BioMed Central. Today it is the official journal of PReS with co-editors-in-chief Drs Angelo Ravelli and Tadej Avcin.

In 2002, Andrea Ring joined Katie Bitner at the AF, and both have been important drivers of the AF's children's programs. Andrea Ring, the senior director of JA and young adult initiatives, is active in the AF today. In 2003, Kevin Brennan, Senior Vice President for Public Policy (1999–2006) and current AF National Advocacy Committee Co-Chair, started advocacy summits at the AF, and in 2005, the Kids Summit program was added for youth grades K–8. The advocacy program has grown a community of youth, young adults, families, and clinicians who advocate for changes in the lives of children with arthritis. In Europe, the European Network for Children with Arthritis and Autoinflammatory Diseases, a network of pediatric rheumatic disease associations (encanetwork.org), formed in Paris in 2002 and represents the country-specific organizations working with children and young people with pediatric rheumatic diseases and their families throughout Europe.

In 2006, the Canadian Pediatric RA formally became a Pediatric Rheumatology Committee of the Canadian Rheumatology Association (CRA). In 2007, Canadian Alliance of Pediatric Rheumatology Investigators (CAPRI) was initiated by Drs Rae Yeung, Ciaran Duffy, Lori Tucker, and Alan Rosenberg. CAPRI is a national multidisciplinary research organization.¹⁷

In 2007, Dr Elizabeth D. Mellins, was the first pediatric rheumatologist to receive an ACR/Rheumatology Research Foundation Investigator award. In 2008, Dr Robert Colbert joined the NIAMS Intramural Research Program (IRP) as chief of the Pediatric Translational Research Branch. He is one of the few pediatric rheumatologists who has attended all the Park City meetings except the first and is a constant promoter of PR. In 2020, Dr Colbert was appointed Clinical Director of the NIAMS IRP. The NIAMS program has had several pediatric fellows in conjunction with Children's National Medical Center beginning in the late 1980s with Dr Raphael Hirsch followed by Drs Ellen Goldmuntz and Lisa Rider.

2010s

The Patient Protection and Affordable Care Act was enacted in 2010, made health insurance available to more people, expanded Medicaid coverage, and supported innovative methods designed to lower health care costs. This improved insurance improved the health insurance coverage in the US of many youth and young adults with rheumatic diseases.

In 2011, the AAP, American Association of Family Practitioners, and the American College of Physicians published a clinical report, "Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home," that provides the first joint framework for transitioning youth to adult-focused health care. Updated guidance was published in 2018 and

reaffirmed by the AAP, AAFP, and ACP in 2023¹⁸ to include the [Six Core Elements of Health Care Transition](#),¹⁹ which provides more detailed quality improvement guidance and has been customized by the ACR, CARRA, AF, and many other organizations and health systems.

The 2012, the FDA Safety and Innovation Act permanently reauthorized BPCA and PREA, making medications for adults more available to the pediatric community. The emerging trend of patient engagement in the early 2000s led to the founding of the Patient-Centered Outcomes Research Institute (PCORI) in 2010 as part of the Affordable Care Act. In 2014, PCORI established PCORInet, a network of networks that could harness the power of substantial amounts of health information to facilitate patient-centered comparative effectiveness research using a common data model and Patient- Powered Research Networks that were disease specific such as PR and community based.

In 2018, Congresswoman Kim Schrier, MD, the only pediatrician in Congress, was elected from Washington State, and she is still in Congress. She collaborated with the coalition to fund the Pediatric Subspecialty Loan Repayment Program.

CARRA continued to grow incorporating as a 501c3 in 2014, and in the 2020s, leaders Norm Ilowite, Laura Schanberg, Yukiko Kimura, and Robert Fuhlbrigge became presidents leading to growth of sites and collaborators. Carol Wallace launched a pre-meeting course that has taught many PR centers how to get started in clinical research. In 2015, a new 21CFR11 Compliant Registry for disease specific pharmacosurveillance and, in 2016, a biorepository were initiated, and intramural grants were offered. Today CARRA is a research network of seven research committees. It has more than 14,000 enrolled youth and young adults and 550 PR members and has been consecutively led by Drs Emily von Scheven, Robert Colbert, and Stacy Ardoin.

In 2014, there was a meeting of advocates that initiated the historic partnership between AF and CARRA with the following members: Vince Del Gaizo (Friends of CARRA), Chris Andersen (Chair, JA Alliance), Colleen Ryan (a parent of a child with rheumatic disease who has chaired national JA conferences and won the Kathy Angel Parent Leadership award), Ann Palmer (President & CEO, AF), Cindy McDaniel (Senior VP, Consumer Health), and Debbie Wright (Friend of CARRA). In 2015, Friends of CARRA merged with the AF. The AF continues today as a major supporter of CARRA's infrastructure and research.

In 2008, Drs Murray Passo, Yukiko Kimura, Beth Gottlieb, and Esi Morgan gathered and approached CARRA about forming a learning network to improve quality of care using quality improvement science. This group formally launched the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) in 2010 and its first registry in 2011. PR-COIN was supported by the AF, the Center for Education and Research in Therapeutics at Cincinnati Children's Hospital Medical Center, and the ACR. In 2015, the Parent Working Group (PWG) was formed and added family engagement to its center agreements. Dr Esi Morgan is principal

investigator, and Kerry Ferraro is chair PWG. Together, they lead this learning network with a patient-centered approach.²⁰⁻²² Today PR-COIN is a network of 21 centers.

Patients, Advocates, Rheumatology Teams Network for Research and Service (PARTNERS) consortium was established in 2013 to 2014, led by Dr Laura Schanberg, funded by PCORI, which created a patient-powered research network integrating patient-reported outcomes with clinical data for juvenile idiopathic arthritis and related diseases. It joined with CARRA, PR-COIN, and three advocacy organizations (AF, Lupus Foundation of America, CureJM) in 2018. PARTNERS created the infrastructure and shared best practices to engage caregivers and patients in the research process.¹⁶

In 2018, Norma Liburd was the first and to date the only pediatric ARP Master awardee. In 2010, Cassie and Friends was founded and is the only charity in Canada dedicated 100% to the pediatric rheumatic disease community.

2020s

In 2022, six key partners came together and advocated for the Pediatric Subspecialty Loan Repayment Program: AAP, ACR, AF, Children's Hospital Association, American Academy of Child & Adolescent Psychiatry, and American Society for Gastrointestinal Endoscopy.

Employing BPCA and/or PREA pediatric labeling changes from 1998 to 2022, a historic milestone, was achieved with more than 1,000 drugs and biologics having undergone labeling changes to include pediatric use information.²³ The ninth edition of *Pediatric Rheumatology* edited by Drs R. Petty, R. Laxer, L. Welderborn, E. Mellins, R. Fuhlbrigge, J. Akikusa, and H. Brunner will be published in 2026.

PR continues to have a smaller workforce per capita of children than most other pediatric subspecialties.²⁴ Data from the American Board of Pediatrics and ACR continue to show a vibrant clinical US PR community. Through June 2023, a total of 626 pediatricians are board certified. ACR membership data show 8% are pediatric rheumatologists with 417 academic and 90 private practice. ARP membership data show 4% are in PR with 33 academic and 19 private practice. Forty-two pediatric rheumatologists are ACR masters and one is an ARP master. Fourteen pediatric rheumatologists have served on the ACR Board: Drs Carol Lindsley, Christy Sandborg, David Glass, Emily von Scheven, Jaime de Inocencio, Karen L. Kerr, Karen Onel, Marisa Klein-Gitelman, Pamela Degotardi, Raphael Hirsch, Robert Allen Colbert, Suzanne Bowyer, Tamar Rubinstein, and Patience White. Nine pediatric rheumatologists have served on the Foundation Board: Drs Colleen Correll, Edward Behrens, Ekemini Ogbu, Jay Mehta, Linda Hiraki, Mara Becker, Marisa Klein-Gitelman, Polly Ferguson, and Robert Allen Colbert. Bryce Binstadt, MD, PhD, is the first pediatric rheumatologist and current President of the ACR Foundation. In addition, the

Chair of the ACR Committee on Pediatric Rheumatology also serves on the Rheumatology Research Foundation board. Three members of the current ARP executive committee are in PR.

The ACR continues to advocate for PR in the areas of clinical practice, research, clinical and scientific workforce, and education. The Committee on Pediatric Rheumatology has been central to these efforts working jointly with the ACR Committee on Workforce Solutions, Committee on Training, and the Government Affairs Committee. Currently, the ACR continues to advocate for funding of PR fellowships, flexibility in PR fellowship training, pediatric rheumatologist and advanced practice provider clinical workforce development in underserved areas, and Medicaid-Medicare parity.

In conclusion, Jim Cassidy's question posed in his 2009 personal history article, "Are we there yet?"²⁵ can now be answered with a resounding "Yes!" There is much more to accomplish in the next 50 years, and thanks to the early work of many, a multitude of PR advocates are up to the challenge.

AUTHOR CONTRIBUTIONS

The author contributed to all of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr White approved the final version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ACKNOWLEDGMENTS

I want to thank all those who were kind enough to connect with me via phone or email to give depth and richness to my learning about the first 50 years of advocacy in Pediatric Rheumatology: Stacy Ardoin, Balu Athreya, Cecily Betz, Bryce Binstadt, Kevin Brennan, Tania Cellucci, Robert Colbert, Ciaran Duffy, Helen Emery, Harry Gewanter, Kerry Ferraro, Maria Ferris, Dawn Hafeli, Jack Klippel, Carol Lindsley, Dan Lovell, Ron Laxer, Esi Morgan, Ross Petty, Patti Rettig, Lisa Rider, Alan Rosenberg, Coleen Ryan, Christy Sandborg, Laura Schanberg, Liz Smith, Charles Spencer, Parag Shah, Jana Lee Taylor, Carol Wallace, Pat Woo, Carolyn Yancy; American Academy of Pediatrics: Laura Laskosz; American College of Rheumatology: Kye Sutphin, Lennie S. McDaniel, and Stephanie Graham; the Arthritis Foundation: Pam Gill, Anna Hyde, Paul Larkin, and Andrea Ring; CureJM: James Minnow; and CARRA: Vince Del Gaizo.

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Facilitating Expedited Drug Approval—the Past, Present, and Future of Clinical Trials for Pediatric Rheumatic Disease

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Introduction

Over the past five decades, pediatric rheumatology has undergone a significant transformation in the design, conduct, and impact of clinical trials, evolving from small, largely exploratory studies to sophisticated, multinational research programs that have reshaped the standards of care for children with rheumatic diseases. Between 1975 and 1995, the field was characterized by single-center trials focused on nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and early conventional disease-modifying antirheumatic drugs (cDMARDs), constrained by small sample sizes, heterogeneous outcome measures, and the absence of standardized disease definitions. The period from 1996 to 2010 was a critical phase of consolidation and framework building, characterized by the introduction of unified disease classification systems, such as the International League of Associations for Rheumatology juvenile idiopathic arthritis (JIA) criteria,¹ the development of consensus outcome measures, and the expansion of multicenter trials evaluating methotrexate and the first biologic therapies. These advances were catalyzed by the formation of collaborative research networks and registries that enabled enrollment at scale and fostered methodologic rigor. From 2011 to the present, the field of pediatric rheumatology has entered a modern era defined by rapid growth in biologic and targeted small-molecule trials, the adoption of innovative trial designs, and the systematic use of registries to assess long-term safety and effectiveness. Together with strengthened regulatory incentives and internationally coordinated consortia, these advances have fundamentally altered the clinical trial landscape, accelerating therapeutic innovation while improving the quality and relevance of evidence generated for children with rheumatic diseases.

Regulatory, ethical, and logistical landscape

Over the past 50 years, the regulatory landscape for pediatric clinical trials has shifted from a largely permissive environment to

one that emphasizes safety, efficacy, and ethical oversight. In the early 1970s, children were often excluded from clinical research, and most medications were prescribed off label without robust pediatric data, exposing young patients with rheumatic diseases to unknown risks. Growing recognition of this problem, along with activism by professional organizations, pediatric research networks, families, and stakeholder organizations, led to pivotal legislative and regulatory changes, most notably the Best Pharmaceuticals for Children Act (BPCA, 2002)² and the Pediatric Research Equity Act (PREA, 2003).³ BPCA encouraged pharmaceutical companies to study their drugs in children by offering a six-month extension of marketing exclusivity. PREA went further by mandating that pharmaceutical companies conduct pediatric studies for new drugs and biologics if they are likely to be used in children or if there is a pediatric correlate of a non-orphan disease occurring in adults. PREA also mandated that the pediatric study plans be submitted before the adult disease counterpart phase 3 trial commences.

In 2012, the US Food and Drug Administration (FDA) Safety and Innovation Act made PREA and BPCA permanent, which has been pivotal for advancing pediatric drug development. In 2012, as part of the FDA Safety and Innovation Act, Congress established the Pediatric Rare Disease Priority Waiver Program. When a company receives FDA approval for a therapy for a pediatric rare disease that qualifies under this program, it is awarded a priority review voucher. This voucher can then be used to expedite the FDA review process for another product that would otherwise not qualify, reducing the standard 10 to 12 months to 6 months. The large financial incentive from the program comes from the fact that the voucher can also be sold or transferred to another company. In 2024, the Center for Drug Evaluation and Research (CDER) E11A Pediatric Extrapolation Guidance for Industry provided recommendations for how to present extrapolation plans in regulatory submissions and how to engage with the FDA during drug development.

Supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K24-AR-078950 to Dr Weiss).

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80028>.

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Submitted for publication January 30, 2026; accepted in revised form February 19, 2026.

Collectively, these laws have facilitated the labeling of numerous drugs for children, including those with JIA and pediatric systemic lupus erythematosus (pSLE). Internationally, guidelines from the European Medicines Agency and the International Council for Harmonisation (ICH) have promoted age-appropriate formulations, dosing, and trial design in a similar manner. Over time, regulatory agencies have increasingly emphasized ethical protections, including obtaining assent from minors and parental consent, while also minimizing trial-related burdens and fostering innovation in pediatric trial methodology. Today, the landscape reflects a delicate balance: ensuring children benefit from advances in medicine while protecting them from unnecessary harm, a paradigm shift that continues to shape the design and conduct of pediatric research worldwide. Progress, however, is still needed as off-label use of medication is still common, accounting for 40% of drugs prescribed in the pediatric population.⁴

Pediatric rheumatology research networks and clinical trials

Several stakeholder organizations have played pivotal and complementary roles in advancing the design, conduct, and global impact of clinical trials in pediatric rheumatology over the past 50 years. The Pediatric Rheumatology Collaborative Study Group (PRCSG), established in 1973, was the first formal pediatric rheumatology research network, laying the groundwork for the development of modern clinical trials in the field. PRCSG pioneered multinational pediatric trials by coordinating studies conducted in the United States and the former Union of Soviet Socialist Republics (USSR). Through rigorously designed, placebo-controlled trials, PRCSG evaluated cDMARDs, including D-penicillamine,⁵ hydroxychloroquine,⁵ oral gold,^{6,7} NSAIDs,^{8,9} and methotrexate,¹⁰ for the treatment of what was then known as juvenile rheumatoid arthritis. These trials demonstrated a lack of efficacy for several of the agents while establishing methotrexate and NSAIDs as effective therapies, thereby defining the therapeutic foundation for JIA. PRCSG subsequently led the first biologic clinical trials in pediatric rheumatology, including the inaugural tumor necrosis factor inhibitor trial of etanercept in JIA,¹¹ which ultimately supported FDA approval for it in polyarticular juvenile rheumatoid arthritis in 1999. Over five decades, PRCSG has maintained a critical role in trial design, execution, and dissemination through sustained partnerships with industry sponsors.

Building on this early momentum, the Paediatric Rheumatology International Trials Organisation (PRINTO) was founded in 1996 to address the growing need for large-scale, multinational pediatric rheumatology trials. PRINTO created the infrastructure necessary to conduct harmonized, rigorously designed clinical trials across diverse geographic and regulatory environments. By enabling the enrollment of sufficiently powered cohorts for rare

pediatric rheumatic diseases, PRINTO has played a crucial role in advancing therapeutic development, validating outcome measures, and securing regulatory approvals in Europe and globally. Its emphasis on standardized protocols, centralized data coordination, and international collaboration has made PRINTO a cornerstone of global pediatric rheumatology clinical trials and research.

In 2000, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) was established to advance collaborative clinical research across North America, with a particular focus on generating real-world evidence. A major milestone was the launch of the CARRA Registry in 2009, the first national registry for pediatric rheumatic diseases, alongside the development of robust trial infrastructure, including centralized site management, standardized contracting, site training, and a dedicated research coordinator network. Today, investigators from more than 120 institutions contribute data to the registry, which has supported landmark interventional and comparative effectiveness studies, including the Trial of Early Aggressive Therapy in Polyarticular JIA (TREAT-JIA).¹² In 2015, the registry was upgraded to be 21 Code of Federal Regulations (CFR) Part 11-compliant, enabling its use for global postmarketing safety surveillance and the assessment of rare but critical long-term outcomes, such as malignancy.

Clinical trial design

The earliest trials of conventional synthetic DMARDs in juvenile rheumatoid arthritis, such as D-penicillamine,⁵ hydroxychloroquine,⁵ oral gold,⁷ and methotrexate,¹⁰ relied on the traditional randomized, placebo-controlled design. Once effective treatments, most notably methotrexate, were established, the continued use of placebo controls in children, particularly those with a high burden of disease, became increasingly difficult to justify ethically. This shift necessitated the development of alternative trial methodologies, including randomized withdrawal designs, open-label pediatric pharmacokinetic studies, and approaches to efficacy extrapolation.

Randomized withdrawal design. The first biologic DMARD studied in JIA, etanercept, was evaluated using the novel randomized withdrawal trial design (RWD)¹¹ (Figure 1). In this framework, all enrolled children receive open-label treatment with the experimental therapy during the initial phase of the trial. Participants who achieve a predefined clinical response, typically a JIA American College of Rheumatology (ACR) 30 response,¹³ were subsequently randomized in phase 2 to either continue the investigational therapy or transition to a placebo. During phase 2, participants were then monitored for a protocol-defined disease flare or time to flare. Children who experienced a mild to moderate flare had the option to restart the active investigational drug in open-label extension (phase 3). The RWD design facilitates

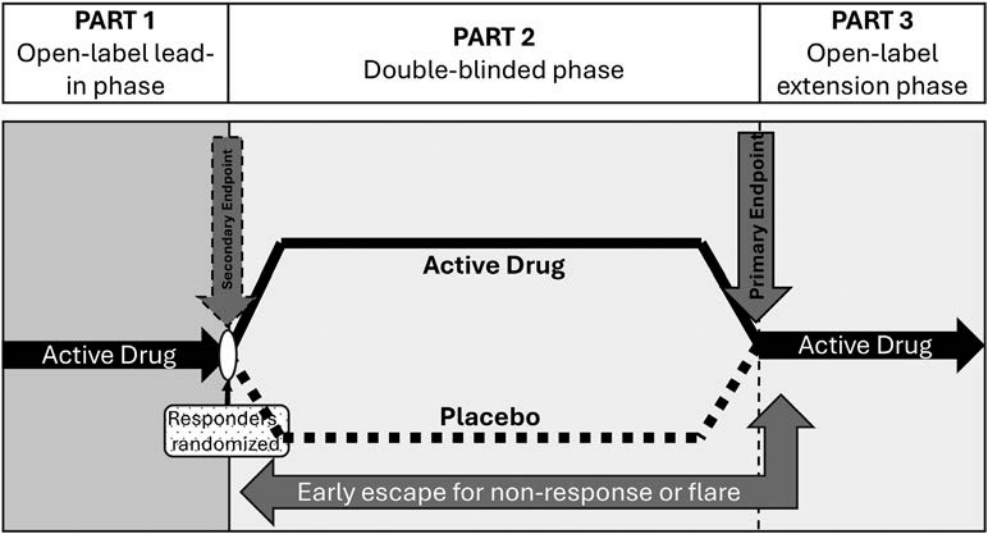


Figure 1. Randomized withdrawal design. Figure adapted from “Pediatric Rheumatology Collaborative Study Group - over four decades of pivotal clinical drug research in pediatric rheumatology.”⁴⁶

efficient assessment of drug efficacy while minimizing placebo exposure and enabling individualized treatment duration. Importantly, this design has greater acceptability among clinicians and families because all participants receive the active experimental therapy immediately after enrolling into the study, which generally coincides with active disease and pain. Further, time on placebo is minimized, and there is an option to resume the drug in phase 3. However, the RWDs introduce selection bias, as only responders advance to randomization in phase 2. Additionally, the principal outcome, time to disease flare, does not directly compare response rates. This design is not suitable for therapies with a prolonged effect or when abrupt discontinuation of the drug raises safety concerns. Despite these limitations, most biologic trials in juvenile arthritis conducted between 1999 and 2020 employed an RWD (Table 1).

Extrapolation studies. In parallel, regulatory pathways evolved to further accelerate pediatric drug development. In 1994, the FDA first proposed extrapolating efficacy data from adult trials when disease pathophysiology and treatment response were sufficiently similar in adult and pediatric populations. Under this paradigm, pediatric development could rely on pharmacokinetic and safety data from relatively small open-label studies in children. In 2019, an FDA/Centers for Excellence in Regulatory Science and Innovation workshop addressed strategies to accelerate drug development for children with polyarticular JIA.¹⁴ After this workshop, the FDA determined that PREA requirements for polyarticular JIA could be satisfied through pharmacokinetic studies supporting extrapolation of efficacy from adult rheumatoid arthritis trials.^{15,16} The FDA further advised that data from children with polyarticular JIA or psoriasis, together with adult trials in rheumatoid arthritis, psoriatic arthritis, or psoriasis,

Table 1. Drug approvals and trial design supporting the approval from 1999 to present*

Drug	Year of FDA pediatric approval	Indication(s)	Trial design supporting pediatric approval
Etanercept	1999	Polyarticular JRA	Randomized withdrawal
Adalimumab	2008	Polyarticular JRA	RCT + open-label extension
Abatacept	2008	Moderate-severe pJIA	Randomized withdrawal
Tocilizumab	2011	Systemic JIA	Randomized withdrawal
	2013	pJIA	Randomized withdrawal
Canakinumab	2013	Systemic JIA	Randomized withdrawal
Golimumab	2020	pJIA; juvenile psoriatic arthritis	Extrapolation from adult RA/PsA + open-label pediatric PK/safety study
Tofacitinib	2020	Polyarticular-course JIA	Randomized withdrawal
Secukinumab	2021	Juvenile psoriatic arthritis; ERA	RCT (randomized withdrawal)
Ustekinumab	2022	Juvenile psoriatic arthritis	Extrapolation from adult PsA + open-label pediatric study
Sarilumab	2024	pJIA	Extrapolation + pediatric open-label PK/safety study
Guselkumab	2025	Juvenile psoriatic arthritis	Extrapolation from adult PsA + pediatric PK/safety study

* ERA, enthesitis-related arthritis; FDA, US Food and Drug Administration; JIA, juvenile idiopathic arthritis; JRA, juvenile RA; pJIA, polyarticular JIA; PK, pharmacokinetics study; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial.

could support extrapolation for juvenile psoriatic arthritis (JPsA) without a dedicated pharmacokinetic study. Consequently, extrapolation for juvenile spondyloarthritis (JSpA) has been applied on a drug-specific basis, rather than a universal one.¹⁷

These regulatory advances culminated in the ICH finalizing the E11A guideline on pediatric extrapolation in December 2024.¹⁸ Extrapolation of adult efficacy data from rheumatoid arthritis and psoriatic arthritis supported the FDA approvals of intravenous golimumab for polyarticular JIA and JPsA in 2020,^{19,20} as well as the FDA approvals of ustekinumab and guselkumab for JPsA.^{19,21} Collectively, these developments reflect a maturation of pediatric trial design and regulatory science, enabling more efficient and ethically sound evaluation of novel therapies. Notably, this extrapolation framework was also applied in pSLE, when belimumab received FDA approval in 2019 based on extrapolation of efficacy from adult lupus trials, supported by pediatric pharmacokinetic, safety, and pharmacodynamic data.²²

Development of pediatric outcome and response measures for use in trials

JIA. Over the past five decades, pediatric rheumatology has also benefited from the development of standardized pediatric outcome and response measures, which have made clinical trials more feasible and robust (Table 2). In the late 1990s, ACR pediatric JIA response criteria were first introduced (eg, JIA Pediatric 30, with additional thresholds such as Pediatric 50, 70, 90, and 100) to quantify graded improvement across six core variables in clinical trials.¹³ Building on this framework, Wallace and colleagues established consensus criteria for clinical inactive disease and remission in JIA in 2004,²³ providing the first uniform definition of remission for oligoarticular, polyarticular, and systemic JIA. The Juvenile Arthritis Disease Activity Score (JADAS)²⁴ was developed in 2009 as a continuous composite index that includes four core measures: physician disease activity assessment, parent/caregiver global assessment, active joint count, and acute-phase reactants. Subsequent work defined cutoffs for states of inactive, minimal, moderate, and high disease activity.²⁵ Additionally, the systemic JADAS was developed and validated for use in systemic JIA by adding a fifth core measure aimed at quantifying the activity of systemic features.²⁶ Likewise, pediatric measures were developed to quantify disease activity in JSpA (the Juvenile Spondyloarthritis Disease Activity Index).²⁷ Objective imaging measures, such as the Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging inflammation and structural scoring systems, were also adapted for pediatric sacroiliac assessment to quantify inflammatory and structural lesions in juvenile SpA.^{28,29} Additionally, standardized flare criteria for JIA³⁰ and JSpA³¹ were developed.

Childhood-onset SLE. For childhood SLE (cSLE), adaptations of adult disease indices, including the Systemic Lupus Erythematosus Disease Activity Index,³² European Consensus Lupus Activity Measure,³³ and Systemic Lupus Activity Measure,³⁴ have been applied and evaluated in childhood cohorts to assess disease activity and correlate with clinical outcomes. In 2009, the PRINTO/ACR provisional criteria for response to therapy in cSLE were developed.³⁵ Building on this work, pediatric-specific definitions of clinically meaningful improvement were developed and validated,³⁶ along with thresholds for minor, moderate, and major clinical responses. Consensus definitions for inactive disease and clinical remission in cSLE were also established.³⁷ Like JIA and JSpA, preliminary criteria for global disease flares in cSLE have been proposed for use in clinical trials.³⁸

Juvenile dermatomyositis. In juvenile dermatomyositis (JDM), a set of disease-specific outcome measures has been developed and validated to facilitate clinical trials in this relatively understudied condition. Core assessments of disease activity include the Disease Activity Score (2003)³⁹ and the Childhood Myositis Assessment Scale (1999),⁴⁰ which provide complementary evaluations of muscle strength and functional capacity. Standardized response to therapy is assessed using the PRINTO/ACR/EULAR response criteria (2008),⁴¹ enabling harmonized outcome evaluation across trials. The Manual Muscle Testing in 8 muscles (2010)⁴² offers a practical and widely adopted measure of muscle strength. Together, these instruments have substantially accelerated therapeutic development in JDM by improving the sensitivity, comparability, and interpretability of clinical trial outcomes.

Juvenile systemic sclerosis. In juvenile systemic sclerosis (jSSc), outcome assessment in clinical trials has focused on a combination of skin, organ-specific, and global severity measures. The modified Rodnan skin thickness score (MRSS), adapted for pediatric use in 2010,⁴³ remains a central measure of skin involvement, whereas overall disease severity is captured using the Juvenile Systemic Sclerosis Severity Score (2017).⁹ PRINTO has led efforts to develop and validate provisional response criteria for jSSc, though these measures remain under active refinement. At present, there are no universally accepted definitions of inactive disease or remission in jSSc.

Patient-reported outcomes. Additionally, cross-cutting patient-reported outcomes have assumed an increasingly prominent role in pediatric rheumatology trials.⁴⁴ Over the past decade, the PROMIS pediatric measures, which are part of the NIH's Patient-Reported Outcomes Measurement Information System, have been integrated into pediatric rheumatology trials to directly capture health-related quality of life, pain interference, fatigue, and other domains from children and adolescents.³¹ Additionally,

Table 2. Pediatric-specific trial response measures and outcomes by disease*

Disease	Core response measures	Disease activity/severity indices	Inactive disease/remission	Flare/damage/other key outcomes
JIA	Pediatric ACR response criteria (JIA ACR 30/50/70/90/100) ¹³	JADAS (10/27/71) ²⁴	Wallace criteria for inactive disease ²³	JIA flare criteria ³⁰
	PRINTO provisional response criteria ²⁵	cJADAS ⁴⁸		JADI ⁴⁹
	Axial JSpA response criteria ⁴⁷	sJADAS ²⁶		SPARCC MRI inflammation and structural scores (for JSpA) ^{28,29}
cSLE	PRINTO/ACR provisional criteria for response to therapy ^{35,36}	JSpADA index ²⁷	Consensus definitions for inactive disease and clinical remission ³⁷	Pediatric global flare criteria ³⁸
		pSLEDAI ³²		
		ECLAM ³³		
JDM	PRINTO/ACR/EULAR response criteria for JDM ⁴¹	SLAM ³⁴	Definitions of inactive disease based on PRINTO criteria ⁵¹	SLICC/ACR Damage Index (adapted for pediatrics) ⁵⁰
		CMAS ⁴⁰		
		MMT-8 ⁴²		
JSSc	PRINTO provisional response criteria (under development/validation)	DAS ³⁹		MDI ⁵²
		MRSS (pediatric use) ⁴³		
		J4S ⁵⁴		
				The Cutaneous Assessment Tool ⁵³

* ACR, American College of Rheumatology; cJADAS, clinical JADAS; CMAS, Childhood Myositis Assessment Scale; cSLE, childhood systemic lupus erythematosus; DAS, Disease Activity Score; ECLAM, European Consensus Lupus Activity Measure; J4S, Juvenile Systemic Sclerosis Severity Score; JADAS, Juvenile Arthritis Disease Activity Score; JADI, Juvenile Arthritis Damage Index; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; JSpA, juvenile spondyloarthritis; JSpADA, JSpA Disease Activity; JSSc, juvenile systemic sclerosis; MDI, Myositis Damage Index; MMT-8, Manual Muscle Testing in 8 muscles; MRI, magnetic resonance imaging; MRSS, Modified Rodnan skin thickness score; PRINTO, Paediatric Rheumatology International Trials Organization; pSLEDAI, Pediatric Systemic Lupus Erythematosus Disease Activity Index; sJADAS, systemic JIA adaptation JADAS; SLAM, Systemic Lupus Activity Measure; SLICC, Systemic Lupus International Collaborating Clinics; SPARCC, Spondyloarthritis Research Consortium of Canada.

physical function is frequently evaluated using the Childhood Health Assessment Questionnaire. Lastly, recognizing the importance of treatment-related harm, the pediatric Glucocorticoid Toxicity Index was developed in the early 2020s to systematically quantify glucocorticoid-associated morbidity in children.⁴⁵

Conclusions

Over the past 50 years, the design, conduct, and impact of clinical trials in pediatric rheumatology have undergone a profound transformation, catalyzed by the establishment of collaborative research networks and registries that have enabled enrollment at scale and enhanced methodologic rigor. Coupled with strengthened regulatory incentives and internationally coordinated consortia, these advances have substantially improved the clinical trial landscape by accelerating therapeutic innovation while increasing the quality, relevance, and generalizability of evidence generated for children with rheumatic diseases. The pace of progress is unlikely to slow. Future advances are expected to include broader adoption of platform and adaptive trial designs, pragmatic and registry-embedded trials, and Bayesian approaches

tailored to small and heterogeneous populations. Advances need to also address barriers to trial enrollment from the perspectives of the patient/family and the clinical team. Continued efforts will focus on refining pediatric-relevant outcome measures by developing harmonized core outcome sets, expanding patient-reported outcomes, and integrating biomarker-driven endpoints. In parallel, advancements in translational science, including biomarker discovery, precision medicine strategies, and preparedness for gene-based therapies, will further shape the next era of pediatric rheumatology clinical research.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Weiss confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Physician-Scientist Pipeline for Pediatric Rheumatology: The Current Landscape and Future Perspectives

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Over the past 50 years, the science of pediatric rheumatology has grown exponentially due to an expansion in the understanding of complex rheumatic conditions and a surge in novel targeted therapeutics. Physician-scientists in the field of pediatric rheumatology have played major roles in these advancements that have improved the care of children, adolescents, and young adults with chronic and often life-threatening systemic inflammatory diseases. Despite the critical role of the physician-scientist in discovering and translating scientific advancements from the bench to the bedside and vice versa, which have catapulted the field of pediatric rheumatology, this role remains an endangered species, with a declining pipeline due to a variety of factors. In this article, we review the current landscape of the physician-scientist pipeline for pediatric rheumatology on the fiftieth anniversary of the formalization of the specialty in North America. We review challenges to maintaining a thriving physician-scientist pipeline and discuss future perspectives.

Introduction

In 1976, building on foundational efforts from early pioneers who conducted research and cared for children, adolescents, and young adults with rheumatic diseases, the subspecialty of pediatric rheumatology was formalized in North America.¹ A year prior, two past presidents of the American Rheumatism Association (ARA; now called the American College of Rheumatology [ACR]), Dr Lawrence Shulman and Dr Gerald Rodnan appointed the Council of Pediatric Rheumatology within the ARA. The landmark international conference, which heralded the formalization of the specialty, was held March 22 to 25, 1976, in Park City, Utah. This conference, organized by the ARA Council of Pediatric Rheumatology, was chaired by Dr Jane Schaller and Dr Virgil Hanson and was also supported by the Arthritis Foundation, the Shriners of North America, and the Jeffrey and Adelaide Lazarus Foundation. With 59 attendees, this conference focused on the current concepts in pathogenesis, advances, and controversies around the care of pediatric rheumatic diseases at the time to propel future directions for the field, including a national program for research, education, and improved therapies.² Over the past 50 years, physician-scientists in pediatric rheumatology have greatly expanded the depth and breadth of knowledge of the pathophysiology of complex rheumatic diseases, advanced biotechnological

interventions, and optimized novel and effective therapeutics. The current spectrum of research in pediatric rheumatology is vast and includes basic, translational, clinical, epidemiologic, and health services as well as research in outcomes and medical education. Physician-scientists have been critical to this growth.

By consensus, physician-scientists are defined as physicians who devote the majority of their professional effort (ie, >50%) to a defined area within the broad continuum of biomedical research at an academic institution, government agency, industry, or independent research centers and institutes.³ A physician-scientist holds a medical degree, often with a PhD or other advanced degree in research methods. The physician-scientist engages in independent biomedical research while often also maintaining a clinical practice, thus functioning at the interface of science and medicine, leading the acceleration of discoveries that would improve the care of patients. This dual role of the physician-scientist as a clinician and scientist is unique because they translate discoveries to bedside practice and vice versa, thereby propelling transformative discoveries and advancements. As physician-scientists provide clinical care, they have a vantage opportunity to inform their research with what is most pertinent and pressing to patients. They also disseminate scientific knowledge to the science and medical communities as well as to patients, patients' families, and the general public.⁴ Thus,

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80073>.

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Submitted for publication March 13, 2026; accepted in revised form April 15, 2026.

maintaining a pipeline for the entry, training, and growth of physician-scientists in pediatric rheumatology is key to supporting continued exponential advancements in the science and clinical care of patients with pediatric-onset rheumatic diseases.

Despite the recognized need for physician-scientists in general, the path to becoming one is often arduous, and interest in a career as a physician-scientist is declining.^{5,6} In particular, the pipeline for pediatric rheumatology physician-scientists has been plagued with challenges in research training, academic career advancement, and building independent biomedical research programs. These challenges have been further compounded by an aging pediatric rheumatology workforce and a notable predicted shortfall in the number of pediatric rheumatologists needed to meet the needs of the field.^{7,8} The objective of this review is to appraise the current landscape of the physician-scientist pipeline for pediatric rheumatology on the fiftieth anniversary of the formalization of the specialty and discuss future perspectives and implications for research in the field.

Methods

For this narrative review, PubMed searches were conducted using the following medical subject heading terms: “Physician Scientist”; “Physician scientist” AND “training” AND “Rheumatology”; and “Physician scientist” AND “training” AND “education” AND “mentoring.” Relevant articles published up to December 2025 were included.

The physician-scientist pipeline for pediatric rheumatology in North America: the current landscape

In the United States, compared to other pediatric subspecialties (including those with lower procedural burden), pediatric rheumatology still has one of the lowest number of physicians per 100,000 children at 0.27 clinical workforce equivalent.⁸ Correll et al⁸ reviewed records from The American Board of Pediatrics, which showed that as of June 2023, the number of board-certified pediatric rheumatologists ≤ 70 years of age was 508. Of these, 88% had a faculty appointment at an academic institution, and 49% primarily worked at a medical school or university. Pediatric rheumatologists self-reported being mostly clinical faculty (71%), and only 15% spent a majority ($\geq 50\%$) of their time in research.⁸ This highlights the small proportion of pediatric rheumatologists who are physician-scientists. The median age of board-certified pediatric rheumatologists was 45 years old, and one-third (32%) of the 508 pediatric rheumatologists planned to retire between age 65 to 69 years. Thus, projected estimates indicate a significant decline in the total active pediatric rheumatology workforce by 2040. With such a small proportion of physician-scientists at baseline, maintaining a vibrant physician-scientist

workforce in pediatric rheumatology will be even more challenging, yet it will remain critical.

Raising awareness of the challenges of the physician-scientist career track in general, and initiatives to enhance the general medical scientific workforce, is long-standing because similar challenges, although to varying degrees, exist in other specialties.⁹ In 1979, James B. Wyngaarden, in his address to the Association of American Physicians titled “The clinical investigator as an endangered species,” highlighted the dwindling numbers of physician-scientists and was one of the initial prominent voices that raised the importance of maintaining this subset of researchers in the biomedical workforce.⁹ Dr Wyngaarden was the president of the Association of American Physicians at the time and would later become the director of the National Institutes of Health (NIH). The concern for a diminishing pool of physician-scientists in medicine in general has been echoed over the past five decades. The NIH Physician-Scientist Workforce Working Group (PSW-WG) was convened and charged by the NIH director at the time, Dr Francis Collins, to examine the current landscape of the physician-scientist biomedical workforce with a view to make recommendations to address the gaps. The report from this group in 2014 cited increases in the cost of medical education, decreases in NIH funding, more attractive financial compensation offered by clinical practice versus research, work-life imbalance, lack of mentorship, and demanding requirements for maintenance of clinical practice as key challenges confronted by physician-scientists.¹⁰

Nearly a decade later, the National Academies of Sciences, Engineering, and Medicine (NASEM) 2023 report on “Trends in the pediatric physician-scientist workforce” also acknowledged the continued decline in the number of physician-scientists plus other similar issues as the PSW-WG 2014 report. The NASEM 2023 report also highlighted specific challenges in pediatrics, including MD-PhD graduates opting for pediatric residencies less often, uncertainties in research funding, an aging physician-scientist workforce, a decline in the number of new physician-scientists entering the workforce, and attrition from research careers at various stages as contributors to the diminishing pool of physician-scientists.¹¹ There is poor retention of midcareer physician-scientists in pediatrics in general, and physician-scientist attrition rates specific to pediatric subspecialties are unknown. It was noted that, on average, $<8\%$ of all pediatric subspecialists self-report spending $>50\%$ of their professional efforts on research, from the American Board of Pediatrics 2023 data on maintenance of certifications. Specifically, 14.2% of pediatric rheumatologists self-reported spending $>50\%$ of their professional effort on research.

Currently, training for a physician-scientist career in pediatric rheumatology is similar to most pediatric subspecialties, beginning with medical school, then residency, and then fellowship (Figure 1).¹² Structured advanced training in research can occur at any of those levels, such as through an MD-PhD program, research-oriented residency program, and/or a graduate degree

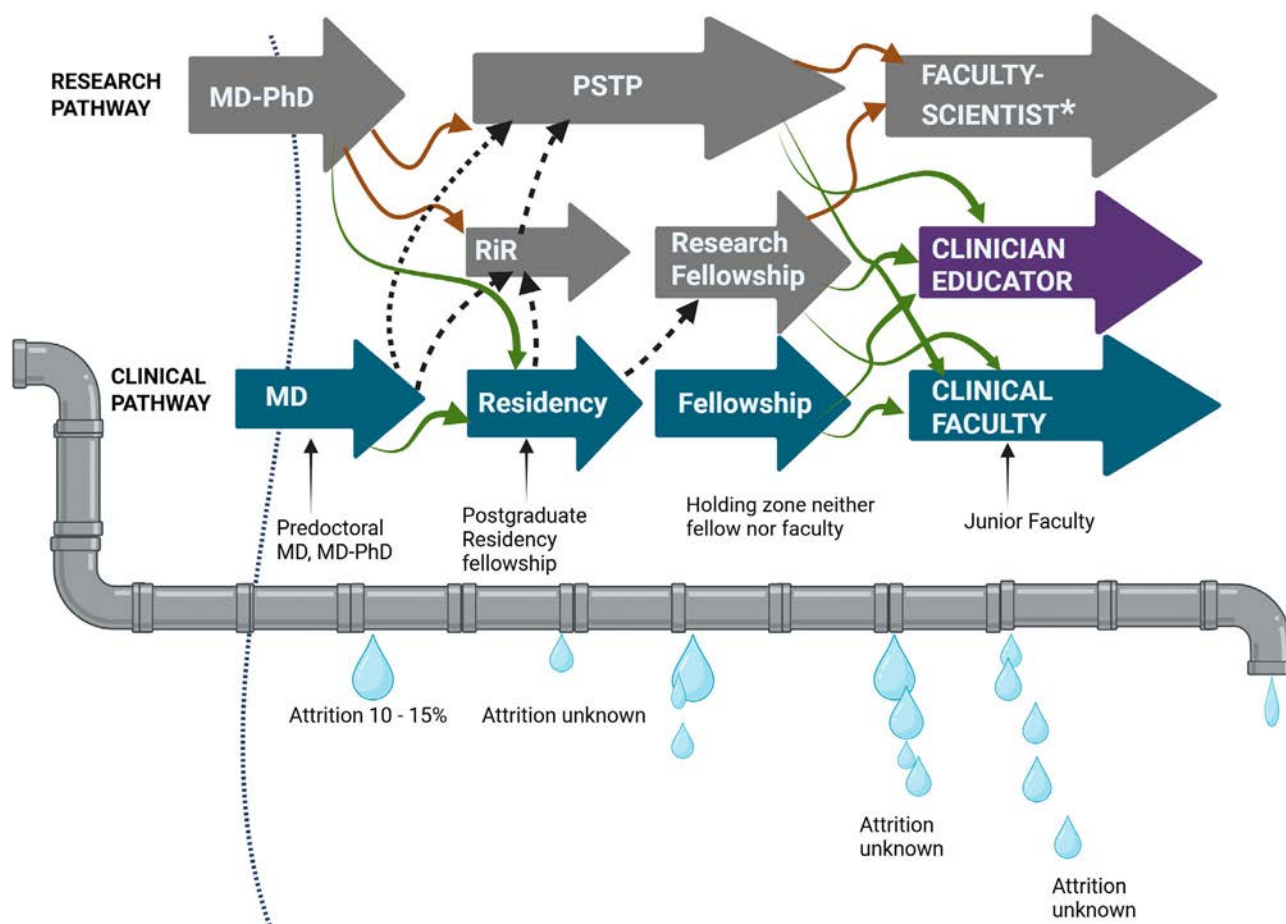


Figure 1. The physician-scientist career path. A schematic representation of the leaky physician-scientist pipeline showing transitions from training to independent research and clinical practice. The block arrows represent training opportunities. The rest of the arrows indicate options for transitions between training programs: red arrows denote transitions within the standard research-based physician-scientist training pathway; black arrows with dotted lines indicate other options for transitions for on-ramps; and green arrows indicate points of physician-scientist attrition from research-focused careers. *Faculty-scientists may also obtain graduate-level training in research, such as master's and/or PhD. PSTP, physician-scientist training program; RiR, research in residency. Source: Adapted from Williams et al.¹³ Used with permission of *JCI Insight*. Permission obtained through Copyright Clearance Center. Re-created in <https://www.biorender.com/> by Dr Ogbu.

in a research domain, such as clinical research, epidemiology, immunology, or public health.^{13–18} However, early exposure to the science of pediatric rheumatology is still a challenge because 40% of pediatric residency programs and medical schools do not have pediatric rheumatologists on faculty, which limits trainee exposure to the field.¹⁹ This lack of exposure to the field of pediatric rheumatology extends to the general public, including primary, secondary, and undergraduate education levels, which are formative periods for decisions on career options, particularly for science, technology, engineering, and mathematics careers.^{8,20–22}

To address the biomedical pipeline challenges, several academic institutions, albeit large centers with a critical mass of faculty researchers and resources, have developed programs to increase local physician-scientist pipelines, which leverage external resources from federal funding and private foundations.^{20,21} The NIH, as the largest funder of biomedical research and training in the United States, has instituted initiatives, such as the predoctoral MD-PhD medical scientist training program,¹³ predoctoral

and postdoctoral T32 research training grants, K08 and K23 mentored career development awards, the K99 and R00 pathway to independence award, and KL2 and TL1 Clinical and Translational Science Awards for qualifying institutions to award to increase earlier exposure to research and foster successful transition to independent research.⁷ The Howard Hughes Medical Institute (HHMI) established its Early Career Physician-Scientist award in 2006, supporting physicians within the HHMI-NIH Research Scholars program. The Burroughs Wellcome Fund created the Physician-Scientist Institutional Awards program in 2017, which was instituted to support academic institutions in developing programs that would encourage an influx of physician-scientists and support effective mentoring.²³ From publicly available records on NIH RePORTER, in the past 10 years, the NIH K24 Midcareer Investigator Award has supported more pediatric rheumatology scientist faculty to devote time to mentoring early physician-scientists in patient-oriented research. All of these mechanisms have been beneficial in

training the physician-scientist workforce, although accurate summative data on the proportion of pediatric rheumatology physician-scientists who have received these awards are not readily available, so direct impact on the field is hard to quantify. Moreover, “success metrics,” such as summative data on the rate of recipients achieving their first independent NIH R01 or R01-type award and at what average age or stage of career, are not readily available.

Specific opportunities to support the development of pediatric rheumatologists interested in a career in research have used joint partnerships between national pediatric and rheumatologic associations and foundations. The Association of Medical School Pediatric Department Chairs Pediatric Scientist Development Program added one new position for pediatric rheumatology in 2026. This position is cofunded by the Rheumatology Research Foundation (RRF), Childhood Arthritis and Rheumatology Research Alliance (CARRA), and the Arthritis Foundation, and it will support a pediatric rheumatology fellow (MD, DO, or MD/PhD) who is pursuing a long-term research career in childhood rheumatic diseases. Other mentored career development awards for pediatric rheumatology physician-scientists are offered separately by the RRF, CARRA, the Arthritis Foundation, and other disease-specific foundations, such as the Lupus Research Alliance. Overall, these opportunities can be leveraged to strengthen the current pediatric rheumatology physician-scientist workforce pipeline, although some specific barriers and facilitators to the field of pediatric rheumatology must be taken into consideration.

Barriers and facilitators to physician-scientist careers in pediatric rheumatology

In 2014, Ogdie et al²⁴ surveyed US-based members of the ACR to determine perceived barriers to and facilitators of a career in rheumatology research. They received 502 (9.2%) responses from surveying 5,448 recipients. However, 72 responses were incomplete, duplicates, or from nonrheumatologists and so were excluded. Of the 430 final respondents included in the report, 62 were pediatric rheumatologists, and 17 were pediatric rheumatology fellows. There were 309 adult rheumatologists and 42 adult rheumatology fellows.²⁴ The majority of respondents (305; 71%) were at academic centers, of which 171 (147 faculty and 24 fellows) were actively pursuing research careers. Of the 171 currently in research, 134 (78%) and 100 (58%) had ≥50% and ≥70% research effort, respectively. The most commonly perceived barriers to a career in research included lack of funding and lack of outstanding mentorship. Provision of these two factors, as well as specific funding for early investigators, protected research time, institutional support, and personal skills or traits (eg, hard work, resilience, initiative, persistence, and passion) were felt to be necessary facilitators for a career in research.

Several of the 430 respondents had received some form of research funding, ranging from foundation fellowship or postdoctoral awards (n = 92; 21%), foundation career development

awards (n = 99; 23%), NIH Loan Repayment Programs (n = 24; 6%), NIH K series or Veterans Affairs career development awards (n = 76; 18%), NIH R01 awards (n = 59; 14%), other NIH awards (n = 71; 17%), and any other grants (n = 141; 33%). However, collectively, attrition across the spectrum of basic, clinical, epidemiologic, and translational research career paths was high at 23% (n = 97), often occurring at a median of 7 years after fellowship training (interquartile range 2–14 years). The most common reasons for attrition from a research career included difficulty in obtaining research funding and lack of departmental and divisional support, which included lack of protected time (Table 1).²⁴ Other reasons included lack of institutional research infrastructure, clear career path, and access to mentorship. Local politics and conflicts, including with division chiefs, were also reasons for leaving. Additional suggestions the authors made for facilitating physician-scientist careers included early research exposure from medical school through fellowship, grant writing training, peer mentoring, formal research training, standards for research training in fellowship or a core research curriculum, career development workshops, improved investigator compensation, and access to loan repayment programs.

With the rising demands of clinical care, the shortfall in the pediatric rheumatology clinical workforce, and clinical care being more financially profitable, protecting time for research is often a challenge for academic health centers. Physician-scientists hold a “dual identity” as both scholars and active practitioners who generate revenue for the health system,²⁵ which is a reality that may be hard to navigate as the workforce shrinks and clinical needs in the field grow. Defining the value proposition for pediatric rheumatology clinical care and research may help address this barrier. In such a relatively new subspecialty, the need for scientific innovation is paramount to advance the field. In the same study by Ogdie et al,²⁴ participants suggested that the ACR had a role in educating department chairs, division chiefs, and fellowship directors on how best to support physician-scientists, including investigators from institutions without strong research

Table 1. Causes of attrition from research careers from on a survey of 97 US-based adult and pediatric rheumatology physician-scientists*

Factor	Physician-scientists (N = 97), n (%)
Difficulty obtaining grant funding	55 (57)
Lack of divisional and departmental support	51 (53)
Better compensation	38 (39)
Lack of mentorship	38 (39)
Tired of writing grants	33 (34)
Personal reasons, such as family or moved to preferred geographic location	26 (27)
Desire to spend more time in clinical care	20 (21)
Industry opportunity	10 (10)
Not enjoying research work	6 (6)

* Source: Adapted from Ogdie et al.²⁴

infrastructure. However, specific details on the preferred scope of education or format to adopt in liaising with department and divisional leadership were not reported.

In Canada, impediments to research careers for physician-scientists, inclusive of pediatric rheumatologists, have been identified as rising medical school tuition costs, salaries and funding for research, and poor mentorship.²⁶ These challenges were further worsened by the termination of the MD-PhD program grants by the Canadian Institutes of Health Research in 2016.²⁶ Thus, a national consensus conference was convened in 2016 to address the declining physician-scientist workforce, specifically to give recommendations for training programs and support for early career physician-scientists.²⁷ It was recommended that an independent national council be established to provide oversight of physician-scientist training programs, offer multiyear funding, and track outcomes. In addition, funding of a physician-scientist trainee was to be viewed as portable and distinct from the operational funding provided to a training program. It was recommended to develop capacity for funding and mentorship support, develop diverse networks of physician-scientists with other scientists, and ensure that research methodologies were integrated in medical school curricula.^{26,27}

Structured research mentorship models in pediatric rheumatology

Lack of effective mentoring is one of the most common barriers to research career success.²³ There have been multipronged structured mentorship approaches to sustain the physician-scientist pipeline from trainee level to independent faculty in pediatric rheumatology. Beyond efforts at the academic institution and federal level, initiatives from the ACR, the RRF, and CARRA have also helped to provide platforms for longitudinal mentorship specific to the pediatric rheumatologist.

The ACR/CARRA Mentoring Interest Group (AMIGO) is a collaboration that started in 2010 following a survey of the ACR and CARRA membership that supported mentorship and networking as key unmet needs in pediatric rheumatology as well as a networking symposium in 2011.²⁸ Mentees and mentors, both from the United States and Canada, are matched based on complementary career paths, including physician-scientist paths in basic, translational, or clinical research, and other reported career development needs. The AMIGO mentors are at the assistant professor level and above. The AMIGO mentees are fellow trainees or junior faculty (instructors or assistant professors). Junior faculty mentors are matched with fellows, and senior faculty mentors (associate professors and full professors) are matched with junior faculty.

A study to evaluate the outcomes of the AMIGO program from 2011 to 2018 was recently published in 2024.²⁹ The results showed continued interest in the program by mentees and mentors, with steady growth in the number of active mentor-mentee

dyads, and overall participation in AMIGO at about 66% (331 of 504) of the entire US and Canadian pediatric rheumatology community. However, the long-term impact of the AMIGO program on the development of the pediatric rheumatology physician-scientist mentee to independence is yet to be systematically determined.

The Rheumatology Research Workshop, annually organized by the ACR Committee on Research, the ACR Early Career Investigator Committee, and the RRF, provides an avenue for education in the rudiments of successful research careers, peer networking, and establishing longitudinal mentorship between early and established pediatric rheumatology physician-scientists. Travel grants are provided for investigators to attend the Rheumatology Research Workshop.

Similarly, CARRA's Early Career Investigator Workgroup identifies the needs of this unique subgroup of researchers and provides support, peer mentoring, and advocacy. CARRA also offers grant mechanisms to not only fund mentored career development projects, but also travel grants for early career investigators to attend the VERITY/Brigham Course in Rheumatology Clinical Research, the annual European Paediatric Rheumatology Congress, and the Eureka International Summer Course on Translational Medicine in Utrecht, the Netherlands.

Pediatric rheumatology physician-scientist pipeline: the global perspective

Maintaining a viable pipeline for physician-scientists in pediatric rheumatology and a thriving independent research career is a shared global responsibility. Although there are national and regional peculiarities in undergraduate and postgraduate training, such as length of training, there are shared themes in the barriers and solutions to research success.^{30–32} The end goal of raising the next generation of successful scientists is the same, and the physician-scientist has a role in driving initiatives that would sustain the research pipeline.³⁰

The Eureka Institute for Translational Medicine was founded in 2008 by Drs Berent Prakken and Salvatore Albani, both pediatric rheumatologists. Based in Italy, this nonprofit supports a global network of universities and research organizations by offering virtual schools and international courses at the graduate and postgraduate levels for clinician-scientists, inclusive of physician-scientists and nonclinician-scientists.^{6,33,34} Specific to pediatric rheumatology, the Eureka Institute for Translational Medicine has had a long-standing partnership with CARRA to support a one-week summer experience in the Netherlands in translational medicine for trainees and early stage investigators. This model has provided longitudinal external mentorship within a scientific community for budding pediatric rheumatology physician-scientists.³⁵ In 2017, there was a meeting of The International Expert Group on the Clinician–Scientist Workforce comprising representatives from the Eureka Institute of Translational Medicine, Association

of American Medical Colleges, Association of Faculties of Medicine of Canada, and Royal College of Physicians and Surgeons of Canada, as well as trainees and independent researchers. Their two-day meeting aimed to identify the current institutional and societal gaps in supporting future physician-scientists and other scientists and generate solutions for addressing those gaps.³⁶ Three key proposed solutions came from this meeting: (1) appropriately articulate the value proposition of clinician-scientists, inclusive of physician-scientists. The value proposition of the clinician-scientist has been hampered by lack of clear definitions and measurable metrics that capture the broad impact of the clinician-scientist within the biomedical sciences and health care stratosphere. (2) Support professionalization and professional identity development of the clinician-scientist. The rationale was the perception that most funding and promotion structures rewarded full-time scientists and clinicians but did not adequately address those combining clinical practice and research. Finally, (3) continue integration of clinical and research training, as through MD-PhD programs, and at the postgraduate and post-doctoral level.³⁶

Similar to North America, the Emerging EULAR Network (EMEUNET), which is a network of young rheumatologists and researchers within EULAR, has initiatives to support emerging researchers in pediatric and adult rheumatology.³⁷ EMEUNET conducted a survey in 2012 to understand the perceptions of the landscape of mentoring for rheumatology in Europe and the benefit of having a structured mentoring program within EULAR. Of the 248 responses from 30 European countries, 52% (n = 128) reported the existence of formal mentoring programs in their countries. Only 2 of 248 reported completing pediatric rheumatology specialty training. However, the majority of responses (82%; n = 181 of 221) agreed with the need for a formal mentoring program through EULAR.

Future perspectives on the pediatric rheumatology physician-scientist pipeline

Physician-scientists will continue to play a key role in future biomedical advancements in the field of pediatric rheumatology. Intentionally building a physician-scientist workforce across the various research categories for pediatric rheumatology remains necessary to maintain this specialty at the cutting-edge of discovery and innovative clinical care delivery. Sustaining a vibrant pediatric rheumatology physician-scientist workforce must involve measures that (1) increase interest in pediatric rheumatology as a career for research as well as clinical care; (2) increase opportunities to engage in research at different career stages; (3) support resiliency in research; (4) decrease departures from the physician-scientist pipeline; (5) promote and sustain effective mentorship systems; and (6) strengthen a diverse, comprehensive scientific community in terms of the focus of science (from bench to bedside), inclusive of those disadvantaged from accessing

opportunities to pursue research careers (such as individuals underrepresented in medicine and trainees from academic institutions without established strong research training or infrastructure).^{38–42}

Preserving entry to the pediatric rheumatology physician-scientist pipeline would require specific consideration when changes to medical school, residency, and fellowship curricular and competencies are being determined.^{43–46} New changes in US pediatric residency program requirements by the Accreditation Council of Graduate Medical Education were proposed in 2025.⁴⁷ These changes include an increase in individualized curriculum time, which could provide an opportunity for additional and earlier exposure to the pediatric rheumatology specialty. An increasing number of publications related to length of subspecialty fellowship training, inclusive of pediatric rheumatology, have emerged. Many note that excellent competency-based clinical training can be achieved in less than the currently prescribed three-year period, and distinct additional training pathways for fellows interested in a long-term career as physician-scientists could be considered.^{48–53} Although flexibility in pediatric rheumatology fellowship training has several merits, the potential impact of curriculum adjustments on physician-scientist training needs to be thoughtfully weighed to sustain interest in this career path and early exposure to research methodology and mentorship. Entrustable Professional Activities have previously been defined for translational scientists, which could be applied to pediatric rheumatology.⁵⁴

Additionally, research training for the pediatric rheumatology physician-scientist should include preparedness for diverse research career trajectories and effective mentorship.^{55–59} The NIH Biomedical Research Workforce Working Group was tasked with developing a model for sustainable and diverse biomedical research workforce. The 2012 executive summary from this group highlighted the limitation of graduate training programs in preparing graduates for diverse careers in research in various aspects (such as academia, pharmaceuticals, and research institutes), and although training should be improved by the programs, it should not add to the length of training.⁶⁰

Supporting resiliency through mentorship is necessary for retention of the pediatric rheumatology physician-scientist workforce. Dr Michelle Kahlenberg, a renowned rheumatology physician-scientist, emphasized the benefit of longitudinal supportive mentorship and openness of mentors in her editorial, “Mentorship of physician scientists: a critical imperative,” discussing both successes and seeming failures in research with their mentees to support resiliency in research.^{61–64} Dr Kahlenberg noted,

“Roughly 90% of grants are not funded. Acceptance rates at top-tier journals vary but run at around 10%. Failure in academic medicine is the norm, not the exception.” (Dr Michelle Kahlenberg)⁶¹

A perspective commentary from the Society for Pediatric Research also supports this stance, noting that effective mentorship is relevant in all stages of the research career, including early and midcareer.²² Effective mentoring builds on a strong mentor-mentee relationship, which is defined as a dynamic, reciprocal relationship in a work environment between an advanced career incumbent (the mentor) and a beginner (the mentee), aimed at promoting the development of both.⁶² Undoubtedly, structured institutional mentoring programs tailored toward the physician-scientist is beneficial for cultivating an effective mentoring atmosphere. In addition, given the success of the unique AMIGO model for fostering networking in the North American pediatric rheumatology community beyond practice location and academic institutional confines, harnessing this already existing model to specifically offer effective mentorship for physician-scientists and track outcomes is feasible and will be of utmost value.

Conclusions

Since formalization of the field in North America 50 years ago, pediatric rheumatologists have continued to improve the care provided to children, adolescents, and young adults with rheumatic diseases, despite a small workforce that is in jeopardy of more significant future shortfalls. The role of the physician-scientist is particularly at risk, yet it is crucial to advancing the understanding of the complex autoimmune and autoinflammatory conditions faced in the clinic and optimizing ways to treat and even cure these conditions. Thoughtful, intentional, multipronged global approaches are necessary to preserve and enhance the pediatric rheumatology physician-scientist pipeline. This will be necessary to advance our understanding of complex and severe immunologic diseases, develop biotechnological interventions, and optimize clinical care that will improve outcomes for children, adolescents, and young adults with rheumatic diseases.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ogbu confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW ARTICLE

Three Decades of Health Care Transition in Rheumatology: Progress, Challenges, and Future Directions

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The revolution of treatment advances for children with rheumatic diseases since the advent of pediatric rheumatology has coincided with the growing recognition that many of these children will continue to require long-term rheumatology care after reaching adulthood. Moreover, it has become evident that effective, systematic approaches are needed to help adolescents and young adults (AYAs) with pediatric rheumatic diseases learn to manage their health independently and succeed in an adult-oriented model of health care. In this narrative literature review, we provide a historical perspective on health care transition and its relevance to the field of rheumatology. Second, we review seminal literature on outcomes of transition and transition-related needs of AYAs with pediatric-onset rheumatic diseases. Third, we describe interventions designed to improve health care transition for AYAs with pediatric rheumatic diseases. Lastly, we discuss remaining knowledge gaps and future directions for the field.

Introduction

Up to 50% of adolescents and young adults (AYAs) with pediatric-onset rheumatic disease are lost to follow-up in the process of moving from a family-centered model of health care to an adult-oriented care.^{1–3} This statistic is especially concerning given the ongoing disease activity and severity in this population. Active disease and requirements for disease-modifying antirheumatic drugs frequently persist into adulthood for individuals with juvenile idiopathic arthritis (JIA),^{4–6} whereas those with childhood-onset systemic lupus erythematosus (cSLE) and juvenile dermatomyositis are at risk for greater long-term morbidity due to more frequent and severe major organ involvement compared to adult-onset counterparts.^{7,8} Less common but highly morbid conditions, such as vasculitis, sarcoidosis, and systemic autoinflammatory diseases, also frequently require ongoing care in adulthood.^{9–11} As concluded from a survey of pediatric rheumatologists, the “rarity, chronicity, and complexity” of pediatric-onset rheumatic diseases pose significant challenges to the care of transitioning AYAs, and more effective health care transition management constitutes a “clear area for improvement.”¹²

The term “transition” was initially defined by the Society of Adolescent Medicine as “the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care

systems.”¹³ This definition has expanded over time to encompass the active and planned process of preparing young people for the adult health system, as well as the transfer (ie, the “hand-off”) and integration into adult care.¹⁴ In this narrative literature review, we discuss (1) the history of health care transition and its contextualization within rheumatology, (2) transition outcomes and challenges to effective transition, (3) interventions aimed at improving transition outcomes, and (4) remaining knowledge gaps and priorities for future study.

Methods. This work constitutes a narrative literature review of published data. It did not involve interaction with human participants or collection of primary data. As such, it did not require oversight by an institutional review board.

Where it all started: The history of health care transition and its relevance to rheumatology

In 1989, the US Surgeon General, Dr C. Everett Koop, held a surgeon general’s conference, “Growing Up and Getting Medical Care,” from which a call to action was issued: develop plans for establishing guidelines for transition and outline the basis of financial coverage.¹⁵ The Maternal and Child Health Bureau (MCHB), directed by Dr Merle McPherson, was tasked with implementing

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80101>.

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Submitted for publication March 19, 2026; accepted in revised form June 1, 2026.

this mandate and subsequently funded a series of special projects related to transition, as well as the first national resource center on transition, Got Transition. In 2002, the first consensus statement on transition by the American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), and American College of Physicians (ACP)–American Society of Internal Medicine highlighted the growing number of children with special health care needs who were surviving into adulthood.¹⁶ The timing was fitting for the field of rheumatology, in which the development of drugs during the late 1990s and early 2000s—namely targeted biologic therapies—revolutionized the treatment of many rheumatic diseases and shifted the focus from survival to long-term management. The 2002 consensus statement tasked physicians caring for AYAs to develop knowledge and skills to facilitate the transition process. The creation of an individualized health care transition plan, maintenance of a medical summary, and identification of a health care professional who would assume responsibility for the patient's health care transition were among the key recommendations.¹⁶ The British Department of Health called for these interventions with similar urgency in a 2004 National Service Framework publication.¹⁷

Both early statements aligned with a growing recognition of unmet transition needs within rheumatology among health care providers, patients, and families. Rheumatology health care professionals were noted to have a lack of education on the subject of transition.^{18,19} Adolescents with JIA and their caregivers expressed a desire for a more individualized assessment of an adolescent's needs.²⁰ Hersh et al²¹ showed that missed appointments and disease flares were common among AYAs with rheumatic diseases during the transfer period, highlighting the need for systematic care processes to ensure seamless transfer of care. The first description of a coordinated transition program for AYAs with pediatric rheumatic diseases was published by Rettig and Athreya²² in 1991, in which provision of transitional care by an MCHB-funded nurse coordinator and social worker resulted in high retention rates in adult care. Thereafter, additional studies began to show that coordinated efforts to support the transition process for AYAs with JIA and SLE could positively impact quality of life and disease activity, respectively.^{23,24} These efforts paralleled the emergence of dedicated transition interventions for youth with other chronic conditions, such as type 1 diabetes mellitus, inflammatory bowel disease, and kidney transplant, designed to address the high rates of emergency care use and hospitalizations, graft loss, and mortality following transfer to adult care.^{25–27}

The 2010s marked the development of frameworks emphasizing the principles and goals of health care transition, as well as process models to guide health care professionals through actionable steps to achieve effective transitions. The 2011 AAP/AAFP/ACP “Clinical Report on Transition” described the implementation of transition-based practices and became the basis for the widely used process model, “Six Core Elements

of Health Care Transition.” This model aligns with a broader framework in the United States’ national program, Got Transition, which includes advocacy for systems-level and policy changes.^{14,28} These six elements—transition policy/guide, transition tracking and monitoring, transition readiness, transition planning, transfer of care, and transfer completion—continue to be championed today to accomplish the goals of improving AYAs’ ability to manage their health in a developmentally appropriate manner, organizing a seamless transfer between health systems, and ensuring integration and engagement with adult-centered care. The contemporary version 3.0 of the Six Core Elements places greater emphasis on the integration into adult-oriented care in alignment with the 2018 update of the AAP/AAFP/ACP Clinical Report on Transition and therefore includes separate packages tailored to adult and dual internal medicine–pediatrics (Med-Peds) providers (Figure 1) in addition to pediatric providers.^{14,29} Similar guidance was established in other countries, such as the United Kingdom, where the National Institute for Health and Care Excellence (NICE) 2016 Guidelines grew out of the foundation laid by the 2004 National Service Framework. The NICE Guidelines additionally recommend a dedicated transition coordinator to help AYAs navigate both medical care and social services.³⁰ Consensus recommendations, guides, and checklists specific to the care of AYAs with pediatric-onset rheumatic diseases subsequently emerged across Europe^{31–34} and parts of Asia.^{35–37} These resources emphasize the gradual, intentional, years-long processes involving patients, caregivers, pediatric services, and adult services that are required to meet the transitional care needs of AYAs with pediatric rheumatic diseases.

Transition outcomes in rheumatology

The Institute for Healthcare Improvement’s “Triple Aim” is an evaluation framework that has been used as a barometer for effective health care transition based on the achievement of three goals: improving patient experience of care (eg, satisfaction), reducing cost (eg, gaps in care, service use), and improving population health (eg, adherence, disease-specific measures, patient-reported outcomes).³⁸ In the context of rheumatology, the literature to date has described transitions as falling short of achieving these goals. A qualitative systematic review of patients’ experiences transitioning to adult rheumatology highlighted feelings of abandonment, a fear of the unknown, and a perception of invalidation in adult care among youth with childhood-onset rheumatic diseases.³⁹ Regarding cost, there are a number of observational studies that have documented significant gaps in care and poor service use.⁴⁰ For example, the mean time between the final pediatric and first completed adult rheumatology visit has ranged in US studies from seven to nine months,^{21,41,42} despite pediatric rheumatologists’ assertion that seeing an adult rheumatologist within six months of the final

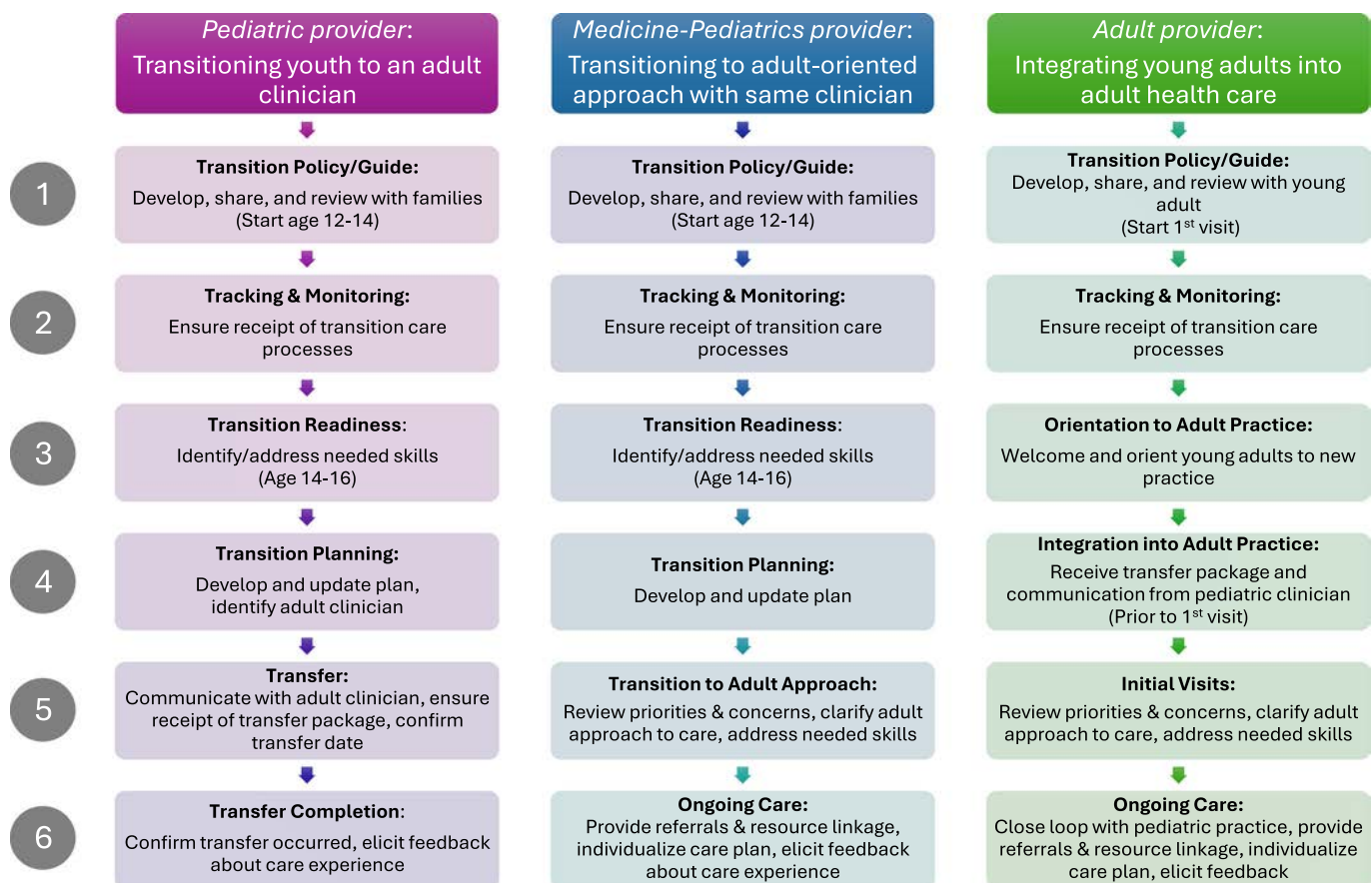


Figure 1. Components of a structured transition process defined by the Six Core Elements of Health Care Transition version 3.0, tailored to different types of practice models that may be transferring or receiving adolescents and young adults with special health care needs. *Source:* White P, Schmidt A, Shorr J, et al. *Six Core Elements of Health Care Transition 3.0*. Got Transition, The National Alliance to Advance Adolescent Health; 2020. Accessed January 8, 2026. <https://www.gottransition.org/six-core-elements/>.²⁹

pediatric rheumatology visit is a “very important” outcome of the transition process.⁴³

With respect to population health outcomes, the impact of care discontinuity on disease-specific measures, patient-reported outcomes, and damage accrual is substantial. Gaps in medical care of more than six months have been shown to correlate with significantly more pain, functional impairments, and overall worse health status among young adults with JIA in Germany.⁴⁴ The peri-transfer period for young adults with JIA is marked by a high prevalence of persistent pain and self-reported anxiety or depression.⁴⁵ Several studies of transferring AYAs with cSLE have demonstrated lower rates of medication adherence, increased emergency care visits, and increased constitutional symptoms, albeit no differences in disease activity measures compared to those remaining in pediatric care.^{46–48} Importantly, alarming rates of end-stage renal disease or death (15%) have been described in young adults with cSLE during the posttransfer period,⁴² as well as increased rates of anxiety, depression, and damage accrual.⁴¹ These findings highlight the consequences of ineffective transitions and the urgent need for

systematic approaches to support AYAs with rheumatic conditions through this vulnerable period.

Barriers to transition care in rheumatology

Barriers to transition care for AYAs with rheumatic conditions span system, patient, and provider levels. At the system level, discontinuity in insurance coverage has been identified as a strong determinant of delays during transfer of care for AYAs living in the United States.^{42,49} However, even among privately insured AYAs with cSLE transferring to adult care, over 25% experienced a gap in care of over 12 months, highlighting the multifactorial nature of transition barriers.⁴⁶ For health care teams, the lack of standardized care processes to support transition leave AYAs with rheumatic conditions ill-prepared for adult-oriented care models across various global contexts. For example, in their single-center US study, Jensen et al⁵⁰ showed that only 40% of AYAs with chronic disease, 56% of whom had a rheumatic disease, reported ever having discussed transition to adult care with their pediatric provider. In Europe, a survey of pediatric

rheumatologists revealed that although 99% of pediatric rheumatologists agree that a formalized process is necessary, over one-quarter worked at centers that did not offer any transition services.⁵¹ Dolezalova et al¹² also cited the lack of standardized clinical guidelines and insufficient planning related to management of the transition process across Europe, highlighting the need for a structured approach. Moreover, the lack of a universally agreed-upon definition of “successful transition” or set of specific measures to use within the Triple Aim framework⁵² complicates local goal-setting efforts by health care providers. For example, with respect to service use outcomes, some studies consider a single visit to the adult rheumatology clinic to constitute a successful transfer,⁵³ others require two visits,⁵⁴ and still others report a “dropout” after two consecutive visits missed.⁵⁵ On the other hand, a retrospective investigation in Turkey required annual adult rheumatology visits for the duration of follow-up to be considered a successful transfer, and only 8.2% of over 2,500 patients met these criteria.⁵⁶

Psychosocial factors emerge as a central barrier to smooth transitions from pediatric-to-adult-centered care. AYAs with rheumatic disease describe emotional difficulties during their transition from pediatric-to-adult-centered care—a time in which even healthy peers undergo significant developmental challenges. They have reported feeling confronted during transition by the long-term nature of their disease, judging the adult health care setting to be “stressful” and “gloomy,” and finding it difficult to “warm up” to adult rheumatologists who did not demonstrate interest in their personal goals.⁵⁷ Emotional attachments to and reliance on pediatric providers are a major challenge.⁴⁹ Young adults with cSLE have attributed “their indecision and delay in deciding crucial components of their healthcare” in the adult health system⁵⁸ to their close relationship with pediatric providers. They have also recommended prioritizing research aimed at mitigating poor psychological outcomes.⁵⁹ Knight et al⁶⁰ proposed a psychosocial model of an “illness experience” and noted that AYAs with cSLE who have negative illness identities described difficulty transitioning to adult care. From the perspective of health care providers, mental health support for patients, resilience and coping strategies, balance in family involvement, and peer support have been identified as psychosocial facilitators of effective transitional care.⁶¹ These studies point to the importance of addressing psychosocial needs of AYAs throughout the transition process.

Equally pressing is a lack of training in transitional care among pediatric and adult rheumatology providers. Following broader dissemination of the AAP/AAFP/ACP Clinical Report on Transition and the Six Core Elements, knowledge about transitional care improved among surveyed pediatric rheumatologist members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). However, there has not been widespread adoption of structured health care transition processes. Only 17% of pediatric rheumatology offices had a transition policy,

and 63% of pediatric rheumatologists did not consistently address the topic of transition with patients.⁶² Knowledge gaps among adult rheumatologists also remain a concern due to discomfort with conditions less commonly seen in adult-onset disease (eg, uveitis and temporomandibular joint arthritis)^{4,63,64} and best practices for transitional care. A survey of adult rheumatologists in the United States found that 37% did not have a plan for receiving patients transitioning from pediatric care, 45% had not received education in transition practices, 75% were not familiar with the 2002 consensus statement, and 93% were unsatisfied with the current transition process.⁶⁵ Further, in a survey of adult rheumatologists in Canada, despite significant interest in learning about transition best practices, 74% had no formal training, only 40% felt comfortable discussing psychosocial concerns, only 13% had sufficient resources to address transition-related concerns, and over 75% lacked time and remuneration for providing transitional care.⁶⁶ Adult rheumatologists in Japan similarly expressed interest but lack of preparation for treating AYAs with pediatric rheumatic diseases.⁶⁷ These findings highlight the need to incorporate transitional care into formal training pathways and address provider-level barriers to integration of AYAs into adult rheumatology care.

Interventions to improve transition outcomes

The previous sections have highlighted the deficiencies in rheumatologic transition care and the need for interventions to address transition barriers and improve outcomes. In the broader context of supporting health care transition of youth with special health care needs, there is evidence that structured health care transition processes improve various outcomes within the Triple Aim, as outlined in systematic reviews by Gabriel et al⁵² and Schmidt et al⁶⁸. Many of the included studies focused on conditions with similar complexity as rheumatic diseases, including type 1 diabetes and inflammatory bowel disease. Those with positive outcomes described multiple intervention components, most commonly related to transfer assistance, transition planning and/or care coordination, and sometimes support for integration in adult care.^{68,69} In pediatric rheumatology, a number of health care transition interventions have been implemented to improve transition outcomes for youth with pediatric rheumatic conditions within various contexts. The outcome measures used to evaluate these interventions vary widely across studies. We categorize the interventions according to a qualitative assessment of their focus: (1) transition policies, (2) transition readiness assessment, (3) designation of a transition coordinator, (4) educational initiatives, and (5) multicomponent transition programs with or without a dedicated transition clinic.

Transition policies/guides. The use of a written transition policy or guide to establish shared expectations about the transition process is a core component of the Six Core Elements. AYAs

have shared their recommendations that a transition policy be clearly displayed, introduced to patients between ages 12 and 14 years old, discussed specifically with each patient, and framed as a process through which AYAs would be supported by their pediatric rheumatologist.⁷⁰ Most often, transition guides are included as one aspect of a multicomponent intervention.^{23,53,71} There is one multicenter study in which implementation of a written transition guide was studied as a discrete intervention. A one-group pretest–posttest design was used to evaluate the effectiveness of a learning collaborative to implement transition guides and demonstrated an average increase in the proportion of AYAs who reported receiving a transition policy and discussing transfer planning with their care team.⁷²

Transition readiness. Several studies focus on the implementation of transition readiness assessments, which are intended to help identify and address gaps in knowledge and self-management skills in AYAs with rheumatic diseases. In a US study, baseline scores of the validated Transition Readiness Assessment Questionnaire (TRAQ) did not predict time to transfer to an adult provider.⁵⁰ However, with the use of a locally adapted readiness assessment that included the TRAQ in Singapore, higher baseline scores were associated with adult clinic attendance, and lower baseline scores were used to personalize patient–family educational interventions.⁷³ Additional studies have also assessed the use of the TRAQ at a single time point across various global contexts, including the United States, Portugal, Turkey, and Serbia.^{74–77} Of note, no associations between socioeconomic status or parental education and results of the TRAQ have been identified.^{75,77} Other transition readiness assessments that have been used in the pediatric rheumatology context include the Transition-Q, a 14-item questionnaire focused solely on self-management skills,⁷⁸ and the Readiness for Transition Questionnaire, which has been used to show that patients were ill-prepared for adult-oriented care.⁷⁹ Disease-specific transition readiness assessment tools include Readiness for Adult Care in Rheumatology, which was developed, validated, and implemented in Canada for use with patients with JIA,⁸⁰ as well as the Transition-KompAZ, developed in Germany, which includes items assessing disease-related knowledge and competencies.⁸¹ Argraves et al⁸² outlined challenges of building a sustainable model for tracking transition readiness in a US outpatient pediatric rheumatology practice but demonstrated that quality improvement methodology and clinical informatics principles could be successfully leveraged; whether this change in process associates with better transition outcomes remains to be determined. Overall, although transition readiness assessments have been used in a variety of settings, their longitudinal use has rarely been evaluated, and it is not well described whether the functional goal of remediating identified gaps has been accomplished as intended.⁸³

Transition coordinator. The designation of a transition coordinator has been considered impactful across a variety of settings. However, the functional role of transition coordinators and their professional backgrounds (eg, nursing, social work, case management) vary across studies. Jensen et al⁵⁴ showed that the integration of a social worker in an American pediatric rheumatology clinic to help patients establish and progress toward transition-related goals, facilitate care coordination, and track patient appointments led to higher rates of successful transition (defined as attendance at two adult rheumatology visits) compared to patients who did not enter the program. In the context of the Aboriginal population in Australia, Mitchell et al⁸⁴ noted that transition coordinators can also function as patient advocates to address language and cultural barriers. A nurse coordinator who addressed logistical challenges and facilitated communication with patients and families was associated with positive transfer outcomes among a Canadian cohort of AYAs with vasculitis, including a mean of four months between the last pediatric and first adult visit and only two no-shows at the first adult visit.¹⁰ Similarly, support from a nursing champion and other nonphysician clinical staff was identified as being an important facilitator of sharing transition guides with patients and families across the CARRA Transition Learning Collaborative.⁸⁵ Most recently, Samuel et al⁸⁶ conducted a randomized controlled trial to test the effectiveness of a patient navigator intervention in reducing rates of short-term care visits among AYAs with chronic diseases (18%–20% of whom had rheumatic diseases) in Canada. The core functions of the navigator were to support patients with adherence to care, engagement with health services, and development of self-management skills. Although there was no overall difference in short-term care use, a statistically nonsignificant reduction in short-term care visits among participants with mental health conditions in the navigator arm suggested that AYAs with mental health needs may benefit more from these types of interventions.

Educational initiatives. Researchers have evaluated endeavors to educate rheumatology providers and patients about transition-related matters. On the provider side, a workshop followed by an observed structured clinical examination on transition care increased adult rheumatology fellows' competence in orienting patients to adult care, eliciting a history from an AYA patient and family, and performing a confidential social history.⁸⁷ From the patient perspective, a French transition program (centered in adult rheumatology but coordinated with pediatric centers) that largely consisted of education about the disease, treatments, and specifics of adult care, led to more regular follow-up for patients with pediatric-onset familial Mediterranean fever.¹¹ In addition, AYAs with rheumatic diseases viewed knowledge of the Six Core Elements as important to their success in navigating the adult health care system and recommended that an "education care plan" about the Six Core Elements be introduced as "a means to independent self-management and self-advocacy."

They also suggested that health care transition be contextualized within other life milestones.⁷⁰ These findings emphasize the value and importance of transition education at multiple levels and highlight the need for co-design of transition interventions with the intended AYA recipients.

Multicomponent transition programs. Given that the goals of health care transition encompass supporting AYAs in learning to manage their own health care as well as ensuring an organized process of preparation, transfer, and integration into adult care, many reports of transition programs have naturally been complex, multicomponent interventions (Table 1). In one of the earliest examples, McDonagh et al⁹¹ designed a transition program for patients with JIA across 10 centers in the United Kingdom that included a transition policy, transition coordinator, individualized transition plan, and informational resources for adolescents, parents, and health professionals. Challenges of this initiative included inconsistent adoption across centers (eg, only 2 of 10 centers used a written transition policy despite provision of the template) and limited feedback regarding the resources developed for the program. Nevertheless, health-related quality of life as assessed by the Juvenile Arthritis Quality of Life Questionnaire improved over a 12-month period despite stable disease activity. Similar transitional care models have been developed and tailored to other contexts.⁹⁶ Hilderson et al⁹² tested the impact of a transition program in Belgium with eight components, including a transition coordinator, patient and parent education, a peer meeting, and transfer plan, for adolescents with JIA. Considered one of the more rigorous evaluations of a transition intervention for rheumatology, the study employed a quasi-experimental, one-group pretest–posttest design as well as a posttest-only comparison with a nonequivalent control group of adolescents who had been transferred to adult rheumatology without the transition program. Compared to the control group, program participants reported higher self-perceived health status, as measured by the Pediatric Quality of Life Inventory. In Germany, a transition pathway led by a case manager consisted of (1) a newly developed questionnaire, (2) education and counseling by a multidisciplinary team based on questionnaire results (including psychological counseling per request), (3) a medical summary, and (4) joint consultation with the pediatric and adult rheumatologist. The mean $\pm$ SD cumulative costs of the education and counseling sessions was 283 ± 164 euros, writing the medical summary 34.2 ± 12.3 euros, and coordinating the transition process 57.3 ± 15.4 euros. The authors considered these costs to be acceptable given the presumed medical complications that would be avoided, but a formal cost-effectiveness analysis was not conducted.⁹³ Balancing the impact and resource use of complex intervention components becomes especially important in health systems with resource constraints.

A growing number of multicomponent transition programs in rheumatology have described the establishment and outcomes of

transition clinics, defined as programs dedicated to the intentional and planned transition of youth with chronic diseases from pediatric-to-adult-centered care.⁹⁷ Many transition clinic models involve joint consultations between pediatric and adult rheumatology providers to facilitate coordination and build familiarity with adult providers; some also integrate allied health professionals to deliver parts of the intervention focusing on disease or self-management education (Table 1). Minden et al⁹⁸ were among the first to describe the creation of a transition clinic with joint pediatric and adult rheumatology transition consultations. This occurred in the context of a broader effort—the Berlin Transition Program—to develop an integrated care pathway for German youth that involved a written transition program, and coordination of individualized transition-specific services with the assistance of a case manager, though no outcome evaluation was described. Stringer et al⁸⁸ described high satisfaction among patients who received multidisciplinary evaluations in a dedicated transition clinic in Canada consisting of a pediatric rheumatologist, adult rheumatologist, pediatric rheumatology nurse, and pediatric physical therapist. Approximately 25% of survey respondents reported no consistent follow-up with an adult rheumatologist, although none of these respondents had been scheduled with the adult rheumatologist taking part in the Halifax transition clinic. Other multidisciplinary transition clinic models used the “Mind the Gap” scale (developed in the United Kingdom by Shaw et al⁹⁹) to demonstrate patient satisfaction with the transition clinic and identify gaps in care.^{100,101} Some transition clinics are physically located in the adult clinic, such as the dedicated adolescent JIA clinic in the Netherlands described by Walter et al⁸⁹, which was associated with (1) a decreased dropout rate, and (2) high self-reported self-management skills after transfer to adult rheumatology. In contrast, Overbury et al⁵³ described a transition clinic in the United States where a Med-Peds residency-trained adult rheumatologist was embedded within a pediatric rheumatology clinic to administer a modular curriculum that included a transition policy, transition readiness assessment, education regarding medications and diagnosis, and counseling on differences between pediatric and adult care. All participants went on to have at least one visit at the adult rheumatology clinic within a median of five months.

Taken together, these studies show that interventions aimed at improving the success of pediatric-to-adult transitions within rheumatology can be implemented in local settings across a wide variety of health systems, cultures, and environments. They also illustrate the relevance of the Six Core Elements in guiding the development and implementation of transition programs.

Remaining knowledge gaps and priorities for future study

Despite the large, growing population of AYAs with special health care needs, the increased recognition of adverse transition

Table 1. Examples of multicomponent interventions to support transition in the rheumatology context*

Study (country)	Recipients (n analyzed)	Core intervention functions (goals)	Form (structures/activities)	Design and outcome evaluation
Dedicated “transition clinic”				
Stringer et al ⁸⁸ (Canada)	Older teens in pediatric rheumatology care with upcoming transfer to adult rheumatology (N = 51)	Facilitate collaboration between pediatric and adult provider; develop transition or transfer plan; increase access to allied health services	Joint consultations by pediatric and adult rheumatologist; transition clinic on pediatric side with nurse and physical therapist	Uncontrolled observational; patient satisfaction; 74% reported regular follow-up with an adult rheumatologist, and 26% without were transferred to provider other than the transition clinic provider
Walter et al ⁸⁹ (the Netherlands)	AYAs transferred to adult rheumatology care (N = 154)	Develop individualized transition plan; enhance communication between pediatric and adult provider; build familiarity with adult provider; increase access to allied health services	Joint consultation by pediatric and adult rheumatologist; adolescent clinic staffed by pediatric providers on adult side with nurse and physical therapist	Uncontrolled observational; patient satisfaction; dropout rate (5.1% in adult clinic, 1.3% in adolescent clinic)
Overbury et al ⁵³ (United States)	AYAs with rheumatology needs (N = 57)	Educate and prepare patients to independently manage care; establish shared expectations for transition process; assess transition readiness	Transition visits on pediatric side with dual Med-Peds rheumatologist who delivered modular curriculum: transition policy, readiness assessment/care plan; medical summary; expectations of adult care; revisions to care plan	Posttest-only comparison with nonequivalent control; no-show rates (15%–16%) equivalent between transition clinic and pediatric rheumatology clinic; first adult clinic attendance rate of 100% (22 of 22)
El Tal et al (Canada) ⁹⁰	AYAs with cSLE transferring from adolescent clinic to adult care (N = 164)	Facilitate collaboration and communication between pediatric and adult provider; educate patients and caregivers; create comanagement structure; build familiarity; collaborate on transition plan	Joint consultation on pediatric side; transition letter (medical summary); adolescent internal medicine–led youth workshop and social work–led caregiver group; joint consultation, followed by alternating care in dedicated AYA clinic on adult side (over four years); postclinic review of progress	Uncontrolled observational; AYA clinic attendance (first visit, second visit); retention in AYAs or graduation to regular adult clinic
Other transition programs				
McDonagh et al ⁹¹ (United Kingdom)	Adolescents with JIA and their parents (N = 308)	Facilitate development and use of individualized transition plans; educate patients and parents ^a	Templates for transition policies and individualized transition plans; review transition plans at every visit; provide informational resources to patients and parents	One-group pretest–posttest and comparison with pseudocontrol group; health-related quality of life improved among participants, albeit no significant difference with pseudocontrols
Hilderson et al ⁹² (Belgium)	Adolescents with JIA and their parents (N = 33 families)	Educate patients and enhance self-management; address psychosocial needs; educate parents; meet peers; develop	Transition coordinator (1) schedules visits to deliver education, (2) provides referral info, (3) develops transfer plan, and (4) joins first adult	Mixed methods with embedded one-group pretest–posttest and posttest only with nonequivalent control; self-perceived health

(Continued)

Table 1. (Cont'd)

Study (country)	Recipients (n analyzed)	Core intervention functions (goals)	Form (structures/activities)	Design and outcome evaluation
Choukair et al (Germany) ⁹³	Adolescents with autoimmune disorders (N = 58)	Facilitate care coordination; assess readiness and provide individualized education to patients; address psychosocial needs; facilitate communication between pediatric and adult provider	Care visit; "adolescent information day" (one-day workshop run in parallel for adolescents and parents)	status (medium effect size of 0.46 for both pre-post and comparative analyses); qualitative themes: improved psychosocial health, little impact on knowledge or self-management behaviors
			Case manager coordinates transition and transfer visits; refer patients to psychology, social-legal team as needed; joint pediatric-adult consultation when possible, otherwise phone or written communication	Uncontrolled observational; total cost of consultation and educational sessions

* AYA, adolescent or young adult; cSLE, childhood-onset systemic lupus erythematosus; JIA, juvenile idiopathic arthritis; Meds-Peds, internal medicine-pediatrics.

^a These functions are as detailed in McDonagh et al. 2006⁹⁴

^b These functions are as detailed in Hilderson et al. 2013⁹⁵

outcomes, and the dissemination of national health policies and guidelines, widespread implementation of structured transition interventions has proved difficult to achieve. According to the National Survey of Children's Health, only 21.8% of youth with special health care needs in the United States received transition services to adult care in 2022 to 2023.¹⁰² This systemic deficiency has resulted in a crisis of accountability, wherein young adults are often left to navigate fragmented systems and gaps in health care access alone. The Six Core Elements is a framework that, by virtue of being an operational roadmap for clinical practice workflow, focuses accountability on health care teams. In contrast, transition frameworks in high-income countries with universal health care, such as the United Kingdom, focus on the integration of social services with a dedicated transition coordinator and/or social service manager, resulting in accountability being shared across health, social, and education service sectors.³⁰ These differences raise questions about who is ultimately responsible for ensuring successful transitions and for providing the resources necessary for high-quality transitional care. The relationships between social drivers and adverse transition outcomes,¹⁰³ as well as the aforementioned psychosocial factors unique to transition-age AYAs with chronic conditions, suggest that deeper integration of social determinants of health with transition and implementation frameworks may be especially important in settings where access to health care is not guaranteed. In the United States, where insurance coverage can have substantial influence on transition outcomes, there are important efforts underway to support reimbursement for transitional care that

may eventually be enacted by governing bodies, as laid out in the 2025 Medicaid and Children's Health Insurance Program Payment and Access Commission report on transitions of care for youth with special health care needs.¹⁰⁴

To support enactment of recommended policies, more widespread adoption by health care organizations, and buy-in from payers, there needs to be stronger evidence that structured transition interventions not only improve health outcomes but can also be sustained and scaled. Future studies should seek to employ more rigorous designs and consider implementation hurdles in the initial design phase. With respect to effectiveness studies, transition research in the context of rheumatology faces similar challenges as other disciplines,⁴⁰ including practicability, ethical concerns about randomization, contamination within practices/organizations necessitating cluster-level evaluations, and underlying heterogeneity of transitional care that make both individual and cluster-level comparisons even more difficult.²³ This is likely why there have been so few randomized controlled trials of transition interventions, only one of which included patients with pediatric rheumatic conditions.⁸⁶ However, this limitation does not preclude study designs from applying the most rigorous quasi-experimental methods whenever possible, describing the interventions in sufficient detail such that they can be replicated or applying established frameworks for the development and evaluation of complex interventions to facilitate implementation.¹⁰⁵ In many cases, this may require broadening from a single disease focus to larger categories of special health care needs.⁶⁸

Scalability is a major concern that has not been adequately addressed to date in transition literature, contributing to the persistently low rates of AYAs with chronic conditions receiving transitional care services. Many “successful” transitional care models that have been described in pediatric rheumatology as well as other contexts are complex, multicomponent interventions. In some cases, the core functions of the intervention are incompletely described, and the necessity of each discrete component for intervention effectiveness is seldom evaluated. Addressing these issues is especially important given that the resource intensity of multicomponent interventions remains a major threat to fidelity, sustainability, and scalability. To date, no studies have evaluated cost-effectiveness of implementation.⁶⁸ As such, there remains a relative paucity of data on transition to adult care in low- and middle-income countries, and literature on the applicability of transition frameworks or adaptability of structured transition interventions in these contexts is still emerging.^{73,96,106,107} Future studies of multicomponent transition programs in rheumatology could draw from the Multiphase Optimization Strategy, a method of building and evaluating complex interventions for optimal effectiveness at the minimum required intensity (“dose-age”).¹⁰⁸ Considering these issues up-front will help to increase the likelihood that effective transition interventions reach the AYAs with rheumatic diseases who need them.

Conclusions

In conclusion, the need to support transition of AYAs with childhood-onset rheumatic diseases from pediatric-to-adult care has been increasingly recognized in the field of rheumatology and in the broader context of caring for children with special health care needs. Existing frameworks for transitional care have long emphasized a number of structured transition processes, and yet, most AYAs still lack necessary transition services, experience gaps in care, and remain at increased risk for poor clinical and psychosocial outcomes. The literature to date evaluating interventions to support transition among AYAs with rheumatic conditions is considerably heterogeneous with respect to which components are included and how they are delivered, which in part reflects the diversity of local contexts in which pediatric and adult rheumatologists practice. Synthesizing what has been gleaned to date can give health care teams a starting point from which to develop their own context-specific care models and processes. From a broader perspective, moving the needle to improve process-related, psychosocial, and clinical outcomes of transition will likely require a three-pronged approach. The first is to consider implementation at the initial design phase, which necessitates co-design with AYAs, their caregivers, pediatric and adult health care teams, health system leaders, and policy-makers. Transition-oriented interventions into adult practices are particularly needed. The second is to clarify the definition of “successful transition” and to include long-term data in evaluating

outcomes and cost-effectiveness. The third is to strengthen the evidence base for innovative models of care by using rigorous study designs, clearly documenting the core functions of the interventions and how their forms are tailored to context, and broadening beyond a single disease focus. Doing so would help increase the chances that health care transition goals can be realized for all AYAs with rheumatic diseases across various health system contexts.

ACKNOWLEDGMENT

The authors thank Patience White, MD, MA, for reviewing the manuscript and contributing her expertise in the history of health care transition and related health policy efforts.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Chang confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW ARTICLE

Juvenile Myositis: Insights on Classification, Pathogenesis, and Therapies Over the Past 50 Years

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The juvenile idiopathic inflammatory myopathies (JIIMs) are rare, serious, multisystem autoimmune diseases affecting children and young people. Fifty years ago, the prognosis for these conditions was poor, with high morbidity and mortality, and very few treatments were available. Since then, there has been major growth in our understanding of the pathogenesis and evidence basis for treatment. Early descriptions considered juvenile dermatomyositis (JDM) to be essentially one disease. Our modern understanding has shown that there are different types of JIIMs, and that although JDM remains the most prevalent, even JDM itself is highly heterogenous. Much progress has been made possible through concomitant growth in the research community with a focus on JIIMs and the fact that the myositis research and clinical communities are highly collaborative internationally. Here, we review the growing understanding of the different types of childhood myositis; the developments in classification, driven in part by recognition of associations of particular phenotypes with specific myositis autoantibodies; the novel insights into pathogenesis of the JIIMs; the therapeutic targets that these have revealed; and the evidence for, and development of, modern treatment care pathways, which have changed radically in recent decades. This has resulted in improved outcomes for children and young people with JIIMs and hope for further groundbreaking developments.

Introduction

Insights into the underlying clinical features and pathomechanisms of childhood-onset (juvenile) idiopathic inflammatory myopathies (JIIMs) date back more than 50 years. Major progress in understanding the clinical features and pathogenesis of JIIM, and in the development of new therapies, has been made in recent decades, related to several key developments in research collaboration, registry development, and research support. National registries for JIIMs were established in the mid-1990s in the United States and United Kingdom and later in other countries, which contained significant patient numbers with detailed clinical data and linked biospecimens.¹ These registries facilitated the advancement of our understanding of the clinical spectrum

and epidemiology of JIIMs, risk factors for poor outcomes, and pathogenesis and biomarkers, as detailed below. Collaborative research networks both across the whole life course in myositis as well as within the juvenile dermatomyositis (JDM) research community were founded in the mid to late 1990s, including the International Myositis Assessment and Clinical Studies (IMACS) Group, the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Paediatric Rheumatology International Trials Organisation (PRINTO), and JDM working groups within both the American College of Rheumatology (ACR) and the Paediatric Rheumatology European Society (PReS).² The international multi-specialty collaborative research environment resulted in the development of validated core set measures and response criteria^{3,4} that facilitated the first multicenter therapeutic trials,⁵

The contributions of the NIH author(s) were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States Government. However, the findings and conclusions presented in this paper are those of the author(s) and do not necessarily reflect the views of the NIH or the US Department of Health and Human Services.

Supported in part by the Intramural Research Programs of the National Institute of Environmental Health Sciences, National Institutes of Health (NIH) (grants Z01 ES101074 and Z01 ES101081). Dr Wedderburn's work was supported by a National Institute for Health and Care Research Senior Investigator Award and the National Institute for Health and Care Research Biomedical Research Centre at Great Ormond Street Hospital.

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80115>.

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Submitted for publication March 5, 2026; accepted in revised form June 16, 2026.

standardization in the classification of myositis,⁶ and the development of therapeutic guidelines and standardized treatment approaches.^{7–9} A biannual international multidisciplinary scientific meeting dedicated to all forms of myositis, the Global Conference on Myositis (GCOM), was established in 2015 and has grown to more than 700 attendees.¹⁰

Another key milestone has been the establishment of myositis-focused patient foundations such as Cure JM and Myositis UK that have supported patients with JIIM and raised funds for research. Founded in 2003 by parents and grandparents, the United States–based Cure JM Foundation started as a volunteer-driven nonprofit dedicated to earlier diagnosis and finding better treatments and ultimately a cure for juvenile myositis (JM). They have funded more than \$30 million in research grants and programs, often funding young investigators, and supported the CARRA biorepository for JDM. Spurred by the parent leaders of Cure JM, *Myositis and You* was published in 2007 as comprehensive handbook for parents and trainees.¹¹ Cure JM also established several centers for specialized care and research on JM and more recently established a Clinical Care Network, connecting more than 40 children's hospitals in the United States and Europe, in which pediatric rheumatologists are focused on delivery of excellent clinical care to patients with JM. The charity Myositis UK (<https://www.myositis.org.uk/>) has been instrumental in supporting progress in research and toward better outcomes for people of all ages living with myositis. Myositis UK has not only provided vital funding for pilot work (which led to far larger awards from government and other funders) but also supported multiple research events, family and patient days, and information-sharing initiatives. Both foundations have supported travel bursaries to enable clinical science and research fellows to attend the international GCOM meeting, and Myositis UK has funded innovative speed funding grants for young investigators at GCOM.

Diagnosis and classification

Myositis in both children and adults was diagnosed for many years according to the Bohan and Peter classification criteria, which used a combination of clinical features (proximal weakness and characteristic DM rashes) and laboratory abnormalities comprising elevation in serum muscle enzymes, electromyography, and inflammatory muscle histology.¹² JDM was the only recognized childhood IIM. It was considered a separate disease from adult myositis, with more frequent calcinosis and vasculopathic features (like cutaneous and gastrointestinal ulceration) and a better prognosis (Figure 1A). In the early 1990s, several myositis autoantibodies were identified in adult patients and found to define phenotypes with distinct clinical features, responses to treatment, outcomes, and HLA risk alleles¹³ (Table 1). These same myositis autoantibodies were then reported in several children with myositis, with similar clinical features as in adults,¹⁴

resulting in proposals to expand myositis classification to include both clinical and serologic subgroups and to be parallel in children and adults.^{13,15} Reclassification was not favored until additional myositis autoantibodies (anti-transcription intermediary factor 1 [TIF1], anti-nuclear matrix protein 2 [NXP2], and anti-melanoma differentiation-associated gene 5 [MDA5]) were identified and found to be present in a significant proportion of patients with JDM. National registries in the United States and United Kingdom defined the array of clinicopathologic and myositis autoantibody subgroups, showing a large degree of overlap in phenotypic features with adult myositis with some important distinctions (Figure 1B).^{16–19}

The EULAR-ACR classification criteria were developed for myositis in 2017 as criteria to be used in research studies.⁴⁶ JIIM was included, and the classification of JIIM and adult myositis is now combined into a single system.⁶ These newer criteria include additional features in the patterns of muscle weakness and the presence of dysphagia and anti-Jo1 autoantibodies and further define muscle biopsy features. Of note, the EULAR-ACR IIM classification criteria are currently undergoing revision to potentially incorporate additional myositis autoantibodies, clinical-pathologic subgroups, and testing procedures, such as magnetic resonance imaging (MRI).⁴⁷

The advent of high-throughput assays with improved reliability in detecting myositis autoantibodies has also led to routine clinical testing for myositis autoantibodies—not only to aid in diagnosis but to understand associated clinical features and potential prognosis.⁴⁸ Currently, many different assays to test for myositis autoantibodies are available, and some carry a risk of false positive or false negative results; future work to standardize assays will be important.⁴⁹

Myositis-specific autoantibodies (MSAs) occur exclusively in patients with IIM, whereas myositis-associated autoantibodies (MAAs) are also seen in overlap myositis and other systemic autoimmune diseases.⁵⁰ Up to 70% of patients with JIIM have at least one myositis autoantibody.⁵¹ The demographics, clinical and pathologic features, and therapeutic responses and outcomes for each autoantibody subset appear, to a degree, to be distinct and share similarities with the corresponding subset of adult IIM (Figure 1B). The role of MSAs in pathogenesis is also emerging, with demonstration of inhibition of their intracellular targets in vitro⁵² and associations with distinct interferon (IFN) and other gene signature pathways⁵³; mouse models of some MSAs recapitulate pathologic and/or clinical features of disease.⁴⁸

Anti-p155/140 (TIF-1γ), the most common MSA in JIIM, has been detected in 18% to 30% of patients with JDM and JDM overlapping with another systemic autoimmune disease. Most children with this autoantibody have typical features of JDM, with widespread photosensitive rashes over the face, trunk, and extremities as well as a higher frequency of cutaneous ulcerations, subcutaneous edema, and lipodystrophy (Figure 1B) and, frequently, a chronic illness course.^{16,17,48} Anti-TIF1γ

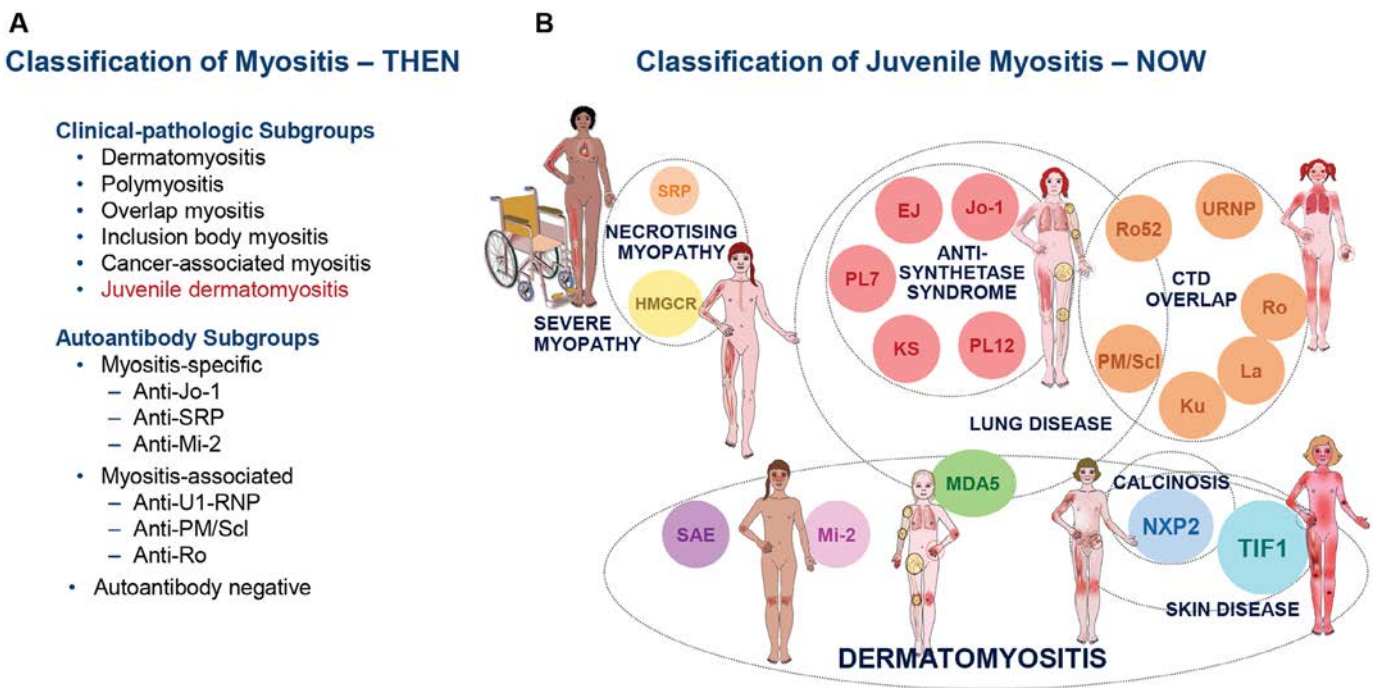


Figure 1. (A) Classification of myositis then. This shows the classification of myositis in the early 1990s, with separation of clinical-pathologic and myositis autoantibody subgroups. Juvenile dermatomyositis was considered a distinct disease from the adult forms of myositis, other subgroups of juvenile myositis were not recognized, and the number of myositis autoantibodies identified was limited. (B) Classification of juvenile myositis now. This represents the classification of myositis today, with integration of clinical subgroups and myositis autoantibodies to together define distinct phenotypes. Most of the subtypes present in adult myositis are now recognized in juvenile myositis, and classification is integrated across the age span. Many more myositis autoantibodies and their associated phenotypes have been identified in recent years. Modified from Rider and Nis-tala,¹⁶ and Betteridge and McHugh 2016.²⁰ HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; MDA5, melanoma differentiation-associated gene 5; NXP2, nuclear matrix protein 2; PM, polymyositis; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TIF1, transcription intermediary factor 1.

Table 1. Key Milestones in Juvenile Myositis Research, Pathogenesis and Therapy*

Year	Milestone	References
1887	Unverricht reports first recognized cases of adult DM	21
1952	ACTH therapy (corticosteroids) introduced as first effective medication for JDM	22
1966	Banker JDM autopsy series details natural history and primary pathologic/ pathogenic features	23
1975	Bohan and Peter classification (diagnostic) criteria	12
1980	Methotrexate introduced as steroid sparing medication	24,25
1983	High dose corticosteroids are standard therapy	26,27
1993	IVIG efficacy established in adult DM	28
1994	Myositis autoantibodies and their phenotypes first recognized in children	14
2002	Type I (αβ) and Type II (γ) IFN expression discovered to be upregulated in JDM muscle	29
2010	First CARRA consensus treatment plan for JDM published towards standardization of initial therapy	9
2013	Rituximab trial published as first major clinical trial and first biologic therapy for JDM	5,30
2013-present	MYOGEN GWAS and ImmunoChip studies confirm HLA ancestral haplotype as major genetic risk factor, identify several other immune SNPs as risks for JDM	31–35
2016	PRINTO randomized trial demonstrates early introduction of Methotrexate superior to prednisone alone in new-onset JDM	36
2017	ACR-EULAR Myositis Response Criteria and Myositis Classification Criteria published; SHARE guidelines for JDM published and widely used across Europe	4,7
2018-2020	JAK inhibitors introduced in JDM	37,38
2021	FDA approval of IVIG for adult DM	39
2023-present	Single-cell and omics studies identify novel pathogenic pathways (innate immunity, neutrophil, mitochondrial, PI3AKT and MAPK); Phase 3 trials in progress for biologic therapies for adult myositis; CAR-T therapy holds promise of remission	40–45

* ACR, American College of Rheumatology; ACTH, adrenocorticotrophic hormone; CAR-T, chimeric antigen receptor T-cell therapy; CARRA, Childhood Arthritis and Rheumatology Research Alliance; DM, dermatomyositis; EULAR, European League Against Rheumatism; FDA, U.S. Food and Drug Administration; GWAS, Genome-Wide Association Study; HLA, Human Leukocyte Antigen; IFN, Interferon; IVIG, intravenous immunoglobulin; JAK, Janus kinase; JDM, juvenile dermatomyositis; JM, juvenile myositis; MAPK, mitogen-activated protein kinase; PI3K/AKT, phosphoinositide 3-kinase; PRINTO, Paediatric Rheumatology International Trials Organisation; SHARE, Single Hub and Access point for pediatric Rheumatology in Europe; SNP, single nucleotide polymorphism

autoantibodies have also been associated with residential UV radiation exposure before diagnosis.⁵⁴ Anti-TIF1 γ can also be associated with clinically amyopathic JDM. In children, this autoantibody is not associated with malignancy, in contrast to adults. The reasons for this difference are unclear, but certain autoantibodies (including anti-Sp4, anti-CCAR1, and others) associated with anti-TIF1 γ appear to attenuate the occurrence of cancer in adults, whereas in JDM, these additional autoantibodies are also present and associated with milder muscle disease.⁵⁵

Anti-NXP2 autoantibodies are present in 15% to 25% of patients with JIIM, but only in JDM and not in other subgroups. Anti-NXP2 is associated with severe weakness and muscle inflammation, muscle atrophy and cramping, joint contractures, mild skin rashes (only Gottron's, heliotrope, and malar rashes), and an increased frequency of calcinosis, although not in all studies (Figure 1B). In some cohorts, internal organ involvement, including dysphagia and cardiac disease, are more frequent.^{56,57}

Anti-MDA5 autoantibodies are present in 6% to 8% of North American and European patients with JDM and 30% of Japanese children. This autoantibody is associated with mild muscle disease as well as frequent fevers, weight loss, adenopathy, arthritis, cutaneous ulcerations, and interstitial lung disease (ILD), which can be rapidly progressive (RP-LD) with associated high mortality (Figure 1B).^{58,59} ILD and RP-LD are more frequent in Asian populations.⁶⁰ Prognosis is good in patients without ILD.⁵⁹

Anti-Mi2 autoantibodies are present in up to 4% of patients with JIIM, exclusively in JDM. They are seen more commonly in Hispanic patients in North America and are associated with more severe weakness and muscle inflammation but also with a good response to glucocorticoid and other immunosuppressive therapy.^{57,61}

Anti-synthetase autoantibodies are present in 2% to 5% of those with JIIM, but up to 25% of adults with IIM. Anti-Jo1 (histidyl-transfer RNA synthetase) is the most common. These patients can have severe muscle weakness, with frequent polyarthritis, ILD, fever, Raynaud syndrome, and mechanic's hands (Figure 1B). They often have a chronic illness course, with disease flares when glucocorticoids are reduced, and increased mortality.^{57,62}

Two autoantibodies define immune-mediated necrotizing myopathy, a form of JIIM that is associated with severe muscle weakness. Muscle biopsy may show myonecrosis, with myophagocytosis by infiltrating macrophages, along with features shared with other forms of JIIM including up-regulation of major histocompatibility complex (MHC) Class I and complement deposition on myofibers.⁶³ Anti-signal recognition particle autoantibodies are present in 2% to 4% of patients with JIIMs, most often African American individuals, and they generally have very severe proximal, axial, and distal weakness; frequent falling episodes; muscle atrophy; markedly elevated serum creatine kinase (CK) levels (>10,000 IU/mL); and increased cardiac involvement and restrictive lung disease. They may also require a wheelchair or other

devices because of severe functional disability (Figure 1B).⁵⁷ They generally do not have cutaneous features of JDM. They typically have a chronic illness course and require multiple immunosuppressive therapies. Patients with autoantibodies to 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) also have severe proximal and distal weakness, falling episodes, highly elevated CK levels, frequent muscle atrophy, joint contractures, arthralgias, dysphagia, weight loss, and a chronic illness course.^{19,64} Although anti-HMGCR autoantibodies in adults are frequently associated with use of statin medications or dietary exposure to statins, statin exposure has not been identified in children.

MAAs are present in 11% to 36% of patients with JIIMs and have been associated with myositis overlapping with another systemic autoimmune disease in children and adults with IIM (Figure 1B). In JIIMs, MAAs overall are associated with increased frequency of Raynaud syndrome and ILD, a chronic illness course, and increased mortality, which increases with the number of MAAs present.¹⁸ Among the MAAs, anti-Ro52 autoantibodies have been associated with worse ILD and more severe disease.⁶⁵ Anti-Ro60 autoantibodies have been associated with panniculitis and weight loss. Anti-polymyositis-scleroderma (PM/Scl) autoantibodies have been associated with higher CK levels and certain cutaneous manifestations, including sclerodactyly, mechanic's hands, Raynaud syndrome, calcinosis, and lipoatrophy. Other MAAs, including Ku and U3RNP, are sometimes seen in scleroderma-overlap myositis.^{17,18}

Areas of future research on myositis autoantibodies will aim to further define distinctive associated illness features among different geographically dispersed populations and races and ethnicities, to use novel technologies to identify myositis autoantibodies in patients who have no identified autoantibodies, and to further define the role of MSAs in pathogenesis. Reliable commercial assays for all autoantibody specificities are needed.⁴⁹ The use of sensitive enzyme-linked immunosorbent assay and other quantitative methodologies to enable following titers over the illness course as biomarkers of disease activity and treatment response is another emerging area.⁶⁶

Pathogenesis

An early description of muscle pathology by Banker and Victor²³ detailed tissue pathology in eight uniformly fatal cases of JDM. This study described key pathologic features, including early perivascular inflammation; vessel intima thickening, sometimes with occlusion; and even muscle infarcts. Early recognition that this necrotizing vasculopathy was present in muscle and other tissues was subsequently confirmed in many studies, found to correlate with prognosis,⁶⁷ and included in the Bohan and Peter classification criteria for JDM.¹² More recently these features were incorporated in the "vascular domain" of an internationally validated consensus muscle biopsy score tool to assess JDM severity.⁶⁸ This cardinal pathologic feature is thought to be

associated with complement deposition on capillary endothelium⁶⁹; this pathology is consistent with more recent studies demonstrating vasculopathy in JDM, detected via endothelial biomarkers such as circulating endothelial cells and endothelial-derived microparticles, as well as angiogenesis proteins, which are associated with IFN-driven pathology.⁷⁰

Early studies revealed increased expression of type I and II MHC (HLA) proteins on muscle fibers compared with age-matched healthy muscle tissue, detectable even early in disease in approximately 90% of JDM cases.⁷¹ Interestingly, overexpression of MHC Class I protein specifically on muscle fibers led to myositis in a transgenic mouse model, with associated muscle inflammation and endoplasmic reticulum (ER) stress, and this model was more severe when the overexpression was initiated in young mice compared with adults.^{72,73} Up-regulation of type I IFN gene expression was also prominently detected in muscle tissue in the first study of gene expression in JDM, in distinction to biopsies from Duchenne muscular dystrophy²⁹ (Table 1). Subsequent analysis of expression of the IFN-driven myxovirus-resistance protein A in muscle biopsy tissue from 103 cases showed that the degree of up-regulation of IFN-driven proteins correlates with muscle weakness and is observed across all MSA specificities.⁷⁴

IFNs drive a readily detectable transcriptional program that includes multiple IFN-stimulated genes (ISGs),⁷⁵ making this signature readily amenable to detection. Early demonstration of IFN-driven gene expression signatures in blood, muscle, and skin of both adult and juvenile^{76,77} DM has been replicated in many studies using a variety of techniques, including measuring ISG scores in whole blood^{78,79} or sorted immune cells, and analyzing IFN-driven proteins in serum (such as Galectin-9 and CXCL10)⁸⁰ or IFN proteins directly using the highly sensitive SIMOA assay.⁸¹ In most of these studies, IFN-driven readouts correlate with muscle weakness, especially before treatment, as well as skin activity in patients with anti-TIF1 γ autoantibodies, and may predict flares.^{76,78,79,82}

The IFN-driven signature is highly evident in muscle tissue both in bulk RNA analyses^{76,83} and, more recently, in spatial transcriptome studies.^{84,85} The higher-powered cellular discrimination enabled by spatial transcriptome data has confirmed that muscle itself can be a source of IFN, in addition to infiltrating IFN-producing immune cells, which include T cells, natural killer cells, and plasmacytoid dendritic cells (pDCs).^{86,87} In addition to type I IFNs, growing evidence supports a role of type II IFN, IFN γ in JDM pathology, including direct detection⁸⁷ and analysis of transcripts that are predominantly driven by IFN γ : class II, major histocompatibility complex, transactivator (CIITA) and CXCL9.⁸⁸

Together, these data, and early clinical efficacy data, have built a strong case for the use of IFN-blocking therapies, whether by blocking signaling through JAK/STATs, blockade of the IFN receptor, or targeting the cytokines themselves (see below). However, the immune system works as an orchestra with many parts

interacting, not through one pathway only, and it is therefore not surprising that many immune processes have been implicated in the pathology of JDM. The dense early inflammatory infiltrate seen in JDM muscle includes T and B cells, monocyte/macrophages, and pDCs.^{89,90} Peripheral blood memory B cells of patients with JDM are expanded pretreatment, and this expansion is driven in particular by CD24hiCD38hi immature B cells, which demonstrate abnormally low interleukin (IL)-10 production, which correlates with the IFN score and likely compromises their immunoregulatory function.^{40,91,92} Within the T cell compartment, a skew toward Th2 or CXCR5+Th17 cells has been observed, with reduced Th1 cells^{40,93} within the CD4+ population. How altered function of blood immune cells reflect those in affected skin or muscle remains to be confirmed.

Transcriptional analysis of blood monocytes in JDM has revealed highly dysregulated mitochondrial biology, functionally altered oxidative phosphorylation, and structural abnormalities of mitochondria.⁹⁴ Ultrastructural studies demonstrate mitochondrial abnormalities in JDM muscle, which has been recently confirmed both in skin samples (obtained by “tape stripping”) by bulk RNAseq⁴¹ and in muscle biopsies by spatial transcriptomics.⁸⁴ There is a complex bidirectional relationship between IFN and mitochondrial biology, with evidence that IFN alters mitochondrial function, but also that oxidized mitochondrial DNA released is a potent ligand for “danger” recognition receptors and thereby can drive IFN production.⁹⁵ Recent evidence suggests that abnormal mitochondria may also be transferred between cells, a possible mechanism of perpetuating pathology.⁹⁶ These studies open a new set of potential therapeutic targets that may prove valuable in ongoing disease activity not controlled by conventional treatment. In parallel with monocytes, neutrophils in JDM are also abnormal, associated with so-called neutrophil extracellular traps,^{97,98} which also contain mitochondrial DNA. Serum proteome studies indicate neutrophil activation in JDM⁴² and the blood biomarker MRP8/14 (also known as calprotectin, or S100A8/A9) is raised in serum in parallel with disease activity⁹⁹ as well as detectable within muscle, released by infiltrating myeloid cells. Additional pathways appear to be up-regulated in chronically active JDM, including prominent dysregulation of p38/MAP kinase, phosphoinositide 3-kinase/AKT, and IL-1 signaling, as well as several cytokines and growth factors and their receptors.⁴³

The underlying genetic background that confers risk of myositis includes the HLA or MHC region on chromosome 6. Large collaborative studies including both adult and childhood-onset IIM have facilitated many novel insights. Thus, the so-called ancestral haplotype, HLA A1-B8-DR3-DQ2 detected in early genome-wide association studies and subsequently confirmed, is a risk factor for inflammatory myositis across all ages in White populations (Table 1).³¹ A detailed analysis of the leading amino acid position conferring risk identified subtle differences between adults and children, whereas MSA-positive subtype-specific

genetics also vary by age at onset.^{32,33} Several other risk loci for DM/JDM, including PTPN22, TYK2 (itself the target of the drug), IRF4, and C4 deficiency, are associated with myositis as well as other autoimmune diseases^{34,35,100} Thus, many parts of the immune system likely play a role in the pathogenesis of JIIM; the next challenge is to dissect which aspects are age-specific as well as to define those pathways that correlate with specific MSAs or phenotypes, or predict an active course despite treatment.

Treatment and prognosis

The last 50 years have brought about tremendous changes in the treatment of JIIMs, and a great deal of success, especially for children with JDM. So-called ancillary treatments (physical therapy, sun protection, proper dietary counseling, and mental health support) are just as important now as they have been since the 1980s.

In a landmark advance, it was apparent in the early 1950s that glucocorticoids were beneficial for patients with JDM, resulting in marked improvement in mortality (Table 1).²² Early articles emphasized the benefits of high doses (up to 2.0 mg/kg/day in divided doses) and prolonged courses of daily oral glucocorticoids, resulting in a decrease in calcinosis and improved outcomes.^{26,27} High doses of intravenous (IV) glucocorticoids (eg, 30 mg/kg methylprednisolone, maximum 1,000 mg) at the outset of treatment likely leads to more rapid improvement, although there are many potential acute side effects.¹⁰¹ Long-term studies have not shown clear benefit of pulse methylprednisolone over time.¹⁰² Before combination therapy was widely practiced, it was universally observed that treatment with glucocorticoids alone was associated with all the well-known undesirable side effects of long-term steroids (Figure 2A).

Accordingly, following demonstration of its efficacy as a second-line agent, methotrexate (MTX) was introduced as a steroid-sparing agent and proved effective when started at treatment outset.²⁴ A subsequent randomized controlled trial (RCT) showed the superior efficacy and tolerability of combination glucocorticoids and MTX in patients newly diagnosed with JDM (Table 1).³⁶

IVIg was first used in childhood myositis in the 1980s. IVIg has been adopted as a widely used, beneficial therapy worldwide. Rigorous observational studies have demonstrated efficacy in children,^{104,105} and a recent RCT proved this in adults with DM³⁹ (Table 1). Based on this experience, groups like CARRA^{8,9} and the Single Hub and Access point for pediatric Rheumatology in Europe⁷ have tried to standardize treatment regimens using available evidence and consensus (Figure 2B; Table 1).

More recently, large case series have demonstrated the likely efficacy of mycophenolate mofetil^{106,107} in addition to, or as an alternative, to MTX. Combination drug therapy has also been more widely used to treat refractory disease and aid in the sparing of glucocorticoids (Figure 2B). Additionally, a sophisticated

analysis has demonstrated the efficacy of cyclophosphamide on JDM disease activity,¹⁰⁸ which previously had traditionally been reserved primarily for ulcerative disease or ILD.

Targeted biologic therapies and small biologically targeted drugs have been the focus of therapeutic development in the last 20 years (Figure 2B).¹⁰⁹ The evidence base for these agents is small, uncontrolled, and not necessarily convincing for all agents. Anti-tumor necrosis factor monoclonal antibody therapies¹¹⁰ have had some efficacy in case series of refractory patients. Rituximab, a B-lymphocyte-depleting biologic therapy, has been studied in a large multicenter RCT of those with refractory JDM and DM/PM.⁵ Although there was apparent efficacy in the sample of children studied, there was no statistical significance, which could be explained by the low power in the subgroup analysis (Table 1).³⁰ An open-label trial of abatacept suggested efficacy for refractory muscle and skin disease, with blinded measures, MRI and biomarkers, including IFNs and chemokines, also showing improvement.¹¹¹

Some of the newest therapies for childhood myositis are directed toward blocking the effects of IFN and other cytokines, primarily aimed at type I and II IFNs. JAK inhibitors (JAKis) block the effects of type I and II IFNs by preventing the phosphorylation of STAT proteins (which, if phosphorylated, would drive ISG transcription). Worldwide there is growing experience with JAKis through case series and a small number of open-label clinical trials,^{37,38} with a high proportion of patients with refractory JDM showing good responses in skin and muscle disease, as well as improvement in ILD and calcinosis in fewer cases. JAKis have been beneficial for patients with refractory JDM with anti-MDA5 autoantibodies, which are associated with high type I IFN responses, in improving lung disease, as well as mortality in adult patients.³⁷ Most recently, monoclonal antibodies targeting IFN β (dazukibart)^{112,113} or the type I IFN receptor (anifrolumab)^{114–116} have shown remarkable success in the treatment of very refractory skin and muscle disease and in the treatment of ulcerative disease in patients with JDM; phase 3 trials are in progress for adult DM.

There is great excitement, now, about the potential for chimeric antigen receptor T cell (CAR-T) therapies in the treatment of childhood myositis and juvenile lupus. To date, reported cases have used CAR-T directed against B cells (CD19)⁴⁴ or B cell maturation antigen⁴⁵ with marked success, including major clinical improvement and near remission in all cases (Table 1). The reported success seems greater than conventional biologic B cell-targeted therapies like rituximab. It is thought that CD19-targeting CAR-T cells are effective against some tissue B cells and not just circulating B cells and that the tissue effect may differentiate CAR-T cell potency.

Although many of the therapies developed over the last 50 years are supported by research evidence from case series or causal modeling rather than RCTs, the outlook for a child with myositis in 2026 is very different than it was in 1966. Although

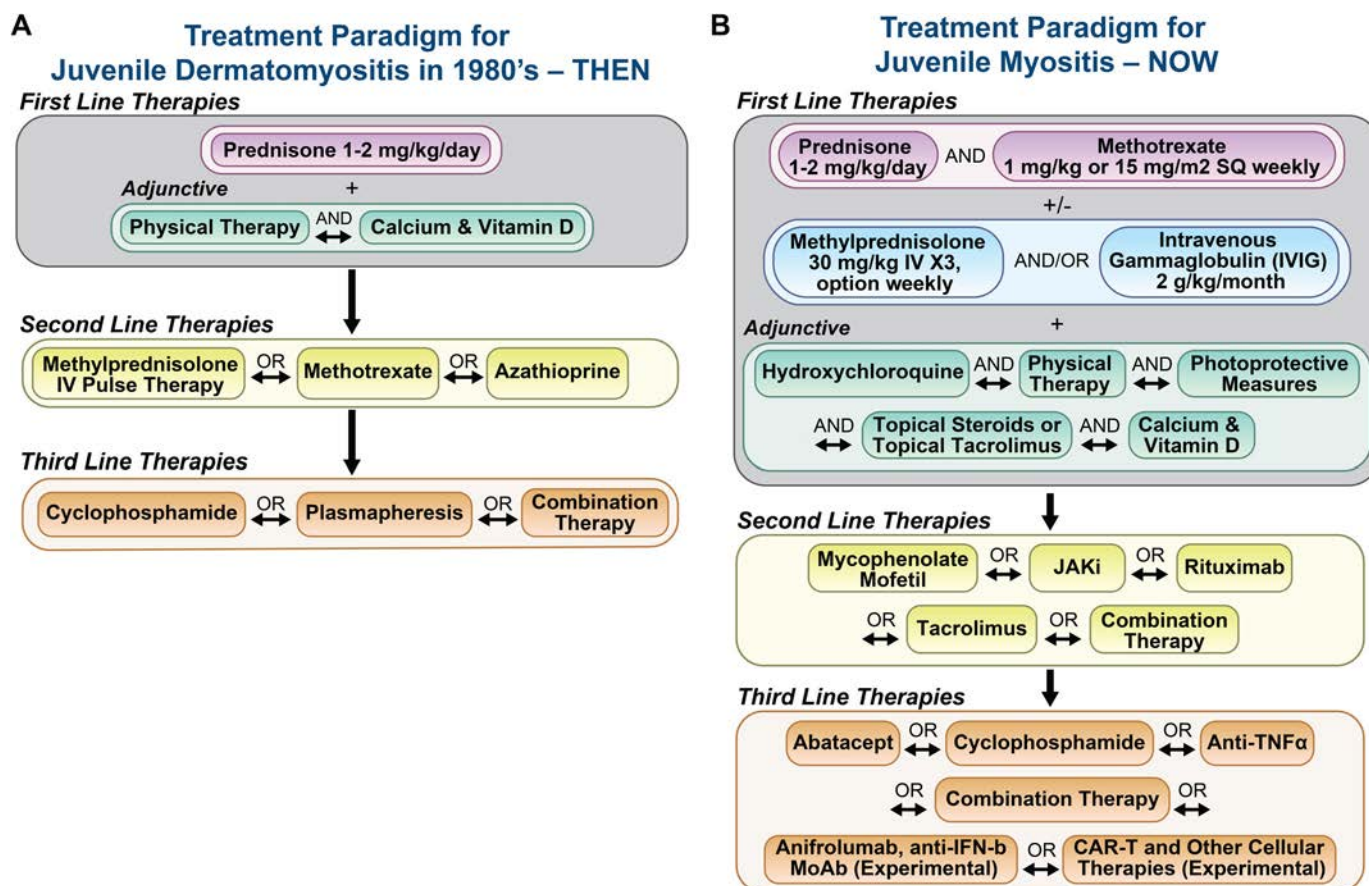


Figure 2. (A) Treatment paradigm for juvenile dermatomyositis then (1980s). Daily oral prednisone therapy was the mainstay of therapy. Second-line therapies were limited, and only cyclophosphamide and plasmapheresis were available for severe patients. (B) Treatment paradigm for juvenile myositis now. A standardized approach to initial therapy now includes daily oral prednisone in combination with methotrexate, with the option to add IV methylprednisolone and/or IV gamma globulin. Several medications are available as second- and third-line therapies, including targeted biologics and drugs and use of combination therapies. Modified from Kim and Rider.¹⁰³ CAR-T, chimeric antigen receptor T cell therapy; IFN- β , interferon- β ; IV, intravenous; IVIg, intravenous Ig; JAKi, JAK inhibitor; MoAb, monoclonal antibody; SQ, subcutaneous; TNF α , tumor necrosis factor α . Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80115/abstract>.

proper epidemiologic studies had not been performed, early reports suggested that JIMs, particularly JDM, had a grim prognosis during the period before specific medication treatment was available. Reportedly one-third of patients died, one-third recovered with some sequelae, and one-third were chronically disabled.¹¹⁷ The course was often described as being monocyclic (in which disease completely remitted after 2 or 3 years of treatment), polycyclic (in which active disease recurrences occurred after periods of medication-free remission), or chronic continuous.²⁷

More recently, several trajectories of disease have been described. In an inception cohort of patients with JDM observed into adulthood, three latent trajectories were described.¹¹⁸ Ten percent of patients were very severe at onset, responded poorly to initial treatment, and remained quite active despite therapy. More than half had a moderate to severe presentation but responded dramatically to initial treatment and had no, or very mild, continuing disease activity. The remainder had a mild to moderate presentation but responded slowly to initial therapy

and continued to have ongoing mild disease activity despite therapy. In the latter group, it was often skin disease that persisted. The best predictor of continued disease activity was an incomplete response over the first 6 months of treatment. A large UK cohort identified similar disease trajectories in JDM, with time since diagnosis, presence of respiration abnormalities, and lipodystrophy as predictors of a subgroup of 11% of patients with high disease activity at presentation and more persistent disease.¹¹⁹ It has been shown by two groups that skin activity responds more slowly and is more persistent than muscle activity.¹²⁰

Although most patients respond well to therapy and mortality is now less than 5% (in most centers much lower), damage is common.¹²¹ In a remarkable series of studies first reported in 2009,¹²² a Norwegian group examined an inception cohort of patients with JDM into adulthood and demonstrated that children with JDM go on to have frequent organ damage, which is predicted by persistent disease activity at 6 months of treatment. They commonly have chronic weakness and may develop

subclinical heart and lung damage and reduced exercise tolerance in these long-term outcome studies. Approximately two-thirds have persistently active disease that is associated with persistent nailfold capillary abnormalities.¹²³ More than one-fourth have reduced bone mineral density and metabolic abnormalities, with hyperlipidemia and central adiposity.

Calcinosis is a potentially devastating long-term complication of the JDM subtype of JIIM. It occurs in approximately 30% of patients in most series and is associated with a chronic disease course and longer disease duration.¹²¹ In one inception cohort, the only baseline clinical predictor of calcinosis was more extensive vascular disease, as determined by underlying nailfold capillary vasculopathy.¹²⁴ There is no evidence-based treatment for calcinosis; however, aggressive treatment of the underlying disease often leads to the regression of calcinosis.

The outcomes of JIIMs have clearly improved remarkably in the last 50 years, but there are still many challenges faced by these patients. Further refinement of treatment approaches with the adaptation of consensus treat-to-target recommendations with the aim of rapid induction of inactive disease and resultant reduction of glucocorticoids will hopefully accelerate further improved outcomes.²⁰

Conclusions

In conclusion, huge progress has been made in our understanding, treatment, development of prognostic tools, and knowledge of the long-term outcomes of JM. This rapid growth of knowledge has been driven in part by collaborative networks and organizations, which have been synergistic across pediatric and adult research communities, between clinical and nonclinical researchers, and through strong international partnerships. Much remains to be done, to further understand pathogenesis, improve treatments, and test new therapeutic modalities and targets, but the future of the field is bright.

ACKNOWLEDGMENTS

We thank our mentors, many colleagues and trainees, and the myositis collaborative groups (IMACS, CARRA, UK JDM Cohort and Biomarker Study, Childhood Myositis Heterogeneity Study Group, PRINTO, and PReS JDM Working Party) who have contributed greatly to this work, and most of all we thank the patients with JM for whom we have had the privilege of caring. We give special thanks to Drs Frederick Miller, Paul Plotz (posthumous), Ira Targoff, Andrew Mammen, Adam Schiffenbauer, Lauren Pachman, Sarah Tansley, Neil McHugh, Liza McCann, and David Isenberg for deep mentorship and collaborations.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Rider confirms that all authors have provided the final approval

of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW ARTICLE

Advancements in Diagnosis and Care for Immune Dysregulation and Inborn Errors of Immunity in Pediatric Rheumatology: Our 50-Year Journey

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Caring for children with complex immune disorders is part of the heritage of pediatric rheumatology that extends back to the original founders of the field. Over the past 50 years, pediatric rheumatologists have been central to advancing discovery and pioneering innovative treatment approaches for pediatric patients with multifaceted immune dysfunction. This includes dissecting disease mechanisms and identifying novel genes associated with inflammasome activation, IL-18opathies, type I interferonopathies, monogenic mosaic disorders, and other forms of immune dysregulation. Pediatric rheumatologists have made foundational contributions to the management of patients with these conditions by leveraging their expertise in existing immunomodulatory medications and recognizing new drug targets. In the next 50 years, scientists and clinicians in the field are poised to make substantial innovations in understanding the causes and biomarkers of immune dysregulation. By harnessing the power of precision medicine, cellular therapies, and immune multidisciplinary teams, pediatric rheumatologists will continue to drive discoveries that will improve outcomes for patients with immune dysregulation.

Introduction

A long tradition of caring for children with immune dysregulation. Pediatric rheumatologists have been at the forefront of managing patients with complex immune disorders since the inception of the field at the 1976 meeting of the Council on Pediatric Rheumatology held in Park City, Utah. Well before this landmark conference, the legacy of pediatric rheumatology extended back to 1897 with George Frederic Still's initial description of a chronic joint disease that was unique to children and of a “very uncertain” etiology.¹ In the 1940s, the first center dedicated to children with rheumatic diseases was established at the Canadian Red Cross Memorial Hospital in Taplow, England, by Eric Bywaters, who was later joined by Barbara Ansell.² The founding

of “Taplow” coincided with the decline in incidence of rheumatic fever and the greater appreciation that children suffered from other idiopathic autoimmune conditions. This center is where many founding fathers and mothers of pediatric rheumatology were trained, including John Baum, James Cassidy, Chester Fink, Virgil Hanson, Ross Petty, Jane Schaller, and Patience White.² These individuals and others, Earl Brewer, Jerry Jacobs, Joe Levinson, and J. Sydney Stillman, came together to form the Council on Pediatric Rheumatology within the American Rheumatism Association in the 1970s. It is this group that would ultimately organize the 1976 meeting and establish the field.³ The lineage of most pediatric rheumatologists in North America can be traced back to these individuals. This long line of clinicians formed a

Dr Vogel's work was supported by the National Center for Advancing Translational Sciences, NIH (grant UH3-TR-003908). Dr Volpi's work was supported by the Italian Ministry of University and Research (grant F500002235) and Ricerca Corrente, Italian Ministry of Health. Dr Cooper's work was supported by the National Institute of Allergy and Infectious Diseases, NIH (grant P01-AI-186771). Dr Henderson's work was supported in part by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grants R01-AR-083424 and P30-AR-070253) and NIH (grant UC2-AR-08103). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80127>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80127>.

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Submitted for publication March 20, 2026; accepted in revised form June 16, 2026.

pediatric subspecialty with unparalleled expertise in managing enigmatic inflammatory disorders in children. This review will focus on the remarkable accomplishments of pediatric rheumatologists, alongside immunologists and geneticists, in the discovery and management of immune regulatory disorders with an emphasis on monogenic diseases characterized primarily by autoimmunity, generally defined as disorders of adaptive immunity, hyperinflammation, and/or autoinflammation referring to sterile inflammation resulting from innate immune dysfunction (Figure 1).

The evolving concept of immune dysregulation.

Although immune dysregulation has always existed, nomenclature surrounding this topic has changed over time. Indeed, there were sections in the proceedings of the Park City meeting dedicated to juvenile arthritis in patients with immunodeficiencies, an indication that pediatric rheumatologists appreciated the association between immune dysfunction and autoimmunity in the earliest days of the subspecialty.³ The actual term immune

dysregulation emerged from the field of immunology as there was a greater appreciation that monogenic immune diseases did not always present strictly with features of immunodeficiency. Through the study of a large registry of patients with primary immune deficiencies (PIDs) in France, Fischer et al⁴ noted that over 25% of affected individuals had at least one inflammatory condition, most commonly autoimmune cytopenias. Other studies confirmed this high prevalence of autoimmunity in patients with PIDs.^{5,6} Around this time, an increasing number of defects in immune-related genes were linked with diseases predominantly characterized by autoimmunity, atopy, lymphoproliferation, and/or hyperinflammation. The prototypical example is immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome due to FOXP3 deficiency.⁷⁻⁹ FOXP3 is the lineage-defining transcription factor for Treg cells, and the 2025 Nobel Prize for Medicine was awarded to the three scientists who identified this tolerogenic T cell subset.¹⁰⁻¹² As the human genome project finished and genetic sequencing became more accessible, the universe of monogenic immune disorders expanded

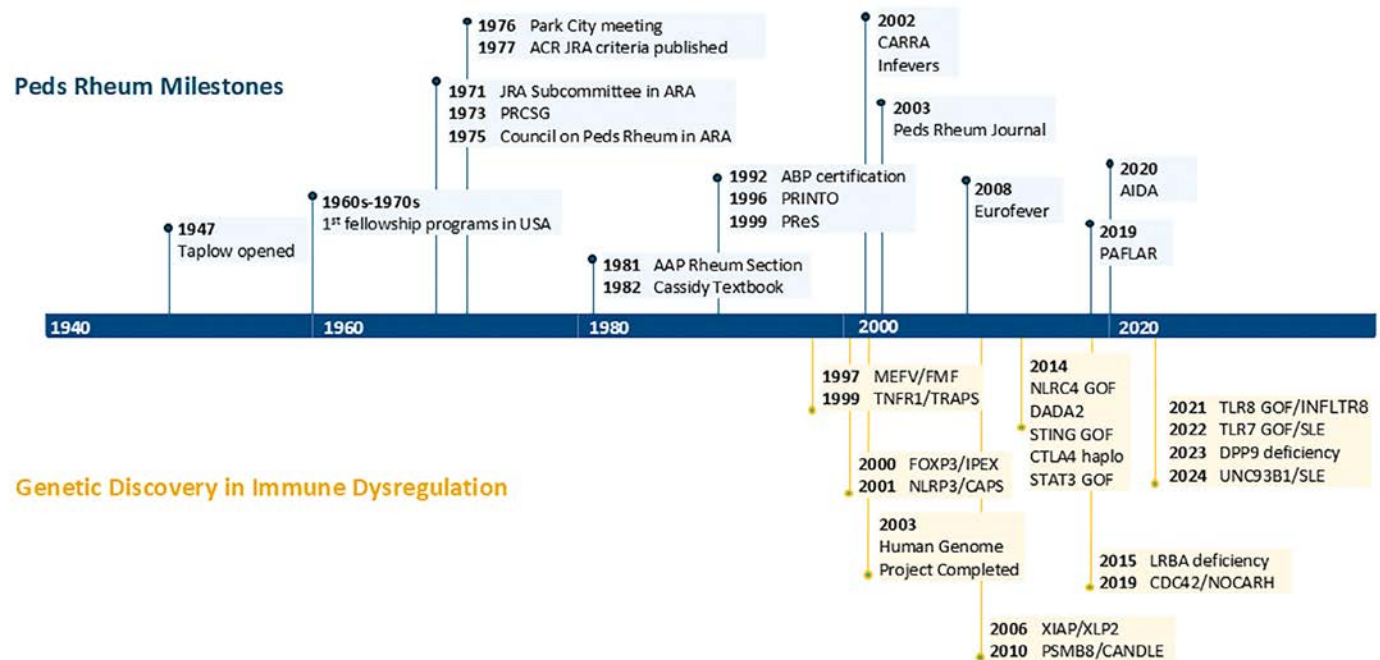


Figure 1. Milestones in Pediatric Rheumatology and genetic discovery in immune dysregulation. The timeline shows landmark events in the history of Peds Rheum as well as the identification of genes associated with immune dysregulation discussed in this review. AAP, American Academy of Pediatrics; ABP, American Board of Pediatrics; ACR, American College of Rheumatology; AIDA, Autoinflammatory Disease Alliance Registry; ARA, American Rheumatism Association; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndrome; CARRA, Childhood Arthritis and Rheumatology Research Alliance; CDC42, cell division cycle 42; DADA2, deficiency of adenosine deaminase 2; FMF, familial Mediterranean fever; GOF, gain of function; haplo, haploinsufficiency; INFLTR8, inflammation, neutropenia, bone marrow failure, and lymphoproliferation caused by TLR8; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome; NOCARH, neonatal-onset cytopenia, autoinflammation, and recurrent hemophagocytic lymphohistiocytosis; PAFLAR, Paediatric Society of the African League Against Rheumatism; Peds, pediatrics; PRCSG, Pediatric Rheumatology Collaborative Study Group; PReS, Paediatric Rheumatology European Society; PRINTO, Paediatric Rheumatology International Trials Organization; PSMB8, proteasome 20S subunit beta 8; Rheum, rheumatology; SLE, systemic lupus erythematosus; STING, stimulator of IFN genes; TLR8, Toll-like receptor 8; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome; UNC93B1, unc-93B1 regulator of TLR signaling; XLP2, X-linked lymphoproliferative syndrome 2.

greatly—over 500 genes have now been linked with human immune diseases.¹³ In particular, primary immune regulatory disorders (PIRDs) were increasingly recognized as technological advancements in sequencing allowed for the identification of variants associated with less fulminant phenotypes, incomplete penetrance, and variable expressivity.

Given these developments, the view of the human immune system as a linear continuum from low function manifested as immunodeficiency with recurrent and opportunistic infections to overactivity characterized by autoinflammation and autoimmunity was abandoned. Instead, a more complex picture evolved in which immune dysfunction is appreciated to be multifaceted, encompassing varying phenotypes from immunodeficiency to autoimmunity, atopy, and more (Figure 2). Recognizing this fundamental change in our understanding, the International Union of Immunologic Societies (IUIS) replaced the term PIDs with inborn errors of immunity (IEIs) to describe germline genetic immune disorders in 2017. The IUIS also recognized immune dysregulation as a subgroup of IEIs.¹³ In this nomenclature system, defects in innate immunity and autoinflammatory disorders are grouped separately from PIRDs. However, many clinicians use the term immune dysregulation more broadly and include interferonopathies and various autoinflammatory diseases under this heading.

The pediatric rheumatologist and advancement in IEIs characterized by immune dysregulation

The contribution of pediatric rheumatologists to our understanding of monogenic diseases with prominent features of immune dysregulation extends from gene discovery to pioneering novel treatments. Because it is impossible to adequately capture

all the individual achievements in the field, this section will highlight a few noteworthy advancements in understanding IEIs primarily manifested as autoimmunity and hyperinflammation.

Diseases of inflammasome activation. Millennia ago, bubonic pressures on the inflammasome selected for *MEFV* variants were famously linked to familial Mediterranean fever (FMF) by Daniel Kastner and others between 1992 and 1997.^{14–16} The link between *MEFV* and FMF, as well as findings in additional diseases such as *TNFR1* in TNFR1-associated periodic syndromes, inspired the concept of autoinflammation (1999), now recognized as a major mechanistic category of inflammatory disease.¹⁷ Beginning in the early 2000s, a collection of discoveries, often led by pediatric rheumatologists, combined to indelibly shape our understanding of human immunopathology.

Inflammasomes (2002). Scientists led by Jurg Tschopp identified a potent innate immune complex that assembled upon danger sensing by the cytosolic protein NLRP3. This NLRP3 inflammasome rapidly catalyzed the specific activation and release of interleukin-1 β (IL-1 β) and IL-18.¹⁸ It was not until 2014 that the protein pyrin encoded by *MEFV* was found to play a role in inflammasome activation.¹⁹

Cryopyrin-associated periodic syndromes and IL-1 blockade (2001–2004). In 2001, pediatric immunologists began to connect *NLRP3* variants to three fever syndromes that were ultimately united under the spectrum of cryopyrin-associated periodic syndromes (CAPSs), which encompasses familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID).²⁰ NOMID in particular was a progressive, severe, and often fatal condition. By 2004, adult and pediatric rheumatologists had shown IL-1 blockade

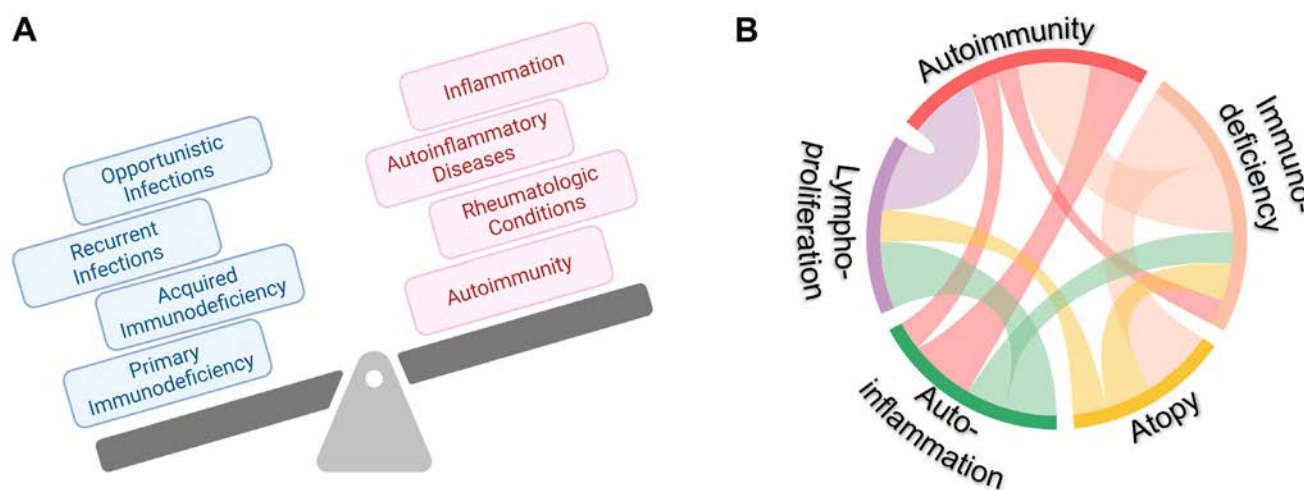


Figure 2. The evolving concept of immune dysregulation. (A) Historical paradigm of immune function. Shown is the historical view of the immune system as linear with function ranging from “low” manifested as immunodeficiency to “high” manifested as inflammation. (B) Complexity of immune dysfunction. Shown is the current concept that immune dysfunction is more complex and can encompass various phenotypes at the same time. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80127/abstract>.

was almost magically effective for CAPSs and ultimately for many other patients with “inflammasomopathies.”^{21,22}

Still's disease and IL-1 (2005). Still's disease is eponymous of 19th century pediatrician George Still, who described patients with fever, rash, adenopathy, and sometimes crippling arthritis—but also systemic hyperinflammation, now called macrophage activation syndrome (MAS).¹ Recently, there has been a movement to unite adult-onset Still's disease and systemic juvenile idiopathic arthritis (JIA) under the term Still's disease.²³ In 2005, pediatric rheumatologists identified an IL-1 signature in systemic JIA.²⁴ Expanding upon the success of anakinra (recombinant human IL-1 receptor antagonist) in CAPSs, they showed that IL-1 blockade was highly beneficial in a small number of children with Still's disease, suggesting a common inflammasome root.²⁴ Subsequently, larger cohort studies confirmed the efficacy of IL-1 inhibition in Still disease.^{25,26}

The rise of IL-18 (2001). After the identification of IL-18 as an “interferon- γ (IFN γ)-inducing factor” and inflammasome substrate in the 1990s, Japanese adult and pediatric rheumatologists were instrumental in showing that IL-18 levels were dramatically elevated in patients with Still's disease relative to other rheumatic and inflammatory diseases.^{27–29} Though neither IL-1 β nor IL-18 had yet shown diagnostic utility in monogenic inflammasomopathies, the connection between IL-18 and Still's disease—particularly in patients with Still's disease with or recovering from MAS—was repeatedly demonstrated.^{30,31}

The IL-18 opathies (2014). A correlation between IL-18 and MAS continued to grow in Still's disease, but a monogenic cause had not yet been identified to place IL-18 upstream. In 2014, pediatric rheumatologists and immunologists at the National Institutes of Health (NIH) and Yale independently discovered *NLRP4* variants and confirmed in vitro that they conferred inflammasome gain of function (GOF) and reported their association with profound serum IL-18 elevation, susceptibility to MAS, and responsiveness to IL-1 blockade.^{32,33} Subsequently, pediatric rheumatologists have contributed to novel genetic associations (*XIAP*, *CDC42*, *DPP9*, and *MEFV*), advocated for US Food and Drug Administration (FDA) approval of IFN γ blockade, and published preliminary evidence in support of therapeutic IL-18 blockade, all corroborating the mechanism that inflammasome-driven IL-18 is a specific driver of MAS.^{34–40}

The concept of autoinflammation; the pantheon of monogenic and syndromic inflammasome-related disorders; the emergence of clinical blood IL-18 measurement; and the therapeutic utility of IL-1, IFN γ , and (hopefully soon) IL-18 blockade represent major advances in the understanding and treatment of human inflammation, with their roots firmly embedded in the history of pediatric rheumatology.

Deficiency of adenosine deaminase 2. Deficiency of adenosine deaminase 2 (DADA2) is a monogenic recessive disease with pleiotropic phenotypes including systemic vasculitis,

early-onset strokes, immunodeficiency, and bone marrow failure. Biallelic mutations in *ADA2* were initially identified as a cause of polyarteritis nodosa and early-onset strokes with vasculopathy by groups in Israel and at the NIH, respectively.^{41,42} The physiologic function of *ADA2* is still unclear, and therefore, the pathophysiology of DADA2 is also unknown. *ADA2* catalyzes the in vitro conversion of free adenosine and 2'deoxyadenosine to inosine and 2'deoxyinosine, respectively. However, this deaminase function of *DADA2* seems limited at physiologic levels of adenosine.⁴³ Recent studies suggest that *ADA2* may function as a nucleic acid modifier in the lysosome.⁴⁴

Although the biologic mechanisms underlying DADA2 remain unresolved, the disease is among the more common monogenic autoinflammatory diseases, with an estimated carrier frequency of 1 in 236 individuals and a disease prevalence of 4 cases per 1 million individuals.⁴⁵ Pediatric rheumatologists have been at the forefront of characterizing *ADA2* gene variants and defining the burden of disease.^{45,46} More than 800 cases have been described in the literature to date, and the mortality rate of DADA2 is about 8%.⁴⁷

A diagnosis of DADA2 can be established by genetic studies (confirming biallelic deleterious variants) or by quantification of plasma *ADA2* activity.⁴⁸ Treatment with tumor necrosis factor inhibitors is effective in resolving vascular inflammation and preventing strokes.⁴⁹ The hematopoietic defects in DADA2 may manifest as pure red cell aplasia, neutropenia, or bone marrow failure.⁴⁶ Hematopoietic stem cell transplant is needed in patients with severe bone marrow failure. Pediatric rheumatologists have led international efforts to establish management guidelines for this disease in the International Consensus Statement for Evaluation and Management of DADA2.⁵⁰

STING GOF/SAVI. The discovery of GOF mutations in stimulator of IFN genes (*STING1*) caused an early-onset systemic vasculopathy cemented the type I interferonopathies as a distinct class of autoinflammation strongly overlapping with autoimmunity.⁵¹ In the initial report, the authors described six patients who presented in infancy with rash that was most prominent in cold-exposed areas (fingers, toes, nose, ears) due to biopsy-proven vasculopathy along with systemic inflammation and interstitial lung disease (ILD). The clinical presentation led to the term STING-associated vasculopathy with onset in infancy (SAVI) to describe the disease. Whole-exome sequencing in the index patient identified a de novo germline mutation in *TMEM173*, which encodes STING. Sanger sequencing confirmed that the other patients also harbored pathogenic variants in this same gene. STING senses intracellular DNA by binding cytosolic cyclic guanosine monophosphate (cGMP)-AMP, a second messenger generated when double-stranded DNA is detected by cGMP-AMP synthase (cGAS). STING activation results in downstream signaling that leads to induction of type-1 interferons. Indeed, peripheral blood mononuclear cells from affected patients had

elevated IFN-stimulated gene expression with no increase upon exposure to the STING ligand, supporting GOF as the disease mechanism. Whereas SAVI is considered a disorder of innate immunity, the elevated type-I interferons trigger autoantibody formation, ILD characterized by a lymphocytic infiltrate, and seropositive arthritis in some patients, blurring the line between autoinflammation and autoimmunity and fitting well within the immune dysregulation phenotype.

Identifying the role of aberrant nucleotide sensing in SAVI greatly contributed to the growing understanding of disease mechanisms that drive type I interferonopathies, a novel class of monogenic diseases characterized by excessive type-1 interferon responses. The work in SAVI added to a body of literature related to other disorders of type-I interferons. This includes Aicardi-Goutières syndrome (AGS), which is characterized by early-onset central nervous system (CNS) inflammation and linked with multiple genes important for nucleotide processing (such as *TREX1*, *RNASEH2A/B/C*, *SAMHD1*, and *ADAR1*).^{52–55} Researchers at multiple institutions had previously reported gene mutations associated with proteasome dysfunction that trigger the unfolded protein responses and lead to production of type-I and -II interferons as the etiology of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE).^{56–58} In total, AGS, CANDLE, and SAVI are prototypical diseases in the type I interferonopathy family, with distinct molecular causes but a shared common final pathway of exaggerated type-I interferon responses. In addition to the innovative work that identified key mechanisms that drive type I interferonopathies, pediatric rheumatologists have been at the forefront of treating patients with this class of disease by repurposing medications that are used for other rheumatologic disorders but are known to inhibit type-1 interferon signaling (JAK inhibitors for JIA and anifrolumab for lupus).^{59–61}

CTLA-4 haploinsufficiency. Building on prior work in murine models, two groups led by the NIH and University Medical Center Freiburg identified several families with severe immune dysregulation caused by heterozygous, autosomal dominant pathogenic variants in *CTLA4*.⁶² Affected individuals exhibited a broad spectrum of autoimmune and inflammatory conditions together with hypogammaglobulinemia and recurrent infections.^{63,64} Pathogenic *CTLA4* mutations impair CTLA-4 trafficking and surface expression, especially on Treg cells, resulting in reduced CTLA-4 availability at the immune synapse. Impaired CTLA-4 surface expression is also seen with biallelic, autosomal recessive *LRBA* mutations due to the role LRBA plays in directing CTLA-4 recycling.^{65,66} Both conditions lead to CTLA-4 insufficiency.

These diseases of CTLA-4 insufficiency have broad-ranging consequences for the regulation of the immune system. CTLA-4 on activated T cells and Treg cells acts as a negative checkpoint competing with CD28 for CD80/CD86 binding on antigen-

presenting cells.⁶⁷ Reduced CTLA-4 surface expression and signaling leads to impaired Treg suppressive function, T cell hyperactivation, and lymphocytic infiltration of organs. Affected individuals usually have hypogammaglobulinemia, with progressive B cell loss over time, expansion of CD21^{low} B cells and T follicular helper cells, and increased apoptosis of switched memory B cells. Treg cell numbers are often in the normal range despite functional impairment.⁶³

Patients with LRBA deficiency tend to have a more severe, earlier-onset phenotype than those with CTLA-4 haploinsufficiency, and CTLA-4 haploinsufficiency shows highly variable penetrance and age at onset, even within families.⁶⁸ This variability in severity and manifestations makes CTLA-4 haploinsufficiency particularly relevant to early evaluation in pediatric rheumatology. Whereas some patients initially present with recurrent infections and lymphadenopathy, others develop autoimmune manifestations first.^{66,69} The clinical presentation often overlaps with more common pediatric rheumatology conditions (arthritis, vasculitis, cytopenias, enteropathy), so CTLA-4 insufficiency is now one of the more frequently recognized IELs in pediatric rheumatology practice.^{70,71}

Early supportive care with intravenous Ig and antibiotic prophylaxis is important to prevent morbidity from infections. The most promising disease-modifying treatment to date is targeted therapy with abatacept (CTLA-Ig) to restore checkpoint signaling.⁷² The early implementation of abatacept in CTLA-4 haploinsufficiency and LRBA deficiency was informed by the favorable safety profile and extensive pediatric rheumatology experience with abatacept in JIA.⁷³ In a large international cohort of 98 patients with LRBA deficiency and CTLA-4 haploinsufficiency, 79% of patients had a sustained clinical response to abatacept, particularly with improvement in lymphoproliferation, enteropathy, and cytopenias.⁷⁴ For patients with severe disease or failure/intolerance of abatacept, hematopoietic stem cell transplantation is considered for definitive therapy.⁷⁵

STAT3 GOF. In 2014, the first description of five individuals with polyautoimmunity, including JIA, and de novo variants in *STAT3* that confer a GOF was published.⁷⁶ This initial report was quickly followed by back-to-back multi-institutional cohorts spearheaded by pediatric rheumatologists. These efforts expanded the number of known patients, and both confirmed several classic clinical findings of STAT3 GOF syndrome (early onset, short stature) and expanded the phenotype to include lymphoproliferation, autoimmune cytopenias, ILD, autoimmune enteropathy, and increased risk of infections.^{77,78} These consequences of significant immune dysregulation remain the defining features of STAT3 GOF among the more than 200 reported patients now in the literature.^{79,80}

Following the original reports, pediatric rheumatologists have continued to work together with colleagues in immunology to identify patients, validate novel variants, refine the cardinal clinical

findings, and uncover the cellular mechanisms and immunopathologic consequences of the variants. STAT3 is a transcription factor classically activated by phosphorylation after JAK activation following cytokine signaling and is critical to numerous developmental and inflammatory pathways. Variants that cause STAT3 GOF are located throughout different functional domains of the protein but have all been validated to confer increased transcriptional capacity in vitro using a luciferase assay.^{77,79} There is evidence that STAT3 variants lead to increased transcription through multiple pathways, including altered phosphorylation kinetics and enhanced DNA binding, and that specific mechanisms may be associated to the protein domain location of the variant.^{77,81} Seminal work on mouse models developed in the laboratories of pediatric rheumatologists revealed a role for effector CD8⁺ T cells in driving the immune dysregulation of STAT3 GOF.^{82,83} Ongoing collaborations between pediatric rheumatologist-scientists and clinical immunologists seek enhanced understanding of the immunopathology and mechanisms of STAT3 GOF and try to extrapolate these findings to deepen our knowledge of more common rheumatic diseases like JIA.^{84,85}

From the moment the genetic etiology of STAT3 GOF was revealed, pediatric rheumatologists have been repurposing available therapies for targeted treatment.⁷⁷ JAK/STAT-mediated cytokine signaling can be dampened with the use of JAK inhibitors, which have emerged as the optimal available management approach for individuals with STAT3 GOF.⁸⁶ The role of bone marrow transplantation in the management of STAT3 GOF is not yet clear, and ongoing work to prospectively evaluate the use of JAK inhibitors in STAT3 GOF and related disorders continues to be spearheaded by pediatric rheumatologists in collaboration with other subspecialists.⁷⁹

Toll-like receptor 7 GOF. Clinical phenotypes that overlap with systemic lupus erythematosus (SLE) have been reported in individuals carrying pathogenic variants in more than 30 genes, including those related to the complement system, type-I interferons, nucleic acid processing, apoptosis, and phagocytosis.⁸⁷ Pediatric rheumatologists have been instrumental in demonstrating the increased rate of monogenic SLE in children compared adults, accounting for 3% to 27% of cases depending on the study population.^{88,89} Most of the genes linked with SLE encode proteins related to the innate arm of immunity. The innate immune system relies on pattern recognition receptors (PRRs) to detect conserved molecular signatures displayed by pathogens and initiate host defenses. Among these, the Toll-like receptor (TLR) family occupies a central position, with each member specialized to recognize distinct pathogen-associated molecular patterns. TLR7, an endosomal receptor, was initially characterized as a sensor of viral single-stranded RNA degradation products such as guanosine.⁹⁰ However, the past decade has witnessed a

profound reconceptualization of TLR7's biologic significance because accumulating evidence established its central role in autoimmune pathogenesis, particularly in SLE.

In 2022, Brown et al⁹¹ provided the first definitive evidence that TLR7 GOF mutations cause human lupus. The study identified a de novo, heterozygous *TLR7* variant (Y264H) in a child with severe, early-onset SLE and demonstrated that this mutation selectively increased sensing of guanosine and 2',3'-cGMP, driving aberrant B cell survival and accumulation of specific B cell types. Critically, when the Y264H variant was introduced into a mouse model, it was sufficient to cause lupus-like disease. Subsequently, the importance of TLR7 in SLE was further confirmed by the finding that *UNC93B1*, a chaperon for TLR7 and TLR8, is also associated with monogenic SLE.^{92,93}

Already in the following four years, another 15 patients with TLR7 GOF from 11 families have been reported with pediatric rheumatologists involved in many of the cases.⁹⁴ Functionally, all mutations increase TLR7 activation upon stimulation. Clinically, most patients are female (80%), suggesting skewed X inactivation may play a role in this disease based on TLR7's location on the X chromosome. A majority of patients were diagnosed with SLE and had antinuclear antibody positivity, whereas complement consumption was noted in a minority of cases. Renal disease was not frequent, with only one patient found to have biopsy-proven lupus nephritis (class III/IV). Patients with non-SLE phenotypes have been reported, including AGS and Evan syndrome.^{95,96}

In total, this work definitively established TLR7 as a monogenic cause of human SLE and confirmed the important role for TLR7 in autoimmune diathesis. Further, these findings immediately suggest novel therapeutic strategies in targeting TLR7 and downstream signaling molecules (myeloid differentiation primary response protein 88 [MyD88]) as rational future interventions for SLE.

TLR8 GOF. Despite the expansion in access to genetic testing, many children suspected of having monogenic immune dysregulation remain undiagnosed. Large cohort studies of patients with suspected IELs indicate that up to 70% of all patients do not have a molecular diagnosis after exome or genome sequencing.⁹⁷ This suggests that new approaches to the analysis of genomic data and alternatives to monogenic drivers of disease need to be considered. Most IELs have been discovered as germline inherited or de novo single-nucleotide variants or structural variants that alter the function of the encoded protein. However, alternative genetic mechanisms are emerging, and in 2021, pediatric rheumatologists identified a cohort of children with early-onset lymphoproliferation, cytopenias, and bone marrow failure due to mosaic and germline variants in *TLR8*.⁹⁸ In this initial cohort, six male children (age 1–16 years) were reported, with five patients having genetic mosaicism, with variants in TLR8 present in a subset (8%–26%) of cells, with four unrelated patients having the same variant (p.P432L). TLR8 is another endosomal PRR encoded on the X chromosome and expressed by myeloid cells

that recognize single-stranded RNA, leading to downstream pro-inflammatory signaling through MyD88 and NF- κ B.⁹⁹ Intriguingly, in most patients, genetic mosaicism was not limited to the hematopoietic compartment and did not confer a selective survival advantage or lead to expansion of a cell type enriched for the variant. Functional studies with patient-induced pluripotent stem cell-derived myeloid cells and primary cells demonstrated that the variants lead to GOF of the protein and stimulated high production of inflammatory cytokines. More recently, an additional four patients were reported, including a female patient with germline disease with symptoms of bone marrow failure before one month of age, demonstrating that TLR8 GOF is an X-linked dominant immune disorder.¹⁰⁰

Clinically, patients suffer from recurrent infections associated with neutropenia and B cell defects, lymphoproliferation including hepatosplenomegaly, expanded CD8 T cells with an activated phenotype, and bone marrow abnormalities including T cell infiltration. Patients have elevated serum cytokines including soluble IL-2R α , IFN γ , IL-18, and IL-12. At least one child had evidence of hemophagocytosis on liver biopsy, and TLR8 GOF may present with features similar to hemophagocytic lymphohistiocytosis (HLH), with granulocyte colony-stimulating factor-refractory neutropenia being one potential clinical differentiator. There is an overall high mortality rate, with 40% of patients (4 of 10) dying, and hematopoietic stem cell transplant is the only known effective therapy.¹⁰⁰ The severe phenotype described here has been termed inflammation, neutropenia, bone marrow failure, and lymphoproliferation caused by TLR8 (INFLTR8). However, a spectrum of TLR8-associated inflammatory disease is emerging with other reports of a family with TLR8 GOF associated with familial anemia, with the genetic variant in that case demonstrating less-robust GOF activity when compared to those identified in patients with INFLTR8, suggesting that strength of signaling may be associated with phenotype.¹⁰⁰ In another family, male siblings with germline TLR8 variants had autoimmunity and inflammation including arthritis and CNS vasculitis.¹⁰¹ In these brothers, whereas the TLR8 protein demonstrated GOF, the protein had reduced half-life with increased TLR7 signaling that the authors propose led to disease.

TLR8 GOF is 1 of approximately 20 monogenic mosaic disorders of immunity classified as “phenocopies” of IELs by the IUIS, with the terminology genetic error of immunity (GEI) used to encompass both germline and mosaic disease.¹⁰² Most mosaic GEIs lead to immune dysregulation and clinical phenotypes relevant to pediatric rheumatologists, for example, lymphoproliferation due to mosaic *FAS* variants and autoimmune inflammatory disease due to mosaic variants in *NLRP3*, *NOD2*, *NLRC4*, and others.^{102,103} This may explain why pediatric rheumatologists have been central to identifying novel genes, like *TLR8*, associated with disease-causing mosaicism. Researchers in the field have also made foundational contributions to our understanding of how to detect somatic mutations

in patients with immune dysregulation. This is technically challenging because the depth of sequencing typically performed with exome and genome may not be sufficient to detect low-frequency variants. New approaches such as high-depth sequencing may overcome this obstacle. Further complicating the picture, mosaic variants are present in healthy individuals as well as patients with immune dysregulation, and thus, classifying variants for further functional evaluation will be important for the field to advance diagnosis and discovery.¹⁰⁴

Future directions for pediatric rheumatology and immune dysregulation

Moving forward, pediatric rheumatologists are poised to make substantial contributions to the field of immune dysregulation that will likely surpass the progress made in the last 50 years. There is an expanding toolbox of novel diagnostics that can be used to dissect immune responses, including assays developed by researchers in the field. Pediatric rheumatologists are leading the way in using anticytokine and cellular therapies to treat immune dysregulation and are developing innovative models to deliver care to affected patients.

Diagnostics and precision medicine. There is an ever-increasing number of assays that can be used to characterize the immune system, a process often termed immunophenotyping. Immunophenotyping typically involves quantifying circulating immune cells and proteins to identify aberrant immune pathways that may be informative for diagnosis and treatment. Clinicians can track immune-related biomarkers tailored to a patient's genetic diagnosis to aid in management. Leveraging immunophenotyping is also important in the substantial proportion of patients with immune dysregulation who do not have an identified monogenic defect. Because these individuals lack a genetic diagnosis and do not typically fit into a known disease paradigm, it can be extremely challenging to predict their clinical course or select appropriate treatments without insight into the nature of their immune system dysfunction. In this way, pediatric rheumatologists are increasingly using immunophenotyping to deliver personalized medicine to patients with immune dysregulation and are expected to continue to pioneer this approach in the future.

Pediatric rheumatologists have made substantial advances in identifying biomarkers that can be used for immunophenotyping. In addition to IL-18, discussed above, researchers in the field have made significant progress in accurately evaluating type-I and -II interferons, pivotal cytokines in immune dysregulation. Although IFN γ (IFN-II) plays a central role in cytokine storm syndromes, measurement of IFN γ in the peripheral blood remains challenging due to its tissue location.^{38,105} Studies of patients with HLH/MAS have shown that sCD25 (also called IL-2R α , a marker of T cell activation) and CXCL9 (a chemokine induced by IFN γ) are reliable biomarkers that can be used in diagnostic

evaluation and therapeutic monitoring.^{106,107} Accurate assessment of circulating type-I interferon is also difficult because this family of cytokines is potent at very low concentrations and is quickly consumed locally. Therefore, transcriptional quantification of IFN-stimulated genes, known as the IFN-I signature, is often used as a surrogate to quantify IFN-I activity.¹⁰⁸ Although this approach is used in research laboratories, it is technically challenging to implement in the clinic. Recently, pediatric rheumatologists and pathologists teamed up to develop a test that simultaneously captures both IFN-I and IFN γ activity.¹⁰⁹ This flow cytometry-based IFN signature has been successfully implemented in the clinical setting, first by the Diagnostic Immunology Laboratory at Nationwide Children's Hospital, and has quickly grown to be an important tool to identify aberrant IFN responses in patients with immune dysregulation.

In addition to the development of assays for established immunologic patterns, novel pathways and biomarkers associated with pediatric rheumatologic diseases are being developed with advances in transcriptomics, proteomics, and metabolomics. The availability of affinity proteomics, including the aptamer-based Somascan technology, and Olink proximity extension assay has illuminated new insight into the biology of Still's disease, juvenile dermatomyositis (JDM), multisystem inflammatory syndrome in children (MIS-C), and Kawasaki disease.^{110–112}

Therapeutics. Biologic disease-modifying antirheumatic drugs that inhibit inflammatory cytokines have transformed the management of rheumatologic diseases in children. Before the first tumor necrosis factor inhibitors were approved for JIA in the late 1990s through early 2000s, patients with polyarticular disease accrued substantial disability (Figure 3). There now exists an expanding armamentarium of medications that target a wide range of cytokines. As discussed in this review, pediatric rheumatologists are often called to use their unparalleled expertise in anticytokine therapies to treat patients with immune dysregulation. Researchers in the field will continue to be instrumental in identifying novel cytokines and immune pathways to target in patients with immune dysregulation through translational research and biomarker discovery.

Beyond anticytokine medications, cellular therapies such as chimeric antigen receptor (CAR) T cells and bispecific T cell engagers represent the next class of therapeutics with the potential to revolutionize the treatment of immune disorders. Although cellular therapies were initially developed for malignancy-related indications, they are increasingly being used in patients with autoimmunity. The most progress has been made for CD19-CAR T cells in patients with SLE.¹¹³ In the small number of patients studied to date, the results have been extremely promising, with patients with refractory disease entering remission without the need for ongoing immunosuppressive therapy.¹¹³ Case reports have shown similar positive findings for pediatric patients with SLE and JDM.^{114,115} Pediatric rheumatologists are at the forefront of

leveraging cellular therapies to treat children with autoimmunity. Multiple centers are initiating clinical trials that will evaluate CAR T cells in pediatric patients with rheumatologic disorders. The Integrated Multidisciplinary Paediatric Autoimmunity Cell Therapy workgroup was recently established by pediatric rheumatologists in collaboration with other subspecialists to advance the use of this class of therapies in the pediatric population.¹¹⁶ In the next decade, the use of cellular therapies is certain to expand as their targets diversify. This represents a promising intervention for patients with rheumatologic disorders as well as those with immune dysregulation.

Multidisciplinary teams. Immune dysregulation is typically characterized by high disease activity with multisystem involvement that is often outside of the typical pattern encountered in more well-defined diseases. For these reasons, patients with immune dysregulation are difficult to manage because they require coordinated subspecialty care that must be executed rapidly despite the dearth of evidence related to best practices. To address these immense challenges, pediatric rheumatologists have conceptualized and operationalized a team-based approach that brings together clinicians and investigators with expertise in immune dysregulation to deliver high-quality care (Supplementary Figure S1).¹¹⁷ These multidisciplinary teams in immune dysregulation (immMDTs) are often organized around a central clinic or inpatient consult service where patients can be evaluated simultaneously by multiple key subspecialists.

The immMDT model has resulted in important improvements in patient care. By offering a “one-stop” approach, these clinics and consult services reduce the logistical burden on families, minimize fragmented care, and facilitate communication and collaboration among providers. Several immMDTs have developed diagnostic and therapeutic algorithms in an effort to standardize care for patients with immune dysregulation.¹¹⁸ Beyond clinical care, immMDTs are becoming a powerful tool for research and education. A number of immMDTs are currently in operation across the United States and span both inpatient and outpatient settings as well as academic and community hospitals. Early evidence from centers that have adopted immMDTs suggests faster disease-directed care, shorter length of stay, higher physician satisfaction, and improved patient outcomes.^{117–121}

The immMDT model has been increasingly adopted at pediatric centers worldwide and is now expanding into adult care settings. As immune-mediated diseases continue to be redefined by advances in genetics and immunology, the need for high-quality, coordinated care for patients will only increase, and immMDTs offer a scalable and adaptable framework guided by pediatric rheumatologists and experts across subspecialties. In retrospect, this team-based approach to patient care has always been a core value in pediatric rheumatology. The early pioneers in the field at Taplow assembled a multidisciplinary group of clinicians to care for children with rheumatic diseases that encompassed immunologists, ophthalmologists,

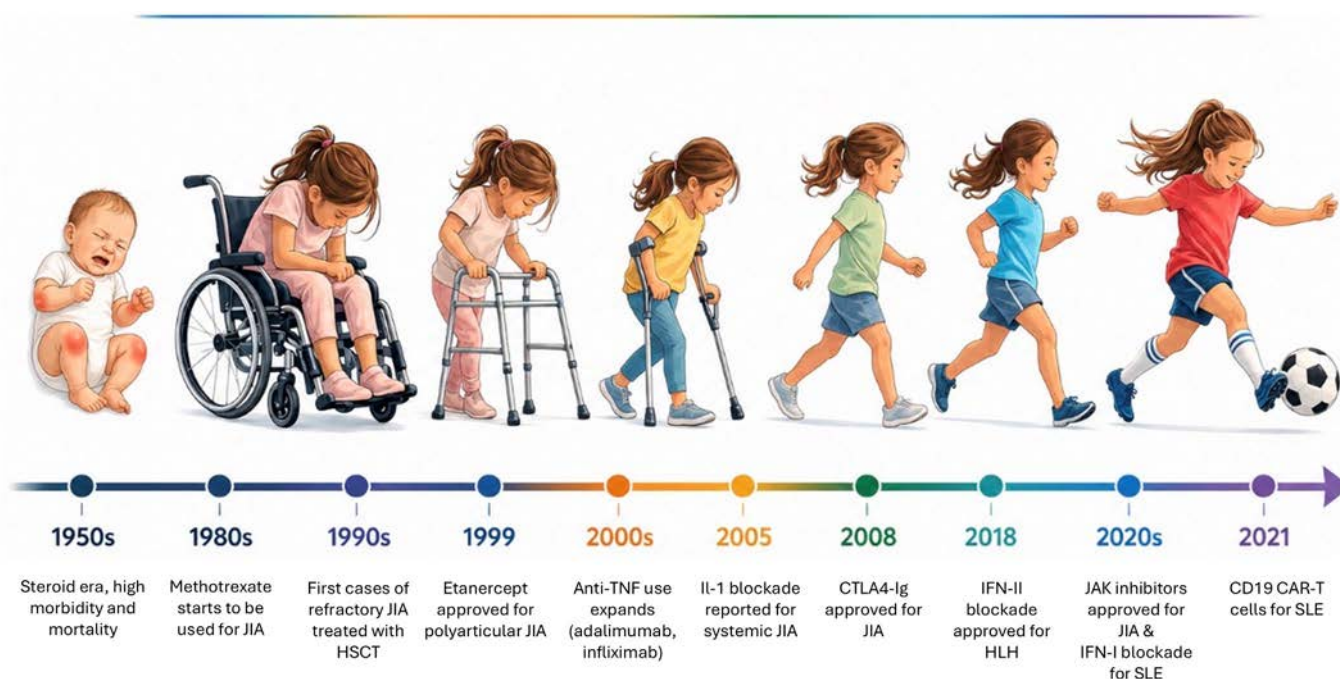


Figure 3. Treatment advances in pediatric rheumatology. The timeline shows therapeutic advances in the field of pediatric rheumatology and US Food and Drug Administration (FDA) approval of medications frequently used to treat immune dysregulation. This figure was made with assistance from OpenAI. CAR, chimeric antigen receptor; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplant; IFN, interferon; IL-1, interleukin-1; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80127/abstract>.

orthopedic surgeons, and pathologists. Perhaps it is with these early pioneers that the concept of immMDTs originally emerged.

Conclusions

In summary, pediatric rheumatologists have made transformational discoveries in defining autoinflammation, dissecting disease mechanisms in interferonopathies, identifying novel genes related to immune diseases, and recognizing the importance of somatic variants in autoimmunity. These accomplishments have provided insights into the nature of inflammatory diseases and suggested biology-informed treatment approaches that have improved outcomes for patients with immune dysregulation as well as those with more common rheumatologic conditions. The next 50 years of pediatric rheumatology are expected to be equally productive given that the field is poised to make substantial advances in personalized medicine and cellular therapies while developing innovative approaches to deliver multidisciplinary care.

ACKNOWLEDGMENTS

We thank our pediatric rheumatology colleagues worldwide for their unwavering dedication, collaboration, and contributions to our field. We also thank the patients and families whose trust and engagement have made this progress possible. Figure 3 was made with assistance from OpenAI.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Henderson confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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EDITORIAL

Reflections on Retractions in Rheumatology Publications

Kelli D. Allen 

The manuscript by Vettori and Iudici in this issue of *Arthritis Care & Research* focuses on retractions in rheumatology-related publications.¹ Prior manuscripts have reported retraction rates in medical journals more broadly, but this appears to be the first to focus on rheumatology, and it is useful to see these metrics for our field specifically. There are several key takeaway points from this report. First, the majority of retractions (75%) were due to misconduct, rather than unintentional errors. This is disheartening yet also important for understanding the heart of the problem. Second, rates of retractions are increasing. Although this is partly due to enhanced vigilance and tools for detecting plagiarism, data fabrication, etc, it likely also reflects an actual increase in instances of misconduct. Third, there is substantial variability in retraction rates across both countries and journals. Although this indicates there are settings in which greater change is necessary, it does not suggest that vigilance and other culture changes are not universally important. Fourth, rates of and reasons for retractions in rheumatology were similar to other medical specialties.

Data presented in this manuscript call for continued reflection on the reasons for publication retractions and how we can address this in the rheumatology field and in medical research more broadly. Although multiple factors contribute to publication misconduct, pressure to publish to achieve professional status is likely a key driver. The degree to which publication pressure leads to misconduct may vary across countries, fields, and institutions. However, pressure to publish is almost universally present in the context of academic medicine, and it has other negative impacts, particularly for early career researchers; it can increase overall work-related stress and lead to an unbalanced emphasis on one aspect of the scientific process. As a rheumatology research community, we have opportunity and an imperative to push back on this paradigm and hold the value of scientific publication in its proper place. High-quality publications are certainly one good indicator that a researcher is conducting rigorous and impactful

science. Yet the primary goal of clinical research publications is to share findings, ultimately advancing collective understanding and improving the care and lives of patients, not to advance the professional status of the authors.

Advances in the availability of artificial intelligence (AI) tools are bringing both new opportunities and challenges in the area of scientific publishing. There are good uses of these tools, including supporting authors who wish to publish in a different language. However, we are seeing increases in fully AI-generated papers and even fabricated data. Unfortunately, these tools are being used to facilitate unethical publication practices, likely for the sake of professional advancement and survival. There will be continued discussions about the appropriate use of AI tools in the context of scientific writing. In wrestling with these questions, and in promoting ethical publications practices overall, it is essential to keep the goal of medical publications at the heart of the discussion.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Allen confirms that the author has provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80011>.

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Submitted for publication January 20, 2026; accepted in revised form January 20, 2026.

Retractions in Rheumatology: Trends, Causes, and Implications for Research Integrity

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Objective. We aimed to describe the trends and main reasons for study retraction in rheumatology literature.

Methods. We reviewed the Retraction Watch database to identify retracted articles in rheumatology. We recorded the main study characteristics, authors' countries, reasons for retraction, time from publication to retraction, and trends over time. Reasons for retraction were classified as scientific misconduct, data/figure errors, or other reasons. Main article features and cause of retractions in rheumatology were compared with a sample of articles from other medical specialties.

Results. A total of 381 (79.5% original articles) rheumatology articles were retracted between 1989 and 2024. Most originated from Asia (68.5%), particularly China (50.7%). Scientific misconduct accounted for 75.3% of retractions, followed by data errors (14.9%) and other reasons (7.6%). Common misconduct types included data fabrication, fake peer review, duplication, and authorship issues. The median time from publication to retraction was 18 months (interquartile range 9–46), with one-third of articles requiring more than 36 months to be retracted. Time to retraction did not improve over time. The number of retractions steadily increased over time from 18 in 2000–2009, 117 in 2010–2019, and 207 in 2020–2023 ($P < 0.001$). Compared with other medical specialties, rheumatology exhibited similar retraction patterns, differing mainly in geographic distribution.

Conclusion. Retractions in rheumatology have risen substantially, largely due to misconduct. This trend may reflect an increase in questionable research practices or improved detection. Strengthening early-career education, institutional oversight, and ethical research culture is essential to enhance transparency and integrity in the field.

INTRODUCTION

Scientific publishing plays a central role in the dissemination of medical knowledge and in supporting research and education within the discipline.¹ However, not all published findings meet the standards of rigor, quality, ethical conduct, and scientific validity. Study validity can be compromised by unintentional errors that naturally occur in research, but in some cases, it may also be undermined by misconduct, including practices such as fraud, plagiarism, or data fabrication.¹ Ensuring accuracy and credibility in research is essential, as scientific evidence underpins medical decision-making and health care policy.

Retraction, the formal withdrawal of a published article, is a key mechanism through which the scientific community safeguards research integrity and prevents the dissemination of misleading information that could compromise patient safety, distort clinical practice, or misguide future research.^{2,3} Although still relatively low, the rate of retraction in medicine has risen in recent

years, with the frequency and causes of retraction varying considerably across medical fields.^{4–6} For instance, the proportion of retractions due to misconduct across medical specialties has been reported to range from 22% to 89%.⁶ When analyzing the reasons for misconduct, plagiarism predominates in some specialties, whereas duplicate publication or data fabrication is more common in others. Similarly, the proportion of articles retracted for unintentional errors is highly variable.⁶ Identifying the patterns and determinants of retractions within specific disciplines is crucial for informing targeted interventions, strengthening editorial and peer-review practices, and ultimately fostering a culture of research integrity. A specialty-focused analysis can reveal field-specific patterns that may be diluted or overlooked in broader biomedical data sets.

To date, no study has specifically examined this issue within the field of rheumatology. We therefore conducted this analysis to characterize retraction patterns in rheumatology, with the aim

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80005>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80005>.

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Submitted for publication October 29, 2025; accepted in revised form December 29, 2025.

SIGNIFICANCE & INNOVATIONS

- The number of retracted articles in rheumatology has increased over time, reflecting either a rise in compromised studies or improved detection.
- Most retractions are due to misconduct, mainly data fabrication, peer-review concerns, and duplicate publication, whereas only about 15% result from errors without misconduct.
- The findings may help inform medical students, rheumatologists, editors, and institutions, promoting a culture of transparency and accountability in research.

of understanding their underlying causes and trends, and to identify potential implications for future improvement.

METHODS

Search strategy. We performed a review of the Retraction Watch database (RWD) (<http://www.retractiondatabase.org>) on January 4, 2025. The RWD is continuously updated and provides a comprehensive list of retracted scientific articles. The RWD identifies retractions through automated searches of article databases (eg, PubMed, Web of Science, Scopus), screening of publisher and journal websites, institutional reports of research misconduct investigations, and reader tips. The RWD is updated daily, but some retractions may still be missed or identified with delay, although its coverage generally exceeds that of other sources such as PubMed and Web of Science.⁷ The data set includes, among other fields, the title of the retracted manuscript, the research area (for example, economics or medicine), the institution and country of the corresponding author, the journal, the type of study (for example, clinical research or meta-analysis), the retraction date, digital identifiers for retraction notices (where available), the DOI of the original article, and the reasons for retraction. To identify articles related to rheumatology, we used a two-step approach. First, we generated a list of rheumatology-related terms starting from an initial draft created using a large language model (ChatGPT o3).⁸ The prompt asked the artificial intelligence (AI) to capture different variations of relevant words (for example “rheumatology,” “rheumatism,” etc). For example, to retrieve articles containing terms such as “rheumatology,” “rheumatologic,” “rheumatism,” or “rheumatoid,” the AI suggested using the root “rheuma” as a keyword. It also accounted for language-specific variations of main disease names. For instance, both “Sjögren” and “Sjogren” were included to capture articles related to Sjögren disease. This process resulted in a list of 65 keywords (Table 1), including the name of the specialty, diseases, major diagnostic tests, treatments, and clinimetric indexes. The list was reviewed for consistency by one of the authors (MI), a rheumatologist. To create the initial shortlist of rheumatology-related

Table 1. Keywords used to identify rheumatology articles (alphabetical order)

ANA	gout	rheuma
ankylosing spondylitis	granulomatosis with polyangiitis	rheumatic
anti-CCP arthritis	HAQ health assessment questionnaire	rheumatism rheumatologic
arthralgia	hyperuricemia	rheumatologist
auto- inflammatory syndromes	IL-6 inhibitors	rheumatology
autoimmune disease	immunosuppressants	rheumatoid arthritis
Behcet	inflammation	rheumatoid factor
Behçet's disease	inflammatory arthritis	rheumatoid nodules
biologic DMARD	JAK inhibitors	rituximab
biological therapy	joint degeneration	sarcoidosis
connective tissue disease	joint erosion	scleroderma
corticosteroids	leflunomide	Sjogren
C-reactive protein	methotrexate	Sjögren's syndrome
CRP	mixed connective tissue disease	spondyloarthropathy
DAS	NSAIDs	spondyloarthritis
DAS28	osteoporosis	sulfasalazine
dermatomyositis	osteoarthritis	synovitis
disease activity score	overlap syndromes	systemic lupus erythematosus
DMARD	PMR	systemic sclerosis
erythrocyte sedimentation rate	polymyalgia rheumatica	TNF inhibitors
ESR	polymyositis	uric acid
fibromyalgia	PsA	vasculitis
GCA	psoriatic arthritis	
giant cell arteritis	remission	

articles, we searched for the presence of at least 1 of the 65 keywords in each row of the Excel file downloaded from retractiondatabase.org. The selected articles were then manually reviewed by the same author (MI) to exclude those not relevant to rheumatology. Discrepancies were resolved by consensus through discussion. To identify medical articles outside the field of rheumatology to use as comparators, we searched the database by filtering the Subject column for articles containing the term “Medicine.” In the RWD, subjects including the word “Medicine” refer to entries within the broader Health Sciences category, which covers a wide range of medical and biomedical specialties such as internal medicine, oncology, cardiology, neurology, surgery, pediatrics, pharmacology, radiology, dentistry, public health, nursing, epidemiology, and related clinical and health-science disciplines. Articles classified under rheumatology were excluded from the comparator set. We classified reasons for retraction into the following categories, adapted from Resnik et al⁹: scientific misconduct (data fabrication, plagiarism, duplication, ethical violations, conflict of interest, authorship issues, lack of informed consent, compromised peer review,

and other/unspecified), errors in data/figure, and other. Information pertaining to the entity initiating or conducting the retraction process (eg, “Investigation by journal/publisher,” “Investigation by institution”) was not considered a substantive reason for retraction. Instead, these cases were grouped separately under the category “Investigation/Administrative,” which records who initiated the retraction but does not represent a specific cause. The impact factors of the journals were assessed using Journal Citation Reports (Clarivate Analytics 2024).¹⁰ We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.¹¹

Statistical analysis. Data were summarized as number (percentage) for qualitative variables and median (interquartile range [IQR]) for continuous variables. Continuous variables were compared with *t*-test, Wilcoxon test, or Kruskal-Wallis test, and categorical variables were compared with χ^2 test or Fisher exact test, as appropriate. We assessed temporal trends using Poisson regression of period counts on an ordinal period index with a log link and an offset for period length (log years); the *P* value is the Wald test for the period coefficient. A *P* value ≤ 0.05 was considered significant. Ethical approval was not required (study not involving human participants). All analyses were performed in R (version 4.4.2).

RESULTS

Main study characteristics. Of the retractions retrieved, 381 (published between 1989 and 2024) were related to rheumatology (Figure 1 shows the flowchart of search strategy). Retracted articles in rheumatology were mostly original articles (*n* = 303; 79.5%), published mainly by authors from Asia (*n* = 261; 68.5%). China accounted for the largest number of retractions (*n* = 193; 50.7%), followed by Japan (*n* = 30; 7.9%). The median number of authors per retracted article was 5 (range 1–46, IQR 3–7), and the median journal impact factor was 3.2 (range 0.2–98.4; IQR 2.5–4.7). In total, articles were retracted from 211 journals, of which 12 had more than five retracted articles (see Supplementary Table S1).

Reasons for retractions. The majority of the articles had multiple reasons for retractions (median 3, IQR 1–4). Most articles had at least one cause of scientific misconduct (*n* = 287; 75.3%), whereas a smaller proportion of articles were retracted due to data errors without misconduct (*n* = 57; 14.9%) or other reasons (*n* = 29; 7.6%). Among the articles retracted for scientific misconduct, the most common issues were data fabrication, concerns with or fake peer review, duplication, and authorship problems (Table 2). Studies retracted for errors without misconduct were published in journals with higher impact factors (median 3.3, IQR 2.8–5.7) than those retracted for misconduct (median 2.9, IQR 2.4–4.3) or for other reasons (median 1.9, IQR 0.8–4.5;

P < 0.001). Figure 2 and 3 show the temporal trends of retraction in rheumatology by reason and by type of misconduct.

Time from publication to retraction. Median time from publication to retraction was 18 months (IQR 9–46, range 1–223), with 118 (31%) and 68 (18%) articles needing more than 36 months and 60 months, respectively, to be retracted. Time needed for retractions was longer for cases of scientific misconduct (18 months, IQR 10.5–46) compared to cases of data errors (13 months, IQR 4–47) or other reasons (5 months, IQR 0–29; *P* < 0.001).

For specific misconduct reasons, time to retraction was shorter for ethical violations, concerns with peer review, lack or withdrawal of informed consent, and plagiarism, whereas it was longer for duplication and authorship issues (see Supplementary Table S2). Time to retraction remained stable over time (median 21 months in 2000–2009, 16 months in 2010–2019, 17 months in 2020–2023; *P* = 0.983).

Temporal trends of retractions and related reasons.

The number of retracted articles increased from 3 in 1990–1999 to 18 in 2000–2009, 117 in 2010–2019, and 207 in 2020–2023 (*P* < 0.001; Figure 2). The year 2023 accounted for the largest number of retractions, with 105 retracted articles (27.5%), of which 101 (96.2%) involved misconduct issues, 92 (87.6%) originated from China, and 74 (70.5%) were published by Hindawi. Similarly, retractions due to misconduct rose from 1 in 1990–1999 to 13 in 2000–2009, 70 in 2010–2019, and 176 in 2020–2023 (*P* for trends < 0.001; Figure 2). Significant upward trends were also observed for retractions due to errors (data not shown), and these trends remained statistically significant even after excluding 2023, the year with a marked spike in retractions.

Comparison between rheumatology and other retracted studies in medicine. Compared with retracted articles in other medical specialties, retracted rheumatology studies exhibited similar patterns in the reasons for retraction, time from publication to retraction, retraction requesters, and publishers involved. The only significant difference was observed in geographic distribution: a higher proportion of retracted rheumatology studies originated from Asia (68.5% vs 58.3%; *P* < 0.001), particularly from China (50.7% vs 38.4%; *P* < 0.001) (Table 2).

DISCUSSION

In rheumatology, the number of retractions has steadily increased in recent years, with most cases attributed to scientific misconduct. The leading causes included data fabrication, concerns about peer review, and duplicate publication, whereas only about 15% of retractions resulted from errors without evidence of misconduct. The average time to retraction was approximately 18 months, with no improvement observed over time. Retractions

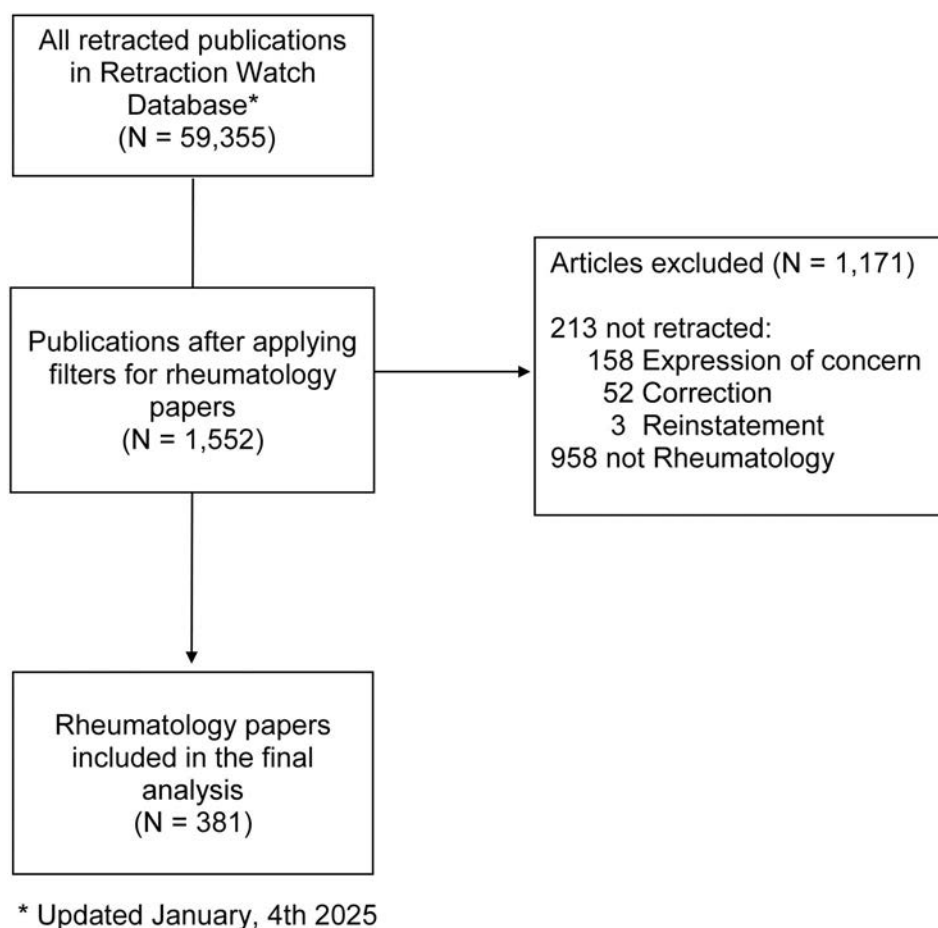


Figure 1. Flowchart of search strategy

occurred more quickly for cases involving ethical violations, lack or withdrawal of informed consent, peer-review concerns, and plagiarism, whereas they took longer for issues related to duplication and authorship disputes. Retracted rheumatology studies showed similar patterns to other medical fields, except for a higher proportion originating from Asia, particularly China.

Retractions in rheumatology, as in other medical fields, have increased in recent years. As in other specialties, it is likely that this rise cannot be explained solely by the growing number of publications. In fact, the incidence of retractions has doubled in cardiology¹² and increased in other fields, from 2.3 per 100,000 publications in 2001 to an estimated 8 per 10,000 publications in 2022.^{4,5} Whether this reflects a general decline in scientific integrity or is instead a consequence of the greater awareness of publication ethics and more effective detection of unreliable work,^{13,14} as advocated by the Committee on Publication Ethics guidelines (2009),¹ remains uncertain. Nonetheless, it is evident that recent years have seen a stronger emphasis on research integrity, greater public scrutiny through online publication, and wider availability of tools to detect plagiarism or redundant studies. Consequently, the rise in retractions may be interpreted not only as evidence of increased misconduct but also as a reflection

of enhanced vigilance and a growing commitment to maintaining scientific standards.¹⁴ For instance, the spike in article retractions observed in 2023 was largely driven by initiatives from certain publishers to eliminate paper mill content and address cases of compromised peer review.¹⁵

Regarding the underlying reasons, most retractions were attributed to research misconduct, whereas those resulting from genuine errors, an unavoidable aspect of scientific work that should not be viewed negatively, were a minority. Although variations exist across specialties,⁶ misconduct regrettably remains the predominant cause of retraction in most areas of medicine,^{6,16–19} with fraud, data fabrication, and fraudulent peer review being the most common forms of misconduct and their incidence showing an increasing trend over time. A meta-analysis on medical publications found that overall, misconduct was responsible for an estimated proportion of 60% of all retractions, whereas error and publication issues were responsible for, respectively, 17% and 9%.⁶ Several factors may explain why authors engage in unethical research practices. The need to maintain a robust publication record to advance an academic medical career, often described as “publish or perish,” has been widely recognized as a key driver.²⁰ Additional contributing

Table 2. Main characteristics of retracted articles*

	Rheumatology (n = 381)	Medicine (n = 15,308)	P value
Article type			0.056
Original article	303 (79.5)	11,828 (77.3)	
Meta-analysis/review	50 (13.1)	1,736 (11.3)	
Case report	16 (4.2)	611 (4.0)	
Commentary/editorial/letter	3 (0.8)	224 (1.5)	
Guidelines	1 (0.3)	56 (0.4)	
Other	8 (2.1)	853 (5.6)	
Continent			<0.001
Asia	261 (68.5)	8,923 (58.3)	
Europe	40 (10.5)	2,248 (14.7)	
North America	22 (5.8)	1,720 (11.2)	
Africa	12 (3.1)	349 (2.3)	
South America	6 (1.6)	123 (0.8)	
Oceania	5 (1.3)	152 (1.0)	
Multiple continents	30 (7.9)	1,610 (10.5)	
Unknown	5 (1.3)	182 (1.2)	
Country			<0.001
China	193 (50.7)	5,881 (38.4)	
International	47 (12.3)	2,257 (14.7)	
Japan	30 (7.9)	743 (4.9)	
United States	14 (3.7)	1,509 (9.9)	
India	3 (0.8)	709 (4.6)	
United Kingdom	3 (0.8)	385 (2.5)	
Reason for retraction			0.309
No. studies with ≥1 reason for scientific misconduct	287 (75.3)	11,485 (77.5)	
No. studies retracted for data errors without misconduct	57 (14.9)	1939 (13.1)	
Other reasons	29 (7.6)	1,389 (9.4)	
Scientific misconduct ^a			
Fabrication of the data	96	3,557	
Concern with/fake peer review	94	4,569	
Duplication	87	3,138	
Issues about authorship	67	1,938	
Lack or withdrawn of informed consent	62	2,233	
Plagiarism	57	2,243	
Ethical violations	20	962	
Conflict of interest	1	136	
Unspecified misconduct	124	4,458	
Error(s) in the manuscript ^a	267	8,760	
Other reasons ^a	311	12,112	
Journal impact factor, median (IQR)	3.2 (2.5–4.7)	3.1 (2.2–5)	0.976
Time from publication to retraction, months, median (IQR)	18 (9–46)	17 (8–42)	0.584
Retractions due to scientific misconduct	18 (10.5–46)	18 (10–40)	
Retractions for data errors	13 (4–47)	13 (4–34)	
Retractions for other reasons	5 (1–29)	5 (1–25)	
N of authors, median (IQR)	5 (3–7)		
Retraction requesters			0.847
Journals or publishers	140 (48.8)	5,647 (49.3)	
Third party ^b	114 (29.9)	4,392 (28.6)	
Company/institution	33 (8.6)	1,419 (9.3)	
Top 5 publishers			0.244
Hindawi	89 (23.4)	3,643 (23.8)	
Elsevier	42 (11.0)	2,012 (13.1)	
Springer	39 (10.2)	1,132 (7.4)	
Wiley	34 (8.9)	1,446 (9.4)	
Taylor and Francis	16 (4.2)	638 (4.2)	
Retraction notice access			
Open access	366 (96.1)	14,754 (96.4)	

* Values are expressed as n (%) unless stated otherwise. IQR, interquartile range.

^a More than 1 reason possible for each study retraction.^b An investigation by any third party that is not the United States Office of Research Integrity.

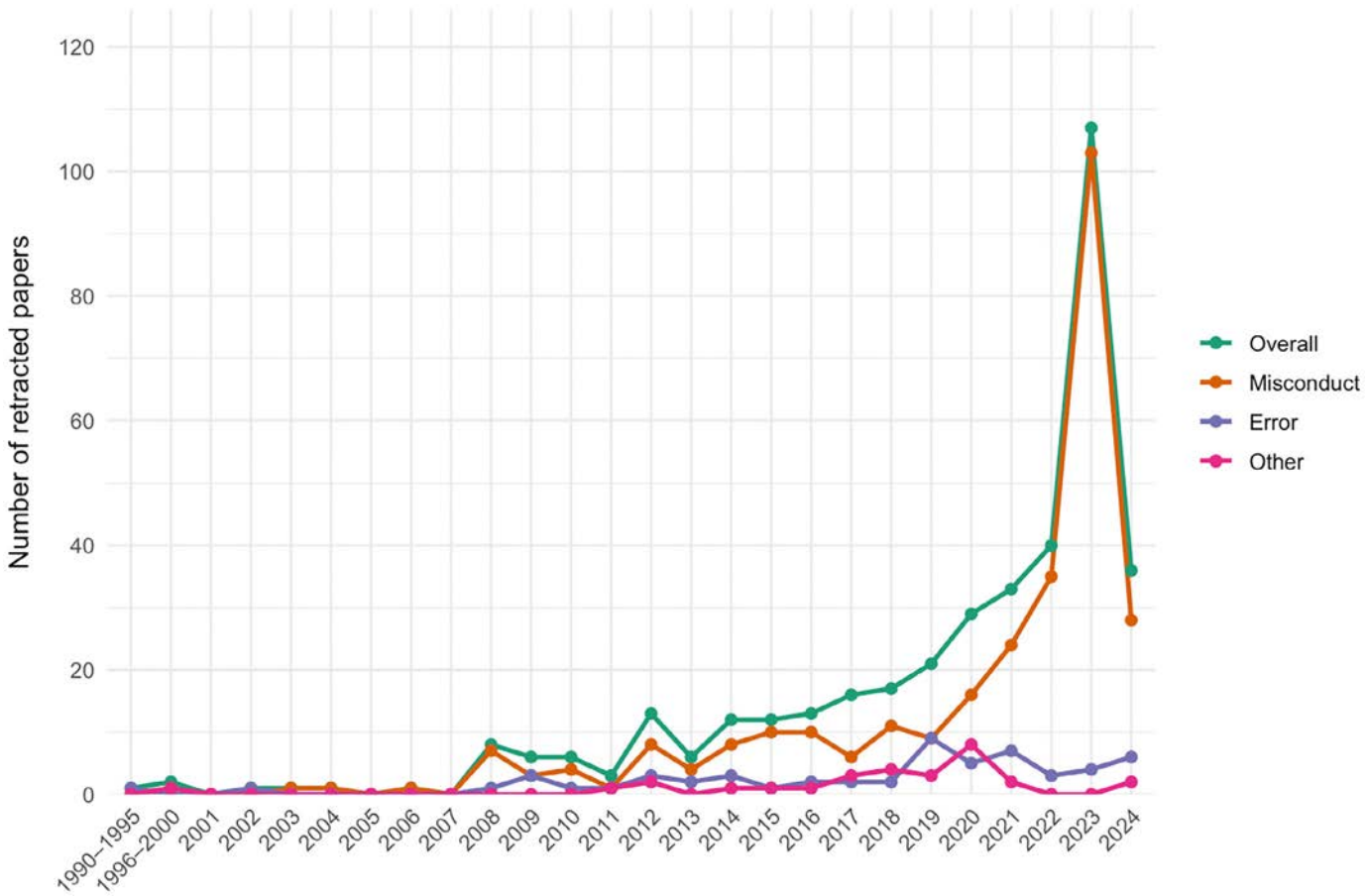


Figure 2. Temporal trends of retraction in rheumatology by reason.

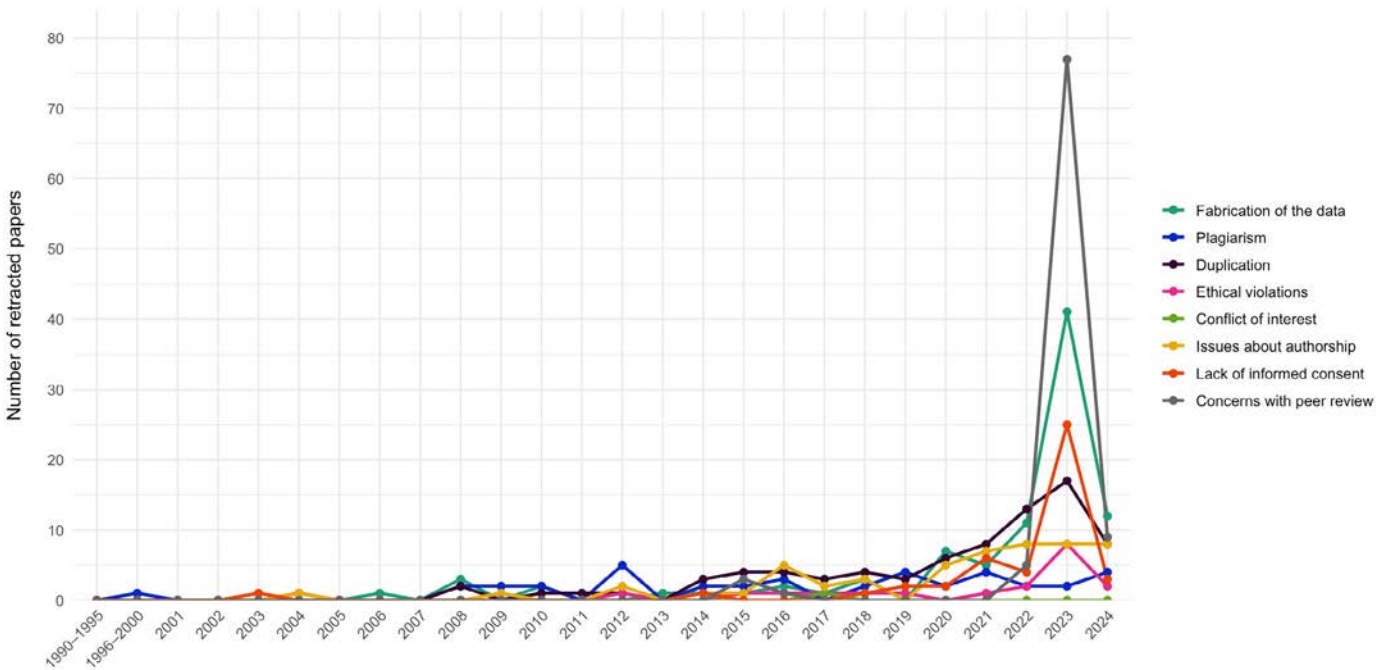


Figure 3. Annual trends in rheumatology retractions by misconduct reason. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80005/abstract>.

factors include inadequate institutional oversight, conflicts of interest, insufficient training in research ethics, and cultural or systemic pressures that prioritize productivity over integrity.^{8,14,21,22} Our findings highlight the need to strengthen education, oversight, and a culture of research integrity in rheumatology, beginning early in training and continuing throughout researchers' careers. Initiatives such as the EQUATOR Network²³ and Responsible Conduct of Research programs²⁴ endorsed by the National Institutes of Health and the European Commission promote transparency, reproducibility, and ethical research practices. Greater consideration and implementation of such initiatives within rheumatology could further enhance research quality and uphold scientific standards. In this context, the advent of AI presents both a concern and an opportunity: whereas these tools may facilitate image manipulation or the creation of fabricated research content, they also offer the potential for enhanced screening and detection methods that could help prevent such issues.

We did not observe any improvement in the time required to retract an article over the years, which has plateaued at approximately 18 months. Notably, about one-third of retractions took more than 36 months to be finalized. This highlights the ongoing challenges in identifying flawed articles and taking timely corrective action to minimize their potential negative impact on the scientific literature.²⁵ Addressing this issue should be considered a research priority, as recent evidence indicates that retracted articles can distort the results of systematic reviews and meta-analyses.²⁵ Adopting standardized workflows, such as those outlined by the National Information Standards Organization Communication of Retractions, Removals, and Expressions of Concern guidelines,²⁶ can streamline decision-making and ensure prompt correction of the scientific record.

About half of the retracted articles originated from China. In a review of retracted articles across medical fields, China and several low- and middle-income countries showed relatively higher retraction rates compared with their overall publication volume.^{27,28} This pattern may reflect multiple factors, including strong performance-based incentives in academic promotion systems, varying levels of oversight and mentorship for early-career researchers,²⁸ and the increasing detection of issues such as paper mills or peer-review manipulation, which may more readily affect regions with rapidly expanding research activity.²⁹

Our study has several limitations. First, as mentioned above, we were unable to estimate the exact proportion of retracted publications relative to all publications in rheumatology, given the wide range of diseases encompassed by this specialty, which are difficult to capture within predefined categories. Second, we could not determine whether the rise in retracted publications reflects an absolute increase in erroneous and/or fraudulent research or, rather, heightened detection. Third, we used impact factor values from the 2024 Journal Citation Reports, which may not reflect the journal's impact factor at the time the retracted articles were

published. However, this approach is common,^{16,30} and prior studies have shown that citation-based journal rankings are relatively stable over time, making contemporary impact factors a reasonable proxy for journals' relative impact.³¹ Fourth, some rheumatology articles, particularly from multidisciplinary journals, may not have been captured, affecting absolute counts. However, this is unlikely to have altered the main conclusions. Finally, it remains uncertain whether these retractions have had a negative impact on subsequent research or patient care. Future research is needed to clarify these points. Strengths of our study include its originality in the field and its systematic approach to characterizing retraction trends, causes, and geographic distribution.

In conclusion, the number of retracted articles in rheumatology has continued to rise over time, primarily due to questionable research practices. This trend may reflect either an increase in the publication of compromised studies or improved detection of such issues. Unfortunately, retractions capture only a small proportion of cases of scientific misconduct. Surveys among scientists have shown that approximately 2% admitted to having fabricated, falsified, or modified data or results at least once, and 34% acknowledged other forms of intentional misconduct, such as manipulating graphs or unjustifiably removing data from final analyses.²² Moreover, it is also important to note that cases of misconduct or serious errors are identified during peer review or editorial assessment and therefore never reach publication. These findings highlight the need to raise greater awareness of research integrity issues within the scientific community. Our results may help inform medical students, rheumatologists and trainees, editors, and research institutions, thereby supporting efforts to strengthen preventive strategies, improve editorial and peer-review processes, and foster a culture of transparency and accountability in research.

ACKNOWLEDGMENTS

We thank the team behind the Retraction Watch Database for making their data publicly available and for their ongoing efforts to promote research transparency. Open access publishing facilitated by Université de Genève, as part of the Wiley - Université de Genève agreement via the Consortium Of Swiss Academic Libraries.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Iudici confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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BRIEF REPORT

A Rheumatoid Arthritis Training Program for Primary Care Providers on the Navajo Nation

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Objective. The Navajo Nation, the largest Native American reservation, faces a high prevalence of rheumatoid arthritis (RA) and a critical shortage of rheumatology providers. To address this gap, we developed an RA training program for primary care providers (PCPs) using the Project Extension for Community Healthcare Outcomes (ECHO) tele-mentorship model. This study evaluates the impact of the RA ECHO curriculum on PCPs' knowledge, confidence, and self-reported clinical behaviors.

Methods. We designed a 12-week RA curriculum of weekly 60-minute Zoom sessions with expert-led didactics and case discussions. Content was informed by a needs assessment and input from Navajo cultural interpreters. PCPs completed precourse, postcourse, and one-year follow-up surveys assessing medical knowledge (multiple-choice test) and self-reported confidence (five-point Likert scale) in RA diagnosis and treatment. The one-year follow-up also assessed changes in self-reported clinical behaviors. Paired *t*-tests were used to assess score changes over time.

Results. A total of 46 clinicians completed the program across three cohorts. Knowledge scores improved from 46% to 71% postcourse (+25%, 95% confidence interval [CI] 7%–43%, *P* = 0.009) and remained 69% after one year. Confidence scores increased from 2.9 ("neutral") to 3.9 ("somewhat comfortable"; +1.0, 95% CI 0.23–1.74, *P* = 0.01), sustained at one year. One year later, participants reported favorable changes in clinical behaviors including performing more detailed joint examinations and ordering preimmunosuppression laboratory tests and vaccines.

Conclusion. The RA ECHO curriculum improved PCPs' knowledge, confidence, and self-reported clinical behaviors in RA care in the Navajo Nation. This culturally grounded, disease-focused model demonstrates feasibility, acceptability, and scalability as a workforce expansion strategy in settings with limited rheumatology access.

INTRODUCTION

Native American communities experience some of the most pronounced health disparities in the United States, including a disproportionate burden of rheumatologic disease and limited access to specialty care. The Navajo Nation, the largest Native American reservation in the United States, illustrates this inequity acutely. Spanning more than 27,000 square miles across Arizona, New Mexico, and Utah, the Navajo Nation is home to over 170,000 tribal members, many of whom live in rural or remote set-

tings with limited access to subspecialty care.^{1,2} The prevalence of rheumatoid arthritis (RA) among the Navajo (Diné) is estimated to be at least four times the national average, with some studies reporting rates as high as 4.5% to 8%, representing one of the highest known burdens of RA worldwide.^{3,4}

Despite this high prevalence of rheumatologic disease, the Navajo Nation, like many other rural areas, faces a serious shortage of local rheumatology providers. Patients often wait more than six months for rheumatology appointments, and many patients must travel more than 100 miles to receive care. In this

Supported by the Bristol Myers Squibb Foundation (Specialty Care for Vulnerable Populations Award A136614) and Pfizer Global Medical Grants (Independent Medical Education Grant A142712).

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80044>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80044>.

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Submitted for publication October 23, 2025; accepted in revised form March 10, 2026.

SIGNIFICANCE & INNOVATIONS

- This study is the first disease-specific, culturally grounded rheumatology Extension for Community Healthcare Outcomes (ECHO) program designed for and implemented in the Navajo Nation, tailored for a community with one of the highest known burdens of rheumatoid arthritis in the United States.
- This study demonstrates that a focused, telementorship-based curriculum can significantly and sustainably improve primary care providers' knowledge, confidence, and self-reported clinical behaviors in rheumatoid arthritis diagnosis and management.
- Our curriculum integrates Navajo cultural perspectives and community input into rheumatology education—an innovative approach to enhance engagement, trust, relevance, and sustainability.
- Our curriculum illustrates how community-informed rheumatology ECHO programs can be used as a scalable and replicable strategy to quickly expand rheumatology capacity in other underserved or rural communities facing rheumatology workforce shortages.

context, local primary care providers (PCPs) often have no choice but to attempt to diagnose and treat complex rheumatologic conditions with limited specialist support.² Yet, many PCPs report limited training or confidence in diagnosing and managing autoimmune diseases.^{2,5} Even when rheumatology appointments are available, many Diné patients express a preference for receiving care from local, trusted PCPs who are more accessible and who better understand their patients' cultural contexts.²

These challenges exist within a broader national crisis in the rheumatology workforce. The American College of Rheumatology projects that by 2030, demand for rheumatologic services will more than double the available supply of rheumatologists, with shortages disproportionately affecting rural and underserved regions.^{6,7} Workforce expansion strategies that rely solely on increasing the number of trained rheumatologists are unlikely to meet the needs of high-burden communities such as the Navajo Nation in the near term. Innovative models that build rheumatology capacity within primary care, while centering equity and community partnership, are urgently needed.

In response to these challenges, we developed and implemented a telementorship-based RA training program for Navajo Area PCPs using the Project Extension for Community Healthcare Outcomes (ECHO) model. Project ECHO is an educational model designed to expand access to specialty care by training PCPs on specialist-level topics through regular, virtual case-based learning and brief didactics led by a multidisciplinary expert panel.^{8,9} Although the ECHO model has demonstrated success in multiple chronic disease domains, its application in rheumatology,¹⁰ and

specifically in Native American communities, has been limited compared to other specialties.

In response to these gaps, we developed and implemented an RA ECHO curriculum for PCPs serving the Navajo Nation. The curriculum was designed in close partnership with Navajo clinicians, community health leaders, and cultural interpreters and was informed by a formal needs assessment of PCPs practicing in the Navajo Area.² This study describes the design, implementation, and evaluation of the RA ECHO curriculum and assesses its impact on PCPs' knowledge, confidence, and self-reported clinical behaviors related to the diagnosis and treatment of RA. Our findings highlight the potential of community-informed, telementorship-based PCP education to address both workforce shortages and disparities in rheumatology care for underserved populations.

PARTICIPANTS AND METHODS

Program development. The RA ECHO curriculum was developed in 2020 by an interdisciplinary team including members from the University of California, San Francisco (UCSF), the American College of Rheumatology Collaborative Initiatives Division, and clinicians and community health leaders living in and near the Navajo Nation. The curriculum was intentionally focused on a single disease, RA, to promote depth of learning and to ensure relevance to the target population given the high prevalence of RA among the Navajo. RA also lends itself well to the ECHO model because it has clearly defined treatment guidelines. Rather than launching a broad nationwide ECHO curriculum, we intentionally decided to focus on one specific community because we believe meaningful and sustainable improvements in RA care come from educational interventions designed with the community's logistical, cultural, linguistic, and social contexts in mind.

Key partners included three rheumatologists from UCSF, two Navajo Area rheumatologists, a pharmacist familiar with the Indian Health Service (IHS) formulary, and two Navajo cultural interpreters. To design the curriculum, we built on previous work² in which we conducted a formal needs assessment of PCPs working within the Navajo Area health system. This needs assessment study included semistructured interviews and surveys of 15 PCPs (13 physicians, 1 nurse practitioner, and 1 physician associate, all working in either family medicine or internal medicine clinics), which identified core gaps in PCP confidence and knowledge related to RA diagnosis, disease-modifying antirheumatic drug (DMARD) initiation, treatment escalation, and safety monitoring. PCPs also described structural barriers to care delivery, including limited access to laboratories and refrigeration-dependent medications, language discordance, and patient mistrust of Western medicine. Our interdisciplinary team intentionally addressed these community-specific facilitators and barriers to rheumatology care throughout the RA ECHO curriculum. A summary of these community-specific considerations and their

corresponding curricular adaptations is provided in Supplementary Table S1.

Curriculum structure. The RA ECHO program consists of 12 weekly 60-minute Zoom sessions, held during the lunch hour. Each session includes a 20- to 30-minute didactic led by a rheumatologist, followed by an interactive case-based discussion. Didactic topics were selected based on the needs assessment study and covered foundational topics such as distinguishing inflammatory from noninflammatory joint pain, conducting a detailed RA joint examination, and safely initiating and monitoring conventional synthetic DMARDs.

Following the didactic, PCPs engaged in interactive case discussion with the interdisciplinary teaching panel. PCPs were encouraged to submit their own de-identified patient cases using a standardized case presentation form developed by our team. The case presentation form was adapted from existing Project ECHO presentation templates and modified by our interdisciplinary team to emphasize RA-specific clinical elements (eg, duration and characteristics of joint symptoms, musculoskeletal examination, imaging studies, previous immunosuppressive medication trials, etc). Whenever possible, discussions integrated community-based considerations such as traditional healing practices, navigating Navajo language barriers, and other practical considerations such as access to refrigeration for biologic medications. In addition to live webinars, we chose to expand our program beyond the traditional ECHO model by creating a library of asynchronous learning resources for PCPs. These resources included instructional videos demonstrating the RA joint examination and how to calculate RA disease activity scores, recorded lectures, one-page “Quick Start” RA treatment guides, and patient education handouts designed specifically for the Navajo community.

Recruitment and participants. PCPs were recruited from IHS and tribally operated health facilities located within the Navajo Area. At the time of recruitment, there were approximately 70 to 80 PCPs (50–55 full-time equivalent PCPs) working in the Navajo Area, a region that is home to approximately 244,000 Native Americans living in and near the Navajo Nation. Recruitment strategies included direct outreach by local champions, email announcements, word of mouth, and presentations at regional and national meetings. Recruitment specifically targeted PCPs (including physicians, nurse practitioners, and physician associates), but other health care providers were not excluded from participating. To help incentivize consistent attendance, we offered continuing medical education credits. Participants who attended at least 9 of 12 sessions and presented at least one de-identified patient case for discussion received a formal Certificate of Course Completion from the American College of Rheumatology.

Evaluation strategy. We used a pre–post survey design to assess the impact of the curriculum on participants’ knowledge, confidence, and satisfaction. Participants completed a pre-survey before the course began, a postsurvey after the course ended, and a one-year follow-up survey. Each survey included a multiple-choice RA medical knowledge test covering key concepts in diagnosis and treatment. The same knowledge questions were used on the presurvey, postsurvey, and one-year follow-up survey, and participants were not provided with an answer key at any point. Each survey also included confidence questions, in which participants ranked their comfort level with aspects of RA diagnosis and management (eg, distinguishing between RA and osteoarthritis; initiating a patient for the first time on an oral DMARD) on a five-point Likert scale. In the postsurvey, participants also rated each session’s usefulness on a five-point Likert scale (1 being not at all useful, and 5 being extremely useful) and answered open-text questions about the course’s usefulness, quality, and impact. In addition to the knowledge and confidence questions, the one-year follow-up survey also asked participants about self-reported changes in clinical behaviors related to RA, such as how frequently they perform detailed joint examinations or check hepatitis serologies before starting immunosuppression. Self-reported behavior changes were measured on a five-point Likert scale (“much less frequently” to “much more frequently”).

Survey responses were analyzed using descriptive statistics, with means and SDs calculated for continuous variables and response frequencies for categorical variables. Changes in knowledge and confidence among presurvey, postsurvey, and one-year follow-up survey were assessed using paired *t*-tests, with 95% confidence intervals (CIs) and *P* values reported. A two-tailed *P* value of <0.05 was considered statistically significant. To examine the relationship between changes in knowledge and confidence, we calculated the Pearson correlation coefficient between each participant’s change in mean knowledge score and change in mean confidence score from pre- to postcourse. This project was granted exempt status by the UCSF Institutional Review Board because it involved implementation and evaluation of standard educational methods. In the preparation of this manuscript, the authors used ChatGPT for minor language editing and grammar review only; all intellectual and analytical contributions are the authors’ own.

RESULTS

Participation and engagement. A total of 46 clinicians participated in the RA ECHO curriculum across the first three cohorts (Table 1), including 33 physicians (71.7%), 9 nurse practitioners (19.6%), 2 physician associates (4.3%), and 2 optometrists (4.3%). Most participants specialized in either family medicine (52%) or internal medicine (37%). There was also a small number of participants from other specialties who reported frequently seeing patients with RA (two from orthopedic surgery, two from

Table 1. Demographics of provider participants in the RA ECHO curriculum for the Navajo Nation (N = 46)*

Characteristic	Provider participants, n (%)
Sex	
Female	33 (71.7)
Male	11 (23.9)
Other/prefer not to say	2 (4.3)
Race	
American Indian or Alaska Native	3 (6.5)
Asian	9 (19.6)
Black or African American	2 (4.3)
Native Hawaiian or other Pacific Islander	0 (0)
White	28 (60.9)
Other/multiracial	2 (4.3)
Prefer not to say	2 (4.3)
Ethnicity	
Hispanic or Latino	4 (8.7)
Not Hispanic or Latino	40 (87.0)
Prefer not to say	2 (4.3)
Age, y	
<30	0 (0.0)
30–39	17 (37.0)
40–49	16 (34.8)
50–59	10 (21.7)
≥60	3 (6.5)
Profession	
Physician (MD/DO)	33 (71.7)
Nurse practitioner (NP)	9 (19.6)
Physician associate (PA)	2 (4.3)
Other	2 (4.3)
Primary specialty	
Family medicine	24 (52.2)
Internal medicine	17 (37.0)
Orthopedic surgery	2 (4.3)
Optometry	2 (4.3)
Pediatrics	1 (2.2)
Time in practice, y	
<2	7 (15.2)
2–4	7 (15.2)
5–9	14 (30.4)
10–14	8 (17.4)
15–19	1 (2.2)
≥20	9 (19.6)
Indian Health Service employed	
Yes	42 (91.3)
No	4 (8.7)
Prior participation in another ECHO program	
Yes	25 (54.3)
No	21 (45.7)

* ECHO, Extension for Community Healthcare Outcomes; RA, rheumatoid arthritis.

optometry, and one from pediatrics). On average, participants attended 71% of the scheduled teaching sessions. A total of 29 participants (63%) presented at least one de-identified patient case during the course.

Knowledge outcomes. Performance on the multiple-choice RA knowledge test (Figure 1) increased by 25% (95% CI 7%–43%, $P = 0.009$) from a mean presurvey score of 46% correct (95% CI 33%–60%) to a mean postsurvey score of 71%

correct (95% CI 57%–84%). This improvement in knowledge was durable: the mean score on the one-year follow-up survey was 69% correct (95% CI 54%–83%), which was not statistically significantly different compared to the posttest ($P = 0.84$).

Confidence outcomes. Statistically significant improvements were observed in participants' self-reported comfort levels with various aspects of RA diagnosis and treatment (+1 point on the Likert scale, 95% CI 0.23–1.74, $P = 0.013$; Figure 1). Before taking the course, the mean confidence rating was 2.9 (95% CI 2.35–3.44), corresponding approximately to a confidence rating of "neutral." On the postsurvey, the mean confidence rating improved to 3.9 (95% CI 3.29–4.46), corresponding approximately to a confidence rating of "somewhat comfortable." This improved confidence remained stable on the one-year follow-up survey, with a mean confidence score of 3.8 (95% CI 3.29–4.39), which was not statistically significantly different than the posttest mean ($P = 0.808$). Changes in participants' knowledge scores (pre vs post) were strongly positively correlated with changes in self-reported confidence scores ($r = 0.73$, $P = 0.0075$), indicating that participants who demonstrated larger gains in RA knowledge also tended to report greater increases in confidence.

Satisfaction with the curriculum. On the postsurvey, the mean usefulness score ($\pm$ SD) across all sessions was 4.52 (± 0.77) of 5. Of the respondents, 100% stated they would recommend the program to colleagues. Free-text comments praised the practical content, case-based learning, and inclusion of Navajo-specific cultural context. Several participants expressed interest in advanced follow-up curricula and hands-on workshops to practice the joint examination and procedures.

Self-reported clinical behavior change. On the one-year follow-up survey, participants in the RA ECHO program self-reported favorable changes in clinical practice behaviors across multiple domains (Figure 2). Two-thirds of participants (67%) indicated that they now initiate a workup for RA more frequently or much more frequently than before the program. Of the participants, 78% reported performing thorough joint examinations more often, and 67% reported increased use of RA disease activity scores. Confidence in initiating conventional DMARD therapy also improved, with 61% of respondents reporting increased prescribing frequency. For patient-related tasks such as ordering preimmunosuppression laboratory testing and checking vaccination status, more than 75% of participants indicated that they now perform these activities more frequently than before. The most common neutral responses ("about the same") were for diagnosing extra-articular manifestations of RA and initiating biologic DMARDs, suggesting that confidence in these areas may remain more limited.

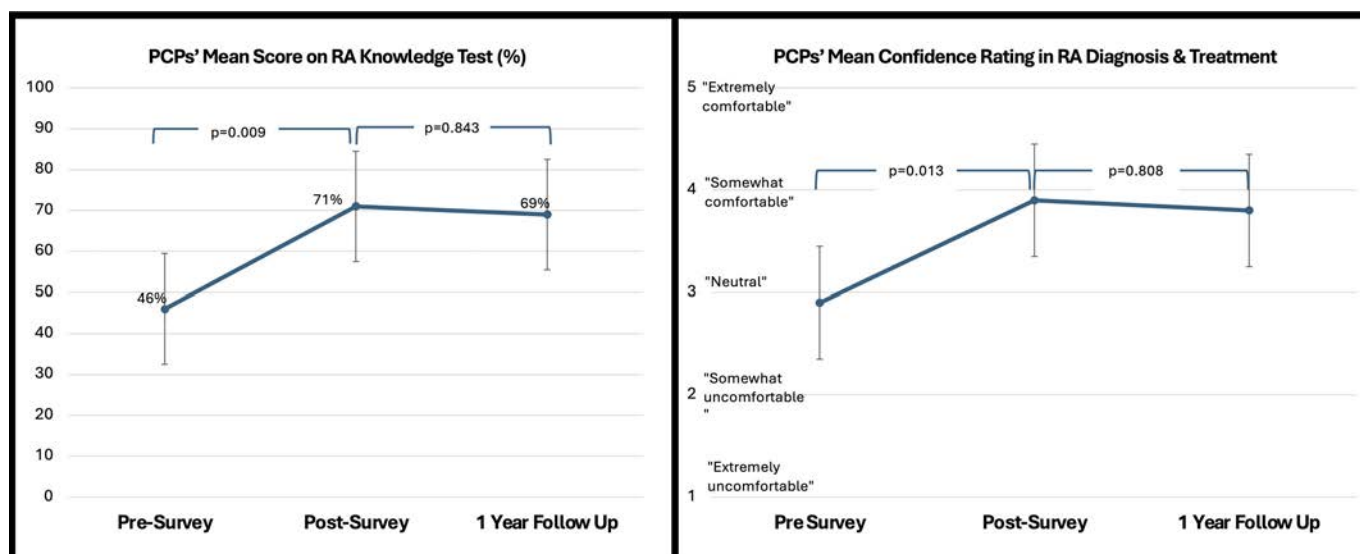


Figure 1. Changes in PCPs' RA knowledge and confidence before and after participating in the RA Extension for Community Healthcare Outcomes curriculum for the Navajo Nation. PCP, primary care provider; RA, rheumatoid arthritis. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80044/abstract>.

DISCUSSION

The RA ECHO curriculum for the Navajo Nation demonstrated high feasibility, strong engagement, and sustained improvements in PCPs' knowledge, confidence, and self-reported clinical behaviors in diagnosing and treating RA. These

results highlight the potential of PCP education interventions as an effective strategy to address the rheumatology workforce shortage in underserved communities. In response to the rheumatology workforce crisis, rheumatologists have an opportunity to seek out new ways to support our primary care colleagues. PCPs are the first, and sometimes only, point of care for patients

"Compared to your clinical practice prior to completing the RA ECHO course, how frequently do you do the following without consultation from a rheumatologist?"

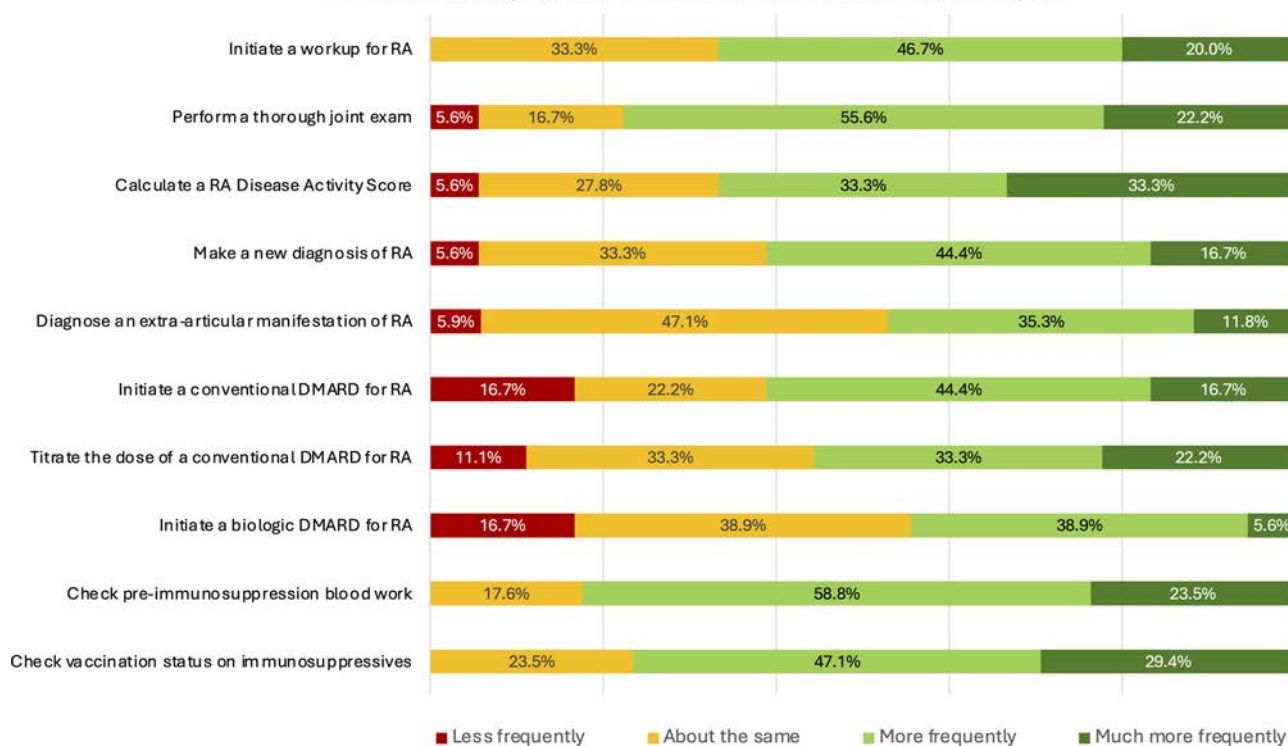


Figure 2. Primary care providers' self-reported clinical behavior changes, reported one year after completing the RA ECHO curriculum for the Navajo Nation. DMARD, disease-modifying antirheumatic drug; ECHO, Extension for Community Healthcare Outcomes; RA, rheumatoid arthritis.

living with rheumatologic diseases. Equipping PCPs with skills to more accurately diagnose and appropriately manage first-line treatment for common rheumatologic conditions has the potential to reduce delays to care, improve patient outcomes and safety, and optimize the use of limited rheumatology resources. The RA ECHO curriculum for the Navajo Nation is an important practical demonstration of an effective and feasible PCP education strategy.

Our program builds upon the ECHO model, an evidence-based, cost-effective, and scalable approach to training PCPs in specialty topics, which has been underused in rheumatology compared to other specialties. Our initiative represents a novel and targeted application of the ECHO model in rheumatology education for clinicians in the Navajo Area, with a specific focus on a single, high-prevalence disease. By concentrating on RA and integrating regionally relevant content, the program achieved depth and relevance that promoted sustained changes in knowledge, confidence, and self-reported clinical practice.

Several key features contributed to the program's success. First, the curriculum was informed by a comprehensive needs assessment,² ensuring that content was closely aligned with the clinical realities and learning priorities of participating clinicians. Second, the program deliberately integrated community-informed and culturally grounded adaptations into the curriculum design rather than treating cultural relevance as merely an adjunct to content delivery. By aligning instructional strategies with Navajo-specific cultural, linguistic, logistical, and structural factors (Supplementary Table S1), the curriculum achieved relevance and feasibility for clinicians practicing in this resource-constrained setting. We believe this approach enhances engagement, trust, and sustainability and offers a replicable framework for adapting rheumatology education to other underserved communities. Third, the interactive, case-based structure of the 12-week course fostered active and sustained participation and helped build a sense of professional community among participants. Finally, we expanded the curriculum beyond the traditional ECHO model by creating an online library of enduring RA educational resources that PCPs can access asynchronously and share with patients and colleagues, thus promoting sustainable impact.

Although our data focus on PCP outcomes, the ultimate goal of this program is to improve the lives of Diné patients living with RA. It is promising that in addition to improvements in PCPs' knowledge and confidence, participants reported meaningful changes in clinical behavior, including performing more thorough joint examinations, increased use of RA disease activity measures, and patient safety considerations such as preimmunosuppression laboratory tests and immunizations. Although these behaviors were not objectively measured in this study, they suggest a potential downstream impact of targeted PCP education on RA care quality and represent an important area for future research.

This study has several limitations. Generalizability beyond the Navajo Nation requires further research. Participants who enrolled in the RA ECHO curriculum for the Navajo Nation may have a greater baseline interest in or knowledge of rheumatology than the broader PCP population, introducing potential selection bias. Additionally, outcomes relied primarily on self-reported measures and knowledge assessments without direct observation of clinical practice or patient-level data. This design was intentional and guided by our Navajo community collaborators. In alignment with their recommendations, we did not access protected patient health information during this early phase of the program, acknowledging the long history of exploitation in Native American communities. Building strong and lasting trust was identified as a critical prerequisite before pursuing patient-level data collection or evaluation.

Despite these limitations, the RA ECHO program demonstrates a scalable, culturally grounded approach for expanding rheumatologic expertise in primary care. Following the completion of the initial three cohorts in the Navajo Nation, we partnered with the Indian Country ECHO initiative to extend the RA ECHO curriculum to providers serving Native American communities nationwide. To facilitate dissemination and broader impact, our curricular materials (including didactic PowerPoint slides, standardized case presentation forms, instructional videos, and accompanying resources) are currently available upon request, and we are actively developing a website that will provide free access to all materials. By making these resources openly available, we aim to support adaptation of this curriculum by other communities facing similar rheumatology workforce shortages while allowing local stakeholders to tailor content to their cultural, clinical, and health system contexts. We are also currently developing additional ECHO courses to address other rheumatologic conditions and broader audiences, including community health representatives, highlighting the program's potential for widespread impact.

Future directions include the formal assessment of patient outcomes, such as time to diagnosis, DMARD initiation rates, disease activity scores, and patient-reported outcomes. This will be conducted in close partnership with local participants to ensure the highest respect for Native patients' health data. Additional strategies, such as incorporating hands-on workshops to teach physical examination and injection techniques, may further enhance the program's impact.

In summary, the RA ECHO program improved PCPs' knowledge, confidence, and self-reported practice behaviors in a population with high unmet rheumatology needs. By combining specialist expertise with culturally grounded, community-informed design, this model demonstrates feasibility, acceptability, and potential for scalability. With careful, community-centered expansion and formal evaluation of patient-level outcomes, rheumatology-focused ECHO programs could become a cornerstone strategy to address

rheumatology workforce shortages and reduce health disparities in underserved regions.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr. The Mandal confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements. All authors contributed to the investigation, formal analysis of the data, and writing, reviewing, and editing of the manuscript.

ROLE OF THE STUDY SPONSOR

The Bristol Myers Squibb Foundation and Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by The Bristol Myers Squibb Foundation or Pfizer.

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Treatment Sequencing and Line of Therapy for Biologics and JAK Inhibitors in Patients With Rheumatoid Arthritis: Implications for Design and Uptake of New Drugs and Predictive Biomarker Diagnostics

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Objective. The opportunity for new biomarker-based tests to predict treatment response and the appropriate use of emerging rheumatoid arthritis (RA) therapies may depend on patients' treatment history. We examined RA treatment sequences and biologic/JAK inhibitor (JAKi) initiation overall and by line of therapy (LoT) to estimate the size of the eligible RA patient population in the United States for a new predictive treatment response test using a population-based RA inception cohort.

Methods. We used an augmented health plan claims database to create an inception cohort of patients with RA and estimated the rate of advanced treatment (biologic or JAKi) addition or switch. Results were stratified by advanced treatment-naïve versus treatment-experienced status and also described specific RA treatment sequences and combinations over time.

Results. Among 37,656 patients with RA, 59,557 new RA treatment initiations were identified. Most patients (85.2%) initiated biologics; the remainder initiated JAKi. Of these, 40.2% used biologics/JAKi as monotherapy. The overall biologic/JAKi addition/switch rate was 25.7 per 100 patient-years (py) (22.7/100 py in biologic-naïve patients and >30/100 py in treatment-experienced patients). Rates varied substantially between prescribers, with an observed add/switch rate in the practices of prescribers in the highest decile (53.8/100 py) more than four-fold greater than rates in the practice of prescribers in the lowest decile (12.1/100 py).

Conclusion. These findings highlight the size and characteristics of the eligible RA population in the United States initiating a new RA biologic or JAKi treatment each year, thus providing valuable insights for stakeholders developing or marketing new RA therapies or biomarker-based diagnostic tests to predict future treatment response.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have an increasing array of treatment options available. After use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), the medications available to patients with RA include biologic DMARDs (bDMARDs) such as tumor necrosis

factor inhibitors (TNFi), other cytokine inhibitors (eg, interleukin-6 receptor [IL-6R], IL-1R), B cell-depleting therapies, and T cell modulators, as well as JAK inhibitors (JAKi), which are in the class of targeted synthetic DMARDs (tsDMARDs). However, the success of these medications to achieve treatment goals (ie, remission or a minimal clinically important difference) in patients with RA is highly variable and challenging to predict. Given the

Supported by Aqtual. Partial support for the infrastructure of the Excellence Network in Rheumatology to Innovate Care and High-Impact Research (ENRICH) practice-based network was provided by the NIH (grant P30-AR-072583). Publication was not dependent on approval by the funding agency.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80025>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80025>.

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Submitted for publication February 14, 2025; accepted in revised form January 7, 2026.

SIGNIFICANCE & INNOVATION

- Improving personalized therapy through development of biomarkers to predict treatment response to rheumatoid arthritis (RA) therapies is of major interest, but the value of such biomarkers depends on the frequency of treatment switching, and performance may be impacted by a patient's treatment history. Using population-based data from 2016 to 2024, we assembled an inception cohort of patients with RA with new-onset disease to assess the rates of RA treatment switching overall, by line of therapy (LoT), and between provider practices.
- We observed that the rate of RA treatment switching (25.7/100 person-years [py] overall) was lowest in biologic-naïve patients (22.8/100 py) and increased (>30/100 py) as patients with RA tried additional LoTs that failed. There was dramatic variability between prescribers of RA medications in the rate at which they switched their patients' RA medications.
- Cycling from one tumor necrosis factor inhibitor (TNFi) to another, as well as cycling from one JAK inhibitor (JAKi) to another, was relatively common. JAKi and abatacept were the most common therapies used after TNFi and thus may be the most fruitful opportunities for predictive biomarkers. As anticipated, given recently recognized safety concerns, JAKi use decreased appreciably after 2020.

uncertainty about the best RA treatment for individual patients, a trial-and-error method is frequently used to select treatment.

Unfortunately, failure to achieve RA treatment goals not only diminishes patients' quality of life due to the disease itself but may also worsen disease-related comorbidities, lead to irreversible radiographic damage, result in adverse events associated with ineffective medications, and be costly.¹⁻³ Moreover, as patients with RA try an increasing number of advanced therapies that fail, treatment response typically falls. For example, the American College of Rheumatology 20% response criteria (ACR20), ACR50, and ACR70 response rates in patients who are biologic naïve are approximately 60%, 40%, and 20%, respectively, whereas in patients with treatment failure of one TNFi, the corresponding treatment response rates are closer to 50%, 30%, and 15%, respectively.^{4,5} Treatment failure may undermine the patient-provider relationship, discourage patients, lead to poor persistence and compliance, and result in future reticence to switch therapies,^{6,7} leading to undercontrolled inflammation. Continued disease activity leads to excess mortality, cost, and burden on health care services.⁸ For these reasons, maximizing the response to patients' initial and subsequent RA treatments is critical.

New blood-based diagnostic tests to predict treatment response are commercially available or are in development. However, the performance of these biomarker tests may vary based on patients' treatment history. These tests may be specific to individual

drugs or mechanisms of action (MOA) and may perform differently in those who are biologic naïve compared to those who are biologic experienced, particularly in those who have multiple prior treatment failures with difficult-to-treat RA.⁹ Identifying the most common treatment sequences used in early RA and examining the rate of switching may be helpful in guiding the development and optimization of biomarker-based response prediction tests and understanding the frequency such tests might be used in clinical practice.

Using national augmented health plan claims data applied to an inception cohort of patients with RA, our objectives were to (1) describe the sequencing pattern of b/tsDMARDs, by specific medications and by line of therapy (ie, the lifetime number of distinct biologics and JAKi that a patient previously received), overall and between providers and (2) examine the rate of RA medication initiation and treatment switching.¹⁰ The rationale underpinning these objectives was to quantify the opportunity for a predictive biomarker test to inform treatment response and estimate the volume of tests that might be used by patients with RA in the United States. Additionally, assuming that not all classes of RA medications would be predicted in the first generation of such a test, the most common sequences of RA treatments would inform which drug classes should be prioritized. The focus of our analysis was on b/tsDMARDs given that biomarker-based tests to predict future effectiveness of csDMARDs were considered unlikely to be cost-effective and that MTX would remain the first-line therapy used by the vast majority of patients with RA.

METHODS

Data source and study period. We used the Komodo Healthcare Map data set, a data schema designed for real-world evidence studies, from January 2016 to March 2024, to create an inception cohort of patients with RA. Komodo's Healthcare Map is composed of event-based, patient-level health care data from 60+ sources. These sources can be grouped into provider-derived (including pharmacy-derived) and payer-derived sources. Together, they comprise health care encounters for over 330 million medically insured patients, including those on Medicare, Medicaid, or commercial insurance, to provide a longitudinal view of a patient's journey. We extracted disease characteristics, treatment history, and medication filling patterns information and focused on use of b/tsDMARDs. Komodo contains data about diagnoses (*International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM]), medications (identified using both pharmacy claims and medical claims coded via the Healthcare Common Procedure Coding System [HCPCS]), and health care resource use.^{11,12}

Newly diagnosed RA study population. Cohort inclusion criteria for the RA cohort required two or more outpatient ICD-10-CM encounters with a diagnosis of RA from rheumatology providers occurring ≥30 days apart and within 365 days in patients ≥18 years of age. A diagnosis of RA was defined by

ICD-10 codes M05.x and M06.x (ignoring M06.1 and M06.4). Continuous medical and pharmacy coverage was required for ≥ 12 months preceding the first RA diagnosis code (baseline) and through the second RA diagnosis code. Using information in the 12-month baseline period and all available prior data, patients with RA with any prior diagnoses of psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis, reactive arthritis, inflammatory bowel disease, polymyalgia rheumatica, hidradenitis suppurativa, or malignancy (excluding non-melanoma skin cancer) were excluded to avoid confounding related to other diseases that might influence treatment switching. Patients with any prior biologic or JAKi use before or during the 12-month baseline period were also excluded to assemble an inception cohort of patients with new-onset RA. Prior csDMARD use was allowed given the nonspecific nature of some RA therapies (eg, hydroxychloroquine for patients with undifferentiated arthritis later diagnosed with RA; use of MTX in other inflammatory arthritis such as psoriatic arthritis). Given that the accuracy of identifying RA in large health plan data sources is greatly enhanced when coupled with prescriptions for DMARDs,¹³ patients in the RA cohort were required to use at least one cs/b/tsDMARD between the first RA diagnosis date and the end of the observation period (March 31, 2024).

RA medication exposure, time, and rate of switching. The treatment sequence of RA medications was examined both by MOA and individual drugs, identifying the sequence of therapy use. This approach informed the frequency of “TNFi cycling” (ie, switching from one TNFi medication to another) and JAKi cycling. The time to switch from one biologic/JAKi to the next was estimated using Kaplan–Meier (KM) curves, overall and stratified by LoT. Patients were censored if they lost coverage or if the data contained more than one biologic or JAKi initiated on the same day. To complement the KM results, the rate of adding or switching to a new biologic/JAKi (hereafter described as the “switch rate”) was estimated per 100 patient-years (py), stratified by LoT and separately by prescribing provider. Subcutaneous and intravenous biologic and JAKi use was identified using various coding systems, including the HCPCS, national drug codes, and generic/brand name. Biosimilar medications were treated as equivalent to their corresponding reference (bio-originator) products for the purposes of analysis. Comedications commonly given to patients with RA (eg, glucocorticoids, nonsteroidal anti-inflammatory drugs, opioids) were identified in a similar manner.

Prescriber clustering. The individual prescribing provider was examined as a potential factor influencing the rate of RA treatment switching. Prescribers were identified using National Provider Identification numbers identified for each index RA b/tsDMARDs claim. Patients were assigned to the prescribing provider (available in the raw data) at the time of each RA medication initiation, regardless of whether that provider continued to

refill the medication. In the subgroup analysis that reported treatment switch rates by provider, we required providers to have ≥ 10 eligible patients with RA in the data set to provide stable estimates.¹⁴

Statistical analysis. Descriptive statistics were used to summarize patient characteristics, both at the time of initial bDMARD and JAKi initiation and at the time of each subsequent switch. Age and all other covariates were recomputed at each switch date. Time to switch by LoT was compared using the Wilcoxon rank sum test. The 95% confidence intervals [CIs] comparing LoT reported from Cox proportional hazards models accounted for the clustering of treatment episodes within patients (using a robust sandwich estimator) and also adjusted for age and sex. Sankey plots were used to describe the sequence of treatments by LoT and between specific RA medications. We also created Sankey plots among the subgroup of patients with three or more years of follow-up. A violin plot was used to show the distribution of the switch rates across each prescriber’s practice.

Analyses were conducted using SAS 9.4 (SAS Institute, Inc) and R version 4.3. This study was reviewed and approved by central institutional review boards (Advarra Pro00062070 and Pro00070131).

RESULTS

Cohort characteristics. After applying inclusion and exclusion criteria (Supplemental Table 1) to the health plan data, we identified 110,528 patients with RA who initiated cs/b/tsDMARDs. After restricting to those who initiated one or more b/tsDMARDs during the study period (34.8%), the sample size was 37,656 unique patients with RA initiating 59,557 unique b/tsDMARDs. As shown in Table 1, the cohort was a median age of 54.3 (interquartile range [IQR] 45.1–51.4) years, and 73% were women. Of those with known race and ethnicity (71.5% of total), 68.5% were White, 11.3% were Black, and 13.7% were Hispanic. The median disease duration at the time of first b/tsDMARDs initiation was 0.5 (IQR 0.2–1.2) years, and patients’ previous duration of health plan enrollment was 3.5 (IQR 2.3–3.9) years.

Biologics (90.8%), rather than JAKi (9.2%), were the most common first-line advanced RA treatment initiated (90.8%). Most patients (88.9%) had evidence of prior csDMARD use, the majority of which was MTX. Patient characteristics and treatments of patients initiating a first b/tsDMARD (Table 1) were generally similar to that of those initiating a subsequent b/tsDMARD, except that non-TNFi biologics and JAKi were increasingly prescribed as patients advanced to later LoTs. The proportion using monotherapy (no concomitant csDMARD use) increased from 36.4% (first-line advanced therapy) to almost 50% once patients were on their third or subsequent b/tsDMARD. Use of JAKi peaked in 2019 to 2020 (18.3% of all b/tsDMARD initiations), after

Table 1. Characteristics of patients with RA measured at initiation of the first and each subsequent b/tsDMARD*

	First initiation of b/tsDMARDs	Second and subsequent b/tsDMARD initiations	All initiations of b/tsDMARDs
n	37,656	21,901	59,557
Age, y	54.3 (45.1, 61.4)	54.0 (45.4, 60.4)	54.3 (45.3, 61.1)
≥65 y	5,121 (13.6)	2,235 (10.2)	7,461 (12.5)
Female	27,499 (73.0)	16,812 (76.8)	44,311 (74.4)
Race and ethnicity ^a			
White	18,440 (68.5)	11,172 (71.8)	29,612 (69.7)
Black	3,030 (11.2)	1,528 (9.8)	4,558 (10.7)
Hispanic	3,685 (13.7)	1,911 (12.3)	5,596 (13.2)
Other (eg, Asian, Pacific Islander)	1,767 (6.6)	954 (6.1)	2,721 (6.4)
Insurance ^b			
Commercial	29,563 (79.0)	18,015 (82.3)	47,578 (80.4)
Medicare	4,856 (13.0)	2,085 (9.6)	6,907 (11.7)
Medicaid	2,985 (8.0)	1,782 (8.1)	4,702 (7.9)
Disease duration, y	0.5 (0.2, 1.2)	1.4 (0.8, 2.5)	0.9 (0.4, 1.9)
Health plan enrollment before first RA diagnosis, y	2.5 (1.6, 3.9)	2.3 (1.5, 3.5)	2.4 (1.5, 3.8)
Health plan enrollment before b/tsDMARD initiation, y	3.5 (2.3, 5.1)	4.3 (3.1, 5.7)	3.9 (2.6, 5.5)
Health plan enrollment after b/tsDMARD initiation, y	1.9 (0.9, 3.4)	1.9 (0.9, 3.2)	1.8 (0.8, 3.2)
Calendar year of initiation			
2017	2,434 (6.5)	334 (1.5)	2,768 (4.6)
2018	4,416 (11.7)	1,547 (7.1)	5,963 (10.0)
2019	5,632 (15.0)	2,685 (12.3)	8,317 (14.0)
2020	5,451 (14.5)	3,353 (15.3)	8,804 (14.8)
2021	6,182 (16.4)	3,863 (17.6)	10,045 (16.9)
2022	6,308 (16.8)	4,278 (19.5)	10,586 (17.8)
2023	6,180 (16.4)	4,823 (22.0)	11,003 (18.5)
2024	1,053 (2.8)	1,018 (4.6)	2,071 (3.5)
Line of therapy ^c			
1	37,656 (100)	–	37,656 (63.2)
As monotherapy	13,689 (36.4)	–	13,689 (36.4)
2	–	13,316 (60.8)	13,316 (22.4)
As monotherapy	–	6,058 (45.5)	6,058 (45.5)
3	–	5,267 (24.0)	5,267 (8.8)
As monotherapy	–	2,533 (48.1)	2,533 (48.1)
4	–	2,064 (9.4)	2,064 (3.5)
As monotherapy	–	1,027 (49.8)	1,027 (49.8)
5	–	798 (3.6)	798 (1.3)
As monotherapy	–	389 (48.7)	389 (48.7)
6+	–	456 (2.1)	456 (0.8)
As monotherapy	–	218 (47.8)	218 (47.8)
RA therapy initiated			
bDMARDs	34,183 (90.8)	16,535 (75.5)	50,718 (85.2)
Abatacept	1,458 (3.9)	3,046 (13.9)	4,504 (7.6)
Anakinra	31 (0.1)	53 (0.2)	84 (0.1)
Rituximab	802 (2.1)	486 (2.2)	1,288 (2.2)
Sarilumab	72 (0.2)	605 (2.8)	677 (1.1)
Tocilizumab	565 (1.5)	1,826 (8.3)	2,391 (4.0)
Adalimumab	17,009 (45.2)	3,329 (15.2)	20,338 (34.1)
Certolizumab pegol	1,645 (4.4)	941 (4.3)	2,586 (4.3)
Etanercept	9,361 (24.9)	3,781 (17.3)	13,142 (22.1)
Golimumab	2,007 (5.3)	1,386 (6.3)	3,393 (5.7)
Infliximab	1,233 (3.3)	1,082 (4.9)	2,315 (3.9)
tsDMARDs (JAKi)	3,473 (9.2)	5,366 (24.5)	8,839 (14.8)
Baricitinib	62 (0.2)	175 (0.8)	237 (0.4)
Tofacitinib	2,013 (5.3)	2,371 (10.8)	4,384 (7.4)
Upadacitinib	1,398 (3.7)	2,820 (12.9)	4,218 (7.1)
tsDMARDs (by calendar year) ^d			
2017–2018	478 (7.0)	325 (17.3)	803 (9.2)
2019–2020	1,441 (13.0)	1,694 (28.1)	3,135 (18.3)
2021–2022	1,184 (9.5)	1,923 (23.6)	3,107 (15.1)
2023–2024	370 (5.1)	1,424 (24.4)	1,794 (13.7)

(Continued)

Table 1. (Cont'd)

	First initiation of b/tsDMARDs	Second and subsequent b/tsDMARD initiations	All initiations of b/tsDMARDs
Prior csDMARDs ^e	54,046 (90.7)	20,580 (94.0)	33,466 (88.9)
Methotrexate	45,331 (76.1)	17,579 (80.3)	27,752 (73.7)
Hydroxychloroquine	24,026 (40.3)	10,090 (46.1)	13,936 (37.0)
Sulfasalazine	9,434 (15.8)	4,255 (19.4)	5,179 (13.8)
Leflunomide	12,086 (20.3)	6,086 (27.8)	6,000 (15.9)
Opioids ^f	10,463 (27.8)	6,639 (30.3)	17,102 (28.7)
Oral glucocorticoids ^f	25,654 (68.1)	14,467 (66.1)	40,121 (67.4)

* Data shown are n (%) or median (25th, 75th percentiles) unless specified. bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; tsDMARD, targeted synthetic DMARD (ie, JAKi); JAKi, JAK inhibitor; RA, rheumatoid arthritis.

^a Among the 72% with available race and ethnicity.

^b Among the 99% with available insurance group.

^c Monotherapy is defined as no csDMARD prescription on the day of b/tsDMARD initiation or in the subsequent 90 days.

^d Denominator is the total number of initiations during each time period.

^e Using all available prior data.

^f In the six months before initiation.

which it began to decline (eg, 13.7% of all initiations in 2023–2024).

Treatment sequencing patterns. Figure 1 describes the pattern of treatment switching between RA medication groups. Not only was TNFi the most common first-line therapy (83.1%), but also it was the most common second-line therapy (48.0%), as many patients switched from a first to a second TNFi (ie, TNFi cycling). The next most common second-line therapy was JAKi, followed by abatacept. The details of specific medication switching are shown in Figure 2. Adalimumab and etanercept remained the dominant TNFi used as both first- and second-line advanced therapies. Abatacept was consistently used by a minority of patients with RA at each LoT. Among the lesser-used IL-6 treatments, tocilizumab was used more frequently as an earlier LoT, and sarilumab was used later. B cell-depleting therapies were infrequently used. Results from the subgroup analysis restricting patients with three or more years of follow-up ($n = 11,332$) revealed similar patterns (Supplemental Figure 1a and b). Among the JAKi, use for all three JAKi peaked in 2020, with a subsequent precipitous drop in tofacitinib use (Figure 3, orange line), whereas upadacitinib use dipped briefly in 2022 but then rebounded and then remained relatively flat (green line). Baricitinib use remained low and flat across all years.

Time to switch and switch rate. Time to switch from one b/tsDMARD to another is shown in Figure 4A. The overall switch-free survival at one year was 70.1% and differed according to LoT. The switch-free survival curve was steeper earlier during treatment, and the overall median time to switch was 38.2 (95% CI 36.9–39.5) months. The corresponding rate of switching was 25.7/100 py overall and was lower in b/tsDMARD-naïve patients (22.8/100 py) compared to those with one, two, or three or more prior b/tsDMARDs (switch rate: 31.5, 32.6, and 34.8/100 py, respectively). After accounting for the clustering of treatment episodes within patients and adjusting for age and sex, the time to

switch was approximately 1.4 to 1.5 times shorter in patients who had previously received one or more b/tsDMARDs (Figure 4B, green, blue, and purple curves) compared to patients who were b/tsDMARD-naïve (red curve; $P < 0.001$ for each), with no other pairwise comparisons significant.

Variability in switch rate by rheumatology provider.

Based on results in the subgroup analysis of prescribers with at least 10 patients with RA ($n = 1,726$ providers and $n = 36,406$ initiations, 96.7% of all treatment initiations in the main analysis), the violin plot in Figure 5 shows substantial variability between providers in the rate of switching. As shown in the upper portion of the curve, the providers with the greatest likelihood of starting or switching b/tsDMARDs did so at a rate of approximately 100/100 py (ie, on average, every patient with RA in their practice switched once per year). This rate was approximately three- to five-fold greater than the switch rate of the much larger number of providers in the lower portion of the plot (20–30/100 py). Switch rates for providers in the highest versus lowest decile were 12.1/100 py and 53.8/100 py, respectively.

DISCUSSION

In this analysis of a contemporary inception cohort of patients with RA with new-onset disease, we found that the rate of treatment switching of biologics and JAKi varied appreciably according to LoT. Biologic- and JAKi-naïve patients were less likely to switch than those with previous treatment failure of one or more b/tsDMARDs. We also observed substantial variability between providers in the rate of switching, with a more than four-fold difference in the advanced therapy rate of switching for RA patients of rheumatology providers in the lowest versus highest deciles. We also observed that despite literature and a conditional recommendation from the ACR suggesting that after failure of one TNFi, switching MOA is likely advisable,¹⁵ TNFi cycling remains common, even contemporarily. Several explanations

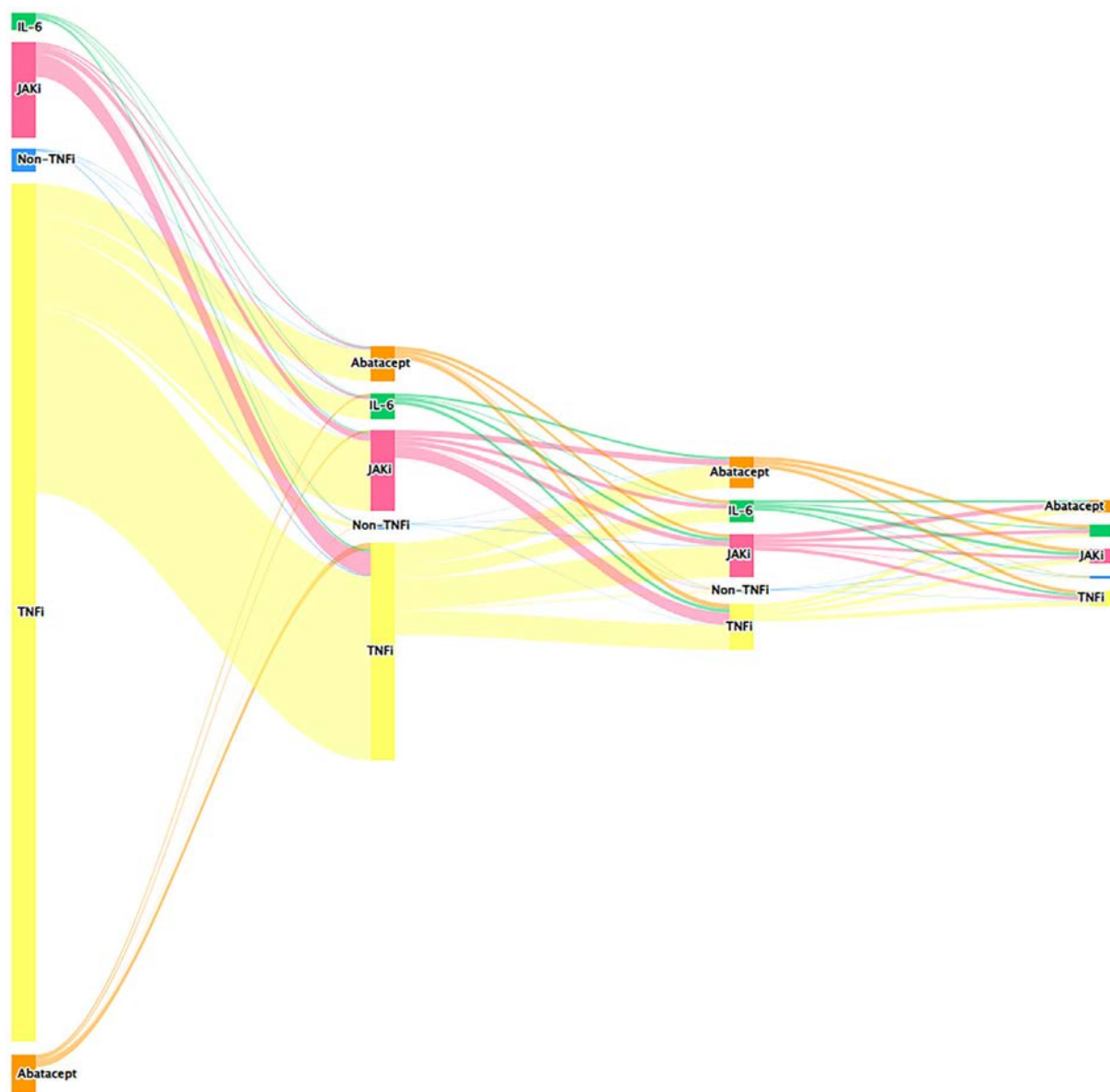


Figure 1. Treatment switching among biologics and JAKi by mechanism of action for lines of therapy 1 to 4 (n = 37,656 unique patients with rheumatoid arthritis). IL-6, interleukin-6; JAKi, JAK inhibitor; TNFi, tumor necrosis factor.

may underlie this observation, including requirements from pharmacy formularies or an initial good response to a first TNFi with drug-specific side effects. We also found JAKi cycling was common. However, use of JAKi fell after 2020, likely affected by new safety results from the Oral Surveillance trial (disclosed in 2021, published in 2022)^{16,17} and the associated change in JAKi labeling. The frequency of advanced RA treatment changes likely is partly influenced by the lack of a diagnostic test that can predict response to specific RA medications or even MOA, leaving providers and patients to select their initial and subsequent RA therapy empirically, with the goal of finding the most optimal RA medication for each patient using trial and error, leading to repeated switching over time.

Assuming that there was an accurate and predictive biomarker test that could guide RA treatment selection for biologics and JAKi,^{18,19} the number of biomarker tests to predict treatment response that would be required to manage a population of patients with RA can be estimated. Based on the observed RA treatment switching rate of 25.7/100 py applied to an inception cohort of biologic/JAKi users like the one we assembled, if patients were tested each time they initiated a new RA treatment, a total of 257 RA tests per 1,000 patients with RA would be ordered annually. In a more established RA cohort with prevalent disease, the rate of treatment switching is greater, and thus the corresponding number of annual tests ordered would be somewhat higher. These estimates invoke the assumption that the

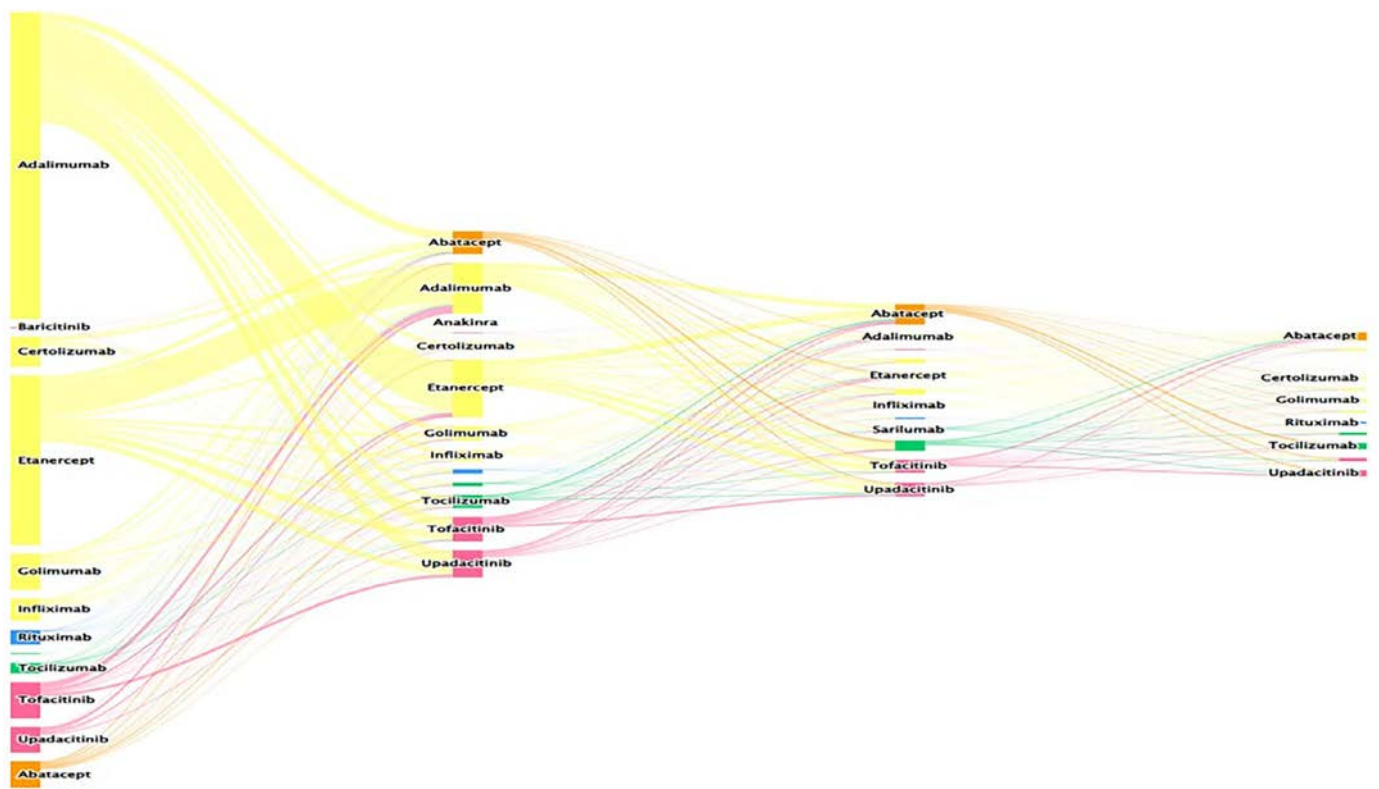


Figure 2. Treatment switching among biologics and JAK inhibitors for specific rheumatoid arthritis medications for lines of therapy 1 to 4 (n = 37,656 patients).

biomarker test results change over time and that patients should be retested at the time of each new treatment switch. At the other extreme, and invoking the maximally conservative assumption that patients with RA only ever need to be assayed once by a diagnostic test that can predict the efficacy of all RA treatments over a patient’s lifetime, then the number of tests ordered reflects

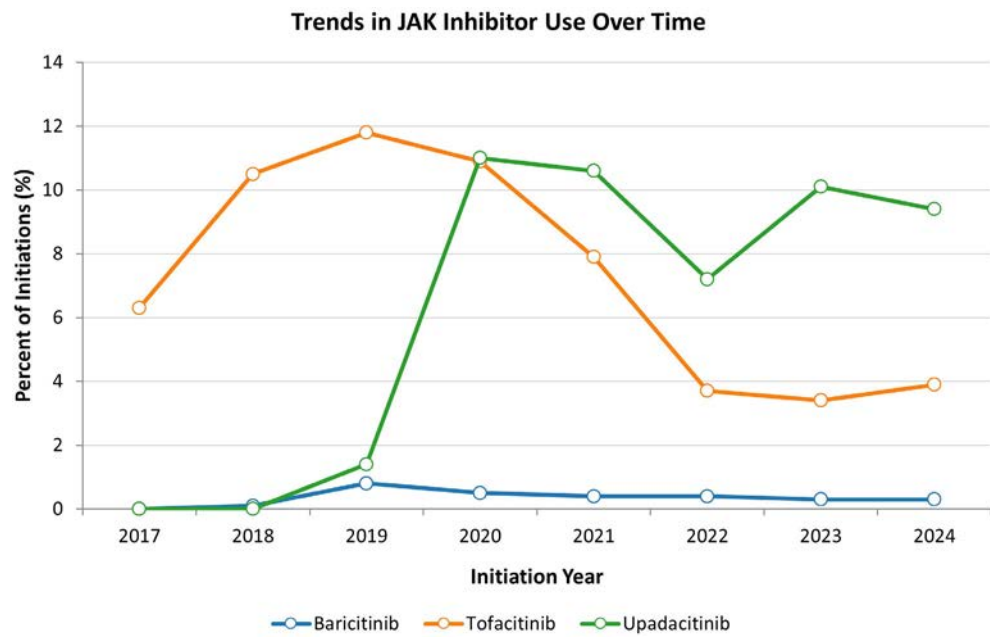


Figure 3. Trends in JAK inhibitor use over calendar time among newly diagnosed patients with rheumatoid arthritis. Data from 2024 reflect only the first three months.

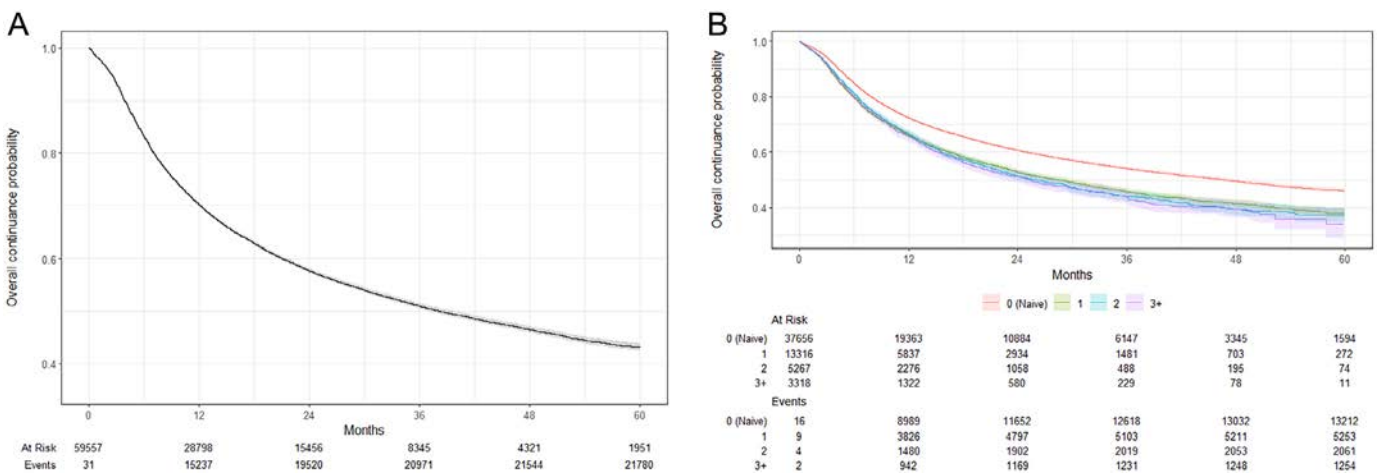


Figure 4. (A) Time to switch to a new biologic/targeted synthetic disease-modifying antirheumatic drug among patients with new-onset rheumatoid arthritis ($n = 37,656$), (B) stratified by line of therapy. Dotted lines denote the 50th percentile (median) for time to switch to a new biologic/JAK inhibitor. The P value for comparison of biologic-naïve patients to patients with exactly one, two, or three or more prior therapies was significant (adjusted $P < 0.0001$), but no other comparisons between line of therapy were significant. The analysis was also adjusted for age, sex, and clustering of treatment episodes within patients.

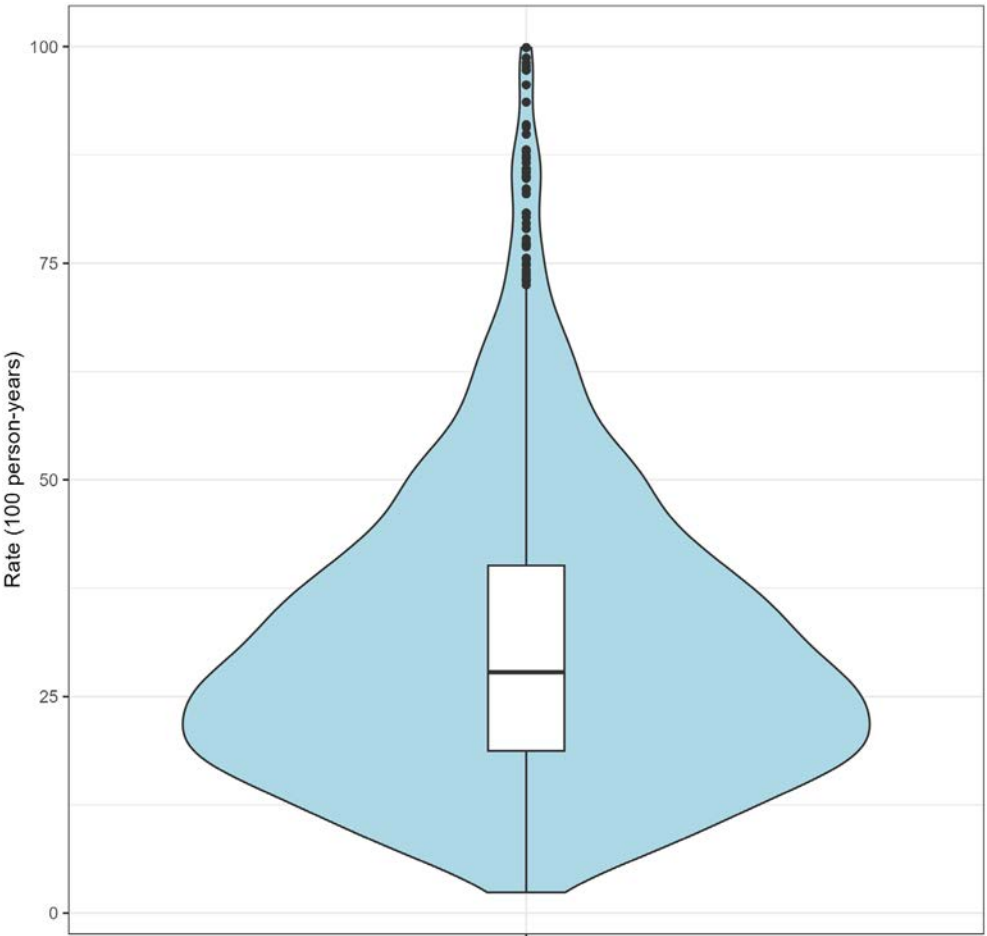


Figure 5. Variability in the rate of biologic and JAK inhibitor treatment switches, by prescriber ($n = 1,726$ prescribers with at least 10 patients with rheumatoid arthritis represented in the analysis; $n = 36,406$ initiations). Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80025/abstract>.

the total number of patients with prevalent RA in the United States. In the United States, there are approximately 1.39 million patients with RA (using an estimated prevalence of 0.54%)²⁰ plus the annual incidence of newly diagnosed RA (approximately 13 new RA cases per 100,000 individuals,¹⁹ which, given the US population size of 340 million people, yields between 4,000 and 5,000 newly diagnosed patients with RA per year). As another consideration, it might be reasonable to consider testing only patients who have an inadequate response to MTX (about 70% of all patients with RA), although predictive biomarker testing for MTX response might be envisioned if it could be made sufficiently cost-effective. In terms of which RA medications might be most useful to predict response/nonresponse based on their frequency of use, TNFi, JAKi, and abatacept would seem to reflect the greatest opportunities given that these are the more commonly used RA treatments in newly diagnosed patients.²¹ However, their prevalence of use must be balanced against the accuracy of prediction for lesser-used RA treatments.

Strengths of our study include a large contemporary cohort with data current through 2024 and application of rigorous methods to create an inception cohort of patients with RA with new-onset disease. Although we recognize the potential for misclassification of new-onset RA, there was a median of 2.5 years of claims data before the first RA diagnosis, increasing the certainty of identifying patients with new-onset RA.²² Additionally, we included patients with a diversity of health plans and insurance types, including commercial and government insurance, increasing the generalizability of our results.

Nevertheless, our results must be contextualized considering our study design. We recognize the potential for misclassification of LoT in the electronic health record (EHR) and claims data. However, we conducted a separately reported validation study (manuscript under review) in the Excellence Network in Rheumatology to Innovate Care and High-Impact Research (ENRICH) practice-based network in which patients had claims data linked to EHR data and patients' self-reported lifetime use of RA therapies was collected on an in-office tablet app.²³ This validation study showed excellent agreement between claims and EHR data and self-reported data as to LoT (crude agreement 84.5%). As another consideration that may impact our results, we only had a median of 1.9 years of follow-up after the first b/tsDMARDs during which to ascertain rates of subsequent treatment switching and LoT, and there were relatively few switches with LoT ≥ 5 ($n = 1,245$, 2.1% of total).²⁴ This led us to combine LoT 3 and above and report the switch rate in this combined group; the switch rate for people with failure of more RA treatments may be even higher than 35/100 py. Finally, we examined RA treatment addition and switching irrespective of the reason for changing therapies. However, we do not expect the reason for changing treatments to impact the potential utility of a predictive biomarker to inform which advanced therapy might next be optimal.

In conclusion, results from this analysis of LoT, switching rates of biologics and JAKi, and treatments patterns in this population-based inception cohort of patients with RA are likely to be useful to a diverse audience of payers, policymakers, and developers of diagnostics and pharmaceuticals. Our findings provide a contemporary look at the sequence of treatments used in patients with RA and may help guide development of new therapies and diagnostic biomarkers to predict treatment response. More specifically, these results may help estimate the market opportunity for new RA treatments and diagnostic tests to predict therapy response. They may also inform the potential impact on coverage policies for payers by estimating the size of the potential RA population and the potential health care use and financial impact of such diagnostic test coverage.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Curtis confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

Aqtual had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Aqtual.

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Minimal Important Change and Minimal Clinically Important Difference in Pain and Function With Exercise in Hip Osteoarthritis

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Objective. The objective of this study was to estimate the minimal important change (MIC) and minimal clinically important difference (MCID) for pain and physical function in individuals with hip osteoarthritis (OA) following a physiotherapist-guided exercise intervention.

Methods. Secondary analysis from a randomized controlled trial of 196 adults with hip OA allocated one of two nine-month exercise programs. Patient-reported outcomes measures for hip pain severity (Numeric Rating Scale [NRS], Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain subscale) and physical function (WOMAC physical function subscale, Patient-Specific Functional Scale [PSFS]) were collected at baseline and three and nine months. Global ratings of change in pain and physical function at three and nine months served as anchors.

Results. MIC estimates were 2.1 and 2.4 points for NRS pain at three and nine months, respectively; 2.8 and 3.0 points for WOMAC pain at three and nine months, respectively; 8.7 and 8.3 points for WOMAC physical function at three and nine months, respectively; and –2.1 and –2.0 points for PSFS at three and nine months, respectively. The MCID estimates were 2.0 and 2.4 points for NRS pain at three and nine months, respectively; 2.8 and 3.0 points for WOMAC pain at three and nine months, respectively; 9.2 and 8.3 points for WOMAC physical function at three and nine months, respectively; and –3.5 and –0.7 points for PSFS at three and nine months, respectively.

Conclusion. This study provides robust, context-specific MIC and MCID estimates for outcomes in hip OA following exercise. These values can inform the interpretation and design of exercise-based clinical trials for hip OA.

INTRODUCTION

Hip osteoarthritis (OA) is a prevalent and disabling condition affecting approximately 10% of adults over the age of 60 in high-income countries.¹ Clinical guidelines recommend exercise as a core treatment to manage hip OA.² Clinicians and researchers rely on patient-reported outcome measures to assess treatment efficacy and guide therapeutic decision-making. However, statistical significance alone does not indicate whether an observed change is meaningful to patients. Therefore, there is a need for patient-informed thresholds to aid clinical interpretation.

Interpreting patient-reported outcomes requires understanding whether observed changes are meaningful to patients. The minimal important change (MIC) refers to the smallest within-person change perceived as important,³ whereas the minimal clinically important difference (MCID) represents the smallest between-group difference considered clinically meaningful.⁴ Existing MIC and MCID estimates for hip OA are limited and largely derived from surgical^{5,6} and pharmacological interventions,⁴ in which the magnitude of clinical improvement is typically greater than that expected from exercise-based interventions. These thresholds are often higher because patients

ACTRN: 12619001297112.

Supported by the Australian National Health and Medical Research Council NHMRC (project grant APP1159045). Dr Hall's work was supported by a National Health and Medical Research Council Investigator Grant Emerging Leader 1 (1172928). The funding sources had no role in the design of this study or its execution, analyses, interpretation of the data, or decision to submit results.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80029>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80029>.

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Submitted for publication August 6, 2025; accepted in revised form February 11, 2026.

SIGNIFICANCE & INNOVATIONS

- This study provides the minimal important change (MIC) and minimal clinically important difference (MCID) estimates for pain and function outcomes following physiotherapist-guided exercise in people clinically diagnosed with hip osteoarthritis (OA).
- This study demonstrates higher and more consistent thresholds than previously reported app-based/ group-based estimates, following similar statistical methods to estimate MIC.
- This study highlights the importance of context-specific MIC/MCID values in patient-reported outcome measure interpretations and trial design.
- This study supports refinement of sample size calculations and outcome benchmarks in future exercise-based trials for hip OA.

undergoing surgery or receiving pharmacotherapy anticipate and experience larger symptom improvement compared with behavioral or exercise programs.^{7,8} Therefore, applying these higher thresholds to exercise trials may underestimate clinically meaningful benefit. This highlights the need for context-specific estimates for hip OA exercise interventions.

In hip OA, pain is commonly assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)⁹ pain subscale and the Numeric Rating Scale (NRS).¹⁰ Physical function is often evaluated using the Patient-Specific Functional Scale (PSFS)¹¹ and WOMAC⁹ physical function subscale. One study has reported MCID values for exercise in knee OA,¹² but these are not necessarily generalized to hip OA given differences between the conditions.¹³ In hip OA, only two studies have reported MIC estimates, with 1 point on the NRS and 3.0 to 6.8 points on the Hip Disability and Osteoarthritis Outcome Score (HOOS) function subscale in digitally delivered and group-based programs (noting that the HOOS function subscale is equivalent to the WOMAC physical function subscale).^{14,15} Importantly, no prior studies have provided MIC or MCID estimates derived specifically from physiotherapist-guided exercise. As a result, hip OA exercise trials often rely on thresholds developed in nonexercise contexts or other OA populations, which may not reflect the expected magnitude or nature of benefit in home-based exercise programs. Given that the MIC and MCID are sensitive to interventions and comparators and are context specific,^{3,16–19} the aim of this study is to estimate MIC and MCID for pain (NRS and WOMAC pain subscale) and physical function (WOMAC physical function subscale and PSFS) in people with hip OA following an exercise program with follow-up at three and nine months.

PATIENTS AND METHODS

This is a secondary analysis from a superiority, two-group comparative effectiveness randomized controlled trial in Australia.

The trial protocol²⁰ and primary outcomes²¹ were previously reported. Ethics approval was obtained by The University of Melbourne Human Research Ethics Committee (12710). This trial was registered in the Australian New Zealand Clinical Trial Registry (ACTRN: 12619001297112) and has been completed.

Participants ($n = 196$) with symptomatic hip OA were recruited between October 2019 and September 2022 from the community across metropolitan Melbourne, Australia. Key eligibility criteria included clinically diagnosed hip OA,²² NRS pain ≥ 4 of 10, the ability to safely participate in exercise, and exclusion of individuals scheduled for or awaiting hip arthroplasty. The inclusion and exclusion criteria are detailed elsewhere.²⁰

Participants were randomized to either a combination of aerobic physical activity and resistance exercise or resistance exercise only. Both groups received nine individual online consultations with a physiotherapist over three months and continued their program independently thereafter. All participants were prescribed a home-based progressive lower limb resistance exercise program, and the combined exercise group was prescribed moderate-intensity aerobic physical activity targeting 150 min/wk. Further details of the exercise programs can be found elsewhere.^{20,21} The patient-reported outcome measures were obtained at baseline and three and nine months. Hip pain was assessed via NRS (0–10), in which 0 = no pain and 10 = worst pain possible,²³ and the WOMAC pain subscale (0–20), in which higher scores indicate more pain.⁹ Physical function was assessed via the WOMAC function subscale (0–68), in which 0 = no difficulty and 68 = extreme difficulties.⁹ For the PSFS,¹¹ at baseline, participants listed up to five daily living activities for which performance was limited by hip symptoms and rated these on a 0 to 10 scale in which 0 = unable to perform and 10 = able to perform at the same level as before injury or problem. A total score was calculated as the sum of the ratings for each activity divided by the number of activities, with higher scores indicating better function. At three and nine months, participants were asked about the activities they listed at baseline and provided a rating on the same scale.

Participant-perceived global ratings of change²¹ in hip pain and hip-related physical function were collected at three and nine months. For hip pain, participants were asked to “select the option which best represents the overall change in pain of your hip since you began the study,” and for hip physical function, participants were asked to “select the option which best represents the overall change in physical function of your hip since you began the study.” Responses for each were scored using a 7-point Likert scale, where 1 = much worse, 2 = moderately worse, 3 = slightly worse, 4 = no change, 5 = slightly better, 6 = moderately better, and 7 = much better. In line with recommended anchor-based methods, which specify that the anchor threshold should reflect a small but important improvement rather than a trivial fluctuation,²⁴ we classified “moderately better” and “much better” as “improved” and all other responses as “not improved.”

We recognize that some participants may have perceived “slightly better” as important. However, because our anchor did not explicitly distinguish between trivial and important change, we chose a conservative threshold to avoid misclassifying minor fluctuations as clinically important change.

Statistical analyses were performed using Stata version 18.0 (StataCorp, LLC). Continuous variables were summarized as means (SD) or medians (interquartile range), and categorical variables were summarized as frequencies (percentage). Ceiling effects were assessed by identifying participants who scored at the best possible value at baseline. Change scores were calculated as baseline minus follow-up. For outcomes in which higher scores indicate worse symptoms (NRS pain, WOMAC pain, WOMAC physical function), positive change scores represent improvement, and negative scores represent worsening. For the PSFS, in which higher scores indicate better function, negative change scores represent improvement and positive scores represent worsening. An anchor-based approach based on a predictive model using logistic regression analysis was used for MIC estimates.³ A dichotomized anchor is the dependent variable, and the change score is the independent variable. The MIC was determined as the value of the change score corresponding to a predicted probability of 0.5 for reporting minimal improvement. To enhance robustness, bootstrapping with 1,000 replications was used to derive 95% confidence intervals (CIs) for the MIC estimate as previously described.²⁵ The MCID compares the magnitude of change in outcome scores between responders and nonresponders, as determined by an anchor. It is estimated as the difference in mean change scores between responder and nonresponder groups. This approach reflects between-group minimal meaningful change by contrasting patients who experienced clinically significant improvement with those who did not. Complete methodologic estimates can be accessed in the Supplementary Material.

RESULTS

Of 196 participants, 97 (49%) were allocated to the aerobic and resistance exercise group and 99 (51%) were allocated to the resistance-only group. Table 1 presents participant characteristics. Complete outcome data were available for 186 (95%) participants at three months and 174 (89%) participants at nine months. Of these, 65% ($n = 120$) and 62% ($n = 115$) had global improvement in pain and physical function at three months, respectively, and 64% ($n = 111$) and 64% ($n = 111$) had global improvement in pain and physical function at nine months, respectively. The complete change scores of our selected instruments based on the global rating change categories are shown in Figure 1; the number of participants according to the seven global rating categories at three and nine months are shown at Supplementary Table 1. The MIC and MCID for three- and nine-month estimates are presented in Table 2.

Table 1. Baseline general characteristics of the participants*

Participants (N = 186)	
Age, y	62 (57–66)
Sex	
Female	127 (68%)
Male	59 (32%)
Height, m	1.7 (1.6–1.7)
Bodyweight, kg	78.0 (68.9–90.1)
BMI	27.9 (25.1–31.6)
Education level	
<3 y of high school	0 (0%)
≥3 y of high school	23 (13%)
Some education beyond high school	87 (47%)
Completed tertiary or higher education	76 (40%)
Hip symptom duration, y	3 (1–5)
Hip affected or most affected	
Right	102 (55%)
Bilateral symptoms	111 (60%)
Unilateral symptoms	75 (40%)
Pain severity	
NRS (0–10)	5 (4–6)
WOMAC pain (0–20)	8 (5–10)
Physical function	
WOMAC physical function (0–68)	22 (14–30)
PSFS (0–10)	3.8 (2.3–5.5)

* Data are presented as n (%) or median (interquartile range). Higher scores on the NRS (0–10) indicate more pain, higher scores on the WOMAC pain subscale (0–20) indicate more pain, higher scores on the WOMAC physical function subscale (0–68) indicate worst physical function, and higher scores on the PSFS (0–10) indicate better ability to perform self-selected activities at the same level as before the hip problem. BMI, body mass index; NRS, Numeric Rating Scale; PSFS, Patient-Specific Functional Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

For WOMAC pain, no participants scored 0 of 20, and for WOMAC physical function, only one participant scored 0 of 68 at baseline. Only two participants scored 0 of 10 on the PSFS. These negligible proportions indicate that insufficient measurement range was unlikely to constrain improvement or bias MIC estimates.

DISCUSSION

This study estimates both MIC and MCID for recommended outcomes in individuals with hip OA following a nine-month home-based exercise program guided by a physiotherapist during the first three months. Exercise is the core recommended treatment to manage hip OA,^{2,22} yet interpretation of outcomes remains largely statistically driven. Our findings provide context-specific thresholds for interpreting clinically meaningful within- and between-group change in hip OA following home-based exercise guided by physiotherapists.

Our MIC estimates for pain on the NRS (2.2 points at three months and 2.4 points at nine months) and WOMAC pain subscale (2.8 points at three months and 3.0 points at nine months) are higher than other MIC estimates in people with hip OA using

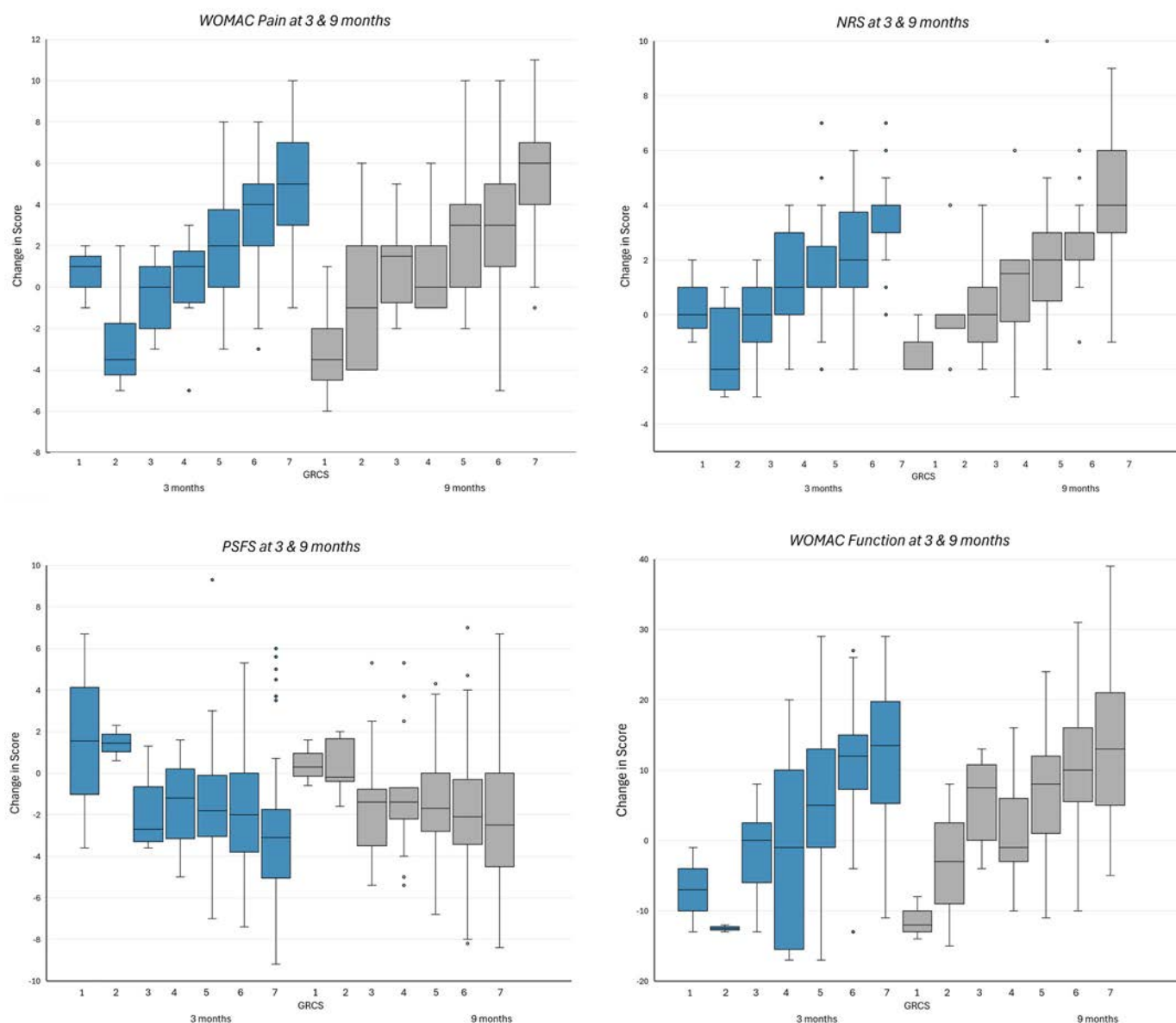


Figure 1. Change scores by GRCS. 1 = much worse, 2 = moderately worse, 3 = slightly worse, 4 = no change, 5 = slightly better, 6 = moderately better, and 7 = much better. The box includes the first to the third quartile, horizontal line represents the median, circles indicate outliers, and error bars represent extreme values. GRCS, global rating of change scale; NRS, Numeric Rating Scale; PSFS, Patient-Specific Functional Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

digitally delivered exercise (1.0 points on NRS pain; 0–10 scale)¹⁵ and group-based exercise (1.6 points on WOMAC pain subscale; 0–20 scale).¹⁴ Similarly, our MIC estimates for physical function on the WOMAC physical function subscale (8.3 points at three months and 8.7 points at nine months) were higher than other MIC estimates in people with hip OA using digitally delivered exercise (4.6 points on WOMAC physical function subscale; 0–68 scale)¹⁵ and group-based exercise (2.0 points on WOMAC physical function subscale; 0–68 scale).¹⁴ These differences may reflect variation in intervention type and delivery method (individualized online session vs digital app/groups based). Our methodologic approach²⁵ is consistent with previous work and is therefore

unlikely to explain why our estimates are higher. One potential explanation for higher MIC estimates is the small between-group treatment effects observed in the parent trial (eg, NRS pain: 0.3 [95% CI –0.3 to 0.8] at three months, 0.0 [95% CI –0.7 to 0.6] at nine months; WOMAC physical function: –0.9 [95% CI –3.6 to 1.8] at three months, –1.8 [95% CI –4.6 to –0.5] at nine months). The MIC estimates for PSFS were 2 units at both time points, within the range of 1.0 to 2.5 reported in musculoskeletal conditions other than hip OA.²⁶ Overall, these findings provide the first physiotherapist-guided, home-based, context-specific MIC estimates for hip OA and reinforce the need for setting-specific thresholds.

Table 2. MIC and MCID values for pain (NRS and WOMAC pain subscale) and physical function (WOMAC physical function subscale and PSFS) at 3 and 9 months*

Domain	Outcome measure	Method	Predictive model scores (95% CI)	
			At 3 mos	At 9 mos
Pain	NRS pain	MIC _{pred}	2.17 (1.64 to 3.61)	2.43 (1.09 to 4.12)
		MCID	1.95 (1.41 to 2.50)	2.36 (1.69 to 3.03)
	WOMAC pain	MIC _{pred}	2.82 (1.94 to 4.23)	3.02 (1.86 to 4.59)
		MCID	3.16 (2.34 to 3.98)	3.19 (2.20 to 4.18)
Physical function	WOMAC physical function	MIC _{pred}	8.73 (6.53 to 10.92)	8.25 (6.1 to 10.75)
		MCID	9.15 (6.05 to 12.25)	8.33 (5.29 to 11.37)
	PSFS score	MIC _{pred}	-2.07 (-2.89 to -1.25)	-2.04 (-2.94 to -1.14)
		MCID	-3.49 (-4.25 to -2.73)	-0.70 (-1.63 to -0.23)

* CI, confidence interval; MCID, minimal clinically important difference; MIC_{pred}, minimal important change values via predictive model; NRS, Numeric Rating Scale; PSFS, Patient-Specific Functional Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

This study extends previous research by providing exercise-specific MCID estimates for pain and physical function in people with hip OA. To our knowledge, no prior studies have reported MCID estimates for hip OA following exercise. Our MCID estimates for NRS pain (2.0 and 2.4 points for three and nine months, respectively) and WOMAC physical function (8.3 and 9.2 points for three and nine months, respectively) are notably larger than estimates used to inform sample size calculations in clinical trials,⁴ including our own²¹ (eg, 1.8 points in NRS pain and 6 points in WOMAC physical function). The implications of larger intervention-specific MCID estimates are that fewer participants are required to address research questions and reduce costs associated with larger sample sizes needed to detect meaningful change. Although replication is needed, these values inform more accurate effect size estimations for power calculations in future hip OA exercise interventions. The MCID for PSFS was 3.5 points at three months but was less stable at nine months (0.7 points). This was likely due to poor correlation to the anchor (Supplementary Table 2), possibly shifting patient priorities or difficulty recalling baseline limitations, bringing into question the PSFS's utility in this context.

Contemporary methodologic and regulatory guidance recommends combining anchor-based estimates with complementary approaches and, where possible, reporting multiple thresholds rather than a single MCID value. Current best practice also encourages incorporating patient-centered alternatives such as the smallest worthwhile effect²⁷ and the patient acceptable symptom state,²⁸ which offer conceptually distinct insights into what patients consider meaningful or acceptable. The smallest worthwhile effect was not feasible in the current study because the necessary benefit-burden trade-off judgment was not collected. Integrating such approaches in future trials would strengthen patient-centered interpretation. Importantly, MCID estimates remain central to clinical trial design, sample size justification, and interpretation of treatment effects. As Revicki et al²⁹ articulate, meaningful thresholds should be refined cumulatively across studies and clinical contexts. Our MCID estimates provide new evidence in hip OA and exercise and offer an alternative to

inappropriately extrapolating MCID estimates from surgical, pharmacological, or knee OA studies.

The key strength of this study is its focus on hip OA, which is often underrepresented in OA research or pooled with knee OA, and assessment at multiple time points. A further strength is that the outcomes examined (eg, pain and self-reported physical function) align with Osteoarthritis Research Society International clinical trial recommendations.³⁰ Limitations should be considered. First, our eligibility criteria (eg, NRS ≥ 4 of 10, ability to exercise safely, exclusion of those awaiting arthroplasty) means our sample reflects people with hip OA typically receiving conservative management but may not represent those with very mild or advanced hip OA. Second, MIC and MCID estimates are inherently context dependent and influenced by population characteristics such as baseline symptoms severity, measurement properties, and the methodologic approaches used.^{3,16-19} As such, our resulting thresholds are specific to this physiotherapist-guided, home-based exercise program and may not generalize to digital, group-based, center-based, or other delivery modalities or patient groups. An important consideration of our study is the exclusive use of anchor-based methods to estimate clinically important change. Although widely used, anchor-based thresholds are influenced by sample characteristics, baseline symptom severity, and the choice of anchor, which may restrict their generalizability across settings and patient groups.²⁵⁻²⁸ Global rating of change scales are susceptible to recall bias and current health-state bias, particularly at longer follow-up, which may inflate or attenuate MIC and MCID estimates. Third, although our predictive modeling approach helps mitigate bias, the classification of "responders" may still be compromised. Dichotomizing global rating of change responses into "improved" versus "not improved" can oversimplify patient experience, and the relatively wide CIs for NRS pain at nine months further suggest instability in long-term estimates. In addition, the PSFS demonstrated weak correlation with the anchor at nine months, indicating limited stability of this measure for long-term MIC or MCID estimation. Finally, generating a single MIC/MCID

point estimate for ordinal measures (eg, WOMAC) is inherently limited, as equal numerical changes do not represent equivalent clinical change across the continuum of the scale.

This study provides context-specific MIC and MCID values for pain and physical function outcomes in hip OA following a home-based exercise program prescribed according to widely used guidelines. These estimates enhance clinical interpretation and offer empirically supported parameters for future exercise-based trials.

ACKNOWLEDGMENTS

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australasian University Librarians

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Guerrero confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Maternal and Personal Smoking, Genetic Susceptibility, and Risk of Osteoarthritis: A Population-Based Prospective Cohort Study

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Objective. To investigate the associations of maternal and personal smoking with the risk of knee, hip, hand, and overall osteoarthritis (OA) and the role of genetic predisposition to OA.

Methods. A total of 321,075 UK Biobank participants (mean age 56 years, 55% women) without OA at baseline were included; 29.9% reported maternal smoking, 24.3% reported former smoking, and 9.5% reported current smoking. Maternal smoking around childbirth (yes or no) and personal smoking status (never, former, or current) and dose (pack-years) were self-reported by the participants. Cox proportional hazards models were used to explore the associations of maternal and personal smoking status and personal smoking dose with the risk of OA. Genetic susceptibility of OA was assessed using polygenic risk scores (PRS).

Results. During follow-up, 18,470 (5.8%), 12,064 (3.8%), 6,605 (2.1%), and 52,853 (16.5%) participants developed knee, hip, hand, and overall OA, respectively. Both maternal and personal smoking were positively associated with the risk of knee, hip, hand, and overall OA (maternal smoking hazard ratio [HR] = 1.08–1.23; personal smoking HR = 1.18–1.40). There were significant dose-responsive associations between personal smoking dose and OA risk (P for trend <0.05). The association between maternal and personal smoking and OA risk was similar across different PRS strata.

Conclusion. Both maternal and personal smoking are independently associated with an elevated risk of OA. These associations are universal across different genetic susceptibility of OA.

INTRODUCTION

Approximately 2% of pregnant women worldwide smoke during pregnancy, whereas the rate reaches up to 8% in Europe.¹ Maternal smoking not only increases the risk of preterm birth and neonatal mortality but also predisposes offspring to various chronic diseases later in life.² Osteoarthritis (OA) represents a major contributor to long-term pain and functional impairment, most commonly involving the knee, hip, or hand joints.³ Tobacco exposure may promote the development of OA by disrupting bone metabolism⁴ and inducing systemic inflammation and metabolic abnormalities.^{5,6} Because of the lack of effective therapeutic options for OA,⁷ identifying modifiable risk factors, such as

smoking at different periods, is essential for advancing early prevention efforts and optimizing clinical management.

The association between smoking and OA risk remains inconclusive, and existing evidence predominantly examines personal smoking exposure during adulthood. Although two recent genetic studies suggested a causal relationship between personal smoking and an increased risk of OA,^{8,9} meta-analyses of observational studies revealed no^{10,11} or even an inverse association.^{12,13} This discrepancy may stem from selection bias, particularly in case-control studies in which smokers are often overrepresented among hospital-based controls.¹³ Additionally, body mass index (BMI) may act as a mediator rather than a confounder in the pathway linking smoking to OA, yet most previous

Supported by the National Natural Science Foundation of China (82473719) and Research Innovation Team Project of School of Public Health of Anhui Medical University (kctd200403).

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80064>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80064>.

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Submitted for publication December 18, 2025; accepted in revised form April 9, 2026.

SIGNIFICANCE & INNOVATIONS

- Maternal smoking elevates offspring's osteoarthritis risk, independent of offspring's personal smoking behavior.
- The detrimental effect of smoking on osteoarthritis risk is universal across individuals with different genetic susceptibility to osteoarthritis.

studies have treated it as a covariate,¹⁴ potentially distorting the true relationship. Furthermore, nicotine, the primary addictive component of cigarettes, readily crosses the placenta.¹⁵ Prenatal exposure to nicotine through maternal cigarette smoking can cause intrauterine cartilage dysplasia that persists into adulthood.¹⁶ However, only a few animal studies indicated that prenatal nicotine exposure may increase offspring's susceptibility to OA.^{17,18} To our knowledge, no population-based studies have directly examined the association between maternal smoking and the risk of OA in adulthood. Therefore, we aimed to investigate the associations of maternal and personal smoking with the risk of OA at different sites (ie, knee, hip, and hand) and to evaluate whether the association was modified by genetic predisposition to OA.

METHODS

Study population. The UK Biobank is a nationwide prospective cohort study recruiting over 0.5 million participants aged 40 to 69 years from England, Scotland, and Wales from 2006 to 2010. The cohort has obtained ethical approval from the North West Multi-Centre Research Ethics Committee (21/NW/0157).¹⁹ Written informed consent was obtained from all participants

before their enrollment. Further details can be found on the official website (<https://www.ukbiobank.ac.uk/>). In the present study, we included 321,075 participants who were free of any type of OA at baseline and did not have missing data on maternal smoking or personal smoking (Figure 1).

Exposure assessment: maternal and personal smoking.

Information on maternal and individual smoking was collected via a self-administered touchscreen questionnaire. Maternal smoking status was assessed by asking “Did your mother smoke regularly around the time when you were born?” with options yes and no. This information was available for all participants, except those who reported being adopted during childhood. Personal smoking status was categorized as never, former, or current by asking two questions “Do you smoke tobacco now?” and “In the past, how often have you smoked tobacco?” The type of tobacco smoked was determined based on the question, “What type of tobacco did you usually smoke?” with options including manufactured cigarettes, hand-rolled cigarettes, cigars, or pipes. Participants selecting “do not know” or “prefer not to answer” were excluded.

The duration and frequency of personal smoking was assessed using smoking years and pack per day. Specifically, smoking years were calculated as current age [current smokers] or age at quitting [former smokers] – age at starting smoking. The duration of personal smoking was classified into never, <10, 10 to 20, 20 to 30, and ≥30 years. Pack per day was assessed by asking “About how many cigarettes did you smoke on average each day?” and calculated as number of cigarettes smoked per day/20. The intensity of personal smoking was classified into never, <0.5, 0.5 to 1.0, 1.0 to 1.5, and ≥1.5 pack/day. In combination, the cumulative dose of personal smoking (in pack-years)

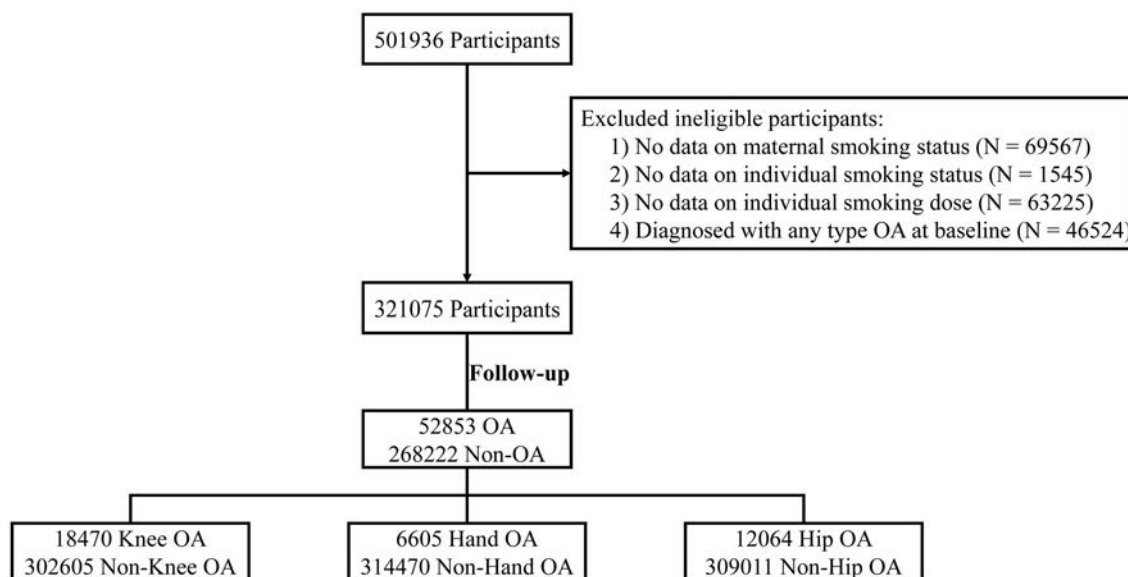


Figure 1. Flowchart of the sample selection from the UK Biobank. OA, osteoarthritis.

was calculated as pack per day $\times$ smoking years, based on their raw values. Accordingly, personal smoking dose was classified into the following categories: never, <10, 10 to 20, 20 to 30, and ≥ 30 pack-years.

Outcome: OA. According to the *International Classification of Diseases, Tenth Revision (ICD-10)*, the incidence of overall OA (M15-M19) and OA at the different sites, including knee OA (ICD-10: M17), hip OA (ICD-10: M16), and hand OA (ICD-10: M15, M18), was identified by the date of first occurrence relative to the date of baseline enrollment. In the UK Biobank, the date of first disease occurrence was derived from self-reports, hospital admissions, primary carer, and death records,²⁰ the validity of which has been supported by previous studies.^{21,22} Participants were tracked from their year of birth until the first occurrence of an event, including OA diagnosis, mortality, withdrawal, or the latest date of data linkage (March 2023 for England, August 2022 for Scotland, and May 2022 for Wales).

Genetic susceptibility of knee and hip OA. Polygenic risk scores (PRS) for OA were constructed using genome-wide association study summary statistics (GWAS) from FinnGen Release 9 (<https://r9.risteys.finnngen.fi/>).²³ To align genomic coordinates with the UK Biobank reference (build GRCh37), FinnGen GWAS data originally mapped to GRCh38 were converted to GRCh37 using liftOver tool provided by the University of California, Santa Cruz Genome Browser and the hg38-to-hg19 chain file (<https://hgdownload.soe.ucsc.edu/goldenPath/hg38/liftOver/>).

Independent GWAS single nucleotide polymorphisms (SNPs; $P < 5 \times 10^{-8}$) were identified by linkage disequilibrium pruning ($r^2 < 0.001$ within 1-Mb windows) using the European reference panel from the 1000 Genomes Project. To ensure data quality, variants with a minor allele frequency < 0.01 , insertion-deletion variants (indels), and ambiguous palindromic SNPs were excluded. PRS were calculated as the weighted sum of risk alleles, with weights corresponding to effect sizes reported in the GWAS. PRS for knee, hip, and overall OA were constructed based on 51, 35, and 49 SNPs, respectively, whereas no SNPs for hand OA were identified; thus, PRS for hand OA cannot be calculated in this study. The continuous PRS variables exhibited an approximately normal distribution (Supplementary Figure S1). Consistent with previous studies,^{24–27} they were grouped into low (first quintile), intermediate (second to fourth quintiles), and high (fifth quintile) genetic risk categories.

Covariates. Potential confounders were determined with reference to prior literature,^{28–30} encompassing socio-demographic characteristics, lifestyle factors, and health history. Sociodemographic information encompassed sex (male or female), ethnicity (White or other), and Townsend Deprivation Index (TDI, measuring socioeconomic status, with higher scores indicating greater deprivation³¹). In the present study, age was

not adjusted for, as follow-up time was used as the time scale in the survival analysis, which inherently accounts for age. Lifestyle factors included BMI, alcohol consumption (never: never or on special occasions only; low: 1–3 times per month; intermediate: 1–4 times per week; and high: daily or almost daily), and physical activity (low: < 600 metabolic equivalents (MET) minutes/week; moderate: $< 3,000$ MET minutes/week; and high: $\geq 3,000$ MET minutes/week).³² The Charlson Comorbidity Index (CCI)³³ was calculated by summing weighted ICD-10 codes for 17 comorbidities and categorized into three levels (0, 1, or ≥ 2 ; details in Supplementary Table S1).

Statistical analysis. Baseline characteristics were stratified by whether the participants developed OA during the follow-up. Variables following a normal distribution are presented as mean (SD), whereas those with skewed distributions are summarized as median (interquartile range). Categorical variables were described as numbers (percentages). Between-group tests were not performed given the very large number of participants.

Cox regression models were used to investigate the associations of maternal smoking (yes or no) and individual smoking status (never, former, or current) or dose (pack-years) with the risks of knee, hip, hand, and overall OA. Schoenfeld residuals were applied to assess the proportional hazards assumption.³⁴ Three models were fitted. Model 1 (univariable model) only included maternal smoking status and personal smoking status (or cumulative dose, duration, and intensity) as two independent variables. Model 2 adjusted for sex, ethnicity, TDI, physical activity, and CCI. Model 3 further adjusted for BMI on top of model 2. In addition, when examining personal smoking status, cumulative smoking exposure (pack-years) was additionally adjusted for after $\log(x + 1)$ transformation to account for differences in prior smoking exposure and to reduce potential residual confounding. Potential effect modification by age (< 60 years vs ≥ 60 years), sex (male and female), and BMI (< 30 vs ≥ 30) was also explored.

To further investigate the role of genetic factors, the analysis was restricted to the subset of participants with available genetic data. Models were adjusted for the OA PRS and the first 10 genetic principal components to account for genetic susceptibility.³⁵ The potential modifying effect of genetic predisposition on the association between smoking and OA risk was evaluated on both the additive and multiplicative scales. Multiplicative interactions were assessed using likelihood ratio tests comparing models with and without the interaction term, whereas additive interactions were evaluated through the relative excess risk due to interaction (RERI) and the attributable proportion (AP).³⁶ All analyses were conducted using the complete dataset, with results presented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Two sensitivity analyses were performed to examine the robustness of the study findings. First, Fine-Gray competing-risk models were fitted to account for the potential competing risk of

death in the association between smoking and OA. Second, missing data for covariates were imputed using chained equations, generating 20 datasets under the assumption that data were missing at random.³⁷ Continuous variables were imputed using predictive mean matching, whereas binary and categorical variable were imputed using binary and polytomous logistic regression, respectively. Associations were subsequently pooled across the imputed datasets using Rubin's rules.³⁸ All statistical analyses were conducted in R (version 4.4.2, <http://www.R-project.org>), with two-sided *P* value <0.05 considered significant.

Data availability. Data were assessed from <https://www.ukbiobank.ac.uk/>. Data and code for this study are available from the corresponding author upon reasonable request.

RESULTS

The baseline characteristics of participants. Of 321,075 participants (mean age 56 years, 55% women) included, 29.9% reported maternal smoking, 24.3% were former smokers, and 9.5% were current smokers. Among these smoking participants, 98.8% reported smoking cigarettes, whereas 1.2% reported smoking cigars or pipes (Table 1).

Participants who developed incident OA during follow-up were more likely to report maternal smoking during pregnancy and personal smoking at baseline, characterized by longer duration, higher intensity, and greater cumulative exposure. They also had higher baseline comorbidity burden and BMI. Baseline characteristics were otherwise comparable across OA subtypes (Table 1).

Maternal and personal smoking status and OA risk.

During the follow-up period, 18,470 (5.75%), 12,064 (3.76%), 6,605 (2.06%), and 52,853 (16.46%) participants developed knee, hip, hand, and overall OA, respectively. In the fully adjusted model, maternal smoking was associated with an increased risk of overall OA (HR 1.14, 95% CI 1.12–1.17), knee OA (HR 1.08, 95% CI 1.04–1.12), hip OA (HR 1.18, 95% CI 1.13–1.23), and hand OA (HR 1.23, 95% CI 1.16–1.31) (Table 2). Personal smoking was also positively associated with incident OA. Notably, both former and current smoking were associated with higher risks of overall, knee, hip, and hand OA (Table 2).

Subgroup analyses indicated significant effect modification by age, sex, and BMI in the associations between smoking and OA. The positive associations between personal smoking and overall, knee, and hip OA were more pronounced among individuals with obesity (BMI ≥30), whereas an opposite pattern was observed for hand OA (Figure 2). Stronger associations of personal smoking with overall and hip OA were observed in women (Figure 2). In addition, the associations of personal smoking with overall and knee OA were more evident among older participants (≥60 years) (Figure 2). For maternal smoking, stronger

associations with hip OA were observed among younger participants (<60 years) and women (Figure 2).

Dose, duration, and intensity of personal smoking and OA risk. After adjusting for potential confounders and maternal smoking, there was a dose-responsive association between the cumulative dose of personal smoking (in pack-years) and the risks of overall, knee, hip, and hand OA (Table 3), with a comparatively weaker association noted for knee OA. Similar results were observed for the association between the duration and intensity of personal smoking and OA risk (Supplementary Table S2 and S3). Specifically, smoking was inversely associated with knee OA (HRs <1.00, *P* for trend <0.05) while showing positive associations with other types of OA (HR >1.00, *P* for trend <0.05) across all smoking metrics.

Maternal and personal smoking and OA risk by PRS.

After accounting for genetic susceptibility to OA, the main findings remained consistent with the main findings (Supplementary Table S4). However, an additive, but not a multiplicative (Figure 3), interaction was observed between personal smoking and OA polygenic risk. Specifically, among current smokers with intermediate genetic risk, the RERI for overall OA was −0.11 (95% CI −0.20 to −0.03), corresponding to an AP of −10%, indicating a negative additive interaction (Supplementary Table S5). Among current smokers with high genetic risk, the RERI was 0.13 (95% CI 0.02–0.24) with an AP of 10%, suggesting a positive additive interaction (Supplementary Table S5). Similar findings were observed for hip OA with respect to maternal smoking exposure (Supplementary Table S5).

Sensitivity analysis. After further accounting for the competing risk of death using Fine-Gray models, the results remained consistent with the primary analysis (Supplementary Tables S6–S9). Besides, the proportion of missing values for covariates was <1.00%, except for physical activity (69,091, 21.52%). Missingness for other covariates was minimal, including alcohol consumption (224, 0.07%), TDI (404, 0.13%), ethnicity (968, 0.30%), and BMI (1,706, 0.53%). Participants with complete data generally exhibited a healthier profile, characterized by fewer comorbidities, lower socioeconomic deprivation, higher levels of physical activity, and lower BMI (Supplementary Table S10). The associations between maternal and personal smoking with the risk of OA after multiple imputation for missing covariates were consistent with the main analysis (Supplementary Tables S11–S14).

DISCUSSION

Using data from the UK Biobank, we found that both maternal smoking and personal smoking were independently associated with increased OA risk in offspring. Moreover, there was an

Table 1. Baseline characteristics of participants*

Characteristics	Non-OA	Overall OA	Knee OA	Hip OA	Hand OA
N	268,222	52,853	18,470	12,064	6,605
Maternal smoking, n (%)	78,901 (29.42)	16,985 (32.14)	5,810 (31.46)	3,894 (32.28)	2,270 (34.37)
Personal smoking status, n (%)					
Never	179,915 (67.08)	32,699 (61.87)	11,586 (62.73)	7,398 (61.32)	3,945 (59.73)
Former	62,429 (23.28)	15,446 (29.22)	5,468 (29.60)	3,647 (30.23)	2,040 (30.89)
Current	25,878 (9.64)	4,708 (8.91)	1,416 (7.67)	1,019 (8.45)	620 (9.38)
Personal smoking duration, n (%)					
Never	179,915 (67.08)	32,699 (61.87)	11,586 (62.73)	7,398 (61.32)	3,945 (59.73)
<10 years	10,209 (3.81)	2,051 (3.88)	715 (3.87)	471 (3.90)	279 (4.22)
<20 years	21,566 (8.04)	4,701 (8.89)	1,679 (9.09)	1,097 (9.09)	548 (8.30)
<30 years	22,464 (8.38)	4,607 (8.72)	1,658 (8.98)	1,112 (9.22)	608 (9.21)
≥30 years	34,068 (12.70)	8,795 (16.64)	2,832 (15.33)	1,986 (16.46)	1,225 (18.55)
Personal smoking intensity, n (%)					
Never	179,915 (67.08)	32,699 (61.87)	11,586 (62.73)	7,398 (61.32)	3,945 (59.73)
<0.5 pack per day	11,099 (4.14)	2,136 (4.04)	699 (3.78)	496 (4.11)	303 (4.59)
<1.0 pack per day	33,091 (12.34)	7,189 (13.60)	2,336 (12.65)	1,706 (14.14)	956 (14.47)
<1.5 pack per day	32,817 (12.24)	7,707 (14.58)	2,718 (14.72)	1,773 (14.70)	965 (14.61)
≥1.5 pack per day	11,300 (4.21)	3,122 (5.91)	1,131 (6.12)	691 (5.73)	436 (6.60)
Personal smoking dose, n (%)					
Never	179,915 (67.08)	32,699 (61.87)	11,586 (62.73)	7,398 (61.32)	3,945 (59.73)
<10 pack-years	22,273 (8.30)	4,278 (8.09)	1,466 (7.94)	987 (8.18)	577 (8.74)
<20 pack-years	24,199 (9.02)	5,197 (9.83)	1,798 (9.73)	1,249 (10.35)	629 (9.52)
<30 pack-years	17,095 (6.37)	4,059 (7.68)	1,343 (7.27)	966 (8.01)	533 (8.07)
≥30 pack-years	24,740 (9.22)	6,620 (12.53)	2,277 (12.33)	1,464 (12.14)	921 (13.94)
Female sex, n (%)	143,590 (53.53)	31,703 (59.98)	10,017 (54.23)	7,379 (61.17)	4,486 (67.92)
White ethnicity, n (%)	242,822 (90.81)	48,870 (92.73)	16,760 (91.05)	11,469 (95.26)	6,177 (93.80)
Alcohol consumption, n (%)					
Never	52,796 (19.70)	11,904 (22.54)	4,189 (22.69)	2,406 (19.96)	1,649 (25.00)
Low	30,953 (11.55)	5,857 (11.09)	2,072 (11.22)	1,277 (10.59)	713 (10.81)
Intermediate	131,329 (49.00)	24,652 (46.68)	8,644 (46.82)	5,789 (48.02)	2,992 (45.36)
High	52,958 (19.76)	10,402 (19.70)	3,556 (19.26)	2,583 (21.43)	1,242 (18.83)
Physical activity, n (%)					
Low	39,236 (18.47)	7,073 (17.87)	2,364 (17.23)	1,506 (16.51)	888 (18.47)
Intermediate	109,549 (51.57)	19,259 (48.67)	6,616 (48.21)	4,533 (49.71)	2,305 (47.95)
High	63,625 (29.95)	13,242 (33.46)	4,742 (34.56)	3,080 (33.78)	1,614 (33.58)
Charlson Comorbidity Index, n (%)					
0	185,754 (69.25)	25,461 (48.17)	8,673 (46.96)	5,950 (49.32)	2,834 (42.91)
1	41,804 (15.59)	12,025 (22.75)	4,331 (23.45)	2,735 (22.67)	1,541 (23.33)
≥2	40,664 (15.16)	15,367 (29.07)	5,466 (29.59)	3,379 (28.01)	2,230 (33.76)
Age, mean (SD), years	55.03 (8.17)	58.55 (7.36)	58.55 (7.43)	59.64 (7.01)	58.83 (7.14)
TDI, median (IQR)	-2.18 (-3.68 to 0.46)	-2.17 (-3.63 to 0.52)	-2.14 (-3.60 to 0.52)	-2.33 (-3.73 to 0.12)	-2.12 (-3.60 to 0.78)
BMI, mean (SD)	26.90 (4.55)	28.50 (5.16)	29.61 (5.25)	28.13 (4.81)	28.76 (5.39)

* BMI, body mass index; IQR, interquartile range; OA, osteoarthritis; TDI, Townsend Deprivation Index.

additive interaction between smoking and polygenic risk of OA for OA risk. These findings highlight that both maternal and personal smoking exert deleterious effects on the risk of OA, emphasizing the critical importance of smoking prevention and cessation efforts across all stages of life.

The study provides the first population-level evidence that maternal smoking is associated with an increased risk of OA in different joints. This association is independent of both the offspring's personal smoking behavior later in life. Our finding holds critical public health importance, particularly given the current

absence of disease-modifying treatments for OA, and provides further evidence that early life smoking exposure has detrimental, long-term health consequences for offspring. These findings are supported by preclinical evidence. For example, maternal smoking during pregnancy may impair fetal cartilage development, potentially through nicotine, which reduces the expression of type II collagen, aggrecan, and insulin-like growth factor 1 in the offspring's cartilage, leading to delayed fetal articular cartilage development and subsequently reduced cartilage quality.¹⁸ Moreover, maternal smoking has been shown to disrupt pancreatic

Table 2. Association of maternal and personal smoking status with the incidence of osteoarthritis*

Smoking status	OA/total	Model 1		Model 2		Model 3	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Overall OA							
Maternal							
No	35,868/225,189	Reference		Reference		Reference	
Yes	16,985/95,886	1.18 (1.16–1.21)	<0.001	1.18 (1.16–1.21)	<0.001	1.14 (1.12–1.17)	<0.001
Personal							
Never	32,699/212,614	Reference		Reference		Reference	
Former	15,446/77,875	1.06 (0.99–1.12)	0.086	1.15 (1.08–1.23)	<0.001	1.23 (1.16–1.31)	<0.001
Current	4,708/30,586	1.11 (1.03–1.20)	0.006	1.16 (1.08–1.25)	<0.001	1.40 (1.30–1.51)	<0.001
Knee OA							
Maternal							
No	12,660/225,189	Reference		Reference		Reference	
Yes	5,810/95,886	1.14 (1.10–1.19)	<0.001	1.15 (1.11–1.19)	<0.001	1.08 (1.04–1.12)	<0.001
Personal							
Never	11,586/212,614	Reference		Reference		Reference	
Former	5,468/77,875	1.01 (0.91–1.13)	0.814	1.17 (1.05–1.30)	0.004	1.31 (1.18–1.46)	<0.001
Current	1,416/30,586	0.89 (0.78–1.02)	0.089	0.99 (0.87–1.13)	0.937	1.36 (1.19–1.55)	<0.001
Hip OA							
Maternal							
No	8,170/225,189	Reference		Reference		Reference	
Yes	3,894/95,886	1.22 (1.17–1.28)	<0.001	1.21 (1.16–1.26)	<0.001	1.18 (1.13–1.23)	<0.001
Personal							
Never	7,398/212,614	Reference		Reference		Reference	
Former	3,647/77,875	1.12 (0.99–1.28)	0.075	1.13 (0.99–1.28)	0.068	1.18 (1.04–1.35)	0.010
Current	1,019/30,586	1.18 (1.01–1.38)	0.038	1.16 (0.99–1.36)	0.059	1.33 (1.13–1.56)	<0.001
Hand OA							
Maternal							
No	4,335/225,189	Reference		Reference		Reference	
Yes	2,270/95,886	1.29 (1.21–1.37)	<0.001	1.27 (1.20–1.35)	<0.001	1.23 (1.16–1.31)	<0.001
Personal							
Never	3,945/212,614	Reference		Reference		Reference	
Former	2,040/77,875	1.08 (0.90–1.28)	0.420	1.17 (0.98–1.40)	0.076	1.25 (1.05–1.49)	0.011
Current	620/30,586	1.15 (0.93–1.42)	0.213	1.14 (0.92–1.42)	0.218	1.38 (1.12–1.71)	0.003

* Model 1: adjusted for maternal and personal smoking status, as well as personal smoking dose. Model 2: further adjusted for sex, ethnicity, Townsend Deprivation Index, physical activity, and Charlson Comorbidity Index. Model 3: further adjusted for body mass index. CI, confidence interval; HR, hazard ratio; OA, osteoarthritis. Bold values indicate statistical significance ($P < 0.05$).

development via mitochondria-mediated apoptosis of β -cells, thereby promoting systemic inflammation and oxidative stress in the offspring.³⁹ Taken together, these findings suggest that maternal smoking may compromise cartilage development and systemic homeostasis in early life, predisposing the offspring to a higher risk of OA.

Our study also provided evidence of a positive association between personal smoking and OA, consistent with findings from previous cohort studies, although these studies involved smaller sample sizes or short follow-up duration.^{40,41} The observed relationship was further supported by two genetic studies.^{8,9} Nevertheless, most previous studies reported that smoking may be protective^{12,13} against OA or show no^{10,11} significant association. One possible explanation is selection bias because a large number of these studies were hospital based.¹³ Another potential reason is that BMI may act as a mediator rather than a confounder in the association between smoking and OA risk because smokers tend to have lower BMI.¹⁴ Our findings further supported this view as the association between smoking and OA risk was attenuated after adjusting for BMI.

We observed a complex relationship between personal smoking and knee OA. Before adjustment for BMI, smoking status was not associated with knee OA, likely because the lower BMI observed in smokers,¹⁴ which is protective against knee OA, masked the detrimental effect of smoking. After accounting for BMI, there was a positive association between smoking and knee OA. Moreover, cumulative measures of smoking, including duration, dose, and intensity, were also inversely associated with knee OA risk. This counterintuitive trend may partially reflect the indirect effect of smoking through BMI, as well as potential survivor bias or measurement limitations. Importantly, these observations do not alter the overall conclusion that personal smoking increases the risk of knee OA. In addition, personal smoking status and cumulative smoking measures were consistently positively associated with hip and hand OA, regardless of BMI adjustment. This may reflect the relatively stable detrimental effect of smoking on these sites, whereas knee OA is more sensitive to BMI,⁴² which partly explained the inverse association between high exposure of smoking and knee OA risk.

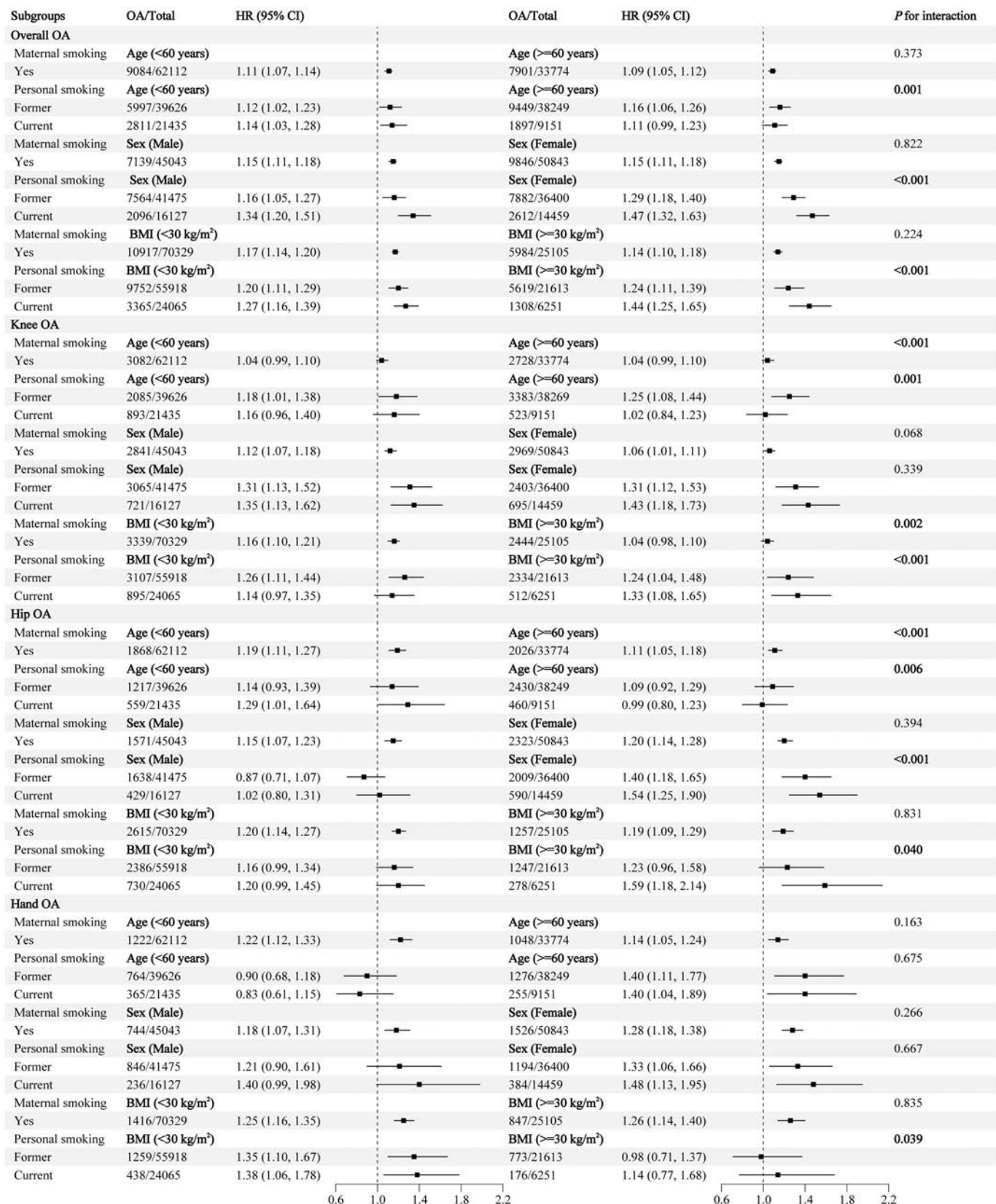


Figure 2. Subgroup analysis for the association between maternal and personal smoking status with the incidence of osteoarthritis. BMI, body mass index; CI, confidence interval; HR, hazard ratio; OA, osteoarthritis.

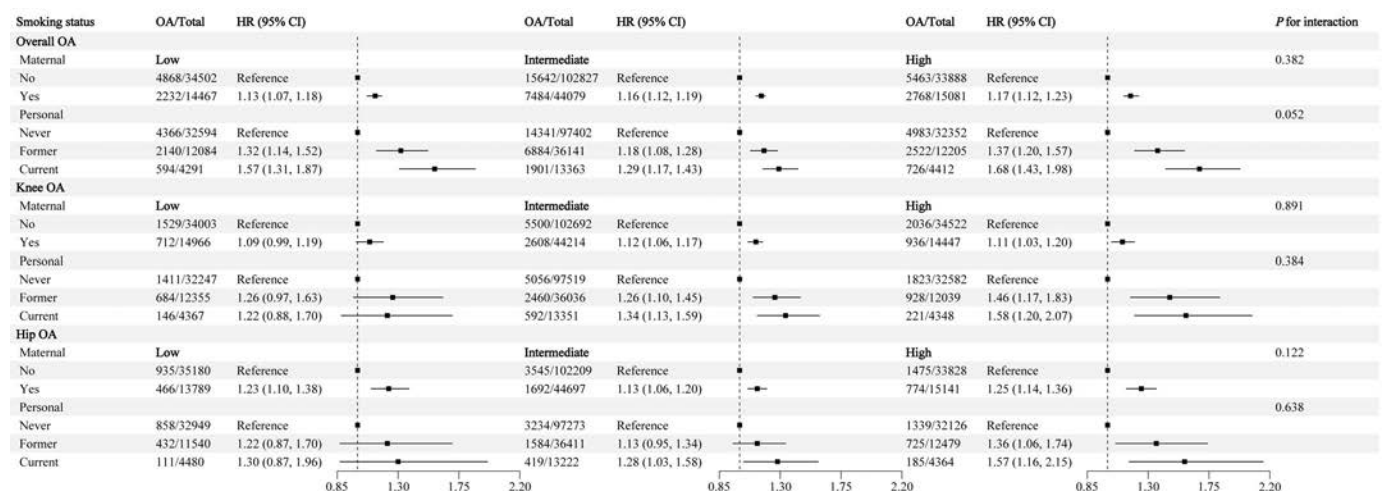
Table 3. Association of personal smoking dose with the incidence of osteoarthritis*

Smoking dose	OA/total	Model 1		Model 2		Model 3	
		HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Overall OA							
Never	32,699/212,614	Reference		Reference		Reference	
<10 pack-years	4,278/6,551	1.05 (1.01–1.09)	0.008	1.07 (1.03–1.10)	0.001	1.07 (1.03–1.11)	<0.001
<20 pack-years	5,197/29,396	1.12 (1.08–1.15)	<0.001	1.12 (1.08–1.15)	<0.001	1.08 (1.05–1.12)	<0.001
<30 pack-years	4,059/21,154	1.17 (1.12–1.21)	<0.001	1.13 (1.09–1.18)	<0.001	1.09 (1.05–1.13)	<0.001
≥30 pack-years	6,620/31,360	1.11 (1.07–1.14)	<0.001	1.03 (0.99–1.07)	0.051	0.97 (0.94–1.01)	0.123
<i>P</i> value for trend		<0.001		<0.001		0.160	
Knee OA							
Never	11,586/212,614	Reference		Reference		Reference	
<10 pack-years	1,466/26,551	1.01 (0.95–1.08)	0.651	1.03 (0.96–1.09)	0.415	1.03 (0.97–1.10)	0.298
<20 pack-years	1,798/29,396	1.10 (1.04–1.16)	0.001	1.07 (1.01–1.13)	0.020	1.02 (0.96–1.08)	0.604
<30 pack-years	1,343/21,154	1.10 (1.03–1.17)	0.004	1.04 (0.97–1.11)	0.306	0.96 (0.90–1.02)	0.218
≥30 pack-years	2,277/31,360	1.08 (1.03–1.14)	0.004	0.95 (0.90–1.01)	0.077	0.86 (0.82–0.91)	<0.001
<i>P</i> value for trend		<0.001		0.629		<0.001	
Hip OA							
Never	7,398/212,614	Reference		Reference		Reference	
<10 pack-years	987/26,551	1.06 (0.98–1.14)	0.155	1.06 (0.98–1.14)	0.157	1.06 (0.98–1.14)	0.146
<20 pack-years	1,249/29,396	1.15 (1.07–1.23)	<0.001	1.15 (1.08–1.24)	<0.001	1.13 (1.05–1.21)	0.001
<30 pack-years	966/21,154	1.18 (1.10–1.28)	<0.001	1.18 (1.09–1.28)	<0.001	1.14 (1.05–1.23)	0.001
≥30 pack-years	1,464/31,360	1.07 (1.01–1.14)	0.044	1.06 (0.99–1.14)	0.084	1.02 (0.95–1.09)	0.642
<i>P</i> value for trend		<0.001		<0.001		0.018	
Hand OA							
Never	3,945/212,614	Reference		Reference		Reference	
<10 pack-years	577/26,551	1.16 (1.05–1.28)	0.005	1.18 (1.07–1.31)	0.001	1.19 (1.07–1.32)	0.001
<20 pack-years	629/29,396	1.12 (1.01–1.23)	0.028	1.13 (1.03–1.25)	0.014	1.10 (0.99–1.21)	0.061
<30 pack-years	533/21,154	1.26 (1.14–1.40)	<0.001	1.23 (1.11–1.37)	<0.001	1.19 (1.06–1.32)	0.002
≥30 pack-years	921/31,360	1.27 (1.17–1.38)	<0.001	1.20 (1.09–1.31)	<0.001	1.13 (1.04–1.24)	0.006
<i>P</i> value for trend		<0.001		<0.001		<0.001	

* Model 1: adjusted for maternal smoking status and personal smoking dose. Model 2: further adjusted for sex, ethnicity, Townsend Deprivation Index, physical activity, and Charlson Comorbidity Index. Model 3: further adjusted for body mass index. CI, confidence interval; HR, hazard ratio; OA, osteoarthritis. Bold values indicate statistical significance ($P < 0.05$).

Subgroup analyses suggested that the effect of personal and maternal smoking on OA may vary according to BMI, sex, and age. Weight-bearing joints such as the knee and hip appear particularly susceptible to combined influence of smoking and

obesity, whereas non-weight-bearing joints like the hand are less affected.⁴² The stronger associations observed in women may reflect smoking-induced reductions in circulating estrogen levels,⁴³ which could adversely affect bone mineral density and

**Figure 3.** Association of maternal and personal smoking status with the incidence of osteoarthritis stratified by polygenic risk score for osteoarthritis. CI, confidence interval; HR, hazard ratio; OA, osteoarthritis.

cartilage metabolism.⁴⁴ The observed age-related differences may reflect cumulative joint damage and prolonged exposure to risk factors, whereas early life exposures, including maternal smoking, could have a greater impact in younger age groups.

In addition, no evidence of multiplicative interaction was observed between genetic susceptibility to OA and either maternal or personal smoking. However, additive interaction analyses suggested heterogeneous patterns. Higher genetic susceptibility to OA appeared to interact synergistically with both maternal and personal smoking. This pattern may reflect the greater vulnerability of cartilage or joint structures in genetically susceptible individuals. Personal smoking could accelerate joint degeneration through mechanisms such as inflammation and oxidative stress,^{5,6} whereas maternal smoking during pregnancy may impair cartilage and bone development in offspring.¹⁸ In contrast, among individuals with intermediate genetic risk, maternal or personal smoking showed a subadditive or antagonistic interaction, the reasons for which remain unclear but may involve protective influences related to BMI or lifestyle factors.

The strengths of our study include the large sample size, long follow-up duration, and the involvement of genetic susceptibility to OA. Additionally, this study was conducted in a large, population-based sample rather than a hospital-based sample, which enhances generalizability and may reduce potential selection bias. However, our study has limitations. First, information on maternal smoking was self-reported, which may have introduced recall bias. Although a prior study has demonstrated that offspring-reported maternal smoking around the time of birth is reasonably reliable,⁴⁵ some misclassification may still occur. Second, this study focused exclusively on maternal and personal smoking, without accounting for other tobacco exposures (eg, secondhand or environmental smoke), potentially leading to unmeasured confounding. Lastly, the UK Biobank participants are healthier than the general population,⁴⁶ potentially limiting the generalizability of our OA risk estimates.

In this large, population-based cohort, both maternal smoking and personal smoking are associated with an elevated risk of OA, with genetic susceptibility potentially modulating these associations. These findings underscore the importance of smoking prevention and cessation, both prenatally and in adulthood, as part of the strategies to reduce OA burden.

ACKNOWLEDGMENTS

This research has been conducted using the UK Biobank resource under application number 96569.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding

authors, Drs H. Zhang and Cai confirm that all authors have provided the final approval of the version to be published and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Comparative Performance of LFA-REAL, SLEDAI, and BILAG for Detecting Clinically Meaningful Changes in Lupus Activity

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Objective. This study aimed to compare the performance of the Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL), British Isles Lupus Assessment Group Index (BILAG), and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) in detecting the clinician's perception of improvement and worsening disease and identifying patients requiring treatment escalation.

Methods. This was a prospective, observational study conducted at four centers. Adults with systemic lupus erythematosus were evaluated at a baseline and follow-up visit. Disease activity was assessed using SLEDAI, BILAG, and LFA-REAL at both visits by the same physician. At the follow-up visit, the Clinician Global Impression of Change (CGIC) was recorded to classify patients as improved, worsened, or unchanged. Receiver operating characteristic curve analysis was used to evaluate each instrument in detecting clinician-rated change gauged by CGIC with optimal cut-off points determined using the Youden Index.

Results. Of the 163 patients enrolled, 145 (89%) completed a follow-up visit. Based on CGIC, 23% improved, 16% worsened, and 61% remained stable. For detecting CGIC-defined improvement, LFA-REAL had an area under the curve (AUC) of 0.85 (95% confidence interval [CI] 0.77–0.92), compared to 0.75 (95% CI 0.66–0.85) for BILAG and 0.74 (95% CI 0.64–0.84) for SLEDAI. For CGIC-defined worsening, AUCs were 0.86 (95% CI 0.77–0.96), 0.79 (95% CI 0.67–0.90), and 0.76 (95% CI 0.66–0.87). Of those with CGIC-defined worsening, eight (35%) required treatment escalation. LFA-REAL identified a difference of ≥ 10 mm in all eight of these patients, compared to four by BILAG and two by SLEDAI.

Conclusion. LFA-REAL showed comparable performance relative to SLEDAI and BILAG in detecting clinician-rated change. There was a statistically significant advantage over SLEDAI for detection of improvement. These findings support its utility as a metric for disease activity in clinical practice and research.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease characterized by intermittent flares and periods of worsening disease activity.¹ Given its variable and unpredictable course, accurate measurement of disease activity remains a major clinical challenge.^{2–4} Reliable assessment is essential not only for guiding therapeutic decisions in daily practice but also

for evaluating efficacy outcomes in clinical trials.^{4,5} Multiple disease activity instruments have been developed and validated to date, including the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the British Isles Lupus Assessment Group Index (BILAG), and the Physician's Global Assessment (PGA). These instruments—and the composite indices derived from them—are the most widely used tools in clinical trials; however, each has important limitations.^{6–8}

Supported by a grant by the US Department of Defense (award number W81XWH-21-1-0468).

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80034>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80034>.

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Submitted for publication November 13, 2025; accepted in revised form March 3, 2026.

SIGNIFICANCE & INNOVATIONS

- Traditional lupus disease activity instruments like the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group Index (BILAG) may fail to capture meaningful variations in disease activity when compared with the Clinician Global Impression of Change.
- The Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) is a novel and simple disease activity instrument that uses a series of visual analog scales to assess individual symptoms, organ-level activity, and overall disease severity in lupus.
- LFA-REAL demonstrated comparable performance relative to SLEDAI and BILAG in detecting clinically significant improvement and worsening, as determined by the Clinician Global Impression of Change, with a statistically significant difference observed over SLEDAI for detection of improvement.

The SLEDAI includes 24 weighted clinical and laboratory manifestations of SLE derived from expert consensus. However, it omits many less common manifestations and, because each item is scored at maximal weight once the minimum threshold is met, it cannot capture variations in severity.^{3,7} In order to score the SLEDAI accurately, training is needed as well as access to a glossary. The BILAG-2004 index includes a comprehensive set of 97 items categorized across nine organ systems. For each manifestation, clinicians indicate whether findings are new, improving, worsening, the same, or not present compared with the previous month, allowing a clinical impression of change to be captured. These assessments of a patient's progress are integrated with severity descriptors to determine ordinal organ-level scores reflecting mild, moderate, or severe disease activity. Although it distinguishes between varying levels of severity, these categories rely on predefined thresholds, which may be less sensitive to smaller changes in disease activity that do not result in transitions between severity categories. Additionally, the index does not differentiate between multiple active descriptors within the same organ system, meaning if a patient had two active manifestations within one organ, only one score can be assigned for that system.⁹ The complexity of BILAG means that it requires extensive training to complete, which limits its use in routine clinical practice.¹⁰ A much simpler instrument frequently used in lupus studies is the PGA, a visual analog scale that captures the clinician's overall impression of SLE disease activity. This tool addresses several limitations of SLEDAI and BILAG by providing a continuous, linear scale with landmarks for mild, moderate, and severe disease. However, condensing multiple manifestations of varying severity into a single 100-mm score limits its interpretability and precision.^{4,10} Additionally, with no guidance to

focus a clinician's assessment on specific components of disease, interrater reliability can be limited.

The Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) is a novel disease activity instrument that incorporates both clinician-reported outcomes (ClinRO) and patient-reported outcomes.⁷ The ClinRO consist of a series of anchored visual analog scales (0–100 mm each) assessing individual symptoms, organ-level activity, and global disease activity⁵ (see Figure 1). The use of a continuous scale, rather than relying on rigid, glossary-defined thresholds of instruments like SLEDAI and BILAG, allows for a more granular detection of fluctuations in disease activity. Unlike the PGA, which compresses all disease manifestations into a single score, LFA-REAL provides subscales for each individual manifestation, enabling tracking of individual symptom progression and response to treatment across different levels of disease involvement.⁴ This instrument has been validated in several previous studies and demonstrated high interrater reliability.^{3–5,10,11} In this study, we aimed to evaluate the performance of LFA-REAL, BILAG, and SLEDAI in detecting clinically meaningful improvement and worsening based on the Clinician Global Impression of Change (CGIC) and in identifying patients requiring treatment escalation.

PATIENTS AND METHODS

A prospective, observational, longitudinal study was conducted at four lupus centers: Columbia University Irving Medical Center, Medical University of South Carolina, Feinstein Institutes for Medical Research, and Oklahoma Medical Research Foundation. Consecutive patients that met at least 4 of the 11 revised 1997 American College of Rheumatology criteria for SLE were invited to participate.¹² This study was approved by the institutional review board at each participating site, and all participating patients provided informed consent.

Data collection. Patients were evaluated during routine clinical visits with their physicians. Data on demographics, clinical characteristics, and medications use were collected at each visit. Laboratory assessments necessary to calculate disease activity instruments were obtained, including complete blood count, urinalysis, C3, C4, anti-double stranded DNA, complete metabolic panel, and urine protein/creatinine ratio.

Each participant was evaluated at a baseline (visit 1 [V1]) and follow-up visit (visit 2 [V2]), as scheduled by usual care. At both visits, disease activity was evaluated by the Safety of Estrogens in Lupus Erythematosus National Assessment–SLEDAI (SELENA-SLEDAI), scored over a 28-day assessment period, BILAG-2004, the LFA-REAL ClinRO, and the PGA performed by the same physician. At the follow-up visit, the physician rated the CGIC, reflecting perceived change compared to the baseline visit, which was classified as the following: “major or complete improvement,” “significant partial improvement,” “no change or insignificant change,”

“significant moderate worsening,” or “severe worsening.” Due to limited numbers of patients in each individual category, response categories were condensed into improvement, minimal or no change, or worsening. See Supplementary Table 1 to compare the original and condensed CGIC measures.

All disease activity instruments, including SELENA-SLEDAI, BILAG-2004, LFA-REAL, PGA, and CGIC, were scored by trained rheumatologists with experience in evaluating SLE in clinical practice as well as in formal clinical studies. At the follow-up visit, clinicians had access to prior clinical information, including baseline assessments, as part of routine clinical care. Disease activity instruments (LFA-REAL, BILAG, and SLEDAI) were completed during the clinical encounter in no designated order, followed by completion of the CGIC, which reflected the clinician’s overall assessment of change since the previous visit. Decisions regarding treatment escalation or tapering were made by the same physician who scored the instruments based on clinical judgment and standard of care, with no requirement to consider the disease scoring.

Statistical analysis. Descriptive statistics were used to summarize demographic and baseline clinical characteristics of the participants. Categorical variables are reported as frequencies and percentages and numerical variables as means and SDs. To calculate the global BILAG score, BILAG A was graded at 12 points, BILAG B at 8 points, and BILAG C at 1 point.¹³ Changes in disease activity scores were calculated for all instruments by subtracting the baseline score from the follow-up value ($V2 - V1$), resulting in Δ LFA-REAL, Δ BILAG, and Δ SLEDAI.

Spearman’s correlation coefficients were used to assess bivariate correlations between changes in disease activity measures. Correlation strength was interpreted using predefined thresholds as follows: very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), and very strong (0.80–1.00). Violin plots were generated to visualize the change in disease activity instruments (Δ LFA-REAL, Δ BILAG, and Δ SLEDAI) across CGIC categories (improvement, no change, or worsening). Differences across the three groups were compared using one-way analysis of variance. Receiver operating characteristic (ROC) curve analysis was performed to assess the ability of each disease activity instrument to detect clinically significant improvement and worsening based on CGIC. The area under the curve (AUC) with 95% confidence intervals (CIs) was calculated for each instrument, and DeLong’s test was used to compare AUCs between instruments. Optimal cut-off values for each score were identified using the Youden Index, and sensitivity, specificity, positive predictive value, and negative predictive value were calculated for these optimal thresholds as well as for other additional exploratory cut-off values that were selected based on proximity to the Youden-derived optimal thresholds while accounting for the scoring structure and clinical usability of each instrument.

As a subgroup analysis, each case classified as worsening by CGIC was analyzed individually to determine whether LFA-REAL, BILAG, and SLEDAI scores increased at follow-up (V2) compared to baseline (V1). A second subgroup analysis was performed among patients with CGIC-defined worsening who required escalation of treatment, which was defined as the addition or dose increase of glucocorticoids or immunosuppressants, as determined by the treating physician during the follow-up visit. A difference of ≥ 10 mm in the LFA-REAL (representing an increase of 10% or higher of each symptom score) was considered clinically significant, based on the results from the ROC curve analysis. We used SPSS version 24.0 (IBM), RStudio version 2024.04.1 (Posit Software), and GraphPad Prism version 9.5.0 (GraphPad Software) for analyses.

RESULTS

The population included 163 patients of whom 141 (87%) were female. The mean age was $41.1 \pm \text{SD } 13$ years, and the mean disease duration was $17.4 \pm \text{SD } 9.2$ years. Overall, 65 patients (40%) identified as White, 64 (39%) as Black, 21 (13%) as Asian, and 40 (25%) as Hispanic. At the initial visit, mean SLEDAI was $5.5 \pm \text{SD } 5$, BILAG $7.1 \pm \text{SD } 7.3$, and LFA-REAL $51.4 \pm \text{SD } 52$ mm. In total, 33 patients (20%) had asymptomatic disease, 111 (68%) mild to moderate disease, and 19 (12%) severe disease at baseline, according to the physician’s assessment. Further demographic and baseline clinical characteristics of the patients are depicted in Table 1.

At the baseline visit, LFA-REAL demonstrated a strong correlation with SLEDAI ($r = 0.67$; 95% CI 0.59–0.72) and a very strong correlation with BILAG ($r = 0.80$; 95% CI 0.75–0.85) (Supplementary Figure 1). LFA-REAL showed a very strong correlation with PGA ($r = 0.85$; 95% CI 0.80–0.90), similar to BILAG ($r = 0.82$; 95% CI 0.75–0.89), whereas SLEDAI showed a strong correlation ($r = 0.78$; 95% CI 0.70–0.84) (Supplementary Table 2). Follow-up visits were completed for 145 patients (89%), which occurred after a mean of $4.3 \pm \text{SD } 3$ months from the initial visit. All 145 patients who completed a follow-up visit had complete data for LFA-REAL, BILAG, SLEDAI, and CGIC, with no missing values for these measures. Based on the CGIC rating at follow-up, 34 patients (23%) improved, 23 (16%) worsened, and 88 (61%) had no meaningful change in disease activity compared to baseline according to the clinicians. Among those classified as improved by CGIC, the LFA-REAL decreased a median of 36.5 mm (interquartile range [IQR] 21.2–61.3) from V1 to V2, the BILAG was reduced by 5 points (IQR 0–7), and the SLEDAI by 2 points (IQR 0–5.3). For those with CGIC-defined worsening, the LFA-REAL increased by a median of 30.2 mm (IQR 9.2–35.6), the BILAG by 3 points (IQR 0–8), and the SLEDAI by 1.5 points (IQR 0–4). Patients classified as having no change based on CGIC showed a median difference of 0 mm in LFA-REAL (IQR –20 to 10), 0 points in BILAG (IQR –1 to 0), and

Table 1. Baseline demographic and clinical characteristics of the participants*

Demographic and clinical characteristics	Participants (N = 145)
Sex, n (%)	
Female	124 (85)
Male	21 (15)
Age, mean (SD), y	41.5 (12.9)
Race, n (%)	
White	60 (42)
Black	58 (40)
Asian	18 (12)
Other	9 (6)
Ethnicity, n (%)	
Hispanic	37 (26)
Not Hispanic	108 (74)
Site, n (%)	
CUMC	49 (33)
MUSC	42 (29)
FIMR	27 (19)
OMRF	27 (19)
SLE disease duration, mean (SD), y	17.6 (9.0)
Physician's assessment of disease severity, n (%)	
No disease activity/asymptomatic	31 (21)
Mild/moderate disease activity	96 (66)
Severe disease activity	18 (13)
Disease activity scores at baseline, mean (SD)	
SLEDAI	5.1 (4.5)
BILAG	6.7 (6.8)
LFA-REAL	51.0 (52.9)
Active organ system involvement at baseline, n (%)	
Musculoskeletal	84 (58)
Mucocutaneous	66 (46)
Vasculitis	4 (3)
Cardiorespiratory	3 (2)
Renal	23 (16)
Neuropsychiatric	0 (0)
Constitutional	6 (4)
Hematologic	44 (30)

* BILAG, British Isles Lupus Assessment Group Index; CUMC, Columbia University Irving Medical Center; FIMR, Feinstein Institutes for Medical Research; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; MUSC, Medical University of South Carolina; OMRF, Oklahoma Medical Research Foundation; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

0 points in SLEDAI (IQR −2 to 0) scores between both visits. Further description of the changes in disease activity scores according to CGIC groups is shown in Figure 2.

Figure 3 shows an ROC curve analysis assessing the discriminatory ability of each disease activity instrument to detect a clinically significant change as defined by CGIC. For detecting improvement, the LFA-REAL demonstrated an AUC of 0.85 (95% CI 0.77–0.92), compared with 0.75 (95% CI 0.66–0.85) for BILAG and 0.74 (95% CI 0.64–0.84) for SLEDAI. For detecting worsening, the AUC for LFA-REAL was 0.86 (95% CI 0.77–0.96), compared to 0.79 (95% CI 0.67–0.90) for BILAG and 0.76 (95% CI 0.66–0.87) for SLEDAI. Using DeLong's test, the AUC

for LFA-REAL was significantly greater than that of SLEDAI for detecting clinical improvement (0.85 vs 0.74; $P = 0.034$), and the trend was not significant compared to BILAG (0.85 vs 0.75; $P = 0.070$). For detecting clinical worsening, LFA-REAL showed higher, although not statistically significant, sensitivity compared to SLEDAI (0.86 vs 0.76; $P = 0.088$) and BILAG (0.86 vs 0.78; $P = 0.199$). See Supplementary Table 3.

The best cut-off values for detecting clinically significant improvement and worsening were determined for each activity index using the Youden Index and rounded to the nearest whole number. The optimal thresholds were 10 mm for LFA-REAL and one unit for both SLEDAI and BILAG. At these thresholds, LFA-REAL showed comparable sensitivity and specificity to the other instruments. For detecting improvement, LFA-REAL achieved a sensitivity of 85.3% (95% CI 73.5%–97.1%) compared to 73.5% (95% CI 58.8%–88.2%) for BILAG and 67.6% (95% CI 50.0%–82.4%) for SLEDAI, whereas specificity remained similar across the three instruments (75.7% [95% CI 67.6%–83.8%] for LFA-REAL, 72% [95% CI 64.9%–81.1%] for BILAG, and 75.7% [95% CI 67.6%–83.8%] for SLEDAI). Similarly, for worsening, LFA-REAL yielded a sensitivity of 78.3% (95% CI 60.9%–95.7%), compared to 65.2% (95% CI 43.5%–82.6%) for BILAG and 56.5% (95% CI 34.8%–78.3%) for SLEDAI, whereas specificity remained similar for the three instruments (81.1% [95% CI 73.8%–87.7%] for LFA-REAL, 86.1% [95% CI 79.5%–91.8%] for both BILAG and SLEDAI). Additional details are provided in Table 2 and Supplementary Table 4.

Among the 23 patients with worsening based on CGIC, worsening was associated with worse arthritis in 14 patients, rash in 7 patients, and alopecia in 2 patients. Of the 23 patients with clinical worsening, 8 (35%) required an escalation in treatment as determined by the treating physician, including 5 patients with worsening arthritis and 3 with worsening rash. The remaining 15 patients with CGIC-defined worsening did not receive treatment escalation according to the physician because the degree of worsening was considered mild or clinically manageable without change in therapy. Treatment escalation consisted of initiation or dose increase of glucocorticoids in three patients, a change or dose increase of an immunosuppressant in four patients, and an increase in both therapies in one patient. Among the 34 patients with improvement based on CGIC, 5 (15%) received a taper or reduction in treatment according to the treating physician, including 3 patients with improvement in arthritis, 1 with improvement in rash, and 1 with improvement in alopecia and fatigue. Treatment taper included four patients in which glucocorticoids were reduced or discontinued and one patient with a reduction in immunosuppressant therapy.

The LFA-REAL demonstrated a difference of ≥ 10 mm between visits in 21 (91%) of the 23 worsening cases. In comparison, BILAG detected worsening in 14 patients (61%) and SLEDAI in 12 (52%). Similarly, for worsening cases that required an escalation in treatment, LFA-REAL identified all eight of these patients

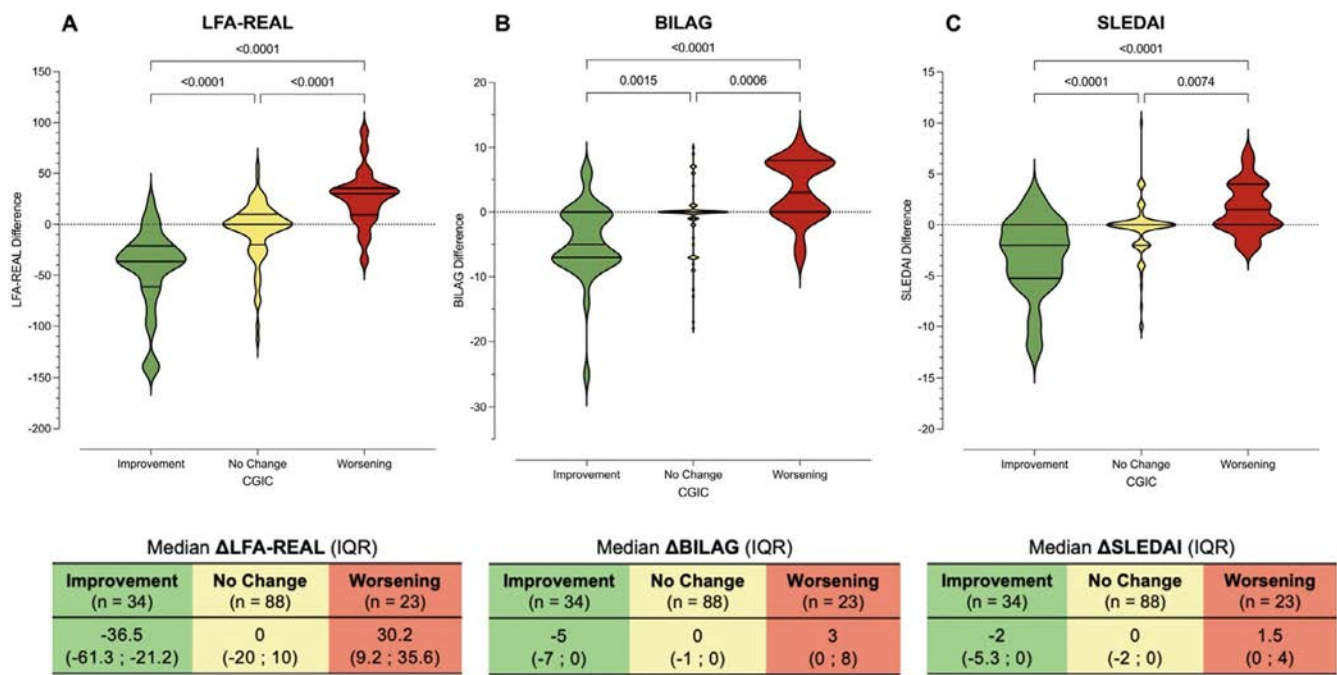


Figure 2. Changes in disease activity scores according to CGIC group. (A) Change in LFA-REAL (V2 – V1) according to CGIC group. (B) Change in BILAG (V2 – V1) according to CGIC group. (C) Change in SLEDAI (V2 – V1) according to CGIC group. BILAG, British Isles Lupus Assessment Group Index; CGIC, Clinician Global Impression of Change; IQR, interquartile range; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; V1, visit 1; V2, visit 2.

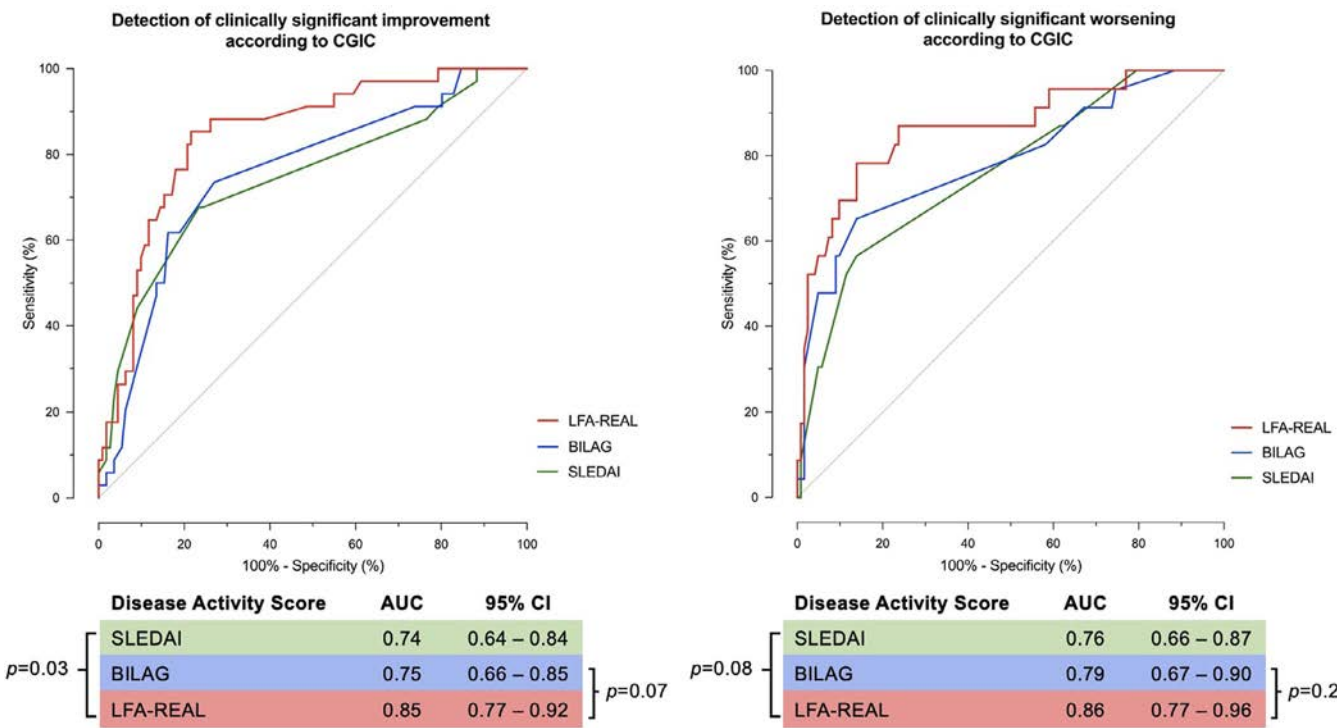


Figure 3. Performance of disease activity indices to identify clinical improvement or worsening according to CGIC group. (Left) ROC curve analysis assessing the ability of each disease activity index to detect clinically significant improvement. (Right) ROC curve analysis assessing the ability of each disease activity index to detect clinically significant worsening. AUC, area under the curve; BILAG, British Isles Lupus Assessment Group Index; CGIC, Clinician Global Impression of Change; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; ROC, receiver operating characteristic; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80034/abstract>.

Table 2. Performance of disease activity indices to identify clinical improvement or worsening according to CGIC group*

Disease activity instruments	Cut-off value ^a	Improvement				Worsening			
		Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)	Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)
LFA-REAL	10.0	85.3 (73.5–97.1)	75.7 (67.6–83.8)	51.8 (38.9–64.7)	94.4 (89.4–98.9)	78.3 (60.9–95.7)	81.1 (73.8–87.7)	43.9 (28.9–59.4)	95.2 (90.7–99)
BILAG	1.0	73.5 (58.8–88.2)	72.0 (64.9–81.1)	45.5 (32.1–58.7)	90.0 (83.5–95.6)	65.2 (47.8–82.6)	86.1 (79.5–91.8)	46.9 (29.0–64.5)	92.9 (87.7–97.3)
SLEDAI	1.0	67.6 (50–82.4)	75.7 (67.6–83.8)	46.0 (31.9–59.6)	88.4 (81.7–94.5)	56.5 (34.8–73.9)	86.1 (79.5–91.8)	43.4 (25.0–61.5)	91.3 (85.8–95.9)

* BILAG, British Isles Lupus Assessment Group Index; CGIC, Clinician Global Impression of Change; CI, confidence interval; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; Spec., specificity.

^a Cut-off values are the closest whole number approximations to the thresholds calculated using the Youden Index.

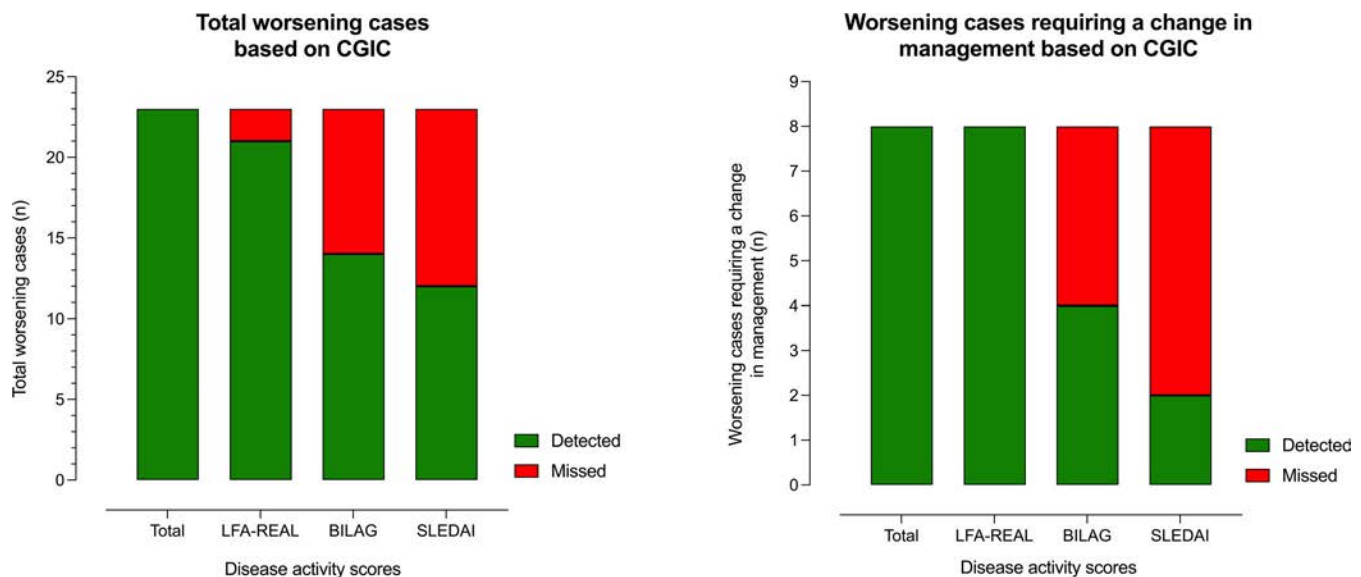


Figure 4. Detection of (Left) total worsening cases and (Right) worsening cases requiring a change in management by each disease activity index. *Change in management consisted in adding or increasing the dose of prednisone in three patients, increasing the dose or changing the immunosuppressant in four patients, and increasing both the steroid and immunosuppressant in one patient. BILAG, British Isles Lupus Assessment Group Index; CGIC, Clinician Global Impression of Change; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80034/abstract>.

as having clinically significant worsening, compared to four (50%) detected by BILAG and two (25%) by SLEDAI (Figure 4).

When analyzed by system domain, LFA-REAL identified all 14 of 14 cases of musculoskeletal worsening due to arthritis, compared with 6 of 14 detected by BILAG and 4 of 14 by SLEDAI. For mucocutaneous worsening, LFA-REAL detected five of seven rash cases, compared with four of seven detected by both BILAG and SLEDAI. A breakdown of the worsening cases by clinical manifestations can be found in Supplementary Table 5 and Supplementary Figures 2 and 3.

DISCUSSION

Given the natural variability of SLE, characterized by alternating periods of flares and remission, the difficulties in understanding and interpreting clinical trial data, and the increasing requirements by insurance providers and regulators for disease justification in clinical practice, there is a need for efficient and accurate disease activity instruments that can quantitatively and accurately capture changes in clinical status.^{3,4} In this multicenter prospective study, we evaluated the performance of the LFA-REAL, BILAG, and SLEDAI in detecting clinically significant change in lupus activity and found that LFA-REAL demonstrated performance comparable to the traditional disease activity measures, with an advantage observed over SLEDAI for detecting improvement.

All disease activity scores substantially correlated with each other. LFA-REAL demonstrated a significantly greater ability to detect clinician-rated improvement by CGIC (AUC 0.85 vs 0.74;

$P = 0.03$), reflecting a limitation in the SLEDAI for detection of partial improvements that might be meaningful to the patient and clinician but do not cross the threshold for the SLEDAI to stop scoring an item. For example, a patient whose platelet count increases from $4 \times 10^9/L$ to $98 \times 10^9/L$ would have no change in SLEDAI score. Similarly, a patient with severe, function-limiting polyarthritis affecting >20 joints who after treatment is left with only mild arthritis in 2 joints would still receive the same SLEDAI score, despite marked improvement.⁴

The detection of worsening by LFA-REAL in the small number of patients who deteriorated was not statistically different from SLEDAI (AUC 0.86 vs 0.76; $P = 0.08$). However, using a 10-mm cut-off for worsening, the LFA-REAL captured all eight of those patients who deteriorated enough to require treatment escalation, whereas the SLEDAI failed to detect worsening in six of these patients (75%). This likely reflects the same limitation in the SLEDAI, which assigns equal weights to all disease manifestations once a minimal threshold is met, making even a major worsening in an already existing feature impossible to detect.^{3,4} A separate SELINA-SLEDAI Flare Composite Index is often used in clinical trials to compensate for that limitation but would add another layer of effort for use in clinical practice.¹⁴ When examined by system domain, LFA-REAL appeared to more consistently identify worsening driven by musculoskeletal manifestations than by mucocutaneous disease, although these observations are descriptive and based on small numbers.

BILAG and LFA-REAL demonstrated similar performance for detecting clinical change, with no statistically significant differences observed for detection of either improvement (AUC 0.85

for LFA-REAL vs 0.75 for BILAG; $P = 0.07$) or worsening (AUC 0.86 vs 0.79; $P = 0.19$). The BILAG, unlike the SLEDAI, does distinguish between different levels of disease severity—mild, moderate, and severe. However, these thresholds are categorical and restricted and can sometimes lead to either false positive or false negative change because of their threshold definitions. Additionally, because the index consolidates multiple features within a single organ system into one score, it cannot capture changes in individual manifestations in patients with multiple active descriptors.^{3–5} These limitations may be reflected in BILAG's failure to identify a change in clinical status in nearly 40% of patients with CGIC-defined worsening in our cohort, including four of the eight patients (50%) who required treatment escalation.

Our findings are consistent with those of previous studies. D. Jesus et al reported that SLEDAI had limited ability to detect changes in disease activity, failing to identify nearly two-thirds of cases judged by physicians as having clinically meaningful improvement or worsening.¹⁵ Similarly, Fatemi et al found that SLEDAI and BILAG had AUCs of 0.771 and 0.779, respectively, for identifying patients with clinical deterioration requiring treatment escalation, similar to our results.²

Our study has several limitations. Although we identified preliminary optimal cut-off points using the Youden Index, these findings require external validation in independent cohorts to confirm their clinical applicability. Also, the small sample size, particularly the limited number of patients with worsening and improvement, limits the ability to draw conclusions from the data or compare instrument performance between centers. These limited event counts reduce statistical power for subgroup analyses and increase uncertainty around estimates of discrimination and diagnostic performance, raising the risk of both Type I and Type II error. In addition, although treatment escalation or tapering could be linked to the clinical manifestations that worsened or improved between visits, more granular information about the specific features of those manifestations and the exact details of medication adjustments was not collected, limiting more detailed characterization of the drivers of treatment decisions.

The CGIC, although not a formally validated outcome measure in SLE, served as a pragmatic and clinically relevant anchor for this study. However, because it may vary based on an unanchored physician judgment, its use in a smaller sample carries risk of subjective bias. LFA-REAL, like other indices based on visual analog scales, is subject to variability between the physicians scoring them. However, in a separate study conducted by our group, LFA-REAL demonstrated good interrater reliability among different practicing physicians and clinical researchers.^{5,11} Additionally, because the same clinician completed the CGIC and disease activity instruments at both visits, there is potential for influence of one instrument scores on another. In future studies, it will be helpful to ensure that different cohorts of assessors are required to score the instruments in a different order.

Finally, data on the time required to complete each disease activity instrument were not collected. As feasibility and time burden are important considerations for clinical implementation, future studies should prospectively assess completion time, ease of use, and workflow impact of these instruments in real world practice. Future studies should also explore the development and validation of LFA-REAL-based definitions of disease flare, potentially informed by thresholds associated with clinician-defined worsening requiring treatment escalation. Direct comparison with the SELENA flare index and BILAG definitions of flare will also be important to evaluate.

In conclusion, our findings suggest that LFA-REAL may perform at least as well as more complex disease activity measures such as SLEDAI and BILAG in detecting clinically meaningful changes in SLE. Further validation in larger, independent cohorts is needed to support its integration into clinical trial endpoints and treat-to-target strategies.

ACKNOWLEDGMENTS

Large language models were used for checking spelling and grammar.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Askanase confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW ARTICLE

Clinical Significance of Therapeutic Drug Level Monitoring for Mycophenolate in Patients With Extrarenal Systemic Lupus Erythematosus—A Systematic Review and Meta-Analysis

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Objective. Clinical response to mycophenolic acid (MPA) is highly heterogeneous; thus, therapeutic drug level monitoring (TDM) may help improve treatment efficacy. This systematic review and meta-analysis examined therapeutic ranges for MPA levels associated with better outcomes and safety in patients with systemic lupus erythematosus (SLE), particularly those with extrarenal manifestations.

Methods. We performed a comprehensive search of studies evaluating associations between MPA levels and clinical SLE response. Using forest plots, we calculated pooled odds of clinical response by MPA levels and measured the weighted mean differences across outcomes. Analysis was performed in all patients with SLE and separately in patients with extrarenal manifestations.

Results. Among 459 reviewed abstracts, 24 met inclusion. Summarized evidence supported that clinical response was observed at MPA area under the curve at 0 to 12 hours (AUC_{0-12}) ≥ 30 to 35 mg hr/L or trough concentration (C_{trough}) ≥ 1.5 mg/L. At these thresholds, therapeutic MPA levels were associated with 12-fold higher odds (95% confidence interval [CI] 5.44–27.35; $P < 0.0001$; $I^2 = 41\%$) of overall clinical SLE response and 15-fold higher odds (95% CI 4.74–46.89; $P < 0.0001$; $I^2 = 61\%$) of response in patients with extrarenal manifestations. Additionally, MPA levels were 32 units higher (95% CIs 17.35–45.67) in overall responders with SLE and 39 units (95% CI 15.05–62.53) higher in patients with extrarenal manifestations. Although pooled analysis did not show a significant increase in adverse events, individual studies suggested safety concerns at MPA $AUC_{0-12} > 60$ mg hr/L or $C_{trough} \geq 2.5$ to 3 mg/L.

Conclusion. This study highlights the clinical utility of TDM to guide MPA dosing to balance efficacy versus safety in all patients with SLE, including those with extrarenal manifestations.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease that disproportionately affects young female individuals and is a leading cause of premature death in young women.^{1,2} Therefore, precise treatment is crucial to prolong disease-free and damage-free survival in all patients.³ As the SLE treatment armamentarium continues to expand, mycophenolic acid (MPA) remains a key therapeutic for both renal and

extrarenal manifestations of SLE.^{4,5} However, studies have shown a significant heterogeneity in treatment response with fixed MPA dosing, resulting in variability in SLE outcomes and adverse events.^{6,7} Such heterogeneity in treatment response to MPA may be explained by a myriad of clinical factors. These include dose, drug absorption, metabolism, clearance, interactions, genetics, specific disease manifestations, and treatment adherence at individual patient level.⁸ Therapeutic drug level monitoring (TDM) of MPA could circumvent this dilemma by bypassing

Supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant number: 5K23AR084608-02).

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80035>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80035>.

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Submitted for publication January 2, 2025; accepted in revised form March 3, 2026.

SIGNIFICANCE AND INNOVATIONS

- This systemic review and meta-analysis suggest the potential clinical significance of maintaining mycophenolic acid (MPA) levels above a threshold of 30 mg hr/L area under the curve at 0 to 12 hours (AUC_{0-12}) and concentration at 12 hours (C_{12}) >1.5 mg/L to maximize clinical response in systemic lupus erythematosus (SLE) and lupus nephritis (LN), as patients above this cutoff demonstrated 12- to 15-fold higher odds of response, including in those with extrarenal manifestations.
- Additionally, patients with MPA levels above 30 mg hr/L AUC_{0-12} and $C_{12} >1.5$ mg/L had a significant seven-point reduction in SLE disease activity.
- Adverse event rates were not significantly higher at these levels in pooled analysis, though some individual studies suggested potential toxicity at MPA levels $AUC_{0-12} >60$ mg hr/L and trough concentration >2.5 to 3 mg/L.
- Therapeutic MPA levels could be used for clinic monitoring to ensure safe and effective MPA use in SLE. However, longitudinal prospective studies are needed to validate these findings and establish a roadmap to personalize dosing in SLE and LN, balancing safety and efficacy.

clinical variables. This will help optimize MPA dosing per individual patient factors to balance safety and efficacy.^{9,10}

TDM has been successful in renal transplant and lupus nephritis (LN) to guide safe and effective dosing of tacrolimus.^{11,12} A similar strategy could be leveraged for MPA in SLE, in which accurate estimates of MPA plasma concentration could guide optimal MPA dosing. However, TDM of MPA is not routinely used during SLE visits because (1) it is unclear how MPA levels should be routinely measured during visits (eg, area under the curve [AUC] vs trough concentration [C_{trough}] vs peak concentration), (2) thresholds or therapeutic ranges for MPA levels that are associated with better SLE outcomes versus lower adverse events are largely unknown, and (3) limited data are available regarding clinical variables that might influence MPA plasma concentrations. A recent meta-analysis shed new evidence to address existing gaps in TDM for MPA in patients with LN, but results were limited to renal outcomes.¹³ Given that MPA is a key medication for moderate–severe extrarenal SLE manifestations,¹⁴ similar data on TDM for extrarenal manifestations are needed. Objectives of this meta-analysis and systemic review were to (1) examine therapeutic thresholds for MPA levels that are associated with better outcomes and safety in all patients with SLE, and particularly those with extrarenal SLE manifestations, (2) identify clinical variables that affect MPA plasma concentrations to inform dosing and enhanced monitoring in those subgroups, and (3) clarify reliable methods that can be used to measure MPA levels in clinics.

MATERIALS AND METHODS

A comprehensive literature search was performed using Medical Subject Headings (MeSH) headings and keywords in the Medline, Embase, CINAHL, clinicaltrials.gov, and Web of Science databases with references reviewed. Results were limited to articles published between January 1, 1990, and April 30, 2024. The search included the MeSH and keywords “systemic lupus erythematosus” OR “lupus” OR “SLE” OR “lupus nephritis” OR “lupus vasculitis” OR “CNS lupus” OR “discoid lupus” OR “cutaneous lupus” AND “concentrations” OR “weight” OR “measures” OR “levels” OR “quantification” AND “mycophenolate” OR “mycophenol” OR “Cellcept” OR “MMF.” Additional studies were identified through checking the references of articles included for full text review using Medline, Web of Science, and CINAHL. Finally, we manually searched the references and citations in reviews, meta-analysis, expert opinions, and articles selected for full text review until we achieved saturation in results and no new studies were identified. We did not filter studies by language. Study screening was performed using Covidence, after which included studies were organized into an Excel sheet for data abstraction.

During the initial screening, two independent reviewers (DS and CS) screened the retrieved articles by reading the titles and abstracts to identify the studies that met the a priori list of inclusion criteria (Supplementary Table 1). Any discrepancy in the decision to include a study was resolved by an independent reviewer (SG). We included observational and interventional studies on human participants, measuring an association between MPA levels and clinical response (efficacy or safety) in patients with SLE with extrarenal or renal manifestations. Both mycophenolate mofetil (MMF) and MPA were considered. Case reports, expert opinions, narrative reviews, and conference abstracts were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines and checklist were used for the literature identification process¹⁵ (Supplementary Figure 1). A detailed protocol can be found on PROSPERO (CRD42024525955). Quality assessment of observational studies used the Newcastle–Ottawa scale (good: 7–9; fair: 4–6; poor: 0–3).¹⁶ The Cochrane Collaboration Risk Assessment tool was used for interventional studies.¹⁷ Certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.¹⁸ An overall score was generated using the standard guidelines on quality assessment from the Agency of Healthcare Research and Quality and the Cochrane handbook.¹⁹ Two reviewers (DS and CS) independently performed quality assessments, and discrepancies were resolved by the third reviewer (SG).

A data extraction form was developed and pilot tested by the lead investigator (SG). Data abstraction form was then used by two independent reviewers (DS and CS) to abstract an a priori list

of variables including patient demographics, disease characteristics, mycophenolate dose, concomitant SLE therapies, disease activity, response criteria, response rate, other clinical variables (eg, estimated glomerular filtration rate [eGFR], albumin), MPA levels and measurement method, adverse events (toxicity), and other relevant outcomes. When appropriate, authors of the studies were contacted for additional information. Disagreements were settled by two reviewers (ZQ and SG). Studies comparing clinical response in SLE manifestations with higher or therapeutic mycophenolate levels versus a comparator group were included in the meta-analysis. If no comparator group was present, then the findings were systematically reviewed, and narrative synthesis was performed. Given the study design and use of published de-identified aggregate data for pooled analysis, this study was exempted for a review by the University of Wisconsin, Madison, Institutional Review Board office.

Research question. Our research question, structured using the population, intervention, comparator, outcome (PI[E]CO) framework, focused on patients with SLE, including both extrarenal and renal manifestations. We examined whether higher or therapeutic MPA levels, compared with lower or subtherapeutic levels, were associated with clinical response, disease activity scores, adverse events, and variability in MPA concentrations.

Primary objective: identify therapeutic thresholds for MPA level monitoring in SLE. The primary objective of this systematic review and meta-analysis was to define therapeutic thresholds for MPA levels that are associated with safe and effective MPA use in patients with SLE. We examined the following:

1. associations between MPA levels and clinical response in patients with extrarenal SLE and in all patients with SLE (renal and extrarenal),
2. MPA levels and adverse event occurrence in patients with extrarenal SLE and in all patients with SLE including both extrarenal and renal SLE outcomes.

Secondary objectives: clinical variables that affect MPA levels. To understand how clinical variables impact MPA plasma concentrations and how MPA levels can be measured or performed during clinic visits, we did the following:

1. examined associations among clinical variables such as ethnicity, eGFR, albumin, MPA dose, other medicines, and MPA plasma concentrations,
2. summarized data on different methods that were used to measure MPA levels and the potential clinical utility of each method to inform TDM intervention for routine visits.

Statistical analysis. We examined the pooled odds of clinical response in patients with extrarenal SLE manifestations and overall SLE (renal and extrarenal) by high or therapeutic MPA levels versus low or subtherapeutic MPA levels. We defined clinical

response in patients with extrarenal SLE manifestations per primary studies: (1) active SLE or SLE flare defined as British Isles Lupus Assessment Group A or B score,²⁰ (2) active SLE defined as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),²¹ (3) markers of SLE disease activity (low complements and high double-stranded DNA antibody), and (4) SLE response defined by Lupus Low Disease Activity State.²² For LN, definitions included the following: (1) Kidney Disease Improving Global Outcomes complete or partial renal remission and renal or LN flare criteria,²³ and (2) American College of Rheumatology (ACR) complete or partial renal remission and renal or LN flare criteria.²⁴ Clinical response outcomes were analyzed separately. To define safe MPA levels, we compared MPA levels in those with versus without adverse events.

For all analysis, we used forest plots to calculate the pooled odds ratios (ORs; 95% confidence interval [CI]) of clinical response in higher or therapeutic mycophenolate levels versus lower or subtherapeutic levels. Additionally, pooling data from studies reporting differences in MPA levels by clinical response, we calculated the weighted mean difference (95% CIs) in MPA levels by clinical response. Finally, we also calculated weighted mean difference (95% CIs) in SLEDAI score by MPA levels when available. A narrative synthesis was performed for studies without a comparator group or without aggregate data by clinical response or MPA levels. All analyses were completed using a random-effects meta-analysis model and tau2 was calculated using the restricted maximum likelihood method from the metafor package in R (version 3.4.1).²⁵ This model and tau2 method account for between-study heterogeneity by estimating a variance component for the true effect size across studies, and it appropriately weights studies based on their sample size and design characteristics. Heterogeneity was assessed using I^2 . We performed sensitivity analysis stratified by study design to assess the robustness of our findings. Publication bias was evaluated by generating funnel plots. For each objective, certainty of evidence was rated using GRADE recommendations.

RESULTS

Study characteristics. Our literature search yielded 451 articles plus 9 additional articles through manual search. After removing duplicates, 459 articles were included in the initial screening (Supplementary Figure 1). Next, 42 studies met the priori inclusion criteria to determine eligibility for a full text review (Supplementary Table 1). Ultimately, 24 studies were selected for final data extraction and quality assessment,^{6,26–48} prospective cohort (n = 12),^{6,28,31,33,35–37,39,40,45,47} retrospective cohort (n = 10),^{26,27,29,30,32,34,42,43,46,48} clinical trial (n = 1),³⁸ and cross-sectional (n = 1).⁴¹ To avoid duplication, we did not include data abstracted from prior systematic reviews. Instead, we reviewed the original primary studies directly and extracted data from these articles.¹³ A total of 24 observational studies were single center, 9 were completed in Europe,^{6,26,30,31,34,36,39,44,47} 13 were

Table 1. Study and patient demographics*

Author (year)	Study population	LN and/or SLE	MPA level threshold	Outcomes observed by MPA levels	Bias
Neumann et al (2008) ³¹	N = 13; mean age 39.6 years; F = 92%; site: Austria	LN 38%; SLE 68%	C ₁₂ 3.5–4.5 mg/L	1. Active SLE defined as BILAG A/B ^a 2. AEs: infection, anemia, GI upset	NOS: good
Fujinaga et al (2008) ⁴⁰	N = 4; mean age 11.75 years; F = 75%; site: Japan	LN 100%	C ₀ 2–5 mcg/mL	1. LN flare defined as ↑ in UPCR to >1 or ↑ in Cr by 50%	NOS: poor
Roland et al (2009) ^{36b}	N = 20; mean age 41 ± 15 years; F = 65%; wt. 69.5 ± 13.4 kg; site: France	LN 50%; SLE 50%	AUC _{0–4} 28.4 ± 13.6 mg hr/L or C ₀ 3.1 ± 2.2 mg/L	1. SLE activity defined as ↓ complement and ↑ dsDNA levels 2. AEs: GI upset, neutropenia 3. Relevant clinical factors: albumin, wt., CrCl	NOS: poor
Zahr et al (2010) ^{6b}	N = 71; mean age 35 years, F = 86%; BMI 24.3; site: France	LN 84%; SLE 16%	AUC _{0–12} ≥ 35 µg h/mL	1. Active SLE defined as SLEDAI ≥6 and/or BILAG A/B ^a 2. AE: cytopenia 3. Relevant clinical factors: albumin, CrCl, MMF dose	NOS: good
Djabarouti et al (2010) ⁴⁷	N = 26; mean age 46 years; F = 61%; wt. 60 kg; 100% White; site: France	SLE 100%	C ₁₂ ≥ 3 mg/L	1. SLE flare defined as ↑ in SLEDAI by at least three points in six months 2. Relevant clinical factors: albumin, GFR, steroids	NOS: good
Lertdumrongluk et al (2010) ^{35b}	N = 18; mean age 33 years; F = 89%; BMI 22.2; site: Thailand	LN 100%	AUC _{0–12} > 45 mg hr/L	1. LN response per ACR PR definition ^c 2. AEs: GI upset, cytopenia, infection	NOS: good
Sagcal-Gironella et al (2011) ^{33b}	N = 19; mean age 16.9 years; F = 95%; wt. 66.6 kg; AA = 58%; site: United States	LN 84%; SLE 16%	AUC _{0–12} ≥ 30 mg hr/L	1. SLE disease activity defined as BILAG score reduction ^d	NOS: fair
Daleboudt et al (2012) ^{34b}	N = 16; mean age 33.2 ± 12.1 years; F = 94%; wt. 67 ± 11.5 kg; 75% White; site: the Netherlands	LN 100%	AUC _{0–12} 60–90 mg hr/L	1. LN remission per KDIGO guidelines ^e 2. AEs: GI upset, infections	NOS: fair
Kittanamongkolchai et al (2013) ^{38b}	N = 19; mean age 30.5 years; F = 95%; BMI 21.2; 100% Asian; site: Thailand	LN 100%	C ₁ >13 mg/L or AUC _{0–12} > 45 mg hr/L	1. LN response per ACR definition ^c 2. AEs: GI upset, infection	Cochrane: low
Woillard et al (2014) ³⁰	N = 36; mean age 12.0 years; F = 72%; BMI 20.72; site: France	SLE 100%	AUC _{0–12} > 44 mg l ⁻¹ hours	1. Active SLE defined as SLEDAI ≥6 2. Relevant clinical factor: albumin	NOS: poor
Streicher et al (2014) ³⁹	N = 23; mean age 38 years; F = 78%; site: France	SLE 100%	C ₀ ≥ 2.5–3 mg l ⁻¹	1. SLE flare defined as ↑ in SLEDAI by at least three points in 12 months 2. AE: GI upset	NOS: good
Alexander et al (2014) ^{37b}	N = 34; mean age 25 vs 31.1 years; F = 100% vs 84%; 33.5% Asian; site: India	LN 100%	AUC _{0–12} ≥ 30 mg hr/L	1. LN remission per CR KDIGO guidelines ^d 2. AEs: infection, cytopenia 3. Clinical factors: albumin, wt.	NOS: good
Zabotti et al (2014) ^{44b}	N = 5; mean age 34.2 years; F = 80%; site: Italy	LN 100%	AUC _{0–12} 45–60 mg hr/L	1. LN remission per KDIGO guidelines ^e 2. AEs: GI upset, cytopenia	NOS: fair
Abd Rahman et al (2015) ^{45b}	N = 25; median age 32.6 years; F = 80%; wt. 61.1 kg; site: Malaysia	LN 100%	AUC _{0–12} > 30 mg ⁻¹	1. LN response per ACR PR definition ^c 2. AEs: GI upset, infection, cytopenia	NOS: good
Hui-Yuen et al (2016) ^{29b}		LN 100%	G ₆ 35–100 µg/mL or MPA C ₆ 1–5 µg/mL	1. LN remission at three months defined as proteinuria <500 mg/24 hr	NOS: good

(Continued)

Table 1. (Cont'd)

Author (year)	Study population	LN and/or SLE	MPA level threshold	Outcomes observed by MPA levels	Bias
	N = 17; mean age pediatric; F = 63%; 47.1% Black; site: United States				
Yap et al (2020) ^{28b}	N = 88; mean age 43.8 years; F = 88%; 100% Asian; site: China	LN 100%	$C_{12} > 1.5$ mg/L	1. LN flare defined as $\uparrow$ in proteinuria ≥ 1 g/day and/or $\uparrow$ in Cr by $\geq 15\%$ 2. AEs: infections, cytopenia	NOS: good
Katsuno et al (2018) ^{32b}	N = 20; mean age 39.5 years; F = 90%; BMI 19.6; 100% Asian; site: Japan	LN 100%	N/A	1. LN remission per CR KDIGO guidelines ^e 2. AE: infections	NOS: good
Godron-Dubrasquet et al (2020) ^{26b}	N = 27; mean age 12.4 years; F = 89%; site: France	LN 100%	$AUC_{0-3} > 45$ mg hr/L	1. LN response per KDIGO guidelines ^e 2. AEs: GI upset, infections, cytopenia 3. clinical factors: albumin, wt.	NOS: good
Chen et al (2020) ⁴³	N = 67; mean age 12–13 years; F = 96% vs 76%; wt. 45 years; site: China	SLE 100%	$AUC_{0-12} > 50$ μ g hr/mL; $C_{trough} > 1.7$ μ g/mL	1. SLE activity defined as SLEDAI ≥ 6 2. Relevant clinical factors: albumin, steroids	NOS: good
Ye et al (2021) ²⁷	N = 107; mean age 133.83 months; F = 76%; BMI 20.78; site: China	LN 81%; SLE 18%	AUC_{0-24} 100.39 mg hr/L or AUC_{0-12} 50.20 mg hr/L	1. SLE activity measured per SLEDAI score 2. Correlation of SLE comorbidities (AKI, PNA, DM) by MPA level	NOS: fair
Abe et al (2021) ⁴⁸	N = 119; mean age 38 years; F = 85%; wt. 55 kg; 100% Asian; site: Japan	LN 59%; SLE 41%	N/A	1. SLE response defined as LLDAS ^f 2. AE: GI upset, infection, cytopenia	NOS: good
Chariyavilaskul et al (2022) ^{46b}	N = 19; median age 29 years; F = 100%; site: Thailand	LN 100%	$C_{0.5} \geq 2.03$ μ g/mL or $AUC_{0-12} \geq 45$ μ g hr/mL	1. LN response per KDIGO guidelines ^e 2. Correlation b/w MPA AUC and trough levels 3. Relevant clinical factor: albumin	NOS: good
Navamani et al (2022)	N = 25; mean age 15 years; F = 80%; wt. 48.6 kg; 100% Asian; site: India	LN 100%	N/A	1. Active SLE defined by SLEDAI ≥ 6 2. Relevant clinical factor: albumin	NOS: good
Mizaki et al (2023) ⁴²	N = 34; mean age 39 years; F = 82%; wt. 54.7 kg; 100% Asian; site: Japan	LN 100%	AUC_{0-12} 30–45 μ g hr/mL; $C_{max} < 24.4$ μ g/mL	1. No clinical outcomes reported 2. AEs: GI upset, infection	NOS: good

* AA, African American; ACR, American College of Rheumatology; AE, adverse event; AKI, acute kidney injury; AUC_{0-4} , area under the curve at zero to four hours; BILAG, British Isles Lupus Assessment Group; BMI, body mass index; b/w, between; C_{12} , concentration at 12 hours; C_{max} , maximum mycophenolic acid concentration among serial measurements; CR, complete remission; Cr, creatinine; CrCl, creatinine clearance; DM, diabetes mellitus; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; G₆, mycophenolic acid glucuronide 6 hours levels; GI, gastrointestinal; KDIGO, Kidney Disease Improving Global Outcomes; LLDAS, Lupus Low Disease Activity State; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; N/A, not applicable; NOS, Newcastle–Ottawa scale; PNA, pneumonia; PR, partial remission; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; UPCR, urine protein Cr ratio; wt., weight.

^a BILAG A/B: severe to moderate disease activity in at least one organ system.

^b These studies were included in the Wuttiputhanun et al¹³ meta-analysis.

^c ACR CR: normal or $\leq 25\%$ decline of GFR from baseline; UPCR < 0.2 ; inactive urinary sediment. PR: normal or increased eGFR by 25% if the baseline was abnormal; 50% reduction of 24-hour urine protein < 2 g/day; inactive urinary sediment.

^d Reduction in mean time adjusted BILAG score (in percent) = (MTA-BILAGPost-MMF/MTA-BILAGPre-MMF) $\times$ 100%. Pre-MMF was measured up to six months before initiation of MMF; Post-MMF was measured starting two weeks after initiation of MMF.

^e KDIGO CR: proteinuria below 0.5 g/day and stable serum creatinine levels or less than 25% higher than at the start of treatment; PR: more than 50% reduction in proteinuria and no increase in serum creatinine levels; flare: not reaching the criteria for partial response.

^f LLDAS: SLEDAI ≤ 4 , no high steroid use, no major organ involvement, stable or improving clinical condition, absence of flare or new symptoms.

completed in Asia,^{27–29,32,33,35,37,38,40–43,45,46,48} and all were conducted after 2008 (Table 1). The overall Newcastle–Ottawa scale for risk of bias assessment showed 16 “good,”^{6,26,28,29,31,32,35,37–39,41–43,45–48} 4 “fair,”^{27,33,34,44} and 3 “poor”^{30,36,40} (Table 1).

Study population and disease characteristics. Patient demographics per individual studies are summarized in Table 1. Approximately 940 patients with SLE were included. The mean age across studies ranged from 11.7 years (pediatric cohort) to 47 years (adult cohort). The proportion of female participants ranged from 61% to 100%. Among included studies, extrarenal SLE outcomes were assessed in 11 studies^{6,27,30,31,33,36,39,41,43,47,48} (including 1 study that used serological parameters to define active SLE³⁶), whereas 13 studies examined renal outcomes.^{26,28,29,32,34,35,37,38,40,42,44–46}

Association between MPA levels and extrarenal SLE outcomes. A total of 10 studies examined association between MPA levels and extrarenal SLE outcomes.^{6,27,30,31,33,36,39,43,47,48} We performed three different pooled analyses (Table 2). First, we calculated OR (95% CI) of extrarenal SLE response by higher or therapeutic MPA levels including data from four studies (Figure 1).^{6,30,31,43} This analysis showed 15-fold higher pooled odds of response in groups with higher or therapeutic MPA levels (pooled OR 14.91, 95% CI 4.74–46.89; $P < 0.0001$; $I^2 = 61\%$; Figure 1). Next, we calculated weighted mean difference (95% CI) in MPA levels by SLE response using data from six studies (Figure 2).^{6,27,36,39,43,47} We found that MPA levels were higher in responders’ versus nonresponders’ with a weighted mean difference of 38.79 units (95% CI 15.05–62.53); $P = 0.014$; $I^2 = 91\%$; Figure 2). Finally, we calculated the weighted mean difference in SLE disease activity scores by higher or therapeutic MPA levels, including data from four studies that used the same SLEDAI.^{6,33,43,48} In this analysis, SLEDAI score was seven points lower in groups with higher or therapeutic MPA levels (weighted mean difference 6.87, 95% CI 2.74–19.99; $P = 0.0011$; $I^2 = 92\%$; Figure 3). Certainty of evidence was rated as very low for extrarenal outcomes by GRADE, primarily due to imprecision and study limitations. One study, not included in the meta-analysis, noted a significant difference in the mean MPA AUC at 0 to 12 hours (AUC_{0-12}) levels between active versus inactive pediatric patients with SLE (69 vs 38 $\mu\text{g h/mL}$; $P = 0.003$).⁴¹

Association between MPA levels and overall (extrarenal and renal) SLE outcomes. A total of 15 studies examined the association between MPA levels and overall SLE outcomes (renal and extrarenal; Table 2).^{6,26,27,30–32,34–36,39,41,43,45–47} We performed two pooled analyses. The first analysis showed a weight mean difference of 32 in MPA levels in responders compared to nonresponders (95% CI 17.35–45.67; $P \leq 0.0001$; $I^2 = 81\%$; Supplementary Figure 2).^{6,26,27,32,34–36,39,41,43,45,47} The second analysis

estimated 12.2-fold higher odds of overall SLE response (renal response and extrarenal response) by higher or therapeutic MPA levels including data from seven studies (95% CI 5.44–27.35; $P < 0.0001$; $I^2 = 41\%$; Supplementary Figure 3).^{6,26,30,31,34,43,46} Certainty of evidence was rated as very low for overall SLE outcomes by GRADE, primarily due to imprecision and study limitations. Narrative synthesis of one study revealed that MPA C_{trough} (concentration at zero hours [C_0]) between 2 and 5 $\mu\text{g/mL}$ were not associated with reduced LN flare frequency over 6 to 41 months.⁴⁰

Association between MPA levels and adverse events. Three studies examined associations between MPA levels and adverse events in patients with extrarenal SLE (Table 2).^{6,31,36} Our pooled analysis did not demonstrate a statistically significant increase in toxicity for threshold of 60 mg hr/L AUC_{0-12} and ≥ 3 mg/L MPA C_{trough} (pooled OR 1.16, 95% CI 0.45–2.99; $P = 0.77$; $I^2 = 0\%$; Figure 4). Certainty of evidence was rated as very low for adverse events by GRADE, primarily due to imprecision and study limitations. Narrative synthesis of data revealed that the most frequently cited adverse events were gastrointestinal symptoms, followed by cytopenia and infections. Five studies reported no associations between MPA levels and adverse events.^{6,34,35,37,40} One noted higher median MPA maximum MPA concentration among serial measurements (C_{max}) and AUC_{0-12} levels in patients experiencing gastrointestinal side effects (median MPA C_{max} in patients with vs without adverse events 26.3 vs 12.3 $\mu\text{g/mL}$) versus (median MPA AUC_{0-12} in those with vs without adverse events 63.4 vs 45.3 $\mu\text{g h/mL}$).⁴² Another study reported that 37.5% of patients developed mild adverse events at a range of MPA AUC_{0-12} 60 to 90 mg hr/L.³⁴ Meanwhile, a study including patients from Southeast Asia noted a significant correlation between cytopenia and higher MPA levels (median AUC_{0-12} 37.8 mg L^{-1} ; $P = 0.038$).⁴⁵

Sensitivity analysis and publication bias. In sensitivity analyses restricted to prospective or retrospective cohorts, therapeutic MPA levels remained consistently associated with greater odds of clinical response, supporting the robustness of our findings. Visual inspection of funnel plots (Supplementary Figures 4–9) suggests possible publication bias across analyses.

Association between MPA levels and clinical variables. Four examined clinical variables that might affect MPA levels included serum albumin ($n = 9$), weight ($n = 3$), eGFR ($n = 3$), and concomitant steroid use ($n = 2$; Tables 1 and 2). A linear correlation between MPA levels and serum albumin was noted in four studies; two studies reported a weak correlation ($R^2 = 0.22$ and $R^2 = 0.28$; $P = 0.017$ and 0.002); five studies noted no correlation between albumin and MPA levels.^{6,26,30,36,37,41,43,46,47} Additionally, MPA levels did not correlate with weight in two studies (one study observed a weak linear correlation between MPA levels and dose per body weight, $R^2 = 0.129$; $P = 0.037$).^{26,36,37} One study found a

Table 2. Clinical outcomes in pts. w/ SLE w/ extrarenal and renal manifestations by MPA levels*

Author (year)	MMF dose	MPA level target	Outcomes	Conclusion
Djavarouti et al (2010) ^{47a}	2 g/d	$C_{12} \geq 3$ mg/L	- Median MPA levels in pts. w/ SLE w/ flare vs no flare (1.5 vs 3.7); $P = 0.008$ - MPA $C_{12} \geq 3$ mg/L has 92% NPV for SLE flare - Albumin, GFR, and steroids do not correlate w/ MPA levels	Target MPA $C_{12} \geq 3$ mg/L is associated w/ a 92% NPV for SLE flare
Woillard et al (2014) ^{30a}	728 mg/d	$AUC_{0-12} > 44$ mg l ⁻¹ h	21-fold ↑ odds of active SLE w/ MPA level < 44 mg l⁻¹ (95% CI 2.3–196.1; $P = 0.007$) - Albumin does not correlate w/ MPA levels	MPA $AUC_{0-12} > 44$ mg l ⁻¹ h is associated w/ 21-fold lower odds of SLEDAI < 6
Chen et al (2020) ^{43a}	20–40 mg/kg BID	$AUC_{0-12} > 50$ µg h/mL or $C_{trough} > 1.7$ µg/mL	- Mean MPA AUC_{0-12} in pts. w/ active vs inactive SLE (32.4 ± 14.8 vs 55.7 ± 31.1); $P < 0.0001$ - MPA C_{trough} levels higher by 1.2 µg/mL in inactive SLE ($P < 0.0001$) - Significant correlation b/w MPA levels and albumin; steroids	Better SLEDAI w/ target MPA $AUC_{0-12} > 50$ µg h/mL or $C_{trough} > 1.7$ µg/mL
Neumann et al (2008) ^{31a}	1 g BID	C_{12} 3.5–4.5 mg/L	- At MPA levels < 3 mg/L, 29% of samples were from pts. w/ active SLE - All pts. maintained remission w/ MPA level ≥ 3.5 mg/L - Mild AEs in 31% of pts. w/ MPA levels ≥ 4.5 mg/L	MPA C_{12} levels b/w 3.5–4.5 mg/L reduce disease activity and AEs
Sagcal-Gironella et al (2011) ^{33a}	1,973 mg/d	$AUC_{0-12} \geq 30$ mg hr/L	pts. w/ MPA level ≥ 30 mg hr/L had greater percent reduction (36%) in BILAG score; $P = 0.002$	Target MPA $AUC_{0-12} \geq 30$ mg hr/L linked w/ ↑ SLE disease control
Navamani et al (2022) ^{49a}	600 mg/m ²	N/A	- Mean MPA levels in pts. w/ active vs inactive SLE (38.46 ± 14.3 vs 69 ± 19.24); $P = 0.003$ - Albumin does not correlate w/ MPA levels	TDM of MPA AUC_{0-12} may help ↑ SLE disease control
Ye et al (2021) ^{27a}	1,000 mg/d	AUC_{0-12} 50.20 mg hr/L	- Mean MPA level in pts. w/ SLE comorbidities vs not (73.63 ± 41.54 vs 100.4 ± 46.4); $P < 0.001$ ↑ MPA level is associated w/ ↓ risk of DM, AKI, PNA; OR 0.991 (95% CI 0.982–0.999); $P = 0.046$	Target MPA AUC_{0-12} 50.20 mg hr/L ↓ risk of SLE comorbidities (DM, AKI, PNA)
Abe et al (2021) ^{48a}	1.5–2 g/d	N/A	3 of 11 pts. achieved LLDAS w/ MPA C_{trough} 8.3, 6.6, 3.5 µg/mL - LLDAS achievement rate was ↓ in pts. w/ AEs vs no AEs (35% vs 65%; $P = 0.009$)	↑ MPA C_{trough} levels increases LLDAS but increases AE risk
Streicher et al (2014) ^{39a}	2 g/d	$C_0 \geq 2.5$ –3 mg l ⁻¹	- Median MPA levels in pts. w/ SLE flare vs pts. w/o flare (1.6 vs 2.95); $P = 0.048$ - MPA $C_0 \leq 3$ has 80% NPV for SLE flare and did not increase AE risk	Target MPA $C_0 \geq 2.5$ –3 mg l ⁻¹ could reduce SLE flares
Zahr et al (2010) ^{6a}	1,846 mg/d	$AUC_{0-12} \geq 35$ µg h/mL	- Mean MPA level in pts. w/ active vs inactive SLE (26.8 ± 13.6 vs 46.5 ± 16.3); $P < 0.0001$ - MPA AUC_{0-12} correlates w/ lower SLEDAI ($r = -0.64$; $P < 0.0001$) - MPA AUC_{0-12} is associated w/ SLEDAI (OR 0.89, 95% CI 0.83–0.96) - No correlation b/w MPA levels and AEs - Multivariate analysis revealed significant correlation b/w MPA level and serum albumin, CrCl	Target MPA $AUC_{0-12} \geq 35$ µg h/mL is associated w/ ↑ SLE disease control w/o ↑ in AEs
Roland et al (2009) ^{36b}	1,600 mg/d	AUC_{0-4} 28.4 ± 13.6 mg hr/L or C_0 1–5 mg/L	MPA AUC_{0-4} level in pts. w/ low vs normal C3 (26.6 ± 11.4 vs 29.0 ± 14.6); $P = 0.760$	MPA AUC_{0-4} or C_0 can be used for MPA TDM.

(Continued)

Table 2. (Cont'd)

Author (year)	MMF dose	MPA level target	Outcomes	Conclusion
Godron-Dubrasquet et al (2020) ^{36c}	1,190 mg/m ² /day	AUC ₀₋₃ > 45 mg hr/L	2. MPA AUC₀₋₄ level in pts. w/ low vs normal C4 (24.1 ± 8.2 vs 30.7 ± 5.6); $P = 0.362$ 3. MPA C₀ level in pts. w/ low vs normal C4 (1.7 ± 1.2 vs 3.8 ± 2.3); $P = 0.043$ 4. No significant correlation b/w MPA C₀ and C3, dsDNA 5. Mild AEs in three pts. w/ MPA level 17–30. 6. No significant correlation b/w MPA level and albumin, wt., CrCl	Target C ₀ 1–5 mg/L is linked w/ ↑ SLE disease control
Yap et al (2020) ^{38c}	1,047 mg/d	C ₁₂ > 1.5 mg/L	1. 3.6-fold ↑ odds of LN response in pts. w/ MPA level >45 (95% CI 2.4–9.5) 2. Higher MPA level in responders w/ LN by 20 mg hr/L; $P < 0.01$ 3. Mild AEs in 33% of pts. w/ median level 44 4. No significant correlation b/w MPA level and albumin, wt. 1. Lower MPA levels in pts. w/ LN flare by 1.1 mg/L; $P = 0.041$ 2. MPA levels in pts. w/ vs w/o infection (4.3 ± 2.6 vs 1.8 ± 1.2) 3. Mean MPA levels (2.9) in 10 pts. w/ anemia vs pts. w/o anemia (1.7 ± 1.1); $P = 0.004$	MPA-AUC ₀₋₃ >45 mg hr/L is linked w/ 3.6-fold ↑ odds of LN remission MPA C ₁₂ >1.5 mg/L ↓ LN flare but ↑ risk of infections and anemia
Hui-Yuen et al (2016) ^{29c}	600 mg/m ² BID	MPA C ₆ 1–5 µg/mL	1. Mean MPA C₆ level in responders vs nonresponders w/ LN (3.26 ± 2.02 vs 3.02 ± 1.76) 2. Mean MPA-G₆ level in responders vs nonresponders w/ LN (44.2 vs 29.88); $P = 0.5$	MPA C ₆ or G ₆ not associated w/ LN response
Katsuno et al (2018) ^{32c}	1,000 mg BID	N/A	1. Median MPA AUC₀₋₁₂ level in responders vs nonresponders w/ LN (52.6 vs 43.5); $P = 0.09$ 2. C₀ levels correlate w/ MPA AUC₀₋₁₂; $R = 0.73$ 3. Infection in five pts. w/ median MPA level 51.2; $P = 0.92$	TDM of MPA AUC ₀₋₁₂ or C ₀ may allow for ↑ LN disease control
Daleboudt et al (2013) ^{34c}	1.9 g/d	AUC ₀₋₁₂ 60–90 mg hr/L	1. When maintained at MPA levels 60–90, 69% of pts. had complete LN remission and 19% had partial remission 2. Mild AEs w/o significant correlation to MPA level in 37.5% of pts.	Therapeutic MPA levels: MPA AUC ₀₋₁₂ 60–90 mg hr/L
Alexander et al (2014) ^{37c}	1.5–2 g/d	AUC ₀₋₁₂ ≥ 30 mg hr/L	1. ↑ LN response w/ MPA level ≥30; $P = 0.057$ 2. AEs: infection (12%), cytopenia (6%) but no correlation w/ levels 3. Weak but significant linear correlation b/w MPA level albumin as well as wt. ($R^2 = 0.222$, $P = 0.017$; $R^2 = 0.129$, $P = 0.037$)	Target MPA AUC ₀₋₁₂ ≥30 mg hr/L promises ↑ LN response
Chariyavilaskul et al (2022) ^{46c}	1,440 mg/d	C _{0.5} ≥ 2.03 µg/mL or AUC ₀₋₁₂ ≥ 45 µg hr/mL	1. MPA AUC₀₋₁₂ ≥45 µg h/mL associated w/ better LN response 2. MPA C_{0.5} 2.03 µg/mL could be used as a surrogate for AUC₀₋₁₂ ≥45 µg h/mL (sensitivity = 85%; specificity = 88.2%) 3. Linear correlation b/w UPCR ($R^2 = 0.28$), serum albumin, and MPA levels ($R^2 = 0.019$)	MPA C _{0.5} ≥2.03 µg/mL could be a surrogate for AUC ₀₋₁₂ levels and improves renal response rate in LN
Kittanamongkolchai et al (2013) ^{38c}	1.5 g/d	C ₁ > 13 mg/L or AUC ₀₋₁₂ > 45 mg hr/L	1. 89% of pts. w/ LN achieved renal remission w/ MPA C₁ levels >13 mg/L maintained over 24 weeks	Maintaining MPA C ₁ levels >13 mg/L ensures LN

(Continued)

Table 2. (Cont'd)

Author (year)	MMF dose	MPA level target	Outcomes	Conclusion
Mizaki et al (2023) ^{42c}	1,500 mg/d	$C_{\max} < 24.36 \mu\text{g/mL}$ or $\text{AUC}_{0-12} 30-45 \mu\text{g h/mL}$	2. AEs: mild infection in four pts. w/ MPA C_1 levels 9–18 ($P = \text{NS}$) 1. No clinical outcomes reported 2. Median MPA $C_{\max}$ and MPA AUC_{0-12} in pts. w/ GI AEs (26.3 and 63.4) vs w/o GI AEs (12.3 and 45.3); $P < 0.05$	remission w/o risking AEs Maintain $C_{\max}$ levels $< 24.36 \mu\text{g/mL}$ to reduce AEs
Fujinaga et al (2008) ^{40c}	405 mg/m ² BID	C_0 2–5 mcg/mL	1. After maintaining MPA C_0 levels b/w 2–5 for 6–41 months, no LN flares or AE were observed	MPA C_0 levels lie w/in 2–5 mcg/mL $\uparrow$ safety & efficacy
Zabotti et al (2014) ^{44c}	3 g/d	$\text{AUC}_{0-12\text{h}} 45-60 \text{ mg hr/L}$	1. w/ maintaining MPA AUC_{0-12} b/w 45–60; 100% of pts. achieved LN response w/o flares 2. Two pts. had mild transient AEs	Therapeutic range for MPA AUC_{0-12} 45–60 mg hr/L
Lertdumrongluk et al (2010) ^{35c}	1,416 mg/d	$\text{AUC}_{0-12} > 45 \text{ mg hr/L}$	1. Mean MPA level in responders vs nonresponders w/ LN (65.98 ± 23.77 vs 32.08 ± 7.97); $P = 0.002$ 2. AEs did not correlate w/ MPA levels	Maintaining MPA $\text{AUC}_{0-12} > 45 \text{ mg hr/L}$ $\uparrow$ LN disease control
Abd Rahman et al (2015) ^{45c}	1,500 mg/d	$\text{AUC}_{0-12} > 30 \text{ mg l}^{-1}$	1. Median AUC_{0-12} level in responders vs nonresponders (23.2 vs 19.2); $P = 0.103$ 2. $C_{\max}$ in responders vs nonresponders w/ LN (11.9 vs 6.1); $P = 0.016$ 3. 44% of pts. had anemia w/ median AUC_{0-12} level 37.8 mg l^{-1} ; $P = 0.038$	MPA AUC_{0-12} levels $> 30 \text{ mg l}^{-1}$ increases renal response but risk cytopenia

* AE, adverse event; AKI, Acute Kidney Injury; AUC_{0-12} , area under the curve at 0 to 12 hours; BID, twice a day dosing; BILAG, British Isles Lupus Assessment Group; b/w, between; C_{12} , concentration at 12 hours; CI, confidence interval; $C_{\max}$, maximum mycophenolic acid concentration among serial measurements; CrCl, creatinine clearance; C_{rough} , trough concentration; DM, Diabetes Mellitus; dsDNA, double-stranded DNA; G_6 , mycophenolic Acid Glucuronide 6 hours levels; GFR, glomerular filtration rate; GI, gastrointestinal; LLDAS, Lupus Low Disease Activity State; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; N/A, not applicable; NPV, Negative Predictive Value 3; NS, not significant; OR, odds ratio; PNA, pneumonia; pt, patient; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TDM, therapeutic drug level monitoring; UPCR, urine protein creatinine ratio; w/ with; wt, weight; w/o, without.

^a Outcomes are per SLE outcomes analysis (SLEDAI, BILAG, and LLDAS).

^b Outcomes are per serology analysis.

^c Outcomes are per LN outcomes analysis (Kidney Disease Improving Global Outcomes and BILAG).

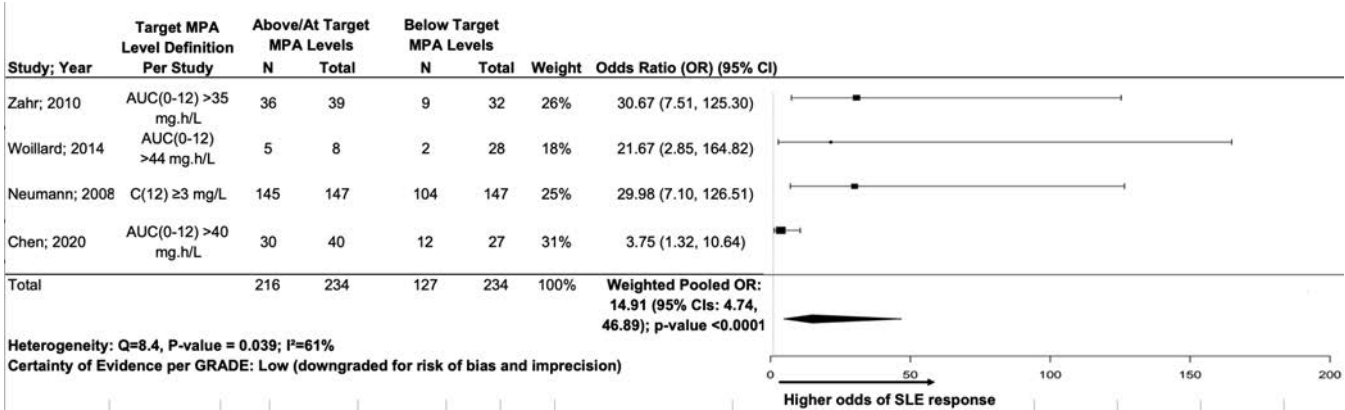


Figure 1. Forest plot showing the odds of clinical response in patients with systemic lupus erythematosus (SLE) with extrarenal manifestations by target mycophenolic acid (MPA) levels. AUC(0–12), area under the curve at 0 to 12 hours; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; OR, odds ratio.

significant association between MPA levels and prednisone use (strength of association not reported).⁴³ Direct correlation between MPA levels and adherence was not measured. One

study noted single-nucleotide polymorphism (SNP) rs2273697 A/G genotype was linked with lower MPA exposure, warranting higher MPA dosing.²⁸ One study reported a

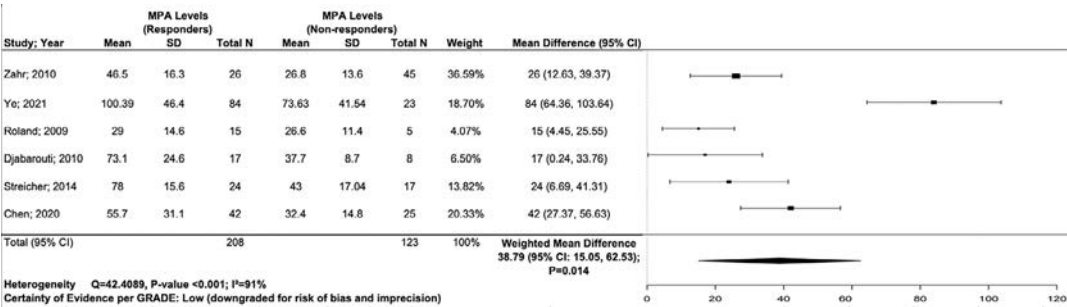


Figure 2. Forest plot showing the weighted mean difference in mycophenolic acid (MPA) levels by clinical response in patients with systemic lupus erythematosus with extrarenal manifestations. CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

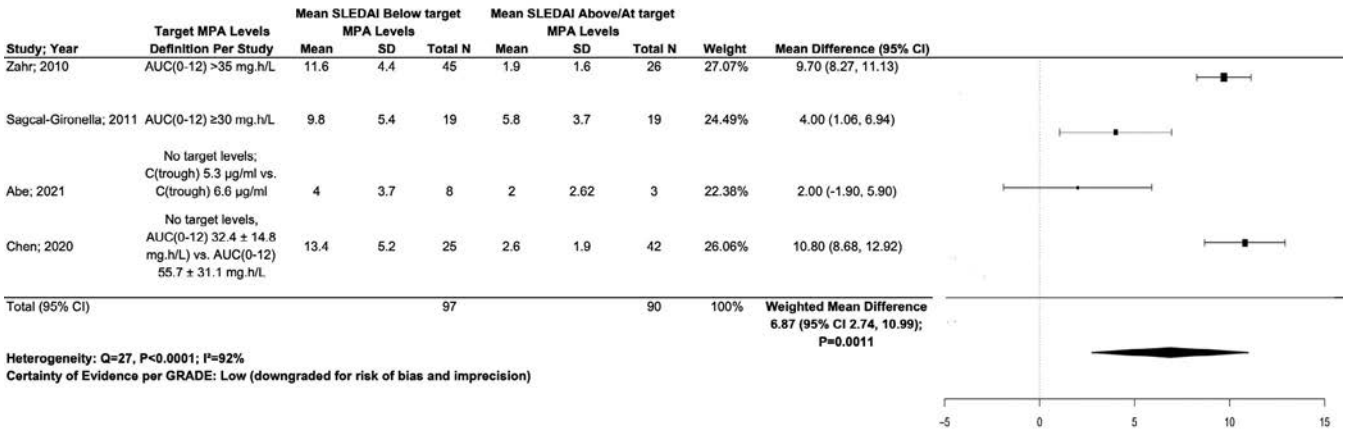


Figure 3. Forest plot showing the weighted mean difference in systemic lupus erythematosus (SLE) disease activity by higher or therapeutic mycophenolic acid (MPA) levels in patients with SLE with extrarenal manifestations. AUC(0–12), area under the curve at 0 to 12 hours; CI, confidence interval; C(trough), trough concentration; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

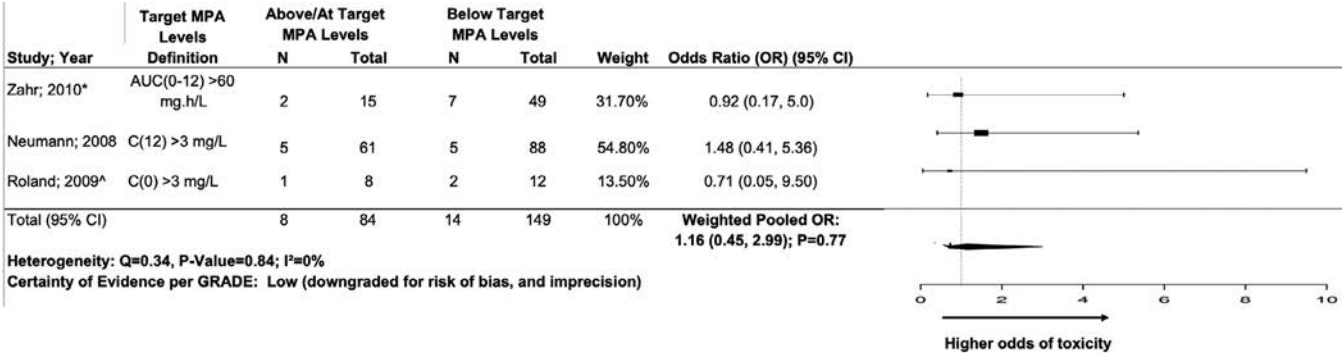


Figure 4. Forest plot showing odds of adverse events/toxicity in patients with systemic lupus erythematosus with extrarenal manifestations by target or higher mycophenolic acid (MPA) levels. AUC(0–12), area under the curve at 0 to 12 hours; C(12), concentration at 12 hours; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; OR, odds ratio. *Zahr et al⁶ excludes patients with low levels and cytopenia due to active lupus; ^C(0) was used for safety analysis given strong R association between C(0) and AUC(0–4) per study.

need to increase the MMF dose from 1 to 2 g/day to achieve a target MPA AUC_{0–12} range of 30 to 60 mg hr/L.³⁷

Measuring MPA levels and therapeutic threshold or therapeutic range for MPA levels. MPA levels were measured using liquid chromatography in 9 studies,^{6,26,30,33,34,37,41,44,46} both mass spectrometry and liquid chromatography in 4 studies,^{32,39,45,47} and enzyme assays in 10 studies,^{27,28,31,35,36,38,40,42,43,48} and 1 study did not specify their measurement technique.²⁹ MPA levels were measured in plasma in 18 studies^{26,27,29–35,38–41,43–47} and serum in 6 studies.^{6,28,36,37,42,48}

Studies used different methods of measuring MPA. To elaborate, AUC MPA levels estimated MPA levels over a time period to obtain a dose: time AUC MPA concentration (AUC time period in hours) was the most common measurement method. A total of 13 studies reported AUC_{0–12}, 1 study reported AUC_{0–24}, whereas one study measured AUC_{0–4} and AUC_{0–3}.^{6,26,27,30,33–38,42–46} Two studies reported and used the C_{max}.^{42,45} Other studies measured MPA predose concentration (C₀).^{36,39,40} Time-dependent assays measured a single MPA level at 1 hour after MPA dose (C₁), 0.5 hours after the last dose (C_{0.5}), and 6 and 12 hours from the last dose (C₆ and C₁₂).^{28,29,31,38,46,47}

Therapeutic thresholds or therapeutic ranges for MPA levels varied across studies. The most used therapeutic threshold was MPA AUC_{0–12} >30 mg hr/L,^{33,37} and a reference range of 30 to 60 mg hr/L was commonly used. Two studies used a therapeutic range of MPA AUC_{0–12} 45 to 60 mg hr/L⁴² and 60 to 90 mg hr/L.³⁴ Studies reporting a single MPA predose concentration (C₁₂) commonly used therapeutic ranges between 1 and 2.5 mg/L (Tables 1 and 2). Therapeutic ranges and thresholds for MPA AUC_{0–12} and C_{0.5–1} levels are shown in Tables 1 and 2.

DISCUSSION

MPA is a key therapeutic in the SLE treatment armamentarium, yet clinical effectiveness and safety of MPA are heterogeneous due

to variability in absorption, metabolism, drug interactions, and other clinical factors.⁸ TDM of MPA could pose a solution for this conundrum by guiding safe and effective dosing of MPA. Our study emphasizes the clinical significance of monitoring MPA levels in all patients with SLE, including extrarenal and renal manifestations. This meta-analysis noted 12-fold higher odds of overall SLE response in patients with an MPA level cutoff ≥30 to 35 mg hr/L AUC_{0–12} or ≥1.5 mg/L C_{trough}. In patients with extrarenal manifestations, this MPA threshold was associated with significantly higher 15-fold odds of clinical response as well as a seven-point reduction in SLEDAI score (95% CI 2.7–11). Additionally, we found MPA levels were 32 units higher (95% CI 17.35–45.67) in overall responders and 39 units (95% CI 15.05–62.53) higher in patients with extrarenal SLE manifestations. Our pooled analysis of adverse events did not demonstrate a statistically significant increase in toxicity at higher exposures (MPA AUC_{0–12} 60 mg hr/L and C_{trough} ≥2.5–3 mg/L). Synthesizing these findings, the evidence supports maintaining MPA levels ≥30–35 mg hr/L AUC_{0–12} or 1.5–2.5 mg/L C₁₂ trough is associated with better clinical response. Although data suggest that adverse events may emerge at MPA levels beyond 60 mg hr/L MPA AUC_{0–12} and ≥2.5 to 3 mg/L C_{trough}. The findings of this meta-analysis and systematic review underscore the importance of TDM for MPA during routine SLE visits including both renal and extrarenal manifestations and could guide MPA dosing, balancing safety versus efficacy in SLE. Additionally, higher-quality longitudinal studies are needed to confirm these findings and inform a workflow for clinical adoption and to guide MPA dosing in SLE.

The 2023 update from EULAR¹⁴ recommends MPA as one of the key therapeutics for management of SLE. Specifically, in extrarenal SLE, the European Renal Association guidelines recommended MPA as first-line therapy for moderately active systemic lupus (SLEDAI > 6).¹⁴ Additionally, the 2024 ACR guidelines recommends mycophenolate as the preferred backbone therapy in the triple-regimen recommendation for patients with class III/IV LN with significant proteinuria.⁵⁰ However, there is variability in plasma concentrations of MPA, resulting in

heterogeneity in clinical response. Moreover, arbitrarily increasing MPA doses can result in toxicity, particularly in groups who are at higher risk of side effects from MPA. Thus, titration of MPA dose based on individual patient factors is needed to balance efficacy and safety in clinical practice.^{8,36,37} TDM can streamline titration of MPA dose, which is widely used in transplant and allows for personalizing MPA dose and reduces the risk of treatment failure by 39%.⁵¹ Likewise, in LN, a recent meta-analysis reported 3.2-fold higher odds (95% CI 1.2–8.4) of renal response with therapeutic MPA levels (AUC_{0-12} 30–60 mg hr/L).¹³ Similar data are lacking for extrarenal manifestations of SLE—more than 50% of patients with SLE. In the absence of such data, patients with extrarenal SLE manifestations often receive suboptimal dosing, thus increasing the risk of flares or adverse events. Supporting this, Woillard et al and Zahr et al both reported low or subtherapeutic MPA plasma levels with standard or fixed MPA dosing resulting in higher lupus flares or active lupus (SLEDAI > 6).^{6,30} Our meta-analysis highlights the potential impact of TDM in SLE by reporting 15-fold higher pooled odds (95% CI 4.74–46.89) of clinical response with higher MPA levels. Across individual studies, efficacy was most consistently observed at exposures above AUC_{0-12} >30 to 35 mg hr/L or MPA C_{12} trough >1.5 mg/L, particularly in patients with SLE with extrarenal manifestations. Higher MPA exposures were also associated with a seven-point reduction in SLE disease activity (95% CI 2.74–19.99); extrarenal responders had 39 mg hr/L higher MPA levels compared to non-responders (95% CI 15.05–62.53).

Upon summarizing evidence on toxicity, we noted no significant associations between higher cutoff/threshold of 60 mg hr/L AUC_{0-12} and ≥ 3 mg/L MPA C_{trough} (pooled OR 1.16, 95% CI 0.45–2.99; $P = 0.77$). Similar findings were noted in a recent study in which the weight mean difference (5.1, 95% CI –5.2 to 15.4) in MPA levels did not differ in patients with versus without adverse events.¹³ Although pooled evidence revealed no statistically significant associations, two studies reported an inverse relationship with cytopenia (anemia) and infections with higher median MPA AUC_{0-12} levels (37.8 mg l^{-1})⁴⁵ and higher MPA C_{12} levels (4.3 mg/L).²⁸ Side effects or adverse events reported in both studies were mild and reversible. No life-threatening events were reported with higher MPA levels. These studies also noted that adverse events could depend on clinical factors such as prednisone dose, Ig level, or variability in drug metabolism due to genotypic variations (SNP rs2273697 A/G genotype).²⁸ Certainty was rated as low across studies. These ratings highlight that although associations were consistent, the strength of evidence was limited and underscored a need for higher-quality longitudinal studies.

A final question that needs to be answered to empower clinicians to use MPA level monitoring in SLE visits is how and when to measure MPA levels. Target levels and reporting methods varied among the studies; however, MPA AUC_{0-12} was the most frequently used, and a therapeutic threshold of >30 mg hr/L was recommended by several studies for clinical use. One study noted

better response rates with MPA AUC_{0-12} levels in the 60 to 90 mg hr/L range.³⁴ The feasibility of using MPA AUC_{0-12} in clinics is questionable given that calculating an AUC_{0-12} requires multiple samples at different intervals following MPA administration. Alternatively, a 12-hour trough MPA level might be easier to reproduce and was the second most common method used.^{36,39,40,43} It was noted that maintaining MPA C_{12} levels at or above 1.5 mg/L was associated with fewer flares and better clinical response. Future studies on the clinical significance and reliability of maintaining levels within the aforementioned therapeutic ranges are needed.

Despite strengths of this study including analyzing the use of TDM of MPA to improve SLE treatment efficacy and balance safety, particularly in patients with extrarenal manifestations, we acknowledge our limitations. First, most studies were conducted in Europe or Asia; only two studies were done in the United States.^{29,33} This could impact generalizability of the summarized evidence. Second, high heterogeneity (I^2 90%) was observed among studies. However, heterogeneity reduced after including only patients with extrarenal manifestations. To further address heterogeneity, we performed sensitivity analysis restricted to prospective or retrospective cohort studies. These confirmed that therapeutic MPA levels were consistently associated with greater odds of clinical response, supporting the robustness of our findings despite variation in study design. Third, most studies used the MPA AUC_{0-12} reporting method; however, real-world clinical feasibility could be limited. MPA C_{12} levels could be feasible, but only three studies measured it. Fourth, only a limited number of studies examined the longitudinal impact and feasibility of using MPA levels in clinics; thus, further data are needed on when and how frequently MPA levels should be monitored during SLE visits. Fifth, the absence of patient-reported outcomes measures in the included studies limits the ability to evaluate the patient perspective on treatment benefit. Finally, as reflected in our GRADE assessment, the certainty of evidence was very low across outcomes, further emphasizing the need for additional longitudinal studies.

In conclusion, in this systemic review and meta-analysis, high or therapeutic MPA levels were associated with 15-fold higher pooled odds of clinical response in patients with extrarenal SLE and 12-fold higher odds of overall response in extrarenal and renal outcomes. Additionally, a clinically significant seven-point reduction in SLE disease activity was noted with higher MPA levels. Across individual studies and pooled analysis, efficacy was most consistently observed at MPA AUC_{0-12} ≥ 30 –35 mg hr/L or C_{12} trough 1.5 to 2.5 mg/L. MPA AUC_{0-12} was a frequently used method; however, 12-hour trough MPA levels might be easier to adopt in nonresearch clinical settings. No statistically significant association between adverse events and higher thresholds was noted; however, several studies suggest that adverse events may emerge at exposures beyond 60 mg hr/L MPA AUC_{0-12} and ≥ 2.5 to 3 mg/L C_{trough} . Future research should

focus on defining a therapeutic range for MPA level that balances safety and efficacy and examining the longitudinal impact of TDM of MPA in SLE. These findings support the clinical utility of TDM to guide precise MPA dosing to enhance efficacy in all patients with SLE, including both extrarenal and renal manifestations. However, ideal testing method, timing of testing, cost-effectiveness, and how to incorporate discussions on TDM to enhance shared decision-making during SLE visits need to be further studied.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Garg confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements. All authors contributed to the investigation, formal analysis of the data, and writing, reviewing, and editing of the manuscript.

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Prevalence of Systemic Lupus Erythematosus in Australia, 2010–2022: A Population-Based Study Using Linked National Administrative Health Data

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Objective. Systemic lupus erythematosus (SLE) is a heterogenous inflammatory condition with widely varying global prevalence estimates. The frequency of SLE in the general population of Australia has been reported to be notably lower than contemporary estimates in countries such as the United States or United Kingdom, at 19 to 39 per 100,000 as opposed to 65 to 97 per 100,000. This study aimed to develop a national SLE cohort using linked administrative data sets and to estimate prevalence using this approach.

Methods. We developed an algorithm to identify SLE cases using the National Health Data Hub, a linked national administrative data asset, which includes data on medications dispensed and medical services subsidized under Australia's universal subsidized coverage schemes, hospital admissions, and deaths. These classification criteria were developed with an expert panel of rheumatologists. Individuals were classified as “certain,” “uncertain,” or “no SLE.” Cohort characteristics were described, and period prevalence (2010–2022) was calculated.

Results. A cohort of 26,788 individuals with SLE were identified, which comprised 16,294 certain cases and 10,494 uncertain cases. The period prevalence of SLE in Australia from 2010 to 2022 was 77 to 127 per 100,000 (certain cases or overall cases). Among the certain cases, just over half had received care for SLE only in an outpatient setting.

Conclusion. This is the first Australian SLE study using comprehensive linked administrative health data, and it identified higher prevalence than previously reported, more closely aligning with international estimates. This algorithm may serve as a foundation for future Australian and international studies seeking to identify SLE in administrative health data sets.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogenous systemic autoimmune rheumatic disease (SARD), with female predominance and a wide variety of manifestations. The underlying etiology is thought to include both genetic and environmental factors.¹

Tracking disease prevalence and regional variation can help uncover possible disease triggers and improve health equity by allowing service delivery to target areas with the most people affected. Given the increasing therapeutic options² and evidence for a “treat to target” approach, the identification of a national cohort is valuable to allow the study and benchmarking of health outcomes.

Supported in whole or in part by the National Health and Medical Research Council (NHMRC). Dr Roper's work was supported by an NHMRC postgraduate scholarship (2038603). Professors Nassar and Nikpour's work was supported by NHMRC Investigator Grants.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80026>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80026>.

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Submitted for publication November 11, 2025; accepted in revised form January 29, 2026.

SIGNIFICANCE & INNOVATIONS

- This article presents a novel electronic phenotyping algorithm for systemic lupus erythematosus (SLE) identification using administrative health data, applicable to settings where outpatient diagnostic codes are unavailable.
- Prevalence estimates identified using this cohort (77–127 per 100,000) were substantially higher than previously reported in Australia and comparable with international figures, suggesting previous under ascertainment.
- The resulting cohort, spanning hospital and non-hospital settings, enables research on the full spectrum of SLE severity and health care use.

Globally, there has been a broad range of prevalence estimates reported for SLE, from 5.05 to 241 per 100,000.^{3,4} This likely reflects true regional variation related to environmental and genetic factors, as well as variation in data sources, definitions, and methodology. As outlined in our recent systematic review,⁵ there are limited Australian data on SLE prevalence, with only four studies of SLE in adults eligible for inclusion in a meta-analysis. All of these were confined to northern Australia, with a specific research focus on identifying SLE among Aboriginal and Torres Strait Islander people. Furthermore, recruitment for most of these studies was from a single town or hospital, and many of these are two to three decades old. Meta-analysis of the existing data estimated the prevalence of SLE in Australia at 19 to 39 per 100,000 in non-Aboriginal Australians^{6–9} and 54 to 166 per 100,000 in Aboriginal and Torres Strait Islander people. In contrast, the overall prevalence in the United States has been recently estimated at 65 to 81 per 100,000¹⁰ and the United Kingdom at 97 to 107 per 100,000.^{11,12} Given its rarity, broad range of clinical manifestations, and spectrum of severity, as well as the diverse range of health care providers involved in diagnosis and management, high-quality prevalence estimates for SLE are difficult to obtain. Most prevalence studies rely on a regionally confined census because random sampling approaches require prohibitively large sample sizes.

Use of administrative health data for case identification provides an alternative approach.¹³ Administrative health data typically encompass information collected during health care services by government agencies for administrative and billing purposes. Examples include hospital admission data and birth and death registries.¹⁴ These data can be linked to create a comprehensive record of an individual's health service use. Linked, population-wide data sets offer a powerful tool for evaluating disease prevalence, patient characteristics, service use, and outcomes. Administrative data are widely used for disease identification, but SLE's clinical heterogeneity and varied management result in nonuniform health service use, which complicates case ascertainment. Furthermore, administrative health data

sources capture different types of information, with some more related to health service contacts rather than diagnostic information. Over a decade ago, a systematic review outlined these challenges,¹⁵ and refining identification methods remains an ongoing area of research.^{16–20} No comprehensive Australian algorithms exist; most studies rely on a single diagnosis (usually based on an *International Classification of Diseases [ICD]* code), which has known limitations.^{17,21}

Alternative cohort or registry data sources may provide complementary information to help ascertain cases and study patterns of care. In Australia, the Optimising Patient Outcomes in Australian Rheumatology (OPAL) data set provides a source of real-world data on patients.²² OPAL captures routine data from over 200 rheumatologists practicing in private and public settings.²² A 2023 OPAL study of 4,260 patients with SLE described medication use, rheumatologist visit frequency, and demographics.²² Although OPAL predominantly reflects private care, it remains a useful reference for understanding prescribing practices and frequency and timing of specialist visits. The aims of this study were to identify a national cohort of people with SLE using administrative health data, to describe cohort demographics and health care use, and to estimate the prevalence of SLE in Australia.

MATERIALS AND METHODS

Study population and design. This is a population-based observational, data linkage study to identify and follow-up with people diagnosed with or receiving health care for SLE in Australia from July 1, 2010, to June 30, 2022.

Data sources. This study used a national linked administrative health data platform, the National Health Data Hub (NHDH), consisting of 11 data sets that are probabilistically linked at the person level.²³ These data sets include information from national data collections and data collections from most Australian states and territories, including New South Wales (NSW), Victoria (VIC), Queensland (QLD), Tasmania (TAS), and South Australia (SA). All data are deidentified before researcher access, and the NHDH follows extensive data governance, privacy, and security protocols, and the consent requirement is waived.²³ Five of the 11 NHDH linked data sets were used in this study and are summarized below and described in detail in Supplementary Material 1:

1. The Medicare Benefits Schedule (MBS) data set (Australia's universal subsidized health care system), including type, date, and cost of service but not including test results.
2. The pharmaceutical benefits scheme (PBS) data set, which captures data on medicines dispensed under the national subsidy scheme and includes most prescription

medicines in routine clinical use in Australia. Unfortunately, belimumab has never been PBS-listed, and anifrolumab was listed only after the study period, so the use of these biologics is not captured.

3. The National Death Index (death data), which includes facts and causes of death from statutory death registrations.
4. Admitted patient care data drawn from the National Hospital Morbidity Database (hospital data).
5. The National non-Admitted Patient episode-level (NAP) data set, including records for public hospital patients attending outpatient clinics.

There is variation in data availability by state: hospital and NAP data collections did not include data from Western Australia (WA) or the Northern Territory (NT), which comprise 11% of the Australian population. Private hospital data for NSW, TAS, and SA were absent, and the NAP data collection was absent for SA. The impact of this on the overall cohort size was estimated to be small (~4%) because of the layered nature of the algorithm (Supplementary Materials 2 and 3).

Case identification. Individuals with SLE were identified using an algorithm detailing specific inclusion and exclusion criteria (Certain inclusion: two or more SLE hospital admissions and more SLE than non-SLE SARD admissions; or one SLE hospital admission plus a non-hospital SLE data point and more SLE than non-SLE SARD admissions; SLE recorded on death data plus a non-death SLE data point, or death before 2014; qualifying specialist visit patterns, medication exposure thresholds, and at least four dsDNA and complement tests. Uncertain inclusion: at least one SLE hospital admission and more SLE than non-SLE SARD admissions; SLE recorded on death data; and at least three relevant specialist or general physician visits, at least two dispensings of HCQ, azathioprine or mycophenolate, and at least three dsDNA and complement tests. Exclusion: non-SLE SARD listed as underlying cause of death where SLE was additional only; three or more dispensing of a non-SLE approved DMARD (i.e. TNFi); failure to meet the relevant visit, dispensing, MPR, pathology, or corroboration thresholds.), consisting of a combination of SLE-related hospitalizations, MBS claims, death records, and claims for dispensed medications (Figure 1 and detailed in Supplementary Material 4). The algorithm has two rule sets, classifying individuals as having “certain” or “uncertain” SLE, allowing the generation of upper and lower bound prevalence estimates. Sensitivity analyses tested the robustness of the algorithm by recalculating certain and uncertain SLE cohorts under alternative rule sets. Decisions that changed cohort size by more than 10% triggered a random review of 5% of affected records for adjudication of the rule based on clinician consultation (Supplementary Material 5). Table 1 illustrates the data items extracted from each

data set, whereas Figure 1 illustrates how these were combined to create the SLE identification algorithm.

Algorithm justification. Hospital data criteria were informed by previously validated ICD-based approaches for SLE identification,^{15,18,19,24,25} which demonstrate higher positive predictive value (PPV) with at least two SLE-coded hospital admissions. We therefore required either multiple SLE-coded episodes (hospital admissions) or a single SLE-coded episode and a supporting outpatient SLE-related claim or medication (eg, hydroxychloroquine) to meet our hospital criteria (Figure 1 and detailed in Supplementary Material 2). Death data criteria were based on ICD coded death certification (details in Supplementary Material 6). The Australian data sets that capture outpatient service use (MBS, NAP, and PBS) do not contain any diagnosis codes. We therefore used a pragmatic and innovative approach to identify individuals who had solely outpatient management of SLE (Figure 1), requiring them to meet criteria related to medication history, outpatient specialist visits, and pathology testing. These three criteria are outlined in Figure 1 and discussed below. These criteria were informed by real-world data from the OPAL data set on how a subset of Australian patients with SLE were treated²² and how each criteria was reviewed, refined, and approved by the five rheumatologist authors, who have practiced across multiple Australian states in the public and private sectors.

1. Medication history (Supplementary Material 7): Most patients use hydroxychloroquine, mycophenolate, or azathioprine during their SLE treatment.^{26,27} An individual was classified as “using” a medication if their medication possession ratio (MPR) was >0.8.^{28,29} Calculation of the MPR is described in Supplementary Material 7. OPAL data informed certain SLE usage durations,²² with the certain SLE cohort requiring more than 20 months use of hydroxychloroquine, more than 15 months of azathioprine, or more than 12 months of mycophenolate. To avoid bias toward highly adherent individuals (real-world data indicates that 51–90% of patients with SLE have an MPR >0.8),^{30,31} the uncertain SLE inclusion rule was less stringent, requiring two dispensings of hydroxychloroquine, mycophenolate, or azathioprine only. Individuals with more than three dispensings of biologic or targeted synthetic medications that have PBS indications restricted to non-SLE inflammatory conditions (ie, tumor necrosis factor [TNF] inhibitors or JAK inhibitors for rheumatoid arthritis or inflammatory bowel disease) were excluded. The threshold of three dispensings was selected based on clinical expert consensus that a short therapeutic trial with a non-SLE medication may occur when there is initial diagnostic uncertainty. Glucocorticoid use was not required for enrollment because it is not specific for SLE.

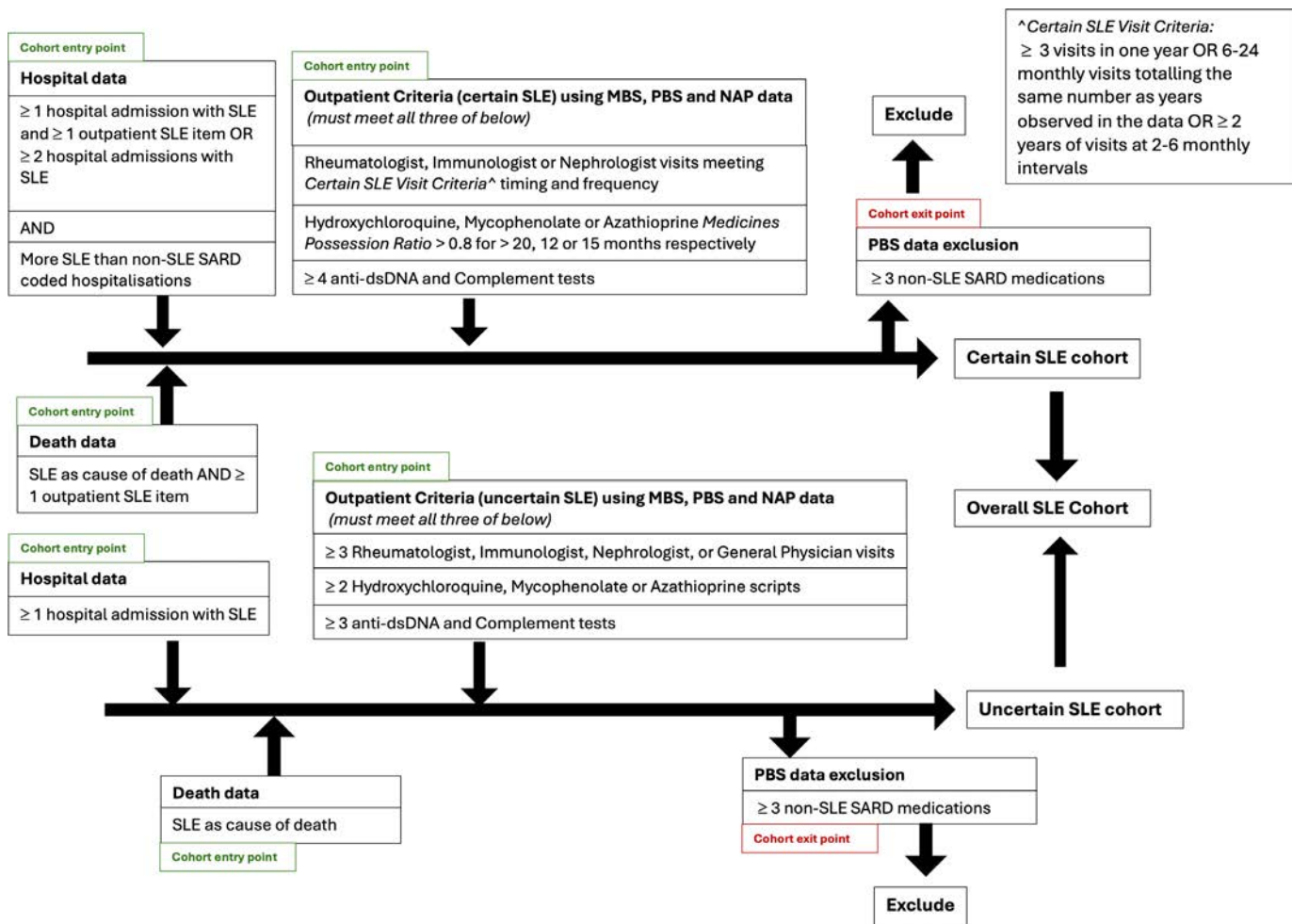


Figure 1. Overview of SLE classification algorithm. Supplementary Material 4 presents the figure in a detailed table format. anti-dsDNA, anti-double-stranded DNA antibodies; MBS, Medicare Benefits Schedule; NAP, non-admitted patient episode level data; PBS, Pharmaceutical Benefits Scheme; SARD, systemic autoimmune rheumatic disease; SLE, systemic lupus erythematosus.

- 2. Outpatient specialist visits (Supplementary Material 3): In Australia, patients with SLE are managed by rheumatologists, immunologists, nephrologists, and general physicians, particularly in rural areas. As per the expert clinician group consensus, stable patients are typically seen annually, with increased visits during flares; however, a subset have frequent flare-related visits that are followed by long gaps in follow-up. The certain SLE visit criteria identify both those with stable, regular visits and those with visit clusters between periods of minimal follow-up. The uncertain SLE cohort only required three visits at any time during the study period.
- 3. Pathology testing (Supplementary Material 8): Anti-double-stranded DNA antibodies (dsDNA) and complement level testing have been recommended to monitor SLE disease activity³² because fluctuations are associated with flares.^{33–35} Expert consultation suggested matching the number of dsDNA and complement tests to the minimum visit count per cohort, meaning that certain SLE

required four tests, and uncertain SLE required three tests.

Statistical analysis. Descriptive statistics for socio-demographic and health service use were reported for all SLE cases. Sociodemographic characteristics included sex, age at diagnosis, country of birth aggregated by region, geographic area of remoteness, and socioeconomic disadvantage quintile based on Australian Bureau of Statistics (ABS) Index of Relative Disadvantage.³⁶ Measures of health care use comprising hospitalizations, medications dispensed, outpatient visits, and specialists seen were determined. Observation time was defined as the period from the first SLE-related item (Table 1) to death or end of follow-up (July 31, 2022). Details of these variables are in Supplementary Material 9.

Period prevalence (July 2010–July 2022) was calculated by dividing all identified SLE cases in each state or territory by the respective midpoint 2015 ABS population estimates, excluding WA and NT. To determine incidence rates, the annual number of

Table 1. SLE-related diagnoses, medications, and health contacts extracted from each dataset*

Hospital data	Inclusion: Hospital admissions with SLE as a principal or additional diagnosis. <i>ICD-10-AM</i> codes M32.1, M32.8, M32.9. Exclusion: More admissions with a non-SLE SARD diagnosis than an SLE diagnosis. Examples of SARD are rheumatoid arthritis, spondyloarthropathies, systemic sclerosis, vasculitis, and idiopathic inflammatory myopathies (full list in Supplementary Material 2).
Death data	SLE as the underlying or additional cause of death: <i>ICD-10-AM</i> codes M32.1, M32.8, M32.9 (details in Supplementary Material 6).
PBS data	Inclusion: Dispensing of hydroxychloroquine, azathioprine, or mycophenolate. Medication adherence criteria are outlined in Figure 1 and in detail in Supplementary Material 7. Exclusion: Chronic dispensing of medications that are not approved for use in SLE in Australia. Examples are biologic agents such as infliximab and adalimumab with restricted PBS indications to inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, and psoriatic arthritis (full list in Supplementary Material 7).
MBS and NAP data	Outpatient visits to rheumatologist, nephrologist, immunologist, or general physician. Visit frequency requirements are outlined in Figure 1.
MBS data	Claims for testing anti-dsDNA and C3 and C4. Testing frequency requirements are outlined in Figure 1 and Supplementary Material 8.

* anti-dsDNA, anti-double-stranded DNA antibodies; C3, complement component 3; C4, complement component 4; *ICD-10-AM*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification*; MBS, Medicare Benefits Schedule; NAP, National non-admitted patient episode level data; PBS, Pharmaceutical Benefits Scheme; SARD, systemic autoimmune rheumatic disease; SLE, systemic lupus erythematosus.

SLE cases was calculated for each state and territory (excluding WA and NT) from 2015 to 2019, allowing for a four-year lookback period to exclude prevalent cases and a two-and-a-half-year minimum follow-up period. The incident date was defined as the first month an individual met the algorithm criteria, and annual incident cases were divided by the mid-year ABS population estimates³⁷ and reported per 100,000 in the population. Incidence rates are reported in Supplementary Material 10.

Individuals diagnosed before aged 15 years were excluded because the adult-based algorithm may not apply due to different care patterns. Also excluded were individuals with data errors (eg, a data item appearing after death date or missing state of residence). For individuals who received care or who resided in multiple states, the first state was used for prevalence calculations.

All data management and analyses were done in R, version 4.4. Ethics approval for this study was obtained from the NSW Population and Health Services Research Ethics Committee (2024/ETH01955) after approval from NHDH data custodians (NG24-0090).

RESULTS

A total of 26,788 SLE cases were identified, of which 16,294 were certain SLE. Of the certain cases, approximately half met outpatient criteria alone, and the remainder were identified by combinations of criteria as demonstrated in Figure 2. Table 2 presents sociodemographic characteristic of the certain, uncertain, and overall SLE cohort, who were predominantly female, with a younger age structure, higher proportion of migrants, and lower proportion of major city residence than the national average.^{38,39}

Table 3 presents the health care use characteristics of the cohort. In the certain SLE cohort, median observation time from the first SLE-related claim to censoring (death or July 31, 2022) was 12 years. There was a total of 2,356 deaths: 14.2 deaths per 1,000 person-years. Just under half (46%) were ever hospitalized with SLE. The most dispensed medication was oral steroids, with 100% of the cohort receiving at least one script for oral steroids at some point during their median 11 years of observation. Similarly, most (88%) of the cohort received at least one script for hydroxychloroquine during the observation period. The proportion of the cohort taking key SLE medications is presented in Table 3. Because belimumab and anifrolumab were not PBS-listed during the study period, data on their use are not available. Of the certain cohort, 72% had seen a rheumatologist, 31% had seen a nephrologist, and 24% had seen an immunologist. Other specialties frequently consulted included obstetricians, dermatologists, ophthalmologists, and general physicians.

Table 4 presents the 2010 to 2022 period prevalence of SLE. The period prevalence of SLE was 77 per 100,000 using the certain definition and 127 per 100,000 using overall cases.

DISCUSSION

This study describes the development of a detailed algorithm to identify Australians with SLE using linked administrative health data sets and incorporating SLE-related hospital admissions, MBS claims, death records, and claims for dispensed medications. To the authors’ knowledge, it is the first algorithm to identify SLE cases using outpatient data in a jurisdiction without diagnostic coding of outpatient events and may serve as a template for other Australian or international researchers in jurisdictions without outpatient diagnostic codes. Using this algorithm to identify SLE, we estimate the prevalence of SLE in Australia to be 77 to 127 per 100,000, which is higher than previously reported⁶⁻⁹ but similar to the contemporary findings in the United States of 81 per 100,000¹⁰ and the United Kingdom of 97 to 107 per 100,000.¹¹

The SLE cohort was predominantly female, which is consistent with established SLE cohorts.²² Compared with the Australian population, a lower proportion of the certain SLE cohort were born in Australia and New Zealand (63% vs 72%³⁹), partly because of higher representation from Asian countries

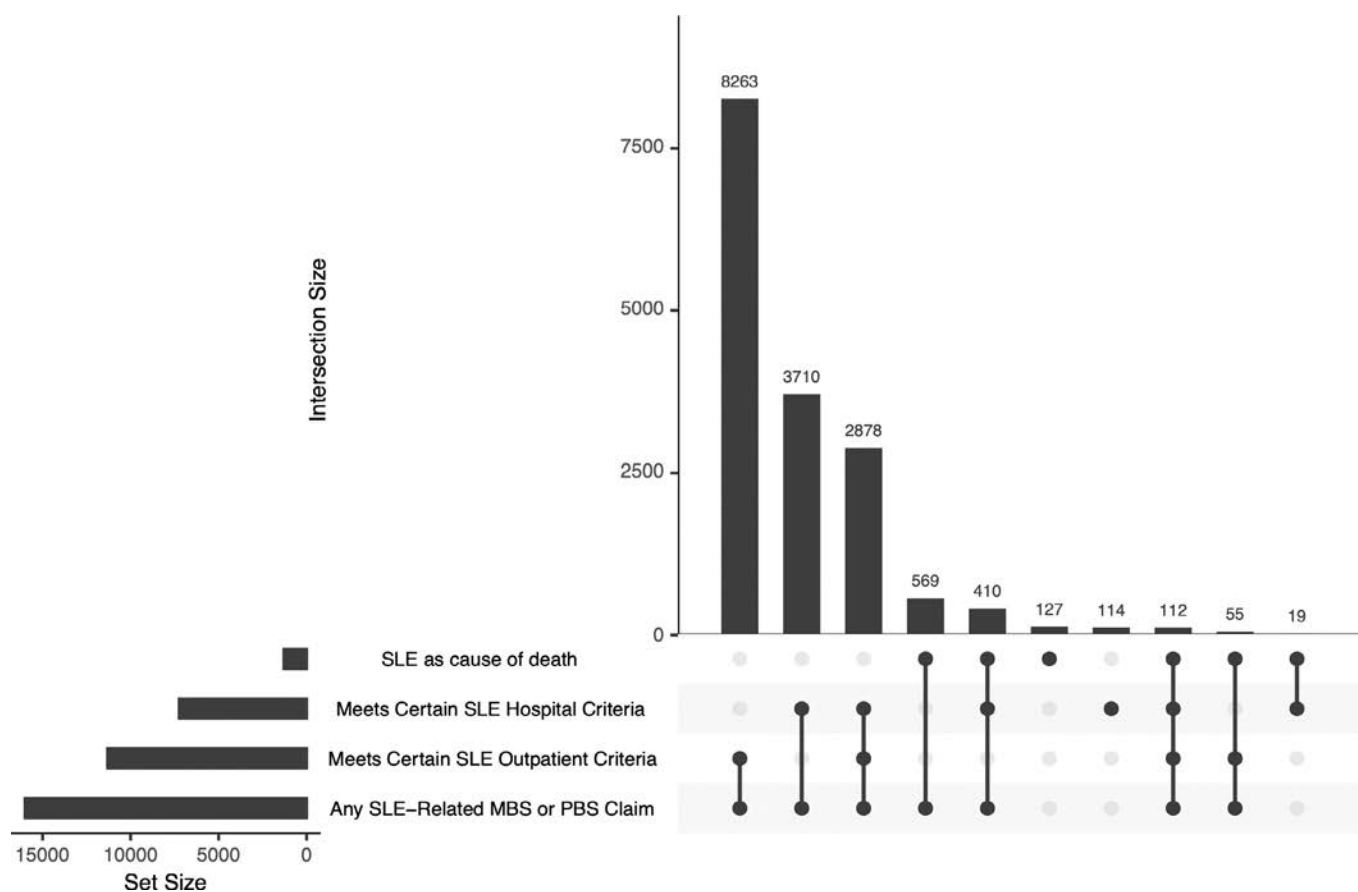


Figure 2. Horizontal bars represent the total people accessing the respective service; columns with circles represent each combination (darkened circles), and vertical bars represent the number of people in the respective combination. For example, the first row represents the total number of people with records related to SLE in the death data set, whereas the first column represents the number of individuals fulfilling certain SLE criteria. Only the 10 most common intersections are shown. MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; SLE, systemic lupus erythematosus.

(12% vs 10.6%).³⁹ The cohort also had greater regional representation (63% vs 72% in major cities³⁸). The distribution of socioeconomic disadvantage was broadly consistent with national figures.

The SLE cohort demonstrated higher health care use than the general Australian population, despite a younger age profile. Median general physician (GP) visits were 10.2 per year compared with a national average of 6.3.⁴⁰ Over the study period, 88% had at least one hospital admission for any indication (although less than half had a hospital admission for SLE care). Although not directly comparable with national annual rates because of the study observation period, this suggests higher hospital use than the general population—for which only 12.7% of Australians aged 15 and over were admitted to the hospital in 2023 and 2024.⁴¹

The SLE cohort demonstrated similar medication usage to confirmed Australian and international SLE cohorts,²² with similar hydroxychloroquine (88% vs 85% OPAL²²) and methotrexate use (28% vs 29% OPAL²²). Only half of our cohort had an MBS claim for visual field testing (a component of hydroxychloroquine screening that is advised in current Australian and New Zealand

guidelines⁴²). Oral steroid use was high in our cohort compared with the OPAL cohort, with 100% filling at least one prescription over the median 11-year observation period versus 65.8% of the OPAL²² cohort reporting glucocorticoid use over 2.3 years. This likely reflects both differing definitions of steroid use and the longer observation period for our cohort. In OPAL, medications are recorded into a bespoke electronic medical record by a rheumatologist. In this context, steroids may be likely to represent maintenance glucocorticoids or current usage. Even if never prescribed maintenance glucocorticoids, most patients with SLE will require steroids for flares at some point—ie, 82% of the Asia Pacific Lupus Collaboration cohort used oral prednisone at least once over just two years.⁴³ Short courses prescribed by a GP for a minor flare between rheumatologist visits may not be recorded in OPAL but would appear in PBS data, as would prescriptions filled for contingency use (ie, travel) and potentially not taken. Our longer time-frame also increases the likelihood of capturing a dispensing.

Although analysis of birth outcomes was outside the scope of the present study, at least 12% of the cohort had a hospital admission for birth. Finally, the mortality rate in SLE was 14.2 per

Table 2. Demographic characteristics of the identified SLE cohort*

Characteristics	Certain SLE, N = 16,294	Uncertain SLE, N = 10,494	Overall ^a SLE, N = 26,788
Female, n (%)	14,099 (87)	8,991 (86)	23,090 (86)
Male, n (%)	2,158 (13)	810 (14)	2,968 (14)
Age at diagnosis, n (%), y ^b			
15–24	978 (6.0)	451 (4.3)	129 (5.3)
25–34	2,151 (13)	1,156 (11)	3,307 (12)
35–44	2,714 (17)	1,562 (15)	4,276 (16)
45–54	3,079 (19)	1,922 (18)	5,001 (19)
55–64	3,143 (19)	2,189 (21)	5,332 (20)
65–74	2,602 (16)	1,855 (18)	4,457 (17)
75–84	1,326 (8.1)	1,073 (10)	2,399 (9.0)
85 and over	301 (1.8)	286 (2.7)	587 (2.2)
Region of birth, n (%)			
Australia/New Zealand	10,206 (63)	6,501 (62)	16,707 (62)
Europe	1,404 (8.6)	1,041 (9.9)	2,445 (9.1)
Asia	1,973 (12)	884 (8.4)	2,857 (11)
Northern Africa and the Middle East	n.p.	n.p.	n.p.
Americas	n.p.	n.p.	n.p.
Sub-Saharan Africa	203 (1.2)	112 (1.1)	315 (1.2)
Missing	1,949 (12)	1,606 (15)	3,555 (13)
Remoteness area, n (%)			
Major cities of Australia	10,393 (64)	6,555 (62)	16,948 (63)
Inner regional Australia	3,429 (21)	2,360 (22)	5,789 (22)
Outer regional Australia	2,055 (13)	1,322 (13)	3,377 (13)
Remote Australia	214 (1.3)	150 (1.4)	364 (1.4)
Very remote Australia	176 (1.1)	87 (0.8)	263 (1.0)
Missing	27 (0.2)	20 (0.2)	47 (0.2)
IRSD quintile, n (%)			
1 (most disadvantaged)	1,486 (20)	855 (19)	2,341 (20)
2	1,398 (19)	869 (19)	2,267 (19)
3	1,167 (16)	758 (17)	1,925 (16)
4	1,724 (24)	1,086 (24)	2,810 (24)
5 (least disadvantaged)	1,510 (21)	1,014 (22)	2,524 (21)

* IRSD, Index of Relative Socioeconomic Disadvantage; n.p., not published; SLE, systemic lupus erythematosus.

^a Overall includes certain and uncertain SLE.

^b Age at meeting algorithm criteria.

1,000 person-years, compared with 18.6 per 1,000 person-years in a recent Italian population-based study⁴⁴ or 15.84 per 1,000 person-years in the United Kingdom.⁴⁵

Although there are currently no validated algorithms for the identification of SLE from Australian administrative data, there has been substantial work in this space internationally, which informed our method. First, hospital data alone captures only 40% to 79% of SLE cases identified using clinician medical record review as the gold standard.^{18,25} This persists even over long periods of observation (remaining at 79.2% after 40 years in a Swedish study²⁴). This likely reflects the exclusion of younger and milder cases never requiring hospitalization and was further demonstrated by a Canadian study demonstrating that 32% of SLE cases identified in Quebec were present in outpatient claims data but absent from hospital records.²⁵ These findings support our inclusion of both hospital and outpatient data as a methodologic strength.

Second, the PPV of a single SLE-coded hospital or outpatient encounter is low but increases with repeat episodes. In Canada, the PPV of a single episode of SLE-coded hospital care was 60%, rising to 87.5% with two or more hospitalizations.²⁵

Similarly, in Norway, the PPV of a single SLE-coded inpatient or outpatient encounter was 47%, increasing to 72% for three or more SLE-coded episodes.¹⁷ Therefore, our hospital criteria require either multiple SLE-coded episodes or an additional supporting claim from a different data source (eg, hydroxychloroquine). Third, clinical heterogeneity, diagnostic complexity, overlapping medication use, and shared specialist care contribute to the misclassification of SARDs in administrative data (for instance, the misclassification of rheumatoid arthritis as SLE). In Norway, half of the false-positive SLE-coded encounters were ultimately diagnosed as another SARD.¹⁷ Similarly, in Estonia, most false-positive SLE-coded care episodes were revised to an alternative SARD.¹⁹ These findings highlight the need for exclusion criteria to minimize SARD misclassification. We applied medication-based exclusions (excluding individuals with SARD-specific but non-SLE therapies, such as TNF inhibitors) and hospital exclusion criteria (more admissions coded as non-SLE SARD than SLE) to reduce this risk. Although these exclusions improve the specificity of the algorithm, SLE has been reported to overlap with many SARDs,⁴⁶ and these cases may have been excluded

Table 3. Health care use and management of individuals in the identified SLE cohort*

Health care utilisation and outcomes	Certain SLE, N = 16,294	Uncertain SLE, N = 10,494	Overall SLE, N = 26,788
Years observed total (post meeting algorithm)	12 (6)	10 (4)	11 (5)
Total deaths (death rate per 1,000 person-years)	2,356 (14.2)	1,342 (13.9)	3,698 (14.1)
Hospitalizations			
Hospital admissions (any cause) per person, median (IQR)	5 (2–12)	4 (1–9)	5 (2–11)
Hospital admissions (SLE) per person, median (IQR)	0 (0–2)	0 (0–0)	0 (0–1)
Ever hospitalized (any cause), %	88	85	87
Ever hospitalized with SLE, %	46	21	36
Receiving dialysis ever, n (%)	304 (2)	80 (1)	384 (1)
Receiving renal transplant, n (%)	344 (2)	65 (1)	409 (2)
Hospitalized for childbirth, n (%)	1,889 (12)	1,146 (11)	3,035 (11)
Medications – ever received, %			
Hydroxychloroquine	88	78	84
Azathioprine	22	13	19
Mycophenolate	25	12	20
Methotrexate	28	27	27
Oral prednisone	100	100	100
Cyclophosphamide	4	2	3
Leflunomide	5	6	5
Ciclosporin	2	1	2
Tacrolimus	4	1	3
Rituximab	1	1	1
IV methylprednisolone	5	4	4
Outpatient visits – ever seeing, %			
Rheumatologist	72	68	71
Nephrologist	31	18	26
Immunologist	24	22	23
General physician (internal medicine specialist)	53	51	52
Obstetrician/gynecologist	37	35	36
Dermatologist	37	37	37
Ophthalmologist	55	48	52
Ophthalmologist or optometrist for automated visual field testing	61	49	56
Annual GP (primary care doctor) visits, median (IQR)	10.2 (6.6–15.6)	10.1 (6.2–15.5)	10.2 (6.5–15.6)
Annual rheumatologist visits, median (IQR)	0.8 (0–1.8)	0.5 (0–1.3)	0.6 (0–1.6)

* GP, general practitioner; IQR, interquartile range; IV, intravenous; SLE, systemic lupus erythematosus.

if their clinical phenotype or management more closely aligned with the non-SLE diagnosis (ie, had more hospital admissions coded as the non-SLE diagnosis or received TNF inhibitor).

A key strength of this study is that it uses population-wide, linked administrative data sets to identify individuals with likely SLE that are informed by existing Australian data as well as international SLE case-finding algorithms, as described previously. Second, Australia's universal health care system enables near-complete capture of real-world health service and medication use via the PBS and MBS data sets, which provides a comprehensive view of this cohort's health care use. Finally, most studies using administrative health data to identify health conditions make assumptions regarding the health care use of individuals with that illness, and the quality of the case identification is dependent on the quality of those assumptions. Our algorithm was informed by both international SLE identification algorithms,^{17–19,26} contemporary Australian data on real-world SLE care,²² and the expert guidance of five rheumatologists with broad experience across public and private sectors in three states.

Although we would ideally have validated our approach with an additional external data set or through review of medical records of cases and noncases, this was not possible. At the time of analysis, the NHDH data governance policies precluded reidentification of records because of privacy principles. In addition, linkage to external SLE registry data would be inadequate because of a lack of non-case records. Nevertheless, we are confident in the value of our approach despite being unable to calculate the sensitivity or specificity of the algorithm. To test the internal validity of our algorithm, we conducted nine separate sensitivity analyses, each varying a single decision rule (Supplementary Material 5). The cohort size and characteristics remained relatively consistent, suggesting that our findings are not unduly influenced by specific parameter choices. However, future validation of this algorithm by reviewing the medical records of a subset of the cohort would be valuable if this becomes possible. We also cannot assume our algorithm has identical performance to those developed in different settings.^{15,18,19,24,25} Structural differences in health systems and data collected (eg, use of insurance claims data¹⁵ or outpatient

Table 4. 2010 to 2022 period prevalence of SLE in Australia, using identified cohort*

State	Certain cases, n	Overall cases, n	Lower bound estimate (certain SLE) prevalence per 100,000	Upper bound estimate (overall SLE) prevalence per 100,000
ACT	454	764	115	193
NSW	6,614	10,669	87	140
QLD	2,984	4,950	62	104
SA	1,124	2,057	66	121
TAS	249	415	48	81
VIC	4,869	7,933	81	132
National, excluding WA/NT	16,294	26,788	77	127

* 2022 was a partial year. ACT, Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; SLE, systemic lupus erythematosus; TAS, Tasmania; VIC, Victoria; WA, Western Australia.

diagnostic codes,^{18,19} which are not collected in Australia) limit direct comparison with international administrative data SLE identification approaches. Furthermore, diagnostic coding systems (ie, ICD/International Classification of Primary Care/Systematized Nomenclature of Medicine) and their accuracy varies, influenced by factors such as clinical coders' expertise (which may differ by national training standards⁴⁷), as well as hospital-specific quality of medical record keeping. Despite these differences in data sources and settings, we were able to calculate similar estimates for SLE to other settings.

Furthermore, although the NHDH has broad coverage, it was not universal. Private hospital and NAP data were incomplete; however, sensitivity analyses suggest minimal impact on overall cohort size because of the layered design of the algorithm. Multiple data sets were missing for the NT and WA, leading to their exclusion. SLE prevalence has been reported to be higher in Aboriginal and Torres Strait Islander people than non-Indigenous Australians,^{5,48} and WA and the NT have higher proportions of Aboriginal and Torres Strait Islander people than Southern Australia (31% of NT and 4% of WA in 2021 census vs 3.5% of Australia excluding these states³⁷). Given these states are small (NT contains <1% of the Australian population and WA approximately 11%), their overall effect on the national estimate is likely minimal, and in the direction of an underestimation. Given their unique demographics, our prevalence figures cannot be presumed to apply to these states, particularly not to the NT.

Future work using this cohort may include and assessment of the geographic distribution of SLE, hospitalizations, and causes of death, and—with appropriate consultation—estimation of disease burden in Aboriginal and Torres Strait Islander people (work outside the scope of our current ethics approvals). Because the NHDH is regularly updated, it will soon be possible to examine trends in use of newer therapies, such as anifrolumab, which were not PBS-listed during the study period.

This study presents the first Australian algorithm to identify SLE using both inpatient and outpatient administrative data. In doing so, it demonstrates that the national prevalence of SLE is higher than previously reported and aligns more closely with international estimates. The cohort identified displays high face validity, with

demographics, medication usage, and health care use patterns comparable with those observed in existing Australian data. By detailing our methodology, including its strengths and limitations, we aim to support transparency and reproducibility. This algorithm may serve as a foundation for future Australian and international studies seeking to identify SLE in administrative health data sets.

ACKNOWLEDGMENTS

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australasian University Librarians.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Roper confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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The Lupus Damage Index Revision Program: Results From the Item Generation and Reduction Phases

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Objective. A data-driven and expert/patient consensus-based project to develop a revised Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) is under way supported by SLICC, ACR, and the Lupus Foundation of America. Our objective is to report the item generation and reduction phase results for a revised SDI.

Methods. Item generation included a literature review by literature review groups and a Delphi exercise of international systemic lupus erythematosus experts and patients. Item reduction involved Delphi rounds in which items with a median appropriateness score of ≤ 4 of 9 were excluded. A 14-member item reduction committee assessed remaining items and removed those that did not reflect the damage construct, were rare, or were not feasible to assess. The clinical domain groups then refined the remaining items and their definitions.

Results. The Delphi panel included 146 individuals from 35 countries. The Delphi exercise nominated 2,256 items, and the literature review identified 117 items. After removing redundancies, 226 candidate items remained. Subsequent Delphi rounds, followed by review by the item reduction committee and clinical domain groups, resulted in 39 items across 13 domains. Eleven items from the original SDI, including proteinuria and cranial neuropathy, were removed and several new items were proposed, including growth failure/reduced final height and adrenal insufficiency. Severity-based subitems are proposed for 17 items (43.6%).

Conclusion. This data-driven and expert/patient consensus-based process has proposed 39 candidate items, some with subitems, and definitions for a revised SDI. Weighting of items and subitems is underway to develop a clinical scoring system.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by flares, inflammation in target

organs, and increased mortality. Over the past 30 years, there has been a remarkable improvement in the survival rates of patients with SLE due to factors such as earlier diagnosis, improved therapeutic modalities, and better management of

Supported by the Lupus Foundation of America and the American College of Rheumatology.

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SIGNIFICANCE & INNOVATIONS

- The current Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) is a robust instrument but is limited by missing items, restricted applicability in pediatric patients, a significant floor effect, and outdated item definitions.
- An international initiative is underway to develop a revised SDI using a multiphase process that is supported by SLICC, ACR, and the Lupus Foundation of America.
- Item generation and reduction phases resulted in 39 candidate defined items to be taken forward to the next stages. Subitems based on severity are possible for 17 (43.6%) of the proposed items.
- Our data-driven and expert/patient consensus-based process aims to develop a more detailed and clinically relevant assessment of organ damage in patients with SLE across the lifespan. It will also better reflect current evidence-based medical practice and is likely to improve sensitivity and responsiveness of the index for future lupus trials and research.

complications.^{1,2} Despite the increased longevity in patients with SLE, a range of comorbidities can arise, a number of which are captured as the accrual of organ damage.^{3,4}

Damage in SLE was originally defined as a health state reflecting irreversible changes that occur in patients with SLE and that may be a consequence of ongoing disease activity, treatment (eg, glucocorticoids), comorbidities, or aging.⁵ Considered a distinct concept from disease activity and health related quality of life, damage serves as a key predictor for morbidity and mortality.⁶ It is therefore crucial to identify patients at risk of damage early enough to implement proactive measures to prevent the onset and progression of damage. In 1996, the Systemic Lupus International Collaborating Clinics (SLICC) group, in collaboration with the American College of Rheumatology (ACR), developed the SLICC/ACR Damage Index (SDI) to quantify irreversible organ damage accrual that occurs in patients with SLE.⁵

The SDI consists of 41 items across 12 organ systems. It captures the accumulation of damage from any cause since SLE diagnosis, regardless of attribution. Generally, items need to be present for six months or more to score. Damage may result from disease activity (eg, renal failure or neurocognitive abnormality), treatment (eg, steroid-induced diabetes or avascular necrosis), intercurrent illness (eg, cancer or surgery), or potentially unrelated events (eg, amputation).⁵ Although widely used in SLE cohort studies,^{5,6} the SDI has several limitations.⁷ Its maximum score is 47, but patients rarely exceed 12, and in most cohorts, up to 50% of patients score 0, reflecting a significant floor effect.⁸ The SDI relies on clinical examination and basic investigations. However, the wider use of sophisticated medical investigations means that this approach does not align with modern medical practice. Similarly, many items in the SDI such as chronic kidney disease now have more “staging” in routine practice, which is not reflected well in the often binary scoring (present or absent) in the SDI. From a pediatric viewpoint, the SDI is limited by missing items, for example, growth restriction. Finally, any damage occurring before the formal diagnosis of SLE, even if associated with a prior, but associated, condition such as antiphospholipid syndrome, discoid lupus, or undifferentiated connective tissue disease, would not be counted in the current SDI. Such limitations may contribute to the lower scores observed in cohorts, which limits the usefulness of the SDI as a primary endpoint in SLE trials.

The SLICC group, in collaboration with the ACR and the Lupus Foundation of America (LFA), initiated an international project to revise the SDI using consensus and evidence-based methods over five key phases. In the first phase, we defined the construct of damage in SLE in the modern era using qualitative methods.⁹ By consensus, a contemporary and expanded conceptual framework was agreed upon; “Damage is a health state related to organ structure and function. The degree of reduced organ function relates to physiologic impairment. Damage can occur before a diagnosis of SLE but should be attributable to SLE. Damage to an organ is irreversible, but the functional consequences on that organ may improve over time through physiological adaptation or treatment.”

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80102>).

[Correction added on 16 September 2026, after first online publication: In Supplementary Table 4, ‘Peripheral’ was changed to ‘Cranial’.]

[Correction added on 16 September 2026, after first online publication: ORCID has been added to Burak Kundakci.]

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80102>.

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Submitted for publication November 14, 2025; accepted in revised form May 5, 2026.

In this article, we report the findings of the item generation and reduction phases of the development of the revised SDI.

MATERIALS AND METHODS

The methodologic approach for development of the revised SDI consists of five stages: updating the construct of damage, item generation, item reduction, item weighting and threshold determination, and assessment of its measurement properties (validity, reliability, and responsiveness). This approach has been successfully used in other rheumatic diseases.^{10–13} Herein, we report the item generation and reduction phases of the revised SDI development. Ethics approval by the University of Manchester was granted on October 13, 2021.

Item generation. This phase aimed to generate a broad list of candidate items reflecting the new construct of damage in SLE, suitable for inclusion in a new damage index. This process involved a literature review and the first round of a Delphi exercise. Literature review groups conducted targeted, nonsystematic literature searches for each organ domain. Searches were primarily performed in MEDLINE (via PubMed) using domain-specific keywords and relevant terms related to SLE and organ damage (eg, terms derived from the current SDI and organ-specific damage items). These searches aimed to identify relevant reviews, cohort studies, patient surveys, and, where condition-specific evidence was limited, indirect evidence from general population studies. Each domain was subsequently reviewed by pediatric subspecialists for content validity, as it applies to patients with childhood-onset SLE.

Delphi panel members were identified through snowball sampling among SLICC members, in other words, initial investigators were asked to invite others that were known to them. We gave guidance requesting them to consider inviting colleagues from a range of clinical expertise, sex, stages of career, and geographic representation. The LFA, Lupus UK, Lupus Europe, and Lupus Canada were invited to nominate two to three patient/caregiver representatives for the Delphi exercise. The Delphi questionnaires were implemented using Qualtrics software (Qualtrics). In the first round of the Delphi exercise, participants provided demographic and professional details, including profession, country of work, age, sex, race and ethnicity (categories taking into account the global constituency: Arab, Black, Chinese, Korean/Japanese, Latin American, South Asian, Southeast Asian, West Asian, White, or another), primary specialty, and measures of clinical experience (years in practice, average number of patients with SLE seen per month). All participants were asked to nominate items (using their own nomenclature) based on the updated construct definition for inclusion in the revised damage index. Items generated by the literature review groups and by the first Delphi round were reviewed, and repetitive and redundant items were removed.

Item reduction. Item reduction involved the second and third rounds of the Delphi exercise, evaluation for further refinement of items by an item reduction committee, and clustering based on organ system by the clinical domain groups. In the Delphi rounds, SLE experts and patients rated items on a 9-point Likert scale, considering the new construct of damage in SLE (in which 1 = not at all appropriate and 9 = completely appropriate). In order to ensure equal voice to patient representatives, clear, layperson-friendly definitions of each item were provided to patient representatives. The Delphi process was designed to give equal weight to all contributors, irrespective of whether they were patients or professionals and irrespective of professional discipline or career stage. All ratings and votes were treated equivalently at each round, with no differential weighting applied to patient versus expert responses. In the second Delphi round, participants also were asked to nominate additional items that they felt may have been omitted or were missing. In the third Delphi round, participants were presented with their own ratings and the group median (with 25th–75th percentiles) for each item, allowing them the opportunity to revise their ratings, if appropriate. Items with a median appropriateness rating less than or equal to 4.0 of 9.0 were removed as this score was clearly in the lower range of appropriateness scores. This approach has been successfully used to develop other criteria.^{11,13} Dillman methods (eg, personalized invitations to participate and follow-up reminders) were used to optimize response rates.¹⁴

Due to insufficient item reduction in the Delphi exercise, an item reduction committee composed of 14 members conducted a thorough assessment of the remaining items. Retained items required a minimum of 10 of 14 (>70%) agreement to be retained. If an item was rejected by five or more committee members due to any of the following reasons, it was excluded: (1) redundant item, (2) assessment is not widely available or feasible, (3) not reflecting the construct of damage and/or related with lupus disease activity, (4) excessively rare.

Remaining items were then reviewed by expert clinical domain groups for further refinement including whether certain items could be “clustered” into a single item and to identify if any grading of severity could be included for relevant items. These clinical domain groups included an organ system lead who is a rheumatologist, three to four organ-specific specialists, a pediatric rheumatologist, and a patient partner.

Item groupings and definitions. Our clinical domain groups including rheumatologists and specialty experts reviewed all final items. For each item, they proposed subitem groupings aligned with current clinical practice, such as severity of ventricular dysfunction, staging of chronic kidney disease, and cognitive impairment severity. These groupings were based on contemporary medical literature and routine practice.

Definitions were derived from current evidence and relevant learned society or professional association guidelines. Where no

formal definition existed, the expert group developed one through consensus based on clinical expertise.

A complete list of participants including the leadership team, the literature review groups, the Delphi panel, the item reduction committee, and the clinical domain groups is shown in Supplementary Table 1.

RESULTS

Delphi panel. We identified 146 individuals from 35 countries, with a mean (range) age of 50.6 (28–79) years. Among the participants, 60.3% were females, and 58.9% identified as White, Latin American (11.0%), Black (7.5%), Korean/Japanese (4.8%), South Asian (4.8%), Arab (3.4%), Chinese (3.4%), Southeast Asian (1.4%), West Asian (0.7%), and another (4.1%). Participants were recruited from a wide range of countries. The largest contributions came from the US (24.0%), Canada (21.2%), and the UK (9.6%), followed by representation from several European, South American, Asian, and African countries. Their clinical experience ranged from 1 to 51 years. This group included 135 medical doctors, 2 allied health professionals, and 9 patients. Of the medical doctors, 120 were rheumatologists, 7 were internists, 5 were nephrologists, 2 were dermatologists, and 1 was an immunologist (Table 1).

Item generation. The literature review groups proposed 117 items across 13 clinical domains, including neuropsychiatric, ocular, endocrine/metabolic, growth and development, reproduction/pregnancy, hematologic, gastrointestinal (GI), renal, cardiovascular, peripheral vascular, pulmonary, musculoskeletal, skin/mucocutaneous, and “others.” The response rate of the first round of the Delphi exercise was 97.9% and resulted in 2,256 “raw” proposed items. After the first Delphi round, we reviewed all nominated items, clustered overlapping items, and harmonized synonymous terms. For example, stroke was proposed by many participants, and some used the term “cerebrovascular accident.” All of these were reduced to a single item. This process led to the removal of 2,040 “raw” items. We then compared the remaining items with those identified through the literature review. All items in the original SDI were nominated in both processes. We found that the first Delphi round generated 103 unique items (46.8%), whereas the literature review generated 4 unique items (1.8%), and 113 items (51.4%) appeared in both exercises (Supplementary Table 2). In total, 220 discrete proposed items were retained.

In the second Delphi round, participants suggested 53 potential additional “raw” items; however, only 6 were retained, as 47 others were deemed to be duplicates or synonyms of existing proposed items. These new items included intracranial hypertension, disordered puberty sequences, limb length discrepancies, low anti-Müllerian hormone levels, lipodystrophy,

Table 1. Participant characteristics of the 146 Delphi panel members

Characteristics	n (%)
Participants	
Medical doctor	135 (92.5)
Allied health professional	2 (1.4)
Patient	9 (6.1)
Sex	
Female	88 (60.3)
Male	58 (39.7)
Age, mean (range), y	50.6 (28–79)
Race/ethnicity	
White	86 (58.9)
Latin American	16 (11.0)
Black	11 (7.5)
Korean/Japanese	7 (4.8)
South Asian	7 (4.8)
Arab	5 (3.4)
Chinese	5 (3.4)
Southeast Asian	2 (1.4)
West Asian	1 (0.7)
Another	6 (4.1)
Country/region	
US	35 (24.0)
Canada	31 (21.2)
UK	14 (9.6)
European (excluding UK)	27 (18.5)
South America	14 (9.6)
Asia	13 (8.9)
Africa	4 (2.7)
Other North America	3 (2.1)
Caribbean	3 (2.1)
Oceania	2 (1.4)
Main specialty (n = 135)	
Rheumatology	120 (88.9)
Internal medicine	7 (5.2)
Nephrology	5 (3.7)
Dermatology	2 (1.5)
Immunology	1 (0.7)
Clinical experience, median (range), y	20 (1–51)
Main type of practice (n = 135)	
Adults	116 (85.9)
Children	9 (6.7)
Young adults	1 (0.7)
Combination	9 (6.7)
Practice environment (n = 135)	
Teaching hospital	128 (94.8)
Community practice	4 (3.0)
Nonteaching hospital	3 (2.2)

and alopecia without scarring. In total, 226 unique items were generated at this stage.

Item reduction. The response rates for the second and third rounds of the Delphi exercise were 95% and 91.7%, respectively. There was stability in median scores and the 25th to 75th percentiles for each item between the second and third rounds. All original SDI items (with two exceptions) were retained with group median appropriateness scores of 7 to 9; “upper GI tract surgery” and “osteomyelitis” were retained with median appropriateness scores of 5. In the third Delphi round, 36 items had a

median score of 4.0 or less, thus reducing the items from 226 to 190 (Table 2).

The item reduction committee then assessed the remaining 190 items, and we excluded items that were rejected by five or more members of the committee (ie, a 70% threshold to retain) due to at least one of the following: redundancy, ascertainment not widely available or feasible, items not reflecting the construct of damage, and excessively rare items (Supplementary Table 3). Consequently, 126 items were removed from the candidate item list.

The remaining 64 items were re-evaluated by the clinical domain groups. Items such as cranial neuropathy, psychosis, and movement disorders were deemed incongruent with the current construct of damage and were consequently removed, as they were more reflective of SLE disease activity. Similarly, very rare items such as bowel stricture, renal infarction, pleural fibrosis, and skin ulceration were also excluded as individual stand-alone items. The clinical domain groups also identified overlapping items and recommended clustering them into single items for clarity and efficiency. For instance, dementia and cognitive impairment were merged into a single item due to them being distinguished only by degree of severity. The items in the hematologic domain overlapped with other clinical domains, and so the domain was removed. Supplementary Table 4 presents the excluded items and their reasons for exclusion by the clinical domain groups. These item reduction phases resulted in 39 proposed candidate items across 13 clinical domains with glossary definitions developed by the clinical domain groups (Table 3 and Figure 1) and a draft index developed (Table 4). Figure 2 summarizes the number of candidate items that were generated and reduced.

Item definitions and subitem proposals. The clinical domain groups were tasked with proposing definitions for each of the items, based on current evidence-based practice, specialty guidelines, and their clinical expertise. In developing precise definitions for each item, potential subitems based on severity for 17 items (43.6%) were proposed (Table 3 and Figure 1). For example, by expert consensus, ischemic heart disease is subdivided as asymptomatic ischemia on testing, symptomatic angina with confirmatory tests, myocardial infarction (clinical presentation and confirmatory tests), and multiple myocardial infarctions and/or coronary artery bypass grafting. Similarly, kidney function impairment is subdivided according to Kidney Disease Improving Global Outcomes (KDIGO) categories of estimated glomerular filtration rate (eGFR).¹⁵ Chronicity findings in the kidney biopsy were also graded according to the classification of the International Society of Nephrology/Renal Pathology Society.¹⁶

DISCUSSION

Using a combined data-driven and expert/patient-based consensus approach, domains, items, and subitems that reflect

Table 2. Summary median scores after the third round of Delphi exercise (in which 1 = not at all appropriate and 9 = completely appropriate)*

Candidate items	Median
Neuropsychiatric	
Ischemic or hemorrhagic stroke	9
Transverse myelitis	9
Cognitive impairment	8
Cranial neuropathy	8
Neurological sequelae (any) from neuropsychiatric SLE	8
Peripheral neuropathy	8
Seizure disorder	8
Dementia	7
Demyelinating disorder including multiple sclerosis	7
Movement disorders (ataxia, tremors, chorea, hemiballismus)	7
Psychosis	7
Executive function disorder	6
Radiographically proven brain atrophy	6
Autonomic disorder	5
Cognitive dyslexia	5
Encephalitis	5
Image changes captured by functional MRI or SPECT	5
Incapacitating headaches	5
Intracranial hypertension	5
Hearing impairment	4.5
Loss of sensation	4.5
Delirium	4
Mood disorder	4
Attempted suicide	3
Insomnia	3
Poor scholastic achievement	3
Tinnitus	3
Ocular	
Chloroquine and hydroxychloroquine maculopathy	9
Cataract	8
Optic atrophy	8
Permanent uniocular or binocular partial or complete loss of vision	8
Retinal necrosis and/or retinal detachment (chorioidopathy, lupus retinopathy, serous retinopathy, retinal thrombosis)	8
Corneal scarring/corneal ulceration	7
Proliferative retinopathy	7
Scleral thinning (as a result of anterior scleritis)	7
Chronic angle closure, open angle glaucoma, and steroid-induced glaucoma	6
Cicatricial ectropion (from DLE)	6
Madarosis (from DLE)	6
Optic neuropathy (due to ischemia or inflammation)	6
Persistent uveitis or scleritis	6
Retinal depigmentation and functional loss	6
Cicatricial conjunctivitis or symblepharon	5
Keratoconjunctivitis sicca	5
Acquired enophthalmos	4
Endocrine/metabolic	
Premature ovarian failure/primary ovarian insufficiency	9
Steroid-induced diabetes	8
Adrenal insufficiency	7
Diabetes mellitus	7
Arterial hypertension	6
Cushing syndrome	6

(Continued)

Table 2. (Cont'd)

Candidate items	Median
Metabolic syndrome	6
Reduced ovarian reserve	6
Testicular dysfunction with reduced sperm count and quality/gonadal dysfunction	6
Cachexia/wasting	5
Chronic fatigue syndrome	5
Erectile dysfunction	5
Hyperlipidemia	5
Hypopituitarism	5
Persistent weight gain	4
Anti-insulin receptor antibodies with recurrent hypoglycemia	3
Eating disorder	3
Hyperthyroidism	3
Hypothyroidism	3
Facial and/or extremity swelling	2
Growth and development	
Growth failure	8
Nontraumatic long bone fractures for children	8
Delayed puberty	7
Reduced final height	7
Disordered puberty sequences, eg, reaching menarche without/with minimal/less than expected growth spurt and breast or pubic hair development	6
Limb length discrepancies	5
Reproduction/pregnancy	
Congenital heart block	7
Hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, and/or eclampsia)	7
Infertility	6
Intra-uterine growth restriction, small for gestational age	6
Miscarriage/fetal loss	6
Obstetric antiphospholipid syndrome	6
Preterm birth	6
Stillbirth	6
Cervical dysplasia	5
Gestational diabetes	5
Low anti-Müllerian hormone levels	5
Neonatal lupus in offspring	4
Placental abruption	4
Hematologic	
Splenectomy (for ITP)	8
Aplastic anemia	7
Bone marrow failure (aplasia, myelodysplasia, or myelofibrosis)	7
Non-Hodgkin lymphoma	7
Spleen infarction	7
Treatment-related myelodysplastic syndrome	7
Antiphospholipid syndrome	6
Functional asplenia	6
Prolonged cytopenia	6
Splenic atrophy	6
Chronic anemia	5
Thrombocytopenia, leucopenia	5
Keloid scar linked to lymph node sampling	3
Gastrointestinal	
Bowel stricture	7
Budd-Chiari syndrome	7
Chronic ascites	7
Chronic liver disease and cirrhosis including nodular regenerative hyperplasia	7

(Continued)

Table 2. (Cont'd)

Candidate items	Median
Chronic peritonitis	7
End-stage liver disease	7
Malabsorption and protein losing enteropathy	7
Mesenteric insufficiency	7
Pancreatic insufficiency or need to use pancreatic enzyme replacement	7
Surgical resection of bowel below the duodenum, spleen, liver, or gallbladder	7
Vasculitis of the mesentery, esophagus, stomach, peritoneum, gallbladder, pancreas, or liver resulting in organ necrosis	7
Gastroparesis	6
Motility disorders including esophageal dysmotility and pseudo-bowel obstruction	6
Dysphagia	5
Myositis with dysphagia	5
Upper gastrointestinal tract surgery	5
Cholecystitis	3
Gastrointestinal bleed	3
Mesenteric adenitis	3
Bariatric surgery	2
Renal	
Chronic kidney disease	9
Decreased eGFR	9
End-stage renal disease	9
Renal biopsy findings (chronicity index > 4 OR interstitial fibrosis > 25% OR tubular atrophy > 25%)	8
Biopsy proven renal microangiopathy due to antiphospholipid syndrome even without GFR less than 50%	7
Chronic subnephrotic proteinuria	7
Proteinuria	7
Renal infarction	7
Renal tubular defect	7
Bladder dysfunction	5
Hemorrhagic cystitis	5
Nephritic syndrome	4
Hematuria	3
Renal calculi	3
Sterile pyuria	2
Cardiovascular	
Cardiomyopathy (ventricular dysfunction)	9
Myocardial infarction ever	9
Accelerated and early atherosclerosis	8
Angina or coronary artery bypass	8
Pericarditis, pericardial thickening, or pericardiectomy	8
Pulmonary hypertension	8
Valve vegetations	8
Carotid endarterectomy/stenting	7
Complete aortic valve stenosis	7
Conduction system disease	7
Myocardial fibrosis	7
Right ventricular dysfunction	7
Valve stenosis	7
Valve thickening	7
Arrhythmias	6
Arterial hypertension	6
Baseline oxygen requirement	6
Diastolic dysfunction	6
Valve regurgitation	6
Aortitis	5

(Continued)

Table 2. (Cont'd)

Candidate items	Median
Cardiogenic shock not due to sepsis	5
QT prolongation	5
Peripheral vascular	
Significant tissue loss ever (eg, loss of digit or limb)	9
Claudication	7
Intracardiac thrombus	7
Minor tissue loss (pulp space)	7
Renal artery stenosis	7
Severe Raynaud phenomenon	7
Thrombosis any (arterial or venous)	7
Venous thrombosis or venous stasis	7
Pulmonary	
Pulmonary fibrosis	9
Pulmonary hypertension	9
Pleural fibrosis, pleurodesis, or pleurectomy for refractory effusions	8
Pulmonary infarction or resection not for malignancy	8
Chronic diffuse alveolar hemorrhage	7
Lobectomy	7
Persistently decreased exercise tolerance/DLco due to ILD or pulmonary emboli	7
Respiratory insufficiency	7
Restrictive lung disease (based on pulmonary function test abnormalities)	7
Diminished lung function (decreased DLco, FEV ₁ , FVC)	6
Bronchiectasis	5
Obstructive airway disease	4
Obstructive sleep apnea	4
Musculoskeletal	
Avascular necrosis/Legg-Calve-Perthes disease/Perthes disease	9
Osteoporosis with fracture	9
Erosive arthritis	8
Fragility fractures	8
Jaccoud arthropathy	8
Joint replacement	8
Atrophy or weakness	7
Muscle atrophy	7
Osteoporosis without fracture	7
Tendon rupture	7
Osteomyelitis	6
Sarcopenia	6
Frailty	5
Osteomalacia	4
Fibromyalgia	3
Osteosclerosis	3
Septic arthritis	3
Chronic gout with erosion and tophi	2
Inflammatory joint pain	2
Skin/mucocutaneous	
Scarring chronic alopecia	9
Scarring (cutaneous)	8
Skin ulceration (excluding thrombosis) for >6 mo	8
Chronic discoid or subacute lesions	7
Cicatricial skin atrophy	7
Hyperpigmentation or hypopigmentation	7
Post venous thrombosis complications	7
Calcinosis	6
Extensive striae	6
Panniculitis	6
Alopecia without scarring	5
Hirsutism	5

(Continued)

Table 2. (Cont'd)

Candidate items	Median
Lipodystrophy	5
Nasal septum perforation	5
Periodontal disease with tooth loss	5
Persistent malar rash	5
Severe livedo reticularis	5
Severe photosensitivity limiting activities of daily living	5
Sjögren syndrome	5
Telangiectasia	5
Xerostomia	5
Easy bruisability	3
Onychodystrophy	3
Others	
Malignancy	8
Organ transplantation (nonkidney)	8
Treatment-related damage	8
Persistent hypogammaglobulinemia	7
Severe or recurrent infections	7
Carcinoma in situ (any site)	6
Work disability	6
Social isolation	4
Poverty	3

* DLco, diffusing capacity for carbon monoxide; DLE, discoid lupus erythematosus; eGFR, estimated glomerular filtration rate; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, interstitial lung disease; ITP, immune thrombocytopenia; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; SPECT, single-photon emission computerized tomography.

the new damage construct in SLE have been developed consisting of 39 candidate items across 13 domains to be taken forward to the next stages. During the item generation phase, just over half of all items were nominated by both literature review and Delphi exercise. The Delphi exercise, which included a wide and diverse group of contributors, provided 103 unique items for further consideration. Our data confirm the value of large group exercises to maximize the scope of new items to consider for a revised index. Novel contributions to the development of the new damage index include the addition of pediatric growth items, use of prediagnosis SLE-related damage, and graded severity subitems.

Eleven individual items from the original SDI were excluded, including cranial neuropathy and proteinuria, or subsumed in newly defined items, including pleural fibrosis and skin ulceration. The neuropsychiatric clinical domain group recommended excluding cranial neuropathy, as this rare manifestation is usually reversible with therapy and more often reflects disease activity than irreversible damage.¹⁷ In the SLICC Inception Cohort, Hanly et al observed that over 50% of cranial neuropathies had resolved by one year. Time to resolution was also significantly shorter than for peripheral neuropathies, supporting the view that cranial neuropathies in SLE are typically manifestations of activity. Moreover, the prevalence of persistent cranial neuropathies that might reflect damage was well below 1%, so this item was excluded on the grounds of both reversibility and rarity.¹⁸ Similarly, multiple studies indicate that SLE psychosis is often transient and reversible and is strongly associated with disease

Table 3. Proposed revised lupus damage index glossary (score only the worst outcome for each item)*

Domain, item, and subitem	Definition and duration
Neuropsychiatric	
Ischemic or hemorrhagic stroke	Imaging evidence (CT or MRI) of infarct or hemorrhage without an associated clinical syndrome. Duration: once item definition is met.
Asymptomatic (imaging only)	
Single symptomatic stroke	Acute focal neurologic deficit persisting more than 24 h with a corresponding CT or MRI abnormality (infarct or hemorrhage) consistent with the clinical syndrome. Duration: once item definition is met.
More than one stroke	Evidence of multiple strokes at different anatomic sites. This item includes ischemic or hemorrhagic spinal cord events. Nonspecific white matter changes on MRI are not considered organ damage. This definition is adapted from the 1999 ACR nomenclature. ³³ Duration: once item definition is met.
Demyelinating disease (including transverse myelitis)	Monophasic or relapsing CNS demyelinating syndrome, based on a combination of clinical findings typical for CNS demyelination and supportive abnormalities on neuroimaging (typically MRI). ³⁴ Includes transverse myelitis, ³⁴ multiple sclerosis, ³⁵ neuromyelitis optica spectrum disorders, ³⁶ SLE-related demyelination, and other causes of demyelinating disease. Isolated optic neuritis is excluded here as any visual loss will be captured elsewhere (see Ocular domain). Duration: 6 mo.
Cognitive impairment	Evidence of cognitive decline from a previous level of performance in one or more cognitive domain (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on the following: concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function AND a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. ³⁷ Duration: 6 mo.
Mild neurocognitive impairment	Cognitive deficits are insufficient to interfere with independence in everyday activities (eg, instrumental activities of daily living) but greater effort, compensatory strategies, or accommodation may be required. Duration: 6 mo.
Major neurocognitive impairment	Cognitive deficits are sufficient to interfere with independence in everyday activities (eg, instrumental activities of daily living). Cognitive deficits must not occur exclusively in the context of a delirium. Duration: 6 mo.
Peripheral neuropathy	Polyneuropathy is a disorder of sensory and motor peripheral nerves characterized by symmetry of symptoms and physical findings in a distal distribution. ³³ Mononeuropathy (single/multiplex) is the disturbed function of one or more peripheral nerves resulting in weakness or sensory dysfunction due to either conduction block in motor fibers or axonal loss. ³³ Requires clinical demonstration of sensory and/or motor deficits on neurologic examination with corresponding abnormalities on electromyography and/or nerve conduction studies. ³³ Small fiber neuropathy is not included as objective testing methods for confirmation of this diagnosis are not readily available in most centers. Duration: 6 mo.
Seizure disorder	Recurrent unprovoked seizures (defined as two or more, at least 24 h apart) with ongoing high probability of recurrence OR a single unprovoked seizure with a high probability of recurrence based on abnormalities identified on brain MRI and/or EEG. Isolated seizure occurring in the context of active SLE is not considered organ damage. Use of anticonvulsant therapy should not be included in the item definition, as this is highly dependent on physician practice patterns and other contextual factors. Duration: 6 mo.
Ocular	
Cataract or antimalarial maculopathy identified without objective visual loss	Cataract and/or antimalarial maculopathy identified <i>without objective visual loss</i> . Duration: 6 mo.
ANY ocular disease resulting in the following:	ANY ocular disease resulting in the following:
Partial visual loss affecting the peripheral visual field alone (uniocular or binocular)	Partial visual loss affecting the peripheral visual field alone (uniocular or binocular). Duration: 6 mo.
Partial visual loss affecting the central visual field alone (uniocular or binocular)	Partial visual loss affecting the central visual field alone (uniocular or binocular). Duration: 6 mo.
Unilateral complete visual loss affecting both central and peripheral visual fields	Unilateral complete visual loss affecting both central and peripheral visual fields. Duration: 6 mo.
Binocular complete visual loss affecting both central and peripheral visual fields	Binocular complete visual loss affecting both central and peripheral visual fields. Duration: 6 mo. Score the worst outcome/stage for the patient. See references. ^{38–40}

(Continued)

Table 3. (Cont'd)

Domain, item, and subitem	Definition and duration
Endocrine	
Premature Ovarian Insufficiency (POI)	POI is the onset of hypergonadotropic hypogonadism before the age of 40 y due to any cause. Criteria for diagnosis: irregular menses for greater than 3 mo without another endocrine disorder (thyroid hormonal dysfunction, hyperprolactinemia) AND elevated FSH > 30 mIU/mL on 2 measurements assessed at least 1 mo apart. Some women with POI present with infertility. ^{31,32} Duration: more than 3 mo.
Diabetes mellitus, including steroid-induced diabetes	Hyperglycemia that fulfills any of the following criteria: (a) fasting plasma glucose $\geq$ 126 mg/dL (7 mmol/L), (b) 2-h plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) with an oral glucose tolerance test, (c) presence of osmotic symptoms (eg, polyuria, polydipsia) of hyperglycemia with a random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L), or (d) HbA _{1c} $\geq$ 6.5. ⁴¹ HbA _{1c} will not be elevated in acute hyperglycemia. Duration: 6 mo.
Adrenal insufficiency	Inadequate cortisol secretion by the adrenal glands. Low early morning (6–9 AM) basal serum cortisol concentration ($\leq$ 3 mcg/dL [80 nmol/L]) is consistent with adrenal insufficiency. Early morning basal serum cortisol concentration ($\geq$ 13 to 14 mcg/dL [$\geq$ 360 to 390 nmol/L]) rules out adrenal insufficiency. When the morning basal serum cortisol concentration is >3 mcg/dL (>80 nmol/L) but <13 to 14 mcg/dL (<360 to 390 nmol/L), a standard ACTH stimulation test should be performed. Peak serum cortisol after ACTH stimulation $\geq$ 18 mcg/dL (500 nmol/L) rules out adrenal insufficiency. ^{42–45} Duration: 6 mo.
Cushing's syndrome	Cushing's syndrome is diagnosed clinically with typical clinical and phenotypic features in a patient taking chronic glucocorticoid therapy. If endogenous Cushing syndrome is present, then confirmation by specialist investigations is required. ^{46–48} Duration: 6 mo.
Testicular dysfunction with reduced sperm counts and quality	Low serum testosterone concentration and/or sperm count associated with elevated serum luteinizing hormone and/or FSH concentrations. Fasting serum total testosterone should be assessed between 8 and 10 AM on at least two occasions. ⁴⁹ Duration: 6 mo.
Growth and development	
Growth failure or reduced final height	Final height lower than the midparental range or $\leq$ 2 SD under the mean race/sex-adjusted height as per national growth charts or the World Health Organization growth chart when measured first at age 18 y and again at or after age 20 y. Duration: once item definition is met.
Gastrointestinal	
Surgical resection of bowel below the duodenum, spleen, liver, or gallbladder: 1 site More than 1 site	Surgical resection (documented in the medical record) of bowel below the duodenum, spleen, liver, or gallbladder. Duration: once item definition is met.
Motility disorders including esophageal dysmotility and pseudo-bowel obstruction	Esophageal dysmotility or pseudo-obstruction are defined by a combination of typical clinical symptoms and confirmatory testing including relevant imaging and motility/manometry studies. ⁵⁰ If due to malignancy, do not score the item here; instead use the Malignancy domain. Duration: 6 mo.
Renal	
Renal function impairment: eGFR 30–59 (G3a–G3b) eGFR 15–29 (G4) eGFR < 15 (G5) OR hemo/peritoneal dialysis OR renal transplantation	Renal function impairment is defined according to the KDIGO categories ¹⁵ of estimated GFR: eGFR > 90 (G1), eGFR 60–89 (G2), eGFR 45–59 (G3a), eGFR 30–44 (G3b), eGFR 15–29 (G4), or eGFR <15 (G5). Duration: renal function impairment must persist for 12 mo or more. Dialysis must be present for 6 mo or more. Transplantation once item definition is met.
Chronicity on renal biopsy: Chronicity index 2–4 Chronicity index > 4	Renal biopsy findings are scored according to modified NIH activity and chronicity indices. ¹⁶ Duration: once item definition is met.
Cardiovascular	
Cardiomyopathy (ventricular dysfunction): Heart failure with preserved EF ($\geq$ 50%) Heart failure with mildly reduced EF (41%–49%) Heart failure with reduced EF ($\leq$ 40%) Heart failure with improved EF	Cardiomyopathy (ventricular dysfunction) is defined using echocardiographic documentation of LVEF ⁵¹ : LVEF $\geq$ 50% with evidence of spontaneous or provokable increased LV filing pressures (eg, elevated natriuretic peptides, noninvasive and invasive hemodynamic measurement). Duration: 6 mo. LVEF 41%–49%, measured by echocardiogram, with evidence of spontaneous or provokable increased LV filing pressures (eg, elevated natriuretic peptides, noninvasive and invasive hemodynamic measurement). Duration: 6 mo. LVEF $\leq$ 40%, measured by echocardiogram. Duration: 6 mo. Previous LVEF $\leq$ 40% with follow-up >40% and improvement persisting for 6 mo or more. Duration: 6 mo.

(Continued)

Table 3. (Cont'd)

Domain, item, and subitem	Definition and duration
Ischemic heart disease	
Asymptomatic ischemia	Asymptomatic ischemia as identified on any of the following: EKG and/or stress testing and/or cardiac MRI. Duration: 6 mo.
Symptomatic angina	Symptomatic angina as confirmed by EKG and/or stress test and/or cardiac catheterization and/or cardiac MRI. Duration: 6 mo.
MI and/or stenting in one coronary artery or one region of a single artery	MI documented by clinical presentation and confirmatory EKG evidence and positive troponins and/or stenting in one coronary artery or one region of a single artery. Duration: once item definition is met.
Multiple MIs and/or coronary artery by-pass grafting and/or stenting in 2 separate regions of 1 artery or 2 or more arteries	Multiple MIs and/or coronary artery by-pass grafting/stenting in 2 separate regions of 1 artery or 2 or more arteries. Duration: once item definition is met.
Vegetations or thickening on any valve	Based on the American Society of Echocardiography guidelines, ⁵² valve vegetation is defined as shaggy, lobulated, or rounded masses typically located on the atrial side of atrioventricular valves (mitral valve and tricuspid valve) or ventricular side of the aortic valve but can be located on any side of any valve. These can occur as the following: Vegetations/thickening without valvular dysfunction. Duration: 6 mo.
Vegetations/thickening without valvular dysfunction	Vegetations/thickening without valvular dysfunction. Duration: 6 mo.
Vegetations/thickening with mild-moderate valvular dysfunction	Vegetations/thickening with mild-moderate valvular dysfunction. Duration: 6 mo.
Vegetations/thickening with severe valvular dysfunction OR valve replacement	Vegetations/thickening with severe valvular dysfunction OR valve replacement. Duration: 6 mo.
Pulmonary hypertension	
Pulmonary hypertension: right heart catheterization showing mean pulmonary artery pressure > 20 mm Hg or echocardiogram showing estimated pulmonary artery systolic pressure > 40 mm Hg	Right heart catheterization showing mean pulmonary artery pressure > 20 mm Hg or echocardiogram showing estimated pulmonary artery systolic pressure > 40 mm Hg. Duration: 6 mo.
Pulmonary hypertension with cor pulmonale	Right heart catheterization showing mean pulmonary artery pressure > 20 mm Hg or echocardiogram showing estimated pulmonary artery systolic pressure > 40 mm Hg AND evidence of alteration of the right heart structure and function due to pulmonary hypertension. See reference. ⁵³ Duration: 6 mo.
Pericarditis, pericardial thickening, or pericardiectomy	Chronic and persisting signs and symptoms of pericarditis and/or pericardial thickening demonstrated on imaging. Surgical removal of part or all of the pericardium surrounding the heart. Duration: 6 mo.
Carotid endarterectomy/stenting	Insertion of an expandable wire mesh tube or coil into the artery to maintain blood flow. Duration: 6 mo.
Vascular	
Arterial thrombosis including organ infarcts other than MI and stroke	Arterial thrombosis with organ infarction of any organ other than the heart or brain. Duration: once item definition is met.
Peripheral ischemia/gangrene with tissue loss: 1 site More than 1 site	Ischemia and/or gangrene with tissue loss due to involvement of a specific vascular structure (artery, vein). Imaging studies such as doppler, or ankle-brachial index test, to identify the vascular structure is recommended but not required for inclusion. ⁵⁴ Duration: 6 mo.
Peripheral arterial disease	Objective evidence of peripheral arterial vascular insufficiency demonstrated by ankle-brachial doppler testing or angiography with or without classic symptoms of intermittent claudication without ischemic damage or gangrene. Duration: 6 mo.
Post-venous thrombosis complications	Extremity swelling, skin discoloration, nonhealing ulceration, and/or amputation. Duration: 6 mo.
Pulmonary	
Pulmonary Fibrosis (PF) mild-moderate PF	Evidence for PF due to any cause ⁵⁵⁻⁵⁸ by HRCT (less than 20% of lung areas) at any time AND impaired PFT with FVC 50%-80% that persists for at least 6 mo. Duration: 6 mo.
advanced PF	Clinical evidence (fine crackles) and/or extensive fibrosis, due to any cause, identified by chest radiograph ²⁹ OR evidence for advanced PF by HRCT (>20% of lung areas) OR impaired PFTs with FVC < 50%. Duration: 6 mo.
Pulmonary infarction or resection not for malignancy	Peripheral wedge-shaped consolidation with a convex medial border on x-ray ⁵⁹ OR CT angiogram (peripheral wedge-shaped broad pleural parenchymal density). Duration: once item definition is met.

(Continued)

Table 3. (Cont'd)

Domain, item, and subitem	Definition and duration
Chronic dyspnea	Chronic dyspnea not related to daily activity with severely impaired PFTs without advanced PF due to any cause including pathology related to the lungs and pleura. Examples include shrinking lung (diaphragmatic elevation by x-ray and/or >20% decrease of FVC in supine position) and pleural fibrosis (x-ray or CT). ^{56,60,61} Duration: 6 mo.
Musculoskeletal	
Avascular necrosis:	
1 site	Regional death of cellular elements of bone, typically in a subchondral location, due to a disruption in the blood supply leading to ischemia, infarction. ^{62–64} Duration: once item definition is met.
More than 1 site	
Osteoporosis with fracture or nontraumatic long bone fractures for children	Low-energy bone fracture or spinal fracture or nontraumatic long bone fractures for children with radiologic evidence of bone loss on bone densitometry. ⁶⁵ Duration: once item definition is met.
Erosive arthropathy	Loss of mineralized tissue at marginal or juxta-articular sites, commonly associated with a break in the cortical lining visualized on plain radiographs, CT, or MRI or demonstrated on 2 planes on ultrasonography. ^{66,67} Duration: 6 mo.
Jaccoud arthropathy	Reducible joint deformities such as swan neck, thumb subluxation, ulnar deviation, “boutonniere,” and Z-thumb, with or without evidence of erosions on plain radiograph. ^{68,69} Duration: 6 mo.
Joint replacement	Elective replacement of any joint(s) due to joint or bone diseases, regardless of the SLE disease activity at the time of joint replacement. ^{70,71} Duration: once item definition is met.
Tendon rupture	Atraumatic rupture of one or more tendons regardless of SLE disease activity at the time of diagnosis of tendon rupture. ^{72,73} Duration: once item definition is met.
Skin/mucocutaneous	
Cutaneous scarring or atrophy (including lipoatrophy):	
Affecting the trunk and/or extremities	Cutaneous scarring or atrophy (including lipoatrophy): in defining this item, the anatomic location and extent should be noted. The scalp is <i>excluded</i> from this item; see Figure 1a. Duration: 6 mo.
Affecting the head and/or neck (excluding the scalp, Figure 1a)	
Dyspigmentation:	
More than 6 mo but less than 12 mo duration	May be hyperpigmentation or hypopigmentation and duration of changes should be considered when scoring this item.
More than 12 mo duration	
Scarring chronic alopecia:	
1 quadrant	The scalp anatomic boundaries are the natural hairline (follicles present) OR, if bald, the frontal border begins 8 cm from the midpoint of the glabella and extends 8 cm left and right from that midpoint. For the back of the head, the theoretical hairline would end at 8 cm below the external occipital protuberance (Figure 1a). ⁷⁴ Divide the scalp into 4 quadrants as shown in Figure 1b. ⁷⁴ Duration: 6 mo.
2 quadrants	
3–4 quadrants	
Malignancy	
Malignancy:	
Non-melanoma skin cancer	Any malignancy diagnosed by a combination of clinical, imaging, and histologic features that confirm cancer. Duration: once item definition is met.
Any other primary malignancy	
Two or more malignancies	
Organ transplantation	
Organ transplantation (non-kidney)	Transplantation of any organ apart from the kidney (see Renal domain). Duration: once item definition is met.

* Items and subitems are presented in their relevant clinical domains. Items with subitems are defined to reflect current guidelines and/or clinical expert opinion. Items and subitems need to be present for a minimum of 6 mo unless otherwise stated in bold. Acute events can be defined once the item occurs. Items occurring after the diagnosis of SLE DO NOT need to be directly attributed to SLE. Items occurring before the diagnosis of SLE should be scored if attributable to an SLE-related process^a by the assessor. Only score the highest scoring subitem for each item. ACR, American College of Rheumatology; ACTH, adrenocorticotropic hormone; CNS, central nervous system; CT, computed tomography; EEG, electroencephalography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EKG, electrocardiogram; FSH, follicle-stimulating hormone; FVC, forced vital capacity; GFR, glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; HRCT, high resolution computerized tomography; KDIGO, Kidney Disease Improving Global Outcomes; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; PF, pulmonary fibrosis; PFT, pulmonary function test; POI, premature ovarian insufficiency; SLE, systemic lupus erythematosus.

^a Examples of an “SLE-related process” before the diagnosis of SLE could include manifestations of antiphospholipid syndrome, interstitial lung disease due to a disease process that evolves into SLE, or deforming inflammatory arthritis that evolves into SLE.

activity. Paholpak et al found that 97.1% of psychotic episodes (36 episodes in 35 patients) fully remitted.¹⁹ Hanly et al reported that more than 80% of psychotic events had resolved by the second annual assessment following the onset of the event.²⁰ Proteinuria, another excluded item, did not reach the threshold for inclusion with the item reduction committee. Its inclusion was also reconsidered and reviewed by the renal clinical domain group. Persistent proteinuria can reflect either inflammatory

activity or chronic damage.²¹ When linked to chronic damage, it is frequently accompanied by other measures of kidney damages, such as reduced eGFR or chronicity features on biopsy, which are already captured in our item list. Furthermore, the growing long-term use of antiproteinuric therapy in patients with lupus nephritis may impact and cause fluctuations in the levels of proteinuria over time. For all the above reasons, the consensus was that proteinuria was excluded.

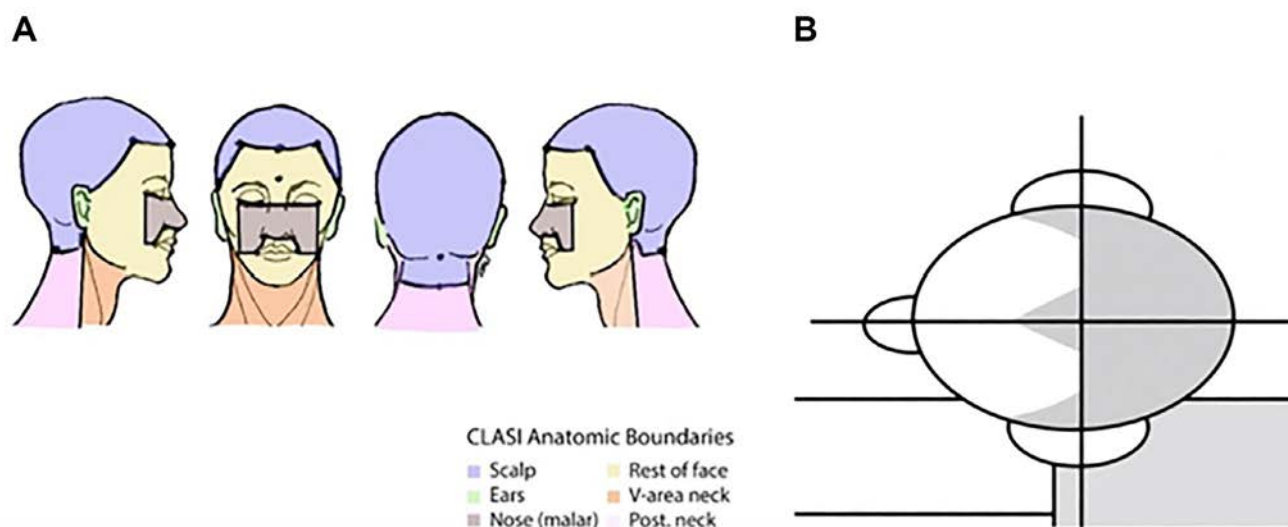


Figure 1. Anatomic boundaries of (A) the scalp and (B) the four quadrants of the scalp using the CLASI boundaries.⁷⁴ CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index. Figure 1B was AI generated by Google Gemini. [Correction added on 16 September 2026, after first online publication: The figure caption has been updated to include the declaration that Figure 1B image was AI-generated using Google Gemini.]

With the exception of surgical resection of bowel below the duodenum, spleen, liver, or gallbladder (not for malignancy) and motility disorders including esophageal dysmotility and pseudo-bowel obstruction, most GI domain items were excluded as they were deemed infrequent (excluded for relevance) by the respective clinical domain group. The Spanish historical cohort study (RELESSER) reported GI damage in 3.7% of 3,658 SLE cases, distributed as follows: infarction or resection involving the bowel, spleen, or liver (2.8%); pancreatic insufficiency (0.3%); stricture or upper GI surgery (0.3%); mesenteric insufficiency (0.2%); and chronic peritonitis (0.2%).²² Liver involvement and other GI manifestations are not included in the 2019 EULAR/ACR Classification Criteria for SLE.^{10,13} However, 25% to 50% of patients with SLE may experience transient liver disease, predominantly subclinical, with mild liver enzyme elevations seen in up to one-third of patients as part of active disease.^{23,24} Despite this, large-scale multicenter studies indicate that liver involvement is a rare cause of morbidity or mortality in patients with SLE.²⁵

Hematology and reproduction/pregnancy were two newly proposed organ systems during the item generation phase. The item reduction committee excluded all reproduction/pregnancy items and half of the hematology items. Reproductive and pregnancy-related items were not deemed consistent with the current construct of damage. For example, pre-eclampsia and adverse pregnancy outcomes have been shown to be risk factors for future cardiovascular disease in women in the general population.²⁶ In addition, congenital heart block, although proposed, does not affect the mother and so does not reflect the damage construct in the mother.

For hematology, items such as aplasia, myelodysplasia, or myelofibrosis due to SLE were excluded as they are rare events that may resolve with treatment. For instance, Chalayer et al studied 30 patients with bone marrow involvement from 19 centers. They

reported that 24 episodes (including relapses) showed a treatment response, with a mean time to resolution of 9 months (range 1–75 months). Several cases of myelofibrosis in this cohort also demonstrated clinical improvement.²⁷ Additionally, the hematology clinical domain group suggested removing splenectomy and splenic infarction to prevent double counting, as these overlapped with items in other organ systems, namely surgical resection of the spleen in the GI domain and arterial thrombosis in the vascular domain.

A novel feature from this phase is the clustering of items under domains and subdivision of some items into subitems. The clinical domain groups recommended clustering related items within each domain. This is similar to the recommendation given by an SLE expert panel in the development of the EULAR/ACR classification criteria, in which items are clustered if they are clinically or physiologically linked.²⁸ For example, mild and major cognitive impairment items are separated only by the degree in severity. Similarly chronic kidney disease is defined in stages aligned to widely used international guidance. Furthermore, the clinical domain groups proposed subdividing items into subitems based on severity or grade. In some instances, the subitems are based on pre-existing internationally accepted categories (eg, KDIGO thresholds for eGFR¹⁵), whereas others are based on expert clinical recommendations (neurocognitive impairment includes mild and major impairment). The ability to delineate subitems offers a more detailed and clinically relevant assessment of organ damage in patients with SLE. It reflects current evidence-based medical practice and is likely to improve sensitivity of the index in SLE populations. This improvement in sensitivity of measuring damage with SLE may result in an amelioration of the floor effect observed in the original SDI and result in improved sensitivity to change. For example, the threshold to score damage in the kidney now includes both chronicity on renal biopsy findings (not previously included) and an eGFR of

Table 4. Patient assessment sheet for proposed revised lupus damage index*

Domain	Item and subitem	
Neuropsychiatric	Ischemic or hemorrhagic stroke:	
	• Asymptomatic (imaging only)	☐ Yes ☐ No
	• Single symptomatic stroke	☐ Yes ☐ No
	• More than one stroke	☐ Yes ☐ No
	Demyelinating disease (including transverse myelitis)	☐ Yes ☐ No
	Cognitive impairment:	
	• Mild neurocognitive impairment	☐ Yes ☐ No
	• Major neurocognitive impairment	☐ Yes ☐ No
	Peripheral neuropathy	☐ Yes ☐ No
	Seizure disorder	☐ Yes ☐ No
Ocular	Ocular damage:	
	• Cataract or antimalarial maculopathy identified without objective visual loss	☐ Yes ☐ No
	ANY ocular disease resulting in the following:	
	• Partial visual loss affecting the peripheral visual field alone (uniocular or binocular)	☐ Yes ☐ No
	• Partial visual loss affecting the central visual field alone (uniocular or binocular)	☐ Yes ☐ No
	• Uniocular complete visual loss affecting both central and peripheral visual fields binocular	☐ Yes ☐ No
Endocrine	• Binocular complete visual loss affecting both central and peripheral visual fields	☐ Yes ☐ No
	Premature ovarian insufficiency	☐ Yes ☐ No
	Diabetes mellitus, including steroid-induced diabetes	☐ Yes ☐ No
	Adrenal insufficiency	☐ Yes ☐ No
	Cushing syndrome	☐ Yes ☐ No
	Testicular dysfunction with reduced sperm counts and quality	☐ Yes ☐ No
Growth and development	Growth failure or reduced final height	☐ Yes ☐ No
Gastrointestinal	Surgical resection of bowel below the duodenum, spleen, liver, or gallbladder:	
	• 1 site	☐ Yes ☐ No
	• More than 1 site	☐ Yes ☐ No
Renal	Motility disorders including esophageal dysmotility and pseudo-bowel obstruction	☐ Yes ☐ No
	Renal function impairment:	
	• eGFR 30–59 (G3a–G3b)	☐ Yes ☐ No
	• eGFR 15–29 (G4)	☐ Yes ☐ No
	• eGFR < 15 (G5) OR hemo/peritoneal dialysis OR renal transplantation	☐ Yes ☐ No
	Chronicity on renal biopsy:	
	• Chronicity index (2–4)	☐ Yes ☐ No
Cardiovascular	• Chronicity index (>4)	☐ Yes ☐ No
	Cardiomyopathy (ventricular dysfunction):	
	• Heart failure with preserved EF (≥50%)	☐ Yes ☐ No
	• Heart failure with mildly reduced EF (41%–49%)	☐ Yes ☐ No
	• Heart failure with reduced EF (≤40%)	☐ Yes ☐ No
	• Heart failure with improved EF (previously ≤40% with follow-up >40%)	☐ Yes ☐ No
	Ischemic heart disease:	
	• Asymptomatic ischemia	☐ Yes ☐ No
	• Symptomatic angina	☐ Yes ☐ No
	• MI and/or stenting in one coronary artery or one region of a single artery	☐ Yes ☐ No
	• Multiple MIs and/or coronary artery by-pass grafting and/or stenting in 2 separate regions of 1 artery or 2 or more arteries	☐ Yes ☐ No
	Vegetations or thickening on any valve:	
	• Vegetations/thickening without valvular dysfunction	☐ Yes ☐ No
	• Vegetations/thickening with mild-moderate valvular dysfunction	☐ Yes ☐ No
	• Vegetations/thickening with severe valvular dysfunction OR valve replacement	☐ Yes ☐ No
	Pulmonary hypertension:	
	• Right heart catheterization showing mean pulmonary artery pressure > 20 mm Hg or echocardiogram showing estimated pulmonary artery systolic pressure > 40 mm Hg	☐ Yes ☐ No
	• Pulmonary hypertension with cor pulmonale	☐ Yes ☐ No
	Pericarditis, pericardial thickening, or pericardiectomy	☐ Yes ☐ No
	Carotid endarterectomy/stenting	☐ Yes ☐ No
Vascular	Arterial thrombosis including organ infarcts other than MI and stroke	☐ Yes ☐ No
	Peripheral ischemia/gangrene with tissue loss:	
	• 1 site	☐ Yes ☐ No
	• More than 1 site	☐ Yes ☐ No

(Continued)

Table 4. (Cont'd)

Domain	Item and subitem	
Pulmonary	Peripheral arterial disease	☐ Yes ☐ No
	Post-venous thrombosis complications	☐ Yes ☐ No
	Pulmonary fibrosis:	
	• Mild or moderate pulmonary fibrosis	☐ Yes ☐ No
	• Advanced pulmonary fibrosis	☐ Yes ☐ No
Musculoskeletal	Pulmonary infarction or resection not for malignancy	☐ Yes ☐ No
	Chronic dyspnea	☐ Yes ☐ No
	Avascular necrosis	
	• 1 site	☐ Yes ☐ No
	• More than 1 site	☐ Yes ☐ No
	Osteoporosis with fracture or nontraumatic long bone fractures for children	☐ Yes ☐ No
	Erosive arthropathy	☐ Yes ☐ No
	Jaccoud arthropathy	☐ Yes ☐ No
	Joint replacement	☐ Yes ☐ No
	Tendon rupture	☐ Yes ☐ No
Skin/mucocutaneous	Cutaneous scarring or atrophy (including lipoatrophy):	
	• Affecting the trunk and/or extremities	☐ Yes ☐ No
	• Affecting the head and/or neck (excluding the scalp)	☐ Yes ☐ No
	Dyspigmentation	
	• More than 6 mo but less than 12 mo duration	☐ Yes ☐ No
	• More than 12 mo duration	☐ Yes ☐ No
	Scarring chronic alopecia:	
	• 1 quadrant	☐ Yes ☐ No
	• 2 quadrants	☐ Yes ☐ No
	• 3–4 quadrants	☐ Yes ☐ No
Malignancy	Malignancy	
	• Nonmelanoma skin cancer	☐ Yes ☐ No
	• Any other primary malignancy	☐ Yes ☐ No
	• 2 or more malignancies	☐ Yes ☐ No
Organ transplantation	Organ transplantation (nonkidney)	☐ Yes ☐ No

* Items and subitems are presented in their relevant clinical domains. Items with subitems are defined to reflect current guidelines and/or clinical expert opinion. Items and subitems need to be present for a minimum of 6 mo unless otherwise stated in the glossary. Items occurring after the diagnosis of SLE DO NOT need to be directly attributed to SLE. Items occurring before the diagnosis of SLE should be scored if attributable to an SLE-related process^a by the assessor. Only score the highest scoring subitem for each item. EF, ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SLE, systemic lupus erythematosus.

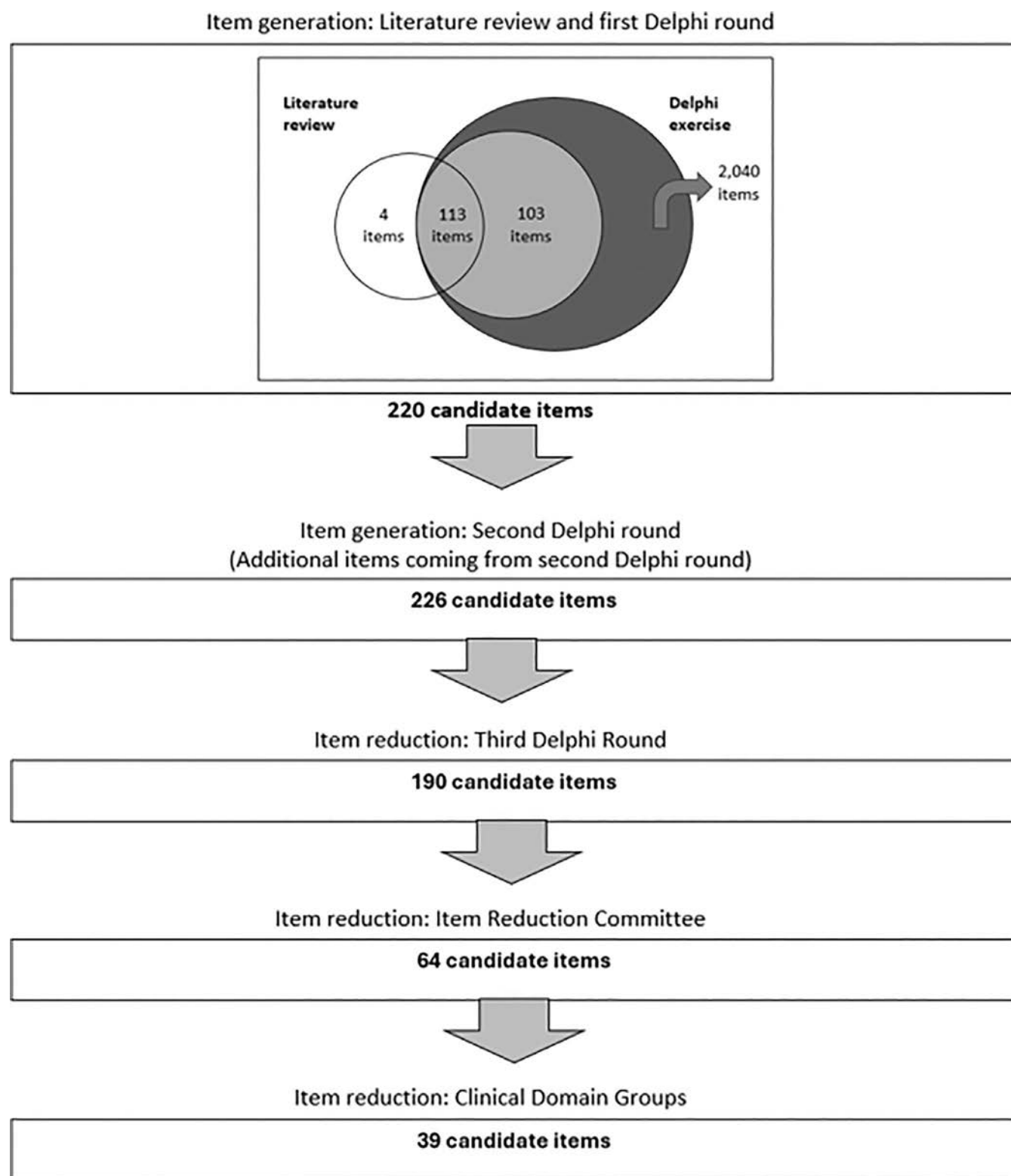
^a Examples of an “SLE-related process” before the diagnosis of SLE could include manifestations of antiphospholipid syndrome, interstitial lung disease due to a disease process that evolves to SLE, or deforming inflammatory arthritis that evolves to SLE. [Correction added on 16 September 2026, after first online publication: The table footnote has been updated to remove the statement “Score only the worst outcome for each item.”]

60% or less, which is a higher eGFR threshold than currently in the SDI (<50%). For pulmonary fibrosis, the chest radiograph (current SDI) has a sensitivity of 63% compared to high resolution computerized tomography (included in our new definition), the current clinical criterion standard²⁹; likewise in pulmonary hypertension, a loud P2 and/or parasternal heave (current SDI) have sensitivities of 30% to 40% compared to the gold standard of right heart catheterization (100% sensitivity) of the new proposed index.³⁰

For each item, we also specifically asked the respective expert group to determine whether a timing of six months or more was an evidence-based way to reflect the construct of damage for that particular item. For most items, the six-month duration was deemed a practical and plausible duration to distinguish activity from damage. For a small number of items, some of the definitions vary from the six-month cut point. For example, ovarian insufficiency requires only a three-month persistence, aligned with international guidance.^{31,32} Similarly, dyspigmentation has a 12-month threshold, reflecting expert opinion that the time reversibility of dyspigmentation can take up to 12 months, beyond which it is likely to be permanent.

Our study has several strengths. First, an inclusive sample of diverse individuals with respect to sex, age, race, clinical experience, and specialties ensures a broad representation of perspectives within both lupus research as well as patient communities. The heterogeneity in our sample population not only adds to the generalizability of study findings but also gives assurance to the insights drawn from the item generation and iterative reduction phases. Our process involved careful refinement across multiple rounds, providing high face validity in capturing a wide range of items covering damage accrual in SLE. In addition, the integration of patient input throughout the study—from study design to item evaluation—reflects a commitment to research that is patient-centric and ensures that this SDI revision is aligned with the needs and perceptions of those living with lupus.

We acknowledge several limitations of this study. First, the reliance on a nonsystematic literature review during the item generation phase may have introduced bias and potentially overlooked relevant literature. To minimize the risk of omitting relevant damage items, we increased the Delphi rounds from two to three. In the first and second rounds of the Delphi exercise,



*2,040 initial ("raw") items were removed following clustering of overlapping items and harmonization of synonymous terms.

Figure 2. Number of candidate items identified during the item generation and item reduction phases of the revised SDI development. SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

we included an open-ended question asking participants to nominate any items that potentially could be relevant for a revised SDI. Second, the underrepresentation of participants from low- and middle-income countries (LMICs) raises questions about the generalizability of the study findings to these regions. To address this gap, we purposely shared our preliminary item list with several LMICs, including countries in Africa. A key reflection from this was that a new index has the potential to support colleagues in LMIC settings to lobby policy makers and payers for better standards of care for their patients. So, although some diagnostics are not yet globally available, retaining these definitions will help raise standards of care for patients with SLE across LMIC settings. LMIC physicians will also be involved in later steps in the index development.

Our item generation and reduction phases have resulted in 39 candidate items to be taken forward to the next stages. The removal of outdated items, items now known to reflect inflammation, and the inclusion of new items, including pediatric items, better reflects the modern construct of damage in SLE across the life course. The inclusion of subitems based on severity or grade is novel. It reflects the evolution in current evidence-based medical practice over the past 30 years and so is likely to improve sensitivity of the index in SLE populations. The next phases will evaluate the item thresholds, how the weight of each item and subitem contributes to the concept of damage in SLE, and the validation of the revised SDI.

ACKNOWLEDGMENTS

This article has been simultaneously co-published by Arthritis Care & Research and Lupus Science & Medicine® and jointly published by Wiley Periodicals LLC and BMJ Publishing Group Ltd. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Bruce confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Integrating Patient-Reported Quality Measures in Systemic Lupus Erythematosus: Development of the American College of Rheumatology Implementation Guide

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Objective. To support high-quality, patient-centered care for systemic lupus erythematosus (SLE), the American College of Rheumatology (ACR) developed evidence-based measures incorporating clinical and patient-reported outcome measures (PROMs). Using the Consolidated Framework for Implementation Research (CFIR), we conducted semistructured interviews with rheumatologists and support staff who piloted these measures. Insights from these interviews informed development of the SLE Quality Measures Implementation Guide for national dissemination.

Methods. Five rheumatology practices were selected to pilot workflows for collecting SLE PROMs recommended in recent ACR guidelines for at least 50 consecutive patients. Measures included physical function (PF) and depression. After data collection, representatives from each practice participated in virtual semistructured interviews. Interviews were recorded, transcribed verbatim, and analyzed thematically using both deductive and inductive techniques. Findings were used to develop the SLE Quality Measures Implementation Guide.

Results. A total of 31 clinicians across five practices participated in the pilot. Interviews with eight participants identified key themes related to innovations, resources, best practices, and challenges in collecting and using SLE PROMs, mapped to CFIR domains. Despite barriers related to workflow, engagement, and resources, PROM implementation in SLE care was well accepted and supported standardized assessment of mental health and PF through communication and electronic health records integration. These insights informed development of the SLE Quality Measures Implementation Guide, featuring guidelines, workflow recommendations, best practices, and educational resources to improve workflow efficiency and enhance patient care.

Conclusion. This study evaluated the implementation of ACR-recommended SLE PROMs and provides actionable recommendations and resources to address challenges through the SLE Quality Measures Implementation Guide.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disease that challenges both patients and clinicians due to its multisystem involvement, variability, and fluctuating course.^{1,2} The heterogeneity of clinical presentations and the difficulty of diagnosing SLE pose significant challenges in treatment,

emphasizing the need for individualized care and consistent monitoring.¹ In addition, managing SLE requires addressing not only the physical manifestations of the disease but also its significant impact on emotional health.^{3,4} This complexity underscores the need to define how to implement coordinated, multidisciplinary, comprehensive care to improve patient outcomes and support overall well-being.^{5,6}

Supported by the Centers for Disease Control and Prevention (CDC). The content is solely the responsibility of the authors and does not necessarily represent the official views of the CDC or the American College of Rheumatology.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80038>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80038>.

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Submitted for publication November 4, 2025; accepted in revised form March 3, 2026.

SIGNIFICANCE & INNOVATIONS

- This is the first study to examine the implementation of American College of Rheumatology (ACR)-recommended patient-reported outcome measures (PROMs) in systemic lupus erythematosus (SLE) clinical care and to identify barriers and facilitators to collect these measures in routine practice.
- We used the Consolidated Framework for Implementation Research to guide and analyze qualitative semistructured interviews and to examine the successes and challenges of implementing PROMs in SLE clinical care.
- Using a consensus-building approach, we combined iterative expert discussions, review of current literature, and feedback from semistructured interviews with trial practices that implemented ACR-developed SLE PROMs to develop the SLE Quality Measures Implementation Guide (<http://slequalitymeasures.kotobee.com>).
- This guide is the first open-source, evidence-based resource to support rheumatologists and care teams in integrating PROMs into routine practice by providing guidance and practical strategies for collecting these measures to inform clinical decisions and advance patient-centered care.

In recent years, there has been increasing recognition of the importance of incorporating and consistently tracking patient-reported outcome measures (PROMs) in the routine care of SLE to improve disease management and support patient-centered care.^{2,7–10} PROMs provide valuable insights into key aspects of patients' perception of how their health is affected by SLE that routine clinical assessments may overlook, allowing standardized and validated assessments of symptoms such as fatigue, pain, emotional well-being, and cognitive function.^{7,11} These dimensions are particularly important in SLE, for which studies have demonstrated that individuals often experience significantly poorer health-related quality of life compared to those with other chronic conditions.^{12–15} Furthermore, studies have shown that the rates of depression and anxiety are up to twice as high in patients with SLE compared to the general population.^{16–20} This increased mental health burden, along with the frequent discordance between clinician assessments and patient experiences highlighted in the literature, emphasizes the need for standardized tools such as PROMs to facilitate shared decision-making and ensure that care is aligned with patient priorities and values.^{21–23}

To support high-quality, patient-centered care, the American College of Rheumatology (ACR) developed evidence-based longitudinal and quality measures that incorporate the use of PROMs, along with key clinical measures, in the management of SLE.⁹ Although the development of these measures represents a significant step toward more individualized care, the routine use of PROMs in clinical practice remains limited.⁷ To address these

gaps and build on the initial phase of this work, which focused on the development of the ACR SLE quality measures,⁹ this study represents part II of the project aimed to (1) investigate the successes and challenges of implementing PROMs for SLE clinical care, and (2) synthesize key implementation findings and tools to inform the development of the SLE Quality Measures Implementation Guide for national dissemination.

METHODS

Selection of practices and data collection. Using purposive sampling, five rheumatology practices participating in the Rheumatology Informatics System for Effectiveness (RISE) registry and using the NextGen electronic health record (EHR) system were selected from approximately 100 NextGen RISE practices for a pilot study. Practices were selected to represent diverse geographic regions across the United States. Each practice was tasked with implementing workflows to collect SLE PROMs recommended in recent ACR guidelines for at least 50 consecutive patients, including measures of physical function (PF; Routine Assessment of Patient Index Data 3 [RAPID-3] or Multidimensional Health Assessment Questionnaire [MDHAQ]) and depression assessment (Patient Health Questionnaire 8 [PHQ-8]).⁹ Practices received support from a NextGen consultant to create structured EHR fields for PROM collection. Data collection for at least 50 PROMs per domain occurred between June 2023 and June 2024.

After data collection was complete, all clinicians (including rheumatologists and medical support staff), as well as practice managers and administrators from the five participating practices, were invited to participate in virtual interviews. Researchers trained in qualitative data collection (CMB, AJ, and JY) conducted interviews via Zoom between August and October 2024. One researcher conducted each interview while other team members took notes. Interviews were guided by a semistructured interview guide based on the domains of the Consolidated Framework for Implementation Research (CFIR) model to explore perceptions about the pilot study and identify barriers and facilitators to SLE PROM implementation. Questions were mapped to CFIR domains and addressed (1) workflows for SLE PROM collection, (2) challenges and opportunities in collecting the measures, (3) practice resources and characteristics, and (4) opportunities to improve current PROM collection and use (Supplementary Material 1). The interview guide was pilot tested and iteratively refined by the research team, the ACR, and collaborating rheumatologists. The study was approved by the University of California, San Francisco, Institutional Review Board. Interviews lasted approximately one hour, were audio recorded, and were transcribed verbatim with transcripts checked for accuracy.

Conceptual framework. Our study was guided by the CFIR model, which offered a comprehensive structure for examining the factors that affect the implementation and collection of SLE outcome measures in routine care. Widely applied in quality improvement and health research,^{24–26} CFIR enables systematic analysis of implementation efforts across multiple levels, helping to describe workflows that overcome challenges and center on opportunities that support adoption and effectiveness of interventions.²⁷ This framework also supports identifying best practices in diverse settings. CFIR consists of five key domains: (1) the implementation process, (2) innovation characteristics, (3) individual characteristics, (4) the inner setting, and (5) the outer setting.^{25,27}

Data analysis. We conducted a thematic analysis of open-ended responses using both deductive and inductive techniques.²⁸ Initially, an experienced qualitative researcher (CN) examined the data, applying deductive codes based on CFIR constructs to identify implementation barriers and facilitators while generating inductive codes to capture emerging ideas across interviews. These preliminary codes were then reviewed collaboratively with the research team, refined, and organized into a comprehensive codebook. Two coders (CW and CH) independently coded the transcripts; coding was reviewed to ensure

consistency, and results were compiled into a matrix to identify key themes. Any discrepancies were resolved through discussion with a third coder (CN). Using an iterative consensus process,²⁹ a qualitative researcher (CN) reviewed the matrix and generated themes and subthemes, supported by illustrative examples, which were then organized and mapped within the five CFIR domains: outer setting, inner setting, intervention characteristics, implementation process, and individual characteristics (Figure 1). Selected quotes were included to highlight important insights, such as innovations, resource availability, effective practices, and challenges related to collecting SLE outcome measures. The study adhered to the Consolidated Criteria for Reporting Qualitative Research guidelines (Supplementary Material 2).

SLE Quality Measures Implementation Guide development. Due to limited resources guiding rheumatologists on PROMs and how to routinely integrate them into clinical workflows, we used a consensus-building approach based on iterative feedback cycles.^{26,30,31} This approach combined expert discussions, review of current literature, and feedback from semi-structured interviews with trial practices that implemented ACR-developed SLE PROMs, with funding support from the Centers for Disease Control and Prevention (CDC). Although these

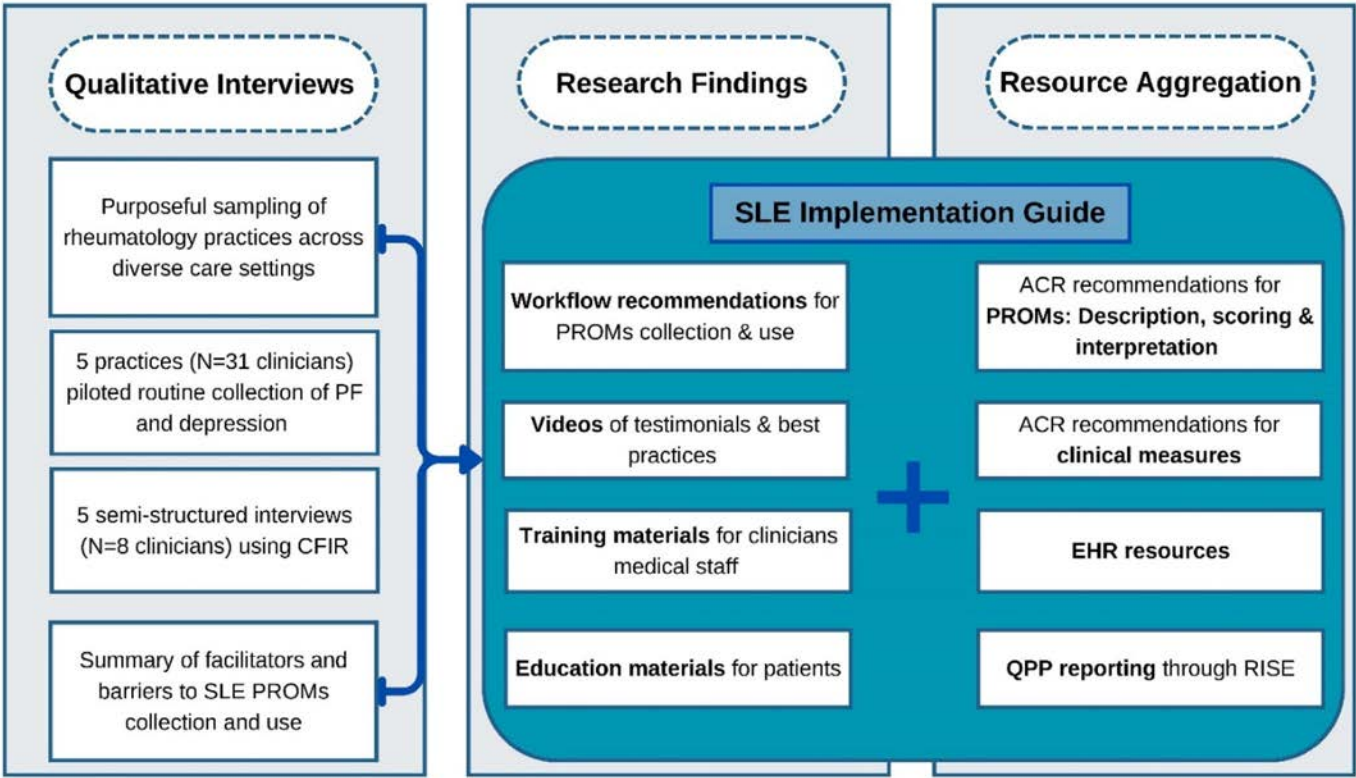


Figure 1. Development of the SLE Quality Measures Implementation Guide: slequalitymeasures.kotobee.com. ACR, American College of Rheumatology; CFIR, Consolidated Framework for Implementation Research; EHR, electronic health record; PF, physical function; PROM, patient-reported outcome measure; QPP, Quality Payment Program; RISE, Rheumatology Informatics System for Effectiveness; SLE, systemic lupus erythematosus. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80038/abstract>.

measures were published and approved by the ACR Board of Directors, they are not yet part of the Centers for Medicare and Medicaid Services' Quality Payment Program (QPP). Insights from the practice interviews, combined with evidence-based resources, informed the development of the SLE Quality Measures Implementation Guide: slequalitymeasures.kotobee.com (Figure 2), which provides practical tools to help rheumatology teams integrate PROMs into patient care. Best practices, challenges, and real-world practice solutions were identified through interviews and incorporated into the implementation guide to ensure real-world relevance. Consensus was operationalized as convergence among the expert team on the acceptability, usability, and feasibility of the guidance for routine clinical implementation. Educational and training materials for patients and staff were developed in response to concerns raised by interview participants and were pilot tested in practices to support more efficient and effective PROM collection and use with feedback gathered and participant suggestions incorporated iteratively. For context, impressions and testimonials from patients and rheumatologists who implemented SLE PROMs were included, highlighting their value and impact on care. In addition to PROMs, the implementation guide also emphasizes implementing clinical quality measures such as consistent hydroxychloroquine use, limiting glucocorticoid exposure, and regular lupus nephritis screening.⁹ The implementation guide was refined through iterative feedback from five rheumatologists and underwent user testing

with team members and stakeholders, with edits made accordingly. Strategies were mapped using the Expert Recommendations for Implementing Change checklist to align with the evidence-based SLE Quality Measures Implementation Guide (Supplementary Material 3).

RESULTS

We conducted interviews with nine participants across the five RISE practices that participated in the pilot study, including five rheumatologists, two practice managers, one nurse practitioner, and one practice administrator. Practice characteristics are summarized in Table 1. Emerging themes and subthemes were organized into the five domains of the CFIR model.

Implementation process. Practices described several strategies for integrating ACR-recommended SLE PROMs into clinical workflows, which contributed to improved efficiency. Standardizing PROM collection at patient check-in helped establish a foundational infrastructure for value-based care (Table 2, quote 1). Structured processes, such as flagging patients with SLE or generating patient lists and embedding PROM forms in charts, enabled consistent identification of patients with SLE and incorporation of PROMs into patient records, streamlining their routine use (Table 2, quote 2). Some practices also implemented EHR alerts as a workflow adaptation to prompt staff to administer

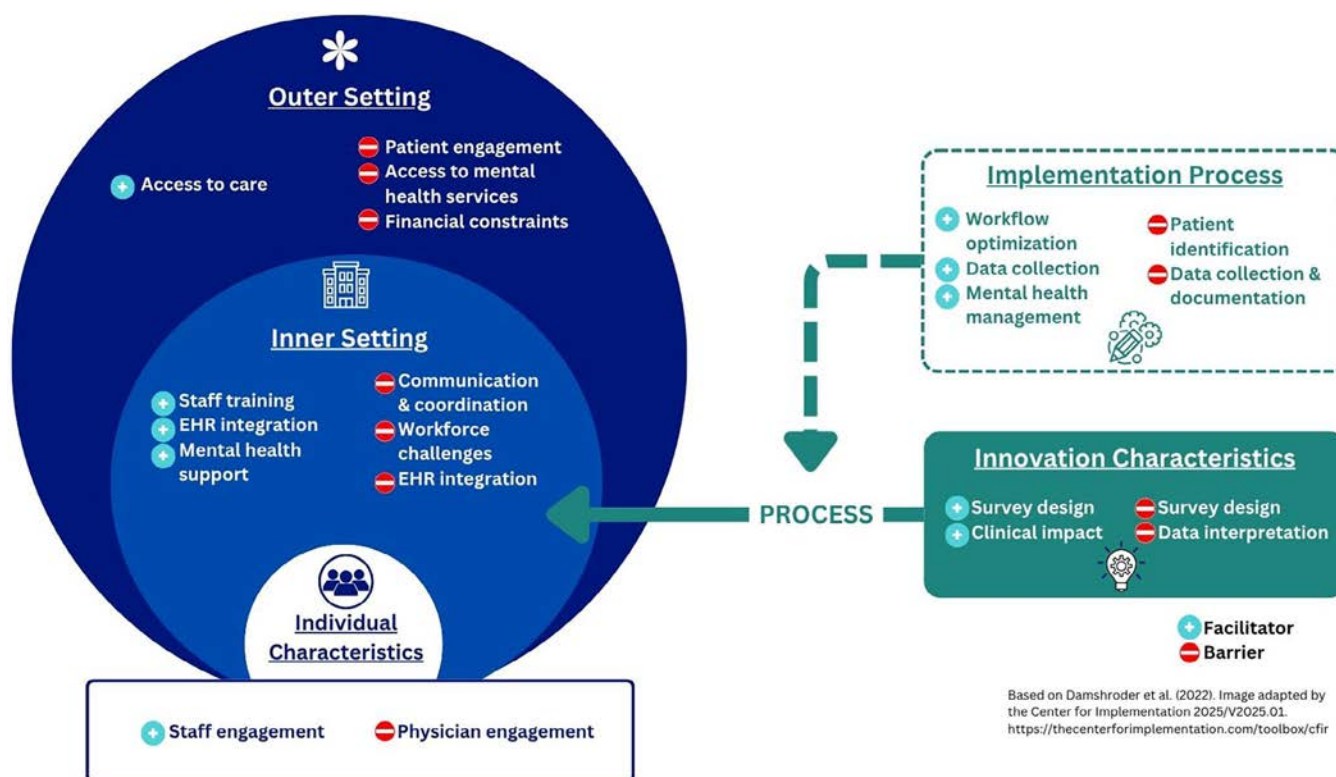


Figure 2. Generated themes as per the Consolidated Framework for Implementation Research domains. EHR, electronic health record.

Table 1. Characteristics of practices interviewed regarding SLE PROM collection*

Characteristic	Practice 1	Practice 2	Practice 3	Practice 4	Practice 5
Geographic division	South	South	South Atlantic	East South Central	South Atlantic
Practice type	Single specialty	Single specialty	Single specialty	Single specialty	Single specialty
Total clinicians at the practice, n	3	9	12	6	24
Clinicians engaged in the pilot, n	3	8	12	6	2
Patients with SLE diagnosis, n	711	566	703	999	883
Physical function Measure	RAPID-3	MDHAQ	HAQ	MDHAQ	MDHAQ
Unique patients' PF score collected per practice for patients with SLE	35	>150	65	>150	50
Unique patients' PHQ-8 responses concerning depression	0 ^a	12	41	183	30

* All participating sites were Rheumatology Informatics System for Effectiveness–affiliated community practices that accept all insurance types. HAQ, Health Assessment Questionnaire; MDHAQ, Multidimensional Health Assessment Questionnaire; PHQ-8, Patient Health Questionnaire 8; PROM, patient-reported outcome measure; RAPID-3, Routine Assessment of Patient Index Data 3; SLE, systemic lupus erythematosus.

^a Practice 1 returned 35 PHQ-8 surveys that were scanned into the electronic health record and were not extractable by the medical record organization, so 0 unique responses were recorded.

PROMs during each visit, further enhancing workflow efficiency (Table 2, quote 3). PF was already being collected by all practices, which facilitated implementation, whereas depression screening was not conducted at baseline. Routine collection of PROMs such as the PHQ-8 at each visit reinforced their integration into clinical workflows (Table 2, quote 4). Most practices reported that using PROMs improved proactive symptom management, especially for mental health, with some initiating treatments such as antidepressants based on elevated PHQ-8 scores (Table 2, quote 5). Despite these successes, several process-related challenges affected consistent implementation. Some practices struggled to reliably identify patients with SLE ahead of visits, which disrupted PROM administration at check-in (Table 3, quote 1). Staff occasionally missed administering PROMs when occupied with other tasks (Table 3, quote 2), and even when patients completed the forms, some scores were not entered into the EHR due to misplaced paperwork, staff oversight, or competing priorities (Table 3, quote 3).

Innovation characteristics. Overall, practices highlighted the value of ACR-recommended PROMs in SLE care as both feasible and impactful tools. Survey design was considered practical, with brief instruments such as the RAPID-3 noted as easy for patients to complete quickly and consistently (Table 3, quote 7). All practices highlighted the positive clinical impact of PROM collection on patient care. PROMs enhanced clinical decision-making by uncovering important mental health concerns that informed treatment planning, an unexpected but highly valued benefit (Table 3, quote 8). PROMs promoted a patient-centered approach by recognizing emotional well-being as key to managing chronic disease (Table 2, quote 9). They also enhanced patient–provider communication, fostering discussions about mental health and enabling timely referrals (Table 2, quote 10). Ultimately, clinicians perceived that PROM-guided SLE care

improved patient satisfaction and well-being, particularly through better mental health outcomes (Table 2, quote 11). On the patient side, as reported by clinicians, all practices noted that PROMs enhanced self-awareness and engagement. Clinicians noted that using structured questions often uncovered previously unrecognized issues, prompting deeper conversations about symptoms (Table 2, quote 12) and that articulating experiences through PROMs helped patients better understand their care and seek support (Table 2, quote 13).

Despite these benefits, several challenges limited the ease of PROM implementation. Survey design was a key barrier, with practices using the MDHAQ to assess patient PF, describing it as lengthy and disruptive to workflow (Table 3, quote 3). One practice noted that emotionally sensitive PHQ-8 items occasionally triggered strong patient reactions, requiring immediate follow-up and clinical support (Table 3, quote 4). Interpreting PROM data also proved difficult in some cases. A few practices reported challenges interpreting PF scores in patients with comorbid conditions like fibromyalgia, in which overlapping symptoms obscured the source of dysfunction (Table 3, quote 5). Others observed that patients misunderstood certain questions or response scales, leading to inaccurate responses (Table 3, quote 6).

Individual characteristics. Individual-level factors, including physician and medical support staff engagement, played an important role in successfully integrating ACR-recommended PROMs into SLE care. Two practices reported that staff commitment, collaboration, and communication enabled effective workflow implementation and sustained use (Table 2, quote 14). In contrast, in one case, PF measures were deprioritized by clinicians, given the shift of focus, resulting in inconsistent use and discussion with patients (Table 2, quote 7).

Table 2. Current practices, benefits, and opportunities in SLE PROM collection: qualitative interview findings*

CFIR domain	Theme	Subtheme	Quotes
Implementation process	1. Workflow optimization	1. Standardizing PROMs collection at check-in	Quote 1: "It's almost like laying down pipes and building plumbing for something to come. It's really helpful because that, what needs to be done in the community practice setting to get us ready for the world of value-based medicine whenever that does hit." (Practice 3)
		2. Flagging patients with SLE	Quote 2: "So [staff member] would run a report and then make a sheet for the front office manager, and she would put the papers in... It's part of the chart..." (Practice 3)
		3. Setting PROM reminder alerts	Quote 3: "We have an alert at the top, so if they have [a lupus diagnosis], it'll just say that they could put it in the alert section. So, when you click on it, you have to acknowledge it too, so that could be helpful..." (Practice 1)
	2. Data collection	1. Routine PROM collection	Quote 5: "My staff gives [the PHQ-8] to the patients every time they come in." (Practice 2)
	3. Mental health management	1. Managing symptoms	Quote 4: "We can always initiate them [patients] on antidepressant therapy in the clinic... and I think that usually makes a big difference." (Practice 4)
Innovation characteristics	1. Survey design	1. Brief mental health questionnaires	Quote 7: "One of the easiest things to implement is the RAPID-3. You get it on one piece of paper. Most patients could do it quickly." (Practice 1)
	2. Clinical impact	1. Enhanced clinical decision-making	Quote 8: "Having something like [the PHQ-8] can be very helpful, because it also changes what your treatment options are, and what you're thinking about doing [treatment plan]." (Practice 1)
		2. Patient-centered care	Quote 9: "In chronic diseases, I think the emotional mental status should be sort of like the fifth vital sign... If you have a tool like [the PHQ-8], just like we do CDAs all the time... it can only take so little time and help patients in such a dramatic way." (Practice 3)
	3.	3. Strong patient-clinician rapport	Quote 10: "Even just in one diagnosis and being able to look at that [PRO forms] and the impacts and really see what's going on with your patients from a mental health perspective is so very important." (Practice 5)
		4. Improved patient satisfaction and well-being	Quote 11: "There was one patient that impressed me in how severely depressed she was... When we got her into counseling and medications... the PHQ-8 went down to a zero from a 20. So that was really nice to see." (Practice 4)
		5. Greater patient awareness of symptoms	Quote 12: "Patients would actually bring it up [their symptoms] and say, 'Gosh, I didn't realize I was feeling this way or thinking these things until you asked the question.'" (Practice 3)
Individual characteristics	1. Staff engagement	1. Commitment and collaboration	Quote 13: "Once they put it on paper, they stare at it and I stare at it, we both have to address it... 'I have a long-standing history of depression, I didn't realize how much it is disabling, I need help.'" (Practice 2)
			Quote 14: "I credit [staff members] for recognizing that, 'Hey, we're doing this.' We need to identify the groups that do the different pieces of work, communicate with them, and then make it happen" (Practice 5)
Inner setting	1. Staff training	1. PROM trainings	Quote 15: "We have an onboarding process, so they're all trained to be able to do all of the things that every MA does... So, we do have an operating procedure for them." (Practice 4)
	2. EHR integration	1. Electronic collection of measures	Quote 16: "So that [PROM form] is printed out for each patient and then that data is entered with that Magic Pen... they do that very fast so that by the time I go into the room, that data is already there." (Practice 2)
		2. Automated score calculation	Quote 17: "There's a pre-built [PROM tool in the EHR] where they just put in the scores, and the EMR automatically calculates it and gives us the score." (Practice 4)
		3. Automated EHR data capture	Quote 18: "So, we have a company called Phreesia that does a pre-visit for our basic data. They can enter it before they arrive in the office or when they first check-in they get a little tablet. It's a multi-page electronic [PROM] form that becomes part of their visit in their chart as informational data." (Practice 3)

(Continued)

Table 2. (Cont'd)

CFIR domain	Theme	Subtheme	Quotes
	3. Mental health support	1. Access to resources	Quote 19: “That actually is just a local website here [at the practice site] with combined resources that are available to everybody. It was available for all the patients that scored high [on PHQ-8]. If it was over four.” (Practice 3)
Outer setting	1. Access to care	1. Proactive referrals for mental health	Quote 20: “You’re making them [patients] recommendations that, ‘You need to go see your primary care, doctor, as soon as possible. You’re not in a good situation,’ and then having them take that form or sending that over to the primary care provider is one option.” (Practice 1)

* CDAI, Clinical Disease Activity Index; CFIR, Consolidated Framework for Implementation Research; EHR, electronic health record; MA, medical assistant; PHQ-8, Patient Health Questionnaire 8; PRO, patient-reported outcome; PROM, PRO measure; RAPID-3, Routine Assessment of Patient Index Data 3; SLE, systemic lupus erythematosus.

Inner setting. Supportive inner setting factors, such as staff training, technological support, and access to in-house mental health support, facilitated the integration of SLE PROMs into routine care. All practices implemented structured onboarding and training to ensure staff could administer and process PROMs consistently (Table 2, quote 15). In addition, technological support via EHR integration played a crucial role in streamlining PROM workflows. Electronic collection of measures using digital tools, such as iPads and “Magic Pens,” enabled staff to input and review responses before the clinician saw the patient, ensuring timely access to data (Table 2, quote 16).

Some practices implemented automatic score calculation, which reduced provider workload and ensured the immediate availability of scores (Table 2, quote 17). One practice used external platforms such as Phreesia to collect PROMs electronically before visits, automatically uploading data into medical records to improve documentation and track patient progress over time (Table 2, quote 18). A few practices also provided mental health resources to connect patients to care, such as printed lists of local services for those with high PHQ-8 scores (Table 3, quote 19).

However, some practices reported communication gaps between providers and staff, which occasionally hindered consistent review and use of questionnaire data (Table 3, quote 15). Workforce challenges such as high staff turnover, physician time constraints, and increased administrative burden also complicated implementation. Ongoing turnover created repeated training demands to maintain workflow consistency (Table 3, quote 16), whereas time constraints during appointments made it difficult to review PROMs, especially when completed on the visit, leading to delays (Table 3, quote 17). Building the necessary PROM infrastructure also required significant administrative effort to coordinate workflows (Table 3, quote 3). EHR integration posed widespread technical and logistical barriers for nearly all practices. PROM forms were often stored in unstructured locations, making them difficult to access during clinical encounters or integrate into progress notes (Table 3, quote 19). Furthermore, the absence of automated data entry and scoring required manual tracking, which increased staff workload and reduced overall efficiency (Table 3, quote 20).

Outer setting. Regarding external factors, all practices emphasized the value of collecting SLE PROMs, particularly PHQ-8, to facilitate proactive referrals and access to mental health services for patients scoring above the threshold (Table 2, quote 20). However, patient engagement also presented challenges, particularly around mental health. One practice reported difficulty engaging older adults in discussions of emotional well-being, noting generational reluctance to disclose mental health concerns (Table 3, quote 21). Survey fatigue was another common issue reported by most of the practices because many patients questioned the need to complete PROMs on every visit despite staff explanations (Table 3, quote 22). Discomfort discussing mental health also emerged as a barrier, with some patients unwilling to share emotional concerns due to stigma or discomfort (Table 3, quote 23). Additionally, most practices reported long wait times for mental health providers, often delaying timely access to specialist care. To address this, many patients initially received mental health support from their primary care physicians while awaiting appointments with specialists such as psychiatrists (Table 3, quote 24). Financial constraints further hindered care: the high cost of physical therapy, including accumulating copays, discouraged some patients from pursuing recommended services (Table 3, quote 25), and limited insurance coverage for mental health care led to substantial out-of-pocket expenses, causing some patients to delay or forgo treatment despite clinical need (Table 3, quote 26).

SLE Quality Measures Implementation Guide development. Results from semistructured interviews with five pilot practices helped identify key challenges and opportunities to integrate PROMs into routine SLE clinical care. Insights from these interviews, combined with ACR guidelines and other evidence-based resources, informed the development of the SLE Quality Measures Implementation Guide (slequalitymeasures.kotobee.com). The SLE Quality Measures Implementation Guide, launched on the ACR website in May 2025, is an online resource designed to support clinicians and staff in implementing SLE quality measures to deliver high-quality, patient-centered care. It includes

Table 3. Barriers to SLE PROM collection: qualitative interviews findings*

CFIR domain	Theme	Subtheme	Quotes
Implementation process	1. Patient identification	1. Gaps in identifying patients with SLE at check-in	Quote 1: "The biggest issue we had was just identifying lupus patients prior to the visit." (Practice 3)
	2. Data collection and documentation	1. Inconsistent collection of PROMs 2. Missed documentation of scores in the EHR	Quote 2: "So, I think if they're [MAs] busy chatting with the patient, they're overlooking or forgetting to administer it." (Practice 4) Quote 3: "There's some data that got missing. I don't know where some of the paperwork went because... sometimes MAs are just forgetting to record [scores]." (Practice 4)
Innovation characteristics	1. Survey design	1. Lengthy PF questionnaire 2. Sensitivity of mental health survey items	Quote 3: "I mean, that's the big thing it's always a challenge of just the amount of time MDHAQ takes [to be filled out by patients]." (Practice 1) Quote 4: "For some people, it's triggering, they'll start crying when they're filling out the form [PHQ-8]." (Practice 4)
	2. Interpretation of data	1. Physician's difficulty interpreting scores with comorbidities 2. Patient difficulty interpreting scores and survey items	Quote 5: "There's a high percentage of people that have fibromyalgia or other associated conditions... There's some other things going on." (Practice 1) Quote 6: "The weakness in PROMs is the patient's own assessment, I find, is often inaccurate. Maybe we don't explain it enough. Sometimes I want to go back and ask if they understood the question [included in the PROM form] on a scale of 0 to 10, or if they're thinking 10 to 0." (Practice 3)
Individual characteristics	1. Physician engagement	1. Inconsistent PF PROs discussion with patients	Quote 7: "[physician name], no he's lazy, he won't do any of it. He does it less than I do." (Practice 1)
Inner setting	1. Communication and coordination	1. Communication gaps	Quote 15: "I did not make our providers totally aware that the questionnaires needed to be looked at [during visit]." (Practice 1)
	2. Workforce challenges	1. Staff turnover 2. Physician time constraints 3. Increased administrative burden	Quote 16: "We just have a lot of staff turnover and so that introduces challenges at the beginning...when there's a new MA." (Practice 4) Quote 17: "The biggest challenge really is the timeframe...we don't have much time...Getting all this done, especially if patients are doing it the day that they come in tends to be a little bit of an issue." (Practice 1) Quote 18: "Setting up the infrastructure within our office, having a system, generating patient flows, getting the staff involved, getting MAs involved, was the hard labor part." (Practice 3)
	3. Integration into EHR	1. Unstructured fields 2. Manual data entry and scoring	Quote 19: "The other challenging factor was that they had to build the [PROM] form in NextGen. And then where it's located in the chart is very difficult to find because it's not tracking over into our chart note." (Practice 4) Quote 20: "I had to manually do all of this [data entry]—follow the scores—because there's just no space. We can't see where the previous PHQ-8 scores are in the EMR." (Practice 4)
Outer setting	1. Patient engagement	1. Difficulty engaging older adults in mental health discussions 2. Survey fatigue 3. Discomfort with mental health topics	Quote 21: "The worst people are usually the elderly in regard to talking about mental health." (Practice 1) Quote 22: "Some patients just say, 'Well, I filled it [PROM form] out last time. Why do I have to do it again?' We keep telling them, 'You have to do it at each clinic visit. It tells us how you're doing. We can score it.'" (Practice 4) Quote 23: "These are things [mental health issues] that patients many times don't voluntarily share and they might not volunteer it because they're not comfortable." (Practice 3)
	1. Access to mental health services	1. Long wait time for mental health services	Quote 24: "It's just the timing of referrals to mental health provider. It usually takes a very long time..." (Practice 1)
	2. Financial constraints	1. High costs of physical therapy 2. Limited insurance coverage	Quote 25: "I think patients are not resistant, but... it's [cost of physical therapy] expensive...the co-pay costs add up, and that's a big hurdle for some of our patients." (Practice 3) Quote 26: "I think it is the fact that a lot of insurers don't cover mental health... That becomes the issue." (Practice 2)

* CFIR, Consolidated Framework for Implementation Research; EHR, electronic health record; EMR, electronic medical record; MA, medical assistant; MDHAQ, Multidimensional Health Assessment Questionnaire; PHQ-8, Patient Health Questionnaire 8; PROM, patient-reported outcome measure; SLE, systemic lupus erythematosus.

detailed guidance on using PROMs recommended by the ACR for SLE along with downloadable forms, scoring instructions, workflows, and explanations to aid understanding.

Reflecting themes from the interviews, the implementation guide also features videos on best practices, patient education materials, staff training resources, and validated translations of PROMs in Spanish. To address common barriers, it includes translated materials in Spanish and offers considerations for collecting PROMs in diverse populations. Additional resources include a downloadable staff training guide to support effective PROM collection and a patient education guide to improve awareness of their importance in SLE care. To further support clinical workflows, the implementation guide also offers tips for succeeding in the QPP.

DISCUSSION

Addressing PROMs in SLE is important to help develop a comprehensive care plans aligned with patients' priorities and values. This study identifies key real-world barriers and facilitators to implementing PROMs in routine SLE care and translates these insights into practical strategies within the ACR SLE Quality Measures Implementation Guide. By applying the CFIR framework across five diverse clinical practices, we developed workflows and digital PROM templates, shaped by clinician beliefs, clinical workflows, organizational readiness, and the availability of digital tools, within the ACR SLE Quality Measures Implementation Guide to support adoption across diverse practices. This guide is the first to enable comprehensive care delivery focused on both clinical and patient-reported outcomes as part of routine SLE care.

Individuals with SLE often have worse-than-average scores on PROMs, resulting in subsequent morbidity, disability, and mortality.³⁰ Therefore, PROMs complement clinical measures to support comprehensive care planning and align treatment plans with patient priorities and values in SLE.³² Although most research has focused on validating these measures and applying them in clinical trials,^{33,34} there is still a notable gap in practical guidance on how to effectively integrate PROMs into routine clinical workflows, particularly across different practices.^{33,35–37} Limited resources to help collect, interpret, and apply PROM data within existing workflows across practices are a significant barrier; however, additional unaddressed barriers, such as time constraints, insufficient training, and uncertainty about the clinical utility of these measures, further limit widespread adoption.^{33,35,38} To directly address this gap, we pilot tested the implementation of ACR-recommended PROMs for SLE^{9,39} across five diverse practices to understand barriers, detractors, and motivators for adopting PROMs as part of routine workflows.

Leveraging the CFIR framework, we identified key barriers and motivators to inform the ACR SLE Quality Measures Implementation Guide. More importantly, CFIR helped us understand how individual beliefs, clinical workflows, and organizational

factors affect the collection and use of SLE PROMs. For example, standardizing check-in procedures and implementing EHR alerts facilitated consistent PROM collection and patient identification. Accordingly, the guide includes a section defining methods for identifying eligible patient lists, either digitally or manually, and provides customizable swim lane diagrams to support workflow implementation across diverse practice settings.

Staff onboarding and training were also reported as essential for sustained PROM use. The guide includes a dedicated medical assistant training module and a “Testimonials and Advice from Rheumatologists and Patients” section that showcases real-world strategies from pilot sites. These include EHR alerts for clinical staff, digital patient identification workflows, and the use of electronic tools to streamline PROM completion during routine SLE visits. Unlike prior studies that focus on PROM psychometrics or trial-based applications, this study explores how PROMs can be embedded in routine workflows by leveraging technology (eg, EHR alerts, and automatic scoring) and staff engagement. The implementation guide incorporates these insights by providing training guides, workflow templates, and culturally adapted materials to support implementation across varied settings.

Poor mental health and PF are associated with poor SLE outcomes. Therefore, assessment of mental health and PF using tools like the PHQ-8 or Patient-Reported Outcomes Measurement Information System (PROMIS)– Short Form Depression and the MDHAQ or PROMIS Physical Function, respectively, were included as recommended PROMs for SLE visits.^{3,9,19} Particularly for the mental health assessment during pilot testing, clinicians reported that using PROMs like the PHQ-8 enabled early identification of depression and more timely intervention. These findings were consistent with prior studies showing that PROMs, including mental health screening, support clinical decision-making and enhance patient-provider communication.^{7,21} The ACR SLE guide curates validated resources, including links to national and regional mental health resources and culturally adapted materials in multiple languages. PF assessments were easier to implement in practices already using instruments such as the MDHAQ for all patients, facilitating higher adoption. However, uncertainty in interpreting PF scores among patients with comorbidities and the length of some questionnaires remained challenges. To address these issues, the SLE Quality Measures Implementation Guide provides recommendations for asynchronous PROM completion (before or between clinic touchpoints). In addition, a section on reimbursement programs, including the Quality Payment Program (QPP) has been incorporated to incentivize practices to measure both PROMs and clinical SLE measures, aiming toward improving overall SLE care quality. The development of a publicly accessible, multimedia-rich, and interactive SLE Quality Measures Implementation Guide tailored to diverse practice settings represents a novel approach to promoting the use of PROMs and clinical SLE measure adoption across clinics.

Despite promising outcomes, several limitations emerged. First, practices faced challenges in reliably identifying patients with SLE, maintaining consistent PROM administration, and interpreting scores in patients with comorbid conditions. Second, survey fatigue and the emotional sensitivity of items (eg, the PHQ-8) occasionally hindered patient engagement. Third, technical barriers, such as unstructured EHR fields and manual data entry, increased staff burden. In addition, the tools were developed and tested only within a single EHR system used by the five pilot practices. External factors, such as limited insurance coverage and long wait times for mental health services, also constrained the impact of PROM-guided care. Lastly, implementation outcome metrics to evaluate the adoption of PROM and clinical measures data collection during SLE visits after launching the SLE Quality Measures Implementation Guide have yet to be assessed.

In conclusion, the ACR SLE Quality Measures Implementation Guide translates real-world insights into actionable strategies for embedding PROMs and longitudinal clinical measures into routine care. It supports scalable, patient-centered SLE management through technology, staff engagement and training, and structured workflows. Finally, the digital SLE guide provides unique yet customizable strategies to embed digital quality measure assessments, particularly PROMs, in routine clinical care to ensure better care delivery standards and improve care quality in SLE.

ACKNOWLEDGMENTS

We would like to thank the many rheumatologists and practice personnel who graciously provided their time to participate in the qualitative interviews presented here and who provided feedback on the SLE Quality Measures Implementation Guide. ChatGPT was used to help shorten the sentences to meet word limits while preserving the original meaning. The generated sentences were then rephrased by the authors to prevent plagiarism.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Garg confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements. All authors contributed to the investigation, formal analysis of the data, and writing, reviewing, and editing of the manuscript.

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Effects of Causal Beliefs About Gout on Public Views About Gout Management: A Randomized Experimental Study

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Objective. Despite well-described biologic causes, the public views unhealthy lifestyle choices as the primary cause of gout. This study investigated how causal beliefs about gout influence the public's views about its management.

Methods. In a randomized study, 201 members of the public viewed one of two 2-minute videos about gout. The videos were identical except for a 45-second section describing the causes of gout using either a biologic explanation (including genetics, kidney disease, age, sex, and diuretic therapy) or a lifestyle explanation (including diet, alcohol, sugary drinks, and weight). Participants completed a questionnaire about gout and its management. Primary outcome was rating of “How likely is it that long-term medications would help gout?” on an 11-point Likert scale.

Results. Participants who viewed the biologic explanation rated hereditary factors and aging as more important causes of gout than those who viewed the lifestyle explanation, and they rated poor diet, alcohol use, and the person's own behavior less highly ($P < 0.001$ for all). In the biologic group, 13 of 99 (13.1%) gave diet or a specific dietary factor as the most important cause compared with 62 of 102 (60.8%) in the lifestyle group. Those in the biologic group were more likely to believe that long-term medication would help gout (mean score 7.6 vs 6.5, $P = 0.001$).

Conclusion. Explaining gout as caused by biologic rather than lifestyle factors affects beliefs about the benefits of long-term medication. Accurate communication about causes of gout could affect the public's beliefs about treatment strategies and may improve long-term medication uptake.

INTRODUCTION

Gout is the most common cause of inflammatory arthritis in adults.¹ It can be treated effectively with long-term urate-lowering therapy (ULT) such as allopurinol, which decreases flares, tophi, and disability.^{2,3} Despite this well-established clinical efficacy, ULT is frequently underprescribed when indicated and is often discontinued by patients after initiation^{4–6}; for example a recent study found that about 63% of people initiating allopurinol did not persist with this therapy for more than a year.⁷ Previous qualitative research has identified several reasons patients discontinue allopurinol, including experiencing gout flares after starting ULT, receiving conflicting or insufficient information about gout from health care professionals, identifying a dietary trigger for gout, believing they did not have frequent

enough flares to warrant medication, and general concerns about taking medication.⁸

Attribution theory describes the origins and consequences of causal beliefs,⁹ which develop through the acquisition of information from cultural depictions of an illness and personal experiences.¹⁰ Causal beliefs help to provide an explanation for and a sense of control over events^{11,12} and also influence treatment adoption because, depending on the cause of an illness, certain treatments make more sense. The impact of causal beliefs held by members of a community is known to have a significant impact on patients living within that system. Although the impact of this has not been previously explored in gout, it has been investigated in other diseases such as depression. A meta-analysis that included 43 cultural groups has found that causal beliefs held by a community strongly influenced their preferred treatment

ACTRN: 12623000455662.

Supported by a grant from the University of Auckland. Mr Fleck's work was supported by an Arthritis New Zealand Summer Scholarship.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80053>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80053>.

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Submitted for publication September 2, 2025; accepted in revised form February 24, 2026.

SIGNIFICANCE & INNOVATIONS

- This is the first randomized study to examine how causal beliefs about gout affect views about its management.
- A brief explanation of either the biologic or lifestyle causes of gout can influence the public's views about gout management, including the necessity of long-term medication.
- Accurate communication about the causes of gout could affect the public's views about its management and improve uptake of ULT.

options. For example, members of an Indian community who conceptualized it as a physical disease favored medication, and those in a Malayan community who viewed it as caused by emotional stress felt that counseling would be the most effective strategy.¹³ These beliefs are clinically relevant as they can influence whether patients seek medical care, their treatment decisions, and adjustment to illness.^{11,14,15}

The pathogenesis of gout involves the development of hyperuricemia leading to the formation of monosodium urate crystals, which deposit in bones, joints, and soft tissue.¹⁶ Studies have attempted to quantify the contribution of genetic variants and diet to risk of hyperuricemia. A meta-analysis of data from 16,760 people without gout from the United States found that three dietary scores based on healthy eating guidelines each explained less than 0.3% of the variance in serum urate, whereas 23.9% of variance in serum urate was explained by genome wide single nucleotide variation.¹⁷ Another study of people with hyperuricemia and gout showed a single genetic variant had substantially larger impact on hyperuricemia than four dietary patterns that were investigated.¹⁸ Other biologic factors, such as renal impairment, age, and diuretic use, also increase the risk of gout.^{1,19–23} Some studies have shown modest reductions in serum urate with the Dietary Approaches to Stop Hypertension (DASH) diet in people with hypertension and hyperuricemia,²⁴ but studies in patients with gout have not shown a sustained impact of dietary change on serum urate. A crossover study of a DASH-based diet showed an initial decrease in serum urate in those randomized to a DASH-based diet compared to patients receiving a usual diet but no difference after the crossover period,²⁵ and a study of dietary education in patients with gout on ULT found that providing education on diet did not lead to a difference in serum urate after six months.²⁶

Despite the compelling evidence for biologic causes of gout, it is a common belief in the community that gout is due solely to lifestyle factors. In previous research, when members of the public were asked about the causes of two identical diseases labeled “gout” or “urate crystal arthritis,” participants viewed “gout” as more likely to be caused by diet, alcohol, and the person's own behavior and “urate crystal arthritis” as more likely to be due to

the effects of aging.²⁷ This randomized experimental study aimed to investigate the impact of different causal beliefs about gout on the public's views about gout management, specifically the need for long-term medication.

MATERIALS AND METHODS

Study design and participants. From June 2023 to April 2024, 201 members of the public were recruited through advertisements on the University of Auckland trials website, posters, and a job search website in Aotearoa/New Zealand. Advertising and participant information was for a study of “video and perceptions of illness” to avoid recruiting a disproportionate number of the public with gout, although participants with gout were not excluded.

Eligible participants were adults aged 18 years or older able to complete a questionnaire in English. Ethical approval was obtained from the University of Auckland Human Participants Ethics Committee (UAHPEC25912), and all participants provided written informed consent. After providing informed consent, participants viewed one of two 2-minute animated videos about gout and then completed a questionnaire about gout and its management. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (<http://anzctr.org.au>; ACTRN12623000455662).

Randomization and masking. A randomization schedule was produced by a biostatistician using a variable block sequence generated in Microsoft Excel (Microsoft Excel for Microsoft 365). Participants were randomized 1:1 to view either the biologic or lifestyle explanation video. The randomization was uploaded to REDCap (Vanderbilt University) by a researcher not involved in the study interviews. As each participant was recruited, their email address was entered into the secure database, and they were emailed either the biologic or lifestyle video automatically by REDCap depending on their randomization.

Procedures. Participants were asked to view the video containing either the biologic or lifestyle description of gout shortly before a 30-minute Zoom interview with a researcher. The interviewer was blinded to group allocation. The participants were asked not to reveal the contents of the video to the researcher. To confirm that the participant had viewed the video, the interviewer asked the participant what disease the video had been about before the interview. If the participant answered incorrectly, it indicated that they had not viewed the video, so they were excluded from the analysis. Participants were able to view the questions over Zoom as they completed the questionnaire.

The two videos were both two minutes long and had identical beginning and end sections, which answered the questions “What is gout?” and “How is gout treated?”. The middle sections of each video, which described the causes, were both 108 words

and 45 seconds in duration. The biologic causes video focused on risk factors such as genetic variants, kidney disease, male sex, age, and diuretic use. The lifestyle causes video described dietary risk factors and being overweight. The full text of each video is shown in Figures 1 and 2, and the links to the videos are available in Supplementary Table 1. Both videos included the same description of gout management, which included reference to medication as well as lifestyle approaches to treatment: “Anti-inflammatory medications can be used to treat the attacks of arthritis. A balanced diet, regular exercise, and a healthy weight are recommended. A long-term daily medication can dissolve the crystals and prevent future attacks.”

Demographic data were collected, and participants were asked whether they had a history of gout or had a close friend or relative with gout. Ethnicity was self-reported using the standard ethnicity question from the 2018 New Zealand census.²⁸

Participants were asked, “If you or someone you know was diagnosed with gout, what do you think are the likely causes of this condition?” They were asked to rate nine potential causal factors: stress or worry, hereditary factors, diet or poor eating habits, aging, alcohol use, pollution in the environment, and the person’s own behavior. These were rated on a five-point Likert scale from “strongly disagree” to “strongly agree.” They were also asked separately to provide the three most important causes of gout in rank order, which were recorded as free text.

After the introduction “We are interested in your thoughts about how likely different types of behavior would help your condition if you were diagnosed with gout,” participants were asked to rate a list of seven potential management strategies: managing stress, regular exercise, stopping or restricting alcohol, long-term medications, changing to a healthier diet, alternative medicine, and losing weight on an 11-point Likert scale from “would not

What is gout?

Gout is a type of arthritis that causes repeated attacks of excruciating joint pain. It often affects the big toe. It is a very common type of arthritis in Aotearoa/New Zealand. At the time of the attack, the joint is hot, red, and tender. The affected person may be unable to sleep, walk, or go to work. Attacks of arthritis come on suddenly and can last for two weeks at a time. Occasionally, the joint can become damaged and deformed.

What causes gout?

High levels of urate in the body cause crystals to form in the joints. These crystals cause the attacks of arthritis.

High levels of urate are usually due to risk factors that can’t be changed. An important risk factor is genes in the DNA that are passed down in families. People are born with these risk factors. Urate is removed through the kidneys, so levels are higher in people with kidney disease. Genes also affect how much urate is removed from the body through the kidneys and the intestines. Gout is more common in older people and men. Other medical conditions can also increase the risk. Some people with heart problems take medication to remove fluid from the body, which increases their risk of high urate levels and gout.

How is gout treated?

Anti-inflammatory medications can be used to treat the attacks of arthritis. A balanced diet, regular exercise, and a healthy weight are recommended. A long-term daily medication can dissolve the crystals and prevent future attacks.

Figure 1. Script for biologic causes video. Section of script that differs from lifestyle explanation in bold.

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What causes gout?

High levels of urate in the body cause crystals to form in the joints. These crystals cause the attacks of arthritis.

A person's diet can affect their urate levels and their risk of gout. Eating large amounts of foods like red meat and seafood can lead to flares of gout. These foods are rich in purines. Purines are chemicals that are broken down to urate in the body. Drinking a lot of alcohol such as beer also increases the urate and risk of gout. Drinking sugary drinks such as cola is another risk factor. Dehydration can also trigger a flare of gout. High levels of urate and gout are also more common in people who are overweight. The more overweight someone is, the more their body holds onto urate.

How is gout treated?

Anti-inflammatory medications can be used to treat the attacks of arthritis. A balanced diet, regular exercise, and a healthy weight are recommended. A long-term daily medication can dissolve the crystals and prevent future attacks.

Figure 2. Script for lifestyle causes video. Section of script that is different from biologic explanation in bold.

help at all" to "very likely to help." This section included the primary outcome, the response to the question, "How likely is it that long-term medications would help gout?"

Participants were asked to imagine that they had been diagnosed with gout, and their views about medications were further explored with another set of questions, including one that was similar to the primary outcome measure: "How likely is it that you would need long-term medication prescribed for gout?" They were also asked how concerned they would be to take long-term medication for gout, how motivated they would be to take long-term medication for gout, how serious gout is as an illness, and how embarrassed they would be to be diagnosed with gout. Answers were given as a rating on an 11-point Likert scale.

Illness perceptions were assessed using the Brief Illness Perception Questionnaire. Before completing this questionnaire, participants were asked to imagine they had been diagnosed with gout and to answer the questions based on how they thought the illness would influence their life. The questionnaire assesses

eight aspects of perceptions of illness on an 11-point Likert scale including consequences (how much gout would affect a person's life), duration (how long gout would continue), personal control (how much control the participant feels they would have over gout), treatment control (how much medication would help), identity (severity of symptoms), concern (how concerned the participant would be about having gout), understanding, and emotional impact.²⁹

As the study advertisements did not specify that the illness being studied was gout, after completing the study interview participants were emailed a debrief sheet that provided further explanation about the study and a link to patient information about gout.³⁰

Statistical considerations. A sample size calculation was performed based on a previous study of disease labels in gout.²⁷ The sample size of 200 participants allowed the detection of at least a two-point difference for a Brief Illness Perception

Questionnaire item with a 90% power and an alpha of 0.05. The primary outcome was the response to the question “How likely is it that long-term medications would help gout?”, measured on an 11-point Likert scale.

Demographic variables were described using number, percentage, mean, and SD. Between-group differences were explored using independent sample *t*-tests.

Participant responses to the question asking them to provide the three most important causes of gout in rank order were grouped into diet, genetics, alcohol, lifestyle, aging, and “other,” based on groupings used in previous studies.^{31,32} Responses were grouped by a researcher who was blinded to the study allocation.

Data were analyzed using IBM SPSS Statistics version 27 (IBM Corp) and SAS version 9.4 (SAS Institute Inc). Main effects of study allocation were modeled using general linear modeling with normal distribution and identity link function for continuous variables to estimate between-group mean differences with and without adjustment for personal or family/friend history of gout. Binary distribution and an identity link function were used to estimate absolute percent difference between groups for the adjusted and unadjusted comparisons. Measures of effect are presented with 95% confidence intervals. To preserve an overall 5% significance level within each of the objectives, additional critical alphas are provided in the footnotes to each table corrected for the number of tests performed using the Bonferroni method. Unadjusted *P* values are provided throughout.

RESULTS

Participants. Between June 30, 2023, and April 11, 2024, 219 participants were recruited. Seventeen participants did not complete the Zoom interview, and one participant’s data were excluded because they did not identify the disease in the video as gout. A total of 201 participants correctly identified the disease

in the video as gout and completed the interview over Zoom with a researcher, 99 in the biologic causes group and 102 in the lifestyle causes group.

Demographic features are shown in Table 1. Of the 201 participants, 152 (75.6%) were female. There were 47 of 201 (23.4%) participants of Asian ethnicity, 21 of 201 (10.4%) were Māori, 124 of 201 (61.7%) were New Zealand European, and 5 of 201 (2.5%) were Pacific peoples. The average age of participants was 40.3 years, ranging from 19 to 87. There were 3 of 201 participants (1.5%) with a history of gout, and 86 of 201 (42.8%) had a family member or close friend with gout.

Causal beliefs. Participant ratings of different potential causes of gout are shown in Table 2. Those in the biologic causes group rated hereditary factors as a more important cause of gout than those in the lifestyle causes group, with a mean rating of 4.6 (SD 0.7) in the biologic causes group compared with mean 3.3 (SD 1.2) in the lifestyle causes group, *P* < 0.001. Those in the lifestyle causes group believed diet or poor eating habits, alcohol, and the person’s own behavior were more important causes of gout (all *P* values < 0.001).

When asked to provide in rank order a list of the three most important causes of gout, 62 of 102 (60.8%) of those in the lifestyle causes group and 13 of 99 (13.1%) of those in the biologic causes group gave either diet in general or a specific dietary factor as the most important cause (*P* < 0.001). In the biologic causes group, 74 of 99 (74.7%) gave genetics as the most important cause compared with 9 of 102 (8.8%) in the lifestyle causes group, *P* < 0.001 (Table 3).

Management strategies. In the biologic causes group, the mean participant rating in response to the question “How likely is it that long-term medicines would help gout?” (the primary outcome measure) was 8.7 (SD 1.4) compared with 7.9 (SD 1.9) in the lifestyle causes group, *P* = 0.001 (Table 4). Consistent with this result, when asked the question, “How likely is it that you

Table 1. Participant characteristics

Demographic variable	All participants, N = 201	Biologic causes, N = 99	Lifestyle causes, N = 102
Gender, n (%)			
Female	152 (75.6)	75 (75.8)	77 (75.5)
Male	48 (23.9)	24 (24.2)	24 (23.5)
Other	1 (0.5)	0 (0)	1 (1.0)
Age (mean [SD], range),	40.3 (18.8), 19–87	41.6 (19.2), 20–87	38.9 (18.3), 19–82
Ethnicity, N (%)			
Asian	47 (23.4)	18 (18.2)	29 (28.4)
Māori	21 (10.4)	16 (16.2)	5 (4.9)
New Zealand European	124 (61.7)	62 (62.6)	62 (60.8)
Other	4 (2.0)	2 (2.0)	2 (2.0)
Pacific peoples	5 (2.5)	1 (1.0)	4 (3.9)
Experience of gout, N (%)			
Personal diagnosis of gout	3 (1.5)	3 (3.0)	0 (0)
Diagnosis of gout in family or close friend	86 (42.8)	46 (46.5)	40 (39.2)

Table 2. Causes of gout, rated on a 5-point Likert scale from 1 “strongly disagree” to 5 “strongly agree”**

Cause	Biologic causes, mean score (SD)	Lifestyle causes, mean score (SD)	Unadjusted mean difference (95% CI)	P	Adjusted mean difference (95% CI)	P
Stress or worry	2.6 (1.1)	2.6 (1.0)	-0.0 (-0.3 to 0.3)	0.83	-0.01 (-0.31 to 0.29)	0.94
Hereditary	4.6 (0.7)	3.3 (1.2)	1.3 (1.0 to 1.6)	<0.001	1.34 (1.07 to 1.60)	<0.001
Diet or poor eating habits	4.0 (0.8)	4.7 (0.5)	-0.7 (-0.9 to -0.5)	<0.001	-0.68 (-0.87 to -0.50)	<0.001
Aging	4.1 (0.8)	3.4 (1.0)	0.6 (0.4 to 0.9)	<0.001	0.65 (0.39 to 0.92)	<0.001
Alcohol use	3.7 (0.9)	4.6 (0.5)	-0.9 (-1.1 to -0.7)	<0.001	-0.93 (-1.13 to -0.72)	<0.001
Pollution	2.3 (0.9)	2.0 (0.9)	0.3 (0.1 to 0.6)	0.009	0.33 (0.08 to 0.58)	0.0095
Chance or bad luck	2.6 (1.2)	2.2 (1.0)	0.3 (0.0 to 0.6)	0.04	0.30 (-0.01 to 0.61)	0.058
A germ or virus	1.9 (1.0)	1.8 (0.9)	0.1 (-0.1 to 0.4)	0.29	0.16 (-0.11 to 0.44)	0.23
The person's own behavior	3.1 (1.2)	3.8 (0.8)	-0.7 (-1.0 to -0.4)	<0.001	-0.70 (-0.99 to -0.41)	<0.001

* Bolded values signify statistical significance. P value for significance adjusted for multiple comparisons using Bonferroni correction; P value for significance = 0.006; adjustment was for personal history of gout or history of gout in a close friend or relative. CI, confidence interval.

would need long-term medication prescribed for gout?”, those in the biologic causes group gave a mean rating of 7.6 (SD 2.2) compared with 6.5 (SD 2.4) in the lifestyle causes group, $P = 0.001$ (Supplementary Table 2). Changing to a healthier diet, reducing alcohol, and losing weight were all given higher ratings by the lifestyle causes group than the biologic causes group (all P values < 0.001).

Both groups viewed lifestyle changes such as regular exercise, stopping or restricting alcohol, changing diet, and losing weight as likely to be effective, with all these management strategies rated above 7.5 on a 0 to 10 scale by both groups. There was no difference between the two groups in motivation to take long-term medications or concern about taking long-term medications or in ratings of how serious gout

is as an illness or how embarrassed they would be if they were diagnosed with it.

Illness perceptions. There were no differences between the two groups in ratings of the eight aspects of illness perceptions (Supplementary Table 3).

DISCUSSION

This experimental randomized study has demonstrated that a brief intervention explaining either the biologic or lifestyle causes of gout affects not only the public's views about the causes of gout but also likely its management, including the need for long-term medication. This was despite there being no difference in

Table 3. Participant listing of most likely cause of gout*

Grouped cause	Biologic causes group: most important cause of gout, n (%), n = 99	Lifestyle causes group: most important cause of gout, n (%), n = 102	Unadjusted percentage difference (95% CI)	P	Adjusted percentage difference (95% CI)	P
Diet	13 (13.1)	62 (60.8)	-47.7 (-59.2 to -36.1)	<0.001	-48.5 (-60.0 to -37.0)	<0.001
Genetics	74 (74.7)	9 (8.8)	65.9 (55.8 to 76.1)	<0.001	65.9 (55.7 to 75.9)	<0.001
Alcohol	2 (2)	16 (15.7)	-13.7 (-21.3 to -6.1)	<0.001	-12.9 (-20.9 to -4.8)	0.002
Lifestyle	2 (2)	3 (2.9)	-0.9 (-5.2 to 3.4)	0.71	-0.89 (-5.3 to 3.50)	0.69
Aging	3 (3)	2 (2)	1.1 (-3.2 to 5.4)	0.66	1.7 (-5.3 to 8.7)	0.64
Other ^a	6 (6.1)	10 (9.8)	-3.7 (-1.1 to 3.7)	0.33	-4.6 (-1.2 to 2.9)	0.23

* Bolded values signify statistical significance. P value for significance adjusted for multiple comparisons using Bonferroni correction; P value for significance = 0.008; adjustment was for personal history of gout or history of gout in a close friend or relative. CI, confidence interval.

^a Other: high cholesterol, liver disease, smoking, stress, kidney disease, weight, urate.

Table 4. Management strategies for gout, scale 0 “wouldn't help it at all” to 10 “very likely to help”**

Management strategy	Biologic causes, mean score (SD)	Lifestyle causes, mean score (SD)	Unadjusted mean difference (95% CI)	P	Adjusted mean difference (95% CI)	P
Managing stress	5.6 (2.6)	5.8 (2.4)	-0.2 (-0.9 to 0.5)	0.57	-0.17 (-0.87 to 0.53)	0.63
Regular exercise	7.8 (2.1)	8.2 (2.0)	-0.4 (-1.0 to 0.1)	0.14	-0.45 (-1.03 to 0.13)	0.13
Stopping/restricting alcohol	7.8 (2.2)	9.0 (1.3)	-1.2 (-1.7 to -0.7)	<0.001	-1.24 (-1.74 to -0.73)	<0.001
Long-term medication	8.7 (1.4)	7.9 (1.9)	0.8 (0.3-1.3)	0.001	0.79 (0.31-1.27)	0.001
Changing to a more healthy diet	8.5 (1.8)	9.3 (1.0)	-0.8 (-1.2 to 0.4)	<0.001	-0.85 (-1.26 to -0.44)	<0.001
Alternative medication	4.9 (2.7)	5.0 (2.6)	-0.1 (-0.9 to 0.6)	0.77	-0.06 (-0.81 to 0.69)	0.87
Losing weight	7.5 (2.2)	8.7 (1.4)	-1.3 (-1.8 to -0.8)	<0.001	-1.29 (-1.81 to -0.77)	<0.001

* Bolded values signify statistical significance. P value for significance adjusted for multiple comparisons using Bonferroni correction; P value for significance = 0.007; adjustment was for personal history of gout or history of gout in a close friend or relative. CI, confidence interval.

the description of treatment options for gout that was provided to the two groups. Therefore, providing accurate information to the public about the causes of gout is a viable strategy for changing illness beliefs and increasing acceptance for the use of long-term medication in the community.

A key finding of this study was that a brief intervention had an impact on causal beliefs, as demonstrated by the differences between groups in what they believed to be the most important cause of gout. This shows that the intervention was effective in influencing causal beliefs and that it was correctly delivered. The video format, containing both audio and visual material, likely contributed to making the intervention understandable and impactful.

The findings align with prior research investigating the impact of causal beliefs in other illnesses. In patients experiencing a first myocardial infarction, four half-hour sessions with a psychologist involving a discussion about causal beliefs and the link between the causes of the disease and the treatment plan resulted in a change in causal attributions and a greater intention to attend cardiac rehabilitation.³³ In another study, members of the public provided with a psychological explanation of a mental illness were more likely to believe the illness to be curable and less likely to believe hospitalization would be essential than those given a biologic explanation.³⁴ This is the first study to demonstrate the efficacy of an intervention aimed at influencing causal beliefs in gout and has also shown that even a very brief intervention can be effective in changing the public's views about gout management.

A practical application of these findings is that they support calls for improvements in the accuracy of information about gout being accessible to the public. Our results indicate that discussion about the causes of gout could be an effective way of improving acceptance of long-term ULT. Inaccurate information about the causes of gout is frequently disseminated to the public through newspapers, films, and television. For example, an analysis of newspaper articles about gout found that unhealthy foods and beverages were reported as the cause in 63% of articles whereas biologic causes were included in 40% of articles.³⁵ Additionally, only 12% of fictional depictions of gout in film and television since 1990 included mention of any biologic cause of gout.³⁶ A previous randomized study demonstrated that these media depictions affect the public's views about both the causes and management of gout.³¹ In the current study, both groups gave high ratings for the likely efficacy of lifestyle interventions, reflecting widespread positive views about the benefits of dietary interventions for gout. The findings from this study strengthen calls for accurate public commentary about the causes of gout, as they indicate that causal beliefs impact views on its long-term management. It highlights the opportunity for public health campaigns that discuss the causes of gout. Our findings also strengthen the justification for development of guidelines for media reporting and depictions of gout, which could be published by nongovernmental organizations or professional groups. Media

guidelines exist for reporting on other diseases such as HIV that have historically had inaccurate depictions in film, television, and newspaper.³⁷ Previous research has shown people with gout frequently experience blame from others as well as inaccurate management advice, which can delay them from receiving effective treatment with ULT.^{38,39} Therefore, improving the accuracy of information about the causes of gout that is accessible to the public is a strategy that could help people with gout receive better support with their management from their communities.

Strengths of this study include that it was randomized, was blinded, and had a large sample size. Incomplete questionnaires were avoided as participants completed them over Zoom with a researcher. The videos were identical other than a short section discussing potential causes of gout, and both contained text discussing medication and lifestyle management strategies. The questionnaires used in the study to evaluate views on illness perceptions and the causes and management of gout have been used in previous gout-related research.^{27,32,40–43} Participants were asked about the need for long-term medication more than once in the questionnaire, and the responses were consistent.

Limitations include the short duration of the study; it is unclear how long the effect of viewing the video lasts, as participants viewed the video shortly before the study interview. No pre-exposure questionnaire was performed to evaluate whether individual participant answers changed before and after the intervention. As both groups were members of the community recruited in the same way, it was assumed that they had similar baseline knowledge about gout. As depictions of gout emphasizing lifestyle causes are very prevalent,^{35,36} repeated exposure to explanations about the biologic causes of gout may be required to maintain an awareness of the efficacy of long-term medication. The study did not include a group examining the effects of a video containing causal information about both biologic and lifestyle factors. This study focused on the views of members of the public; it is unknown whether the intervention would have a similar effect on people with gout themselves and whether beliefs about the benefits of long-term medication translate into actually taking urate-lowering medications.

In summary, this study has demonstrated that a brief intervention describing the biologic causes of gout affects views about the likely benefits and necessity of long-term medication. This confirms the importance of ensuring that accurate information about the biologic causes of gout is accessible to patients and the wider community and demonstrates that even a brief intervention targeting causal beliefs in gout affects views on its management.

ACKNOWLEDGMENTS

Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australasian University Librarians.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Murdoch confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Long-Term Lignan Intake, Whole Grain Foods, and the Risk of Gout: Results From Two Prospective Cohort Studies

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Objective. Multiple plant-based dietary patterns are inversely associated with gout, although the individual constituents driving this association remain unclear. Dietary lignans, a major group of phytoestrogens abundant in plant foods, are metabolized by the gut microflora and may modulate gout risk. We examined the associations between dietary lignan intake, certain whole grain foods rich in lignans, and incident gout.

Methods. We analyzed data from 122,680 individuals in the Health Professionals Follow-up Study and Nurses' Health Study. We administered a food frequency questionnaire every two to four years. We used Cox models to evaluate associations between dietary lignans, whole grain foods, and confirmed gout.

Results. Higher intakes of matairesinol (hazard ratio [HR] comparing extreme quintiles, 0.78; 95% confidence interval [CI], 0.69–0.90; *P* trend = 0.002) and secoisolariciresinol (HR, 0.78; 95% CI, 0.68–0.89; *P* trend = 0.002) were both associated with lower gout risk, whereas pinoresinol and lariciresinol were not associated with gout. We found inverse associations of whole grain cold breakfast cereals (HR for those consuming ≥ 1 serving per day, 0.62; 95% CI, 0.53–0.73), cooked oatmeal/oat bran (HR for those consuming ≥ 2 servings per week, 0.78; 95% CI, 0.70–0.86), and bran added to food (HR for those consuming ≥ 2 servings per week, 0.84; 95% CI, 0.74–0.95), but not dark breads or other cooked breakfast cereals, with gout.

Conclusion. Higher intakes of matairesinol and secoisolariciresinol, as well as whole grain cold breakfast cereals, oatmeal, and added bran, were each significantly associated with lower gout risk. These findings support adherence to healthful plant-based diets for gout and support a potential role of the gut microbiome in gout pathogenesis.

INTRODUCTION

Gout is the most common inflammatory arthropathy worldwide and is causally preceded by hyperuricemia.^{1,2} Gout predominantly affects men, as their serum urate (SU) level remains largely unchanged in adulthood.^{3,4} Conversely, there is a significant correlation between SU and age among women, with levels increasing sharply during and after menopause.^{3,4} Indeed, prior

research has shown that postmenopausal women are at an increased risk of developing gout.⁵ This is primarily thought to be due to the uricosuric effect of estrogen,⁶ which declines during menopause. Conversely, the use of hormone therapy may lower SU; the Heart and Estrogen-Progestin Replacement Study, a randomized trial among 2,756 women, found that those treated with hormone therapy had slightly lower levels of SU after 12 months.⁷ Similar findings have been reported from observational studies.

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Supported by the NIH (grants UM1-CA-186107, U01-CA-167552, R01-AR-065944, R01-AR-056291, R01-DK-120870, R01-DK-126698, R01-HL-035464, and P50-AR-060772). Dr Rai's work was supported by a Doctoral Foreign Study Award from the Canadian Institutes of Health Research. Dr McCormick's work was supported by a Career Development Award from the NIH (grant K99-AR-080243).

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Data described in the article, code book, and analytic code will be made available upon request pending application and approval. Further information including the procedures to obtain and access data is described at <https://www.nurseshealthstudy.org/researchers> and <https://www.hsph.harvard.edu/hpfs/for-collaborators/>.

Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25596>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.25596>.

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Submitted for publication October 16, 2024; accepted in revised form June 17, 2025.

SIGNIFICANCE & INNOVATIONS

- Prior work has shown that dietary lignans, a major group of phytoestrogens abundant in plant-based diets, are metabolized by the gut microflora and can act as weak estrogens; whether these dietary factors are associated with the clinical endpoint of gout remains unknown.
- Higher intakes of two lignans, matairesinol and secoisolariciresinol, are significantly associated with lower gout risk.
- Selected whole grain foods rich in lignans, including whole grain cold breakfast cereals, cooked oatmeal/oat bran, and bran added to food, are also inversely associated with incident gout.
- These findings support adherence to healthful plant-based diets for gout prevention and support a potential role of the gut microbiome in gout pathogenesis.

For example, postmenopausal hormone use was associated with lower SU among women in the Third National Health and Nutrition Examination Survey.⁸ Another study of 61 postmenopausal women in Japan found that hormone therapy reduced SU among those with hyperuricemia.⁹ However, the potential adverse effects associated with hormone therapy use make it impractical for the sole purpose of gout prevention or treatment.

Meanwhile, diet is a well-established modifiable risk factor for gout. For example, conventional purine-loading factors such as red meat,¹⁰ seafood,¹⁰ fructose,¹¹ and alcohol¹² have all been shown to be independently associated with higher gout risk. Conversely, low-fat dairy products,¹⁰ coffee,¹³ and vitamin C¹⁴ are inversely associated with gout risk. More recently, studies have found inverse associations between healthy plant-based¹⁵ or fully vegetarian¹⁶ diet patterns and incident gout, although the individual plant constituents driving this relationship remain unknown. The link between endogenous estrogens and SU/gout suggests that modifiable factors capable of modulating estrogen metabolism may also modulate the risk of gout. To that end, phytoestrogens are a family of plant-derived compounds that bear a structural similarity to 17 β -estradiol (E2) and can exert weak estrogen-like effects by binding to estrogen receptors (ERs).¹⁷ Dietary lignans, including matairesinol, secoisolariciresinol, pinoreesinol, and lariciresinol, form a major group of phytoestrogens in the human diet.¹⁸ They are abundant in many plant-based foods commonly consumed in the western diet (eg, whole grain cereals, flax, fruits, vegetables, red wine, tea, and coffee).¹⁸ These potentially beneficial secondary plant metabolites are metabolized by the gut microbiota to form more bioactive enterolignans, which can then act as weak estrogens and bind with low affinity to ERs.^{18–20} This is particularly relevant to gout, which is associated with gut dysbiosis and partly modulated by diet.²¹

Taken together, the established associations between endogenous estrogen, the gut microbiome, and incident gout combined with the structural similarity of dietary lignans to E2 suggest that long-term dietary lignan intake may be inversely associated with gout risk, although this has yet to be investigated. Therefore, we analyzed data collected in two large ongoing prospective cohorts of US men and women to examine the associations between habitual dietary lignan intake and the risk of incident gout. Moreover, to enhance clinical applicability, we also examined the associations between commonly consumed whole grain foods that are rich in lignans and the risk of gout.

PATIENTS AND METHODS

Study population. The Nurses' Health Study (NHS) was initiated in 1976 when 121,700 female registered nurses (aged 30–55 years) responded to a mailed questionnaire with information about their medical history and lifestyle habits. In 1986, the Health Professionals Follow-up Study (HPFS) was initiated with 51,529 male health professionals (aged 40–75 years) who responded to a questionnaire similar to that used in the NHS. Every two years thereafter, participants continued to provide detailed responses on lifestyle, health behaviors, and medical history (response rate ~90% each cycle) in both cohorts. At baseline, we excluded individuals with prevalent gout, implausible energy intake (defined as <500 or >3,500 kcal/day for women and <800 or >4,200 kcal/day for men), and who were missing data on dietary lignan intake from the study population. The final baseline study population included 43,703 men in the HPFS and 78,977 women in the NHS.

Assessment of dietary intake. In 1984, participants in the NHS completed a 116-item food frequency questionnaire (FFQ) to provide information on their usual intake of various foods and beverages. From 1986 onward, an expanded questionnaire (~130 food items) has been administered to both NHS and HPFS participants every four years to collect updated dietary data. On each FFQ, participants indicated how often, on average, they consumed a predefined portion of ~130 food items over the previous year. Participants selected from nine response categories ranging from “never or less than once per month” to “six or more times per day.” The reliability and validity of the FFQ have been described in detail previously.^{22–25}

Average daily individual lignan intakes (ie, matairesinol, secoisolariciresinol, pinoreesinol, and lariciresinol) were calculated by multiplying each lignan-containing food item's consumption frequency by the lignan content of its specified portion size, and then summing the contributions from all relevant food items. Total lignan intake was calculated as the sum of the four individual lignans. The nutrient composition values were obtained from the Harvard University Food Composition Database, which is based primarily on US Department of Agriculture sources and

supplemented with other data sources as needed. Phytoestrogens from supplements were not included in these calculations.

We additionally identified five of the top contributing sources of dietary lignans that had not been previously studied in relation to incident gout in these cohorts. These foods were dark bread (encompassing wheat, oatmeal, rye, pumpernickel, other whole grain breads, and wheat pita bread), whole grain cold breakfast cereal, cooked oatmeal or oat bran, other cooked breakfast cereals, and bran that is added to food. Participants who reported consuming any cold breakfast cereal were asked to provide information about the type and brand name, which was then matched with data from the cereal manufacturer to estimate whole grain content. Cold breakfast cereals were considered whole grains if they contained at least 25% whole grain or bran content by weight.

Gout case ascertainment. We defined incident gout cases as those meeting the American College of Rheumatology (ACR) survey criteria for gout.²⁶ On each biennial questionnaire, participants indicated whether they had received a diagnosis of gout from a clinician. A supplementary questionnaire with the ACR criteria was mailed to participants who self-reported gout to confirm the diagnosis. As in previous studies using these cohorts, the primary endpoint was incident gout meeting at least 6 of the 11 ACR criteria: (1) more than one attack of acute arthritis, (2) maximum inflammation developed within one day, (3) oligoarthritis attack, (4) redness observed over joints, (5) painful or swollen first metatarsophalangeal joint, (6) unilateral first metatarsophalangeal joint attack, (7) unilateral tarsal joint attack, (8) tophus, (9) hyperuricemia, (10) asymmetric swelling within a joint (or on radiography), and (11) complete resolution of an attack. As part of a prior pilot validation study in the HPFS, two board-certified rheumatologists reviewed the medical records of 50 men who self-reported a gout diagnosis; the concordance rate between their medical record review and the ACR survey criteria was 94%.¹⁰

Covariate assessment. Every two years, participants provided updated information on lifestyle factors (eg, physical activity), new medical diagnoses, and medication use. Self-reported height and body weight were collected at baseline in both cohorts, and weight was updated every two years thereafter. The reproducibility and validity of self-reported body weight have been evaluated previously in a subset of men and women enrolled in these cohorts.²⁷ Self-reported weights were found to be highly correlated with the average of two standardized measurements taken six months apart by trained technicians (Pearson correlation coefficient of 0.97 for both men and women).²⁷ Among women, we also collected information on oral contraceptive use (baseline only), menopausal status, and postmenopausal hormone use.

To minimize confounding by overall diet quality, we identified two diet quality indices using factor analysis (principal components) of 37 prespecified food groups as has been done previously in our cohorts.^{28,29} As lignans are found in many foods common to the human diet, we excluded the top lignan-contributing foods from these 37 groups to avoid overadjusting for lignan intake. We used an orthogonal rotation procedure that resulted in two factors (ie, diet quality indices) that were uncorrelated with one another (Supplemental Figure 1).

Statistics. We calculated person-years of follow-up from the return of the baseline questionnaires until either the gout diagnosis date, death, date of last return of a valid follow-up questionnaire, or the follow-up period ended (January 2012 in HPFS and June 2010 in NHS), whichever came first. We divided lignan intake into quintiles, as this approach does not make assumptions about linearity and minimizes the influence of outliers. To test for a linear trend, we assigned the median intake value of each lignan within each category and modeled this as a continuous variable.

We used prespecified cutoffs to categorize the intake level of food items. For whole grain cold breakfast cereal and dark bread, we used four categories: never or less than one serving per month, one serving per month to one serving per week, two to six servings per week, and one or more serving per day. As oatmeal/oat bran, other cooked breakfast cereals, and added bran each have lower overall intake levels, we used three categories for these foods: never or less than one serving per month, one serving per month to one serving per week, and two or more servings per week. We used the continuous variable for each food item to calculate the *P* value for the trend.

All dietary variables were cumulatively averaged over the entire follow-up to better reflect long-term habitual intake and minimize within-person variation. The values of nondietary covariates were updated every two years to account for changes in these variables over time. To minimize missing covariates, we replaced missing data on body mass index (BMI) and physical activity by carrying forward observations from the preceding questionnaire for one follow-up cycle, and we created missing indicators to handle any remaining missing values.

We used time-varying Cox proportional hazards regression models to evaluate the association between lignan intake and whole grain foods rich in lignans with incident gout. We used age (years) as the time scale and stratified by calendar time in two-year intervals.³⁰ To examine the relation between lignan intake and gout, we adjusted for energy intake (quintiles), BMI (<21, 21–22.9, 23–24.9, 25–26.9, 27–28.9, 29–30.9, 31–32.9, 33–34.9, ≥35, or missing), history of hypertension, history of renal failure (men only), diuretic use, physical activity (quintiles or missing), total vitamin C intake (0–249, 250–499, 500–999, 1,000–1,499, >1,500 mg/day), and both diet quality indices (quintiles). As beer is both an established risk factor for gout¹² and

Table 1. Baseline characteristics of the Health Professionals Follow-up Study and Nurses' Health Study populations according to quintile of total lignan intake*

	HPFS (1986)					NHS (1984)				
	Q1	Q3	Q5	Q1	Q5	Q1	Q3	Q5	Q1	Q5
No. of participants	8,740	8,740	8,740	15,795	15,795	15,795	15,796	15,795	15,795	15,795
Age, mean ± SD, y	53.0 ± 10.0	53.8 ± 9.7	54.1 ± 9.5	49.4 ± 7.3	49.4 ± 7.3	49.4 ± 7.3	50.9 ± 7.1	52.3 ± 6.9	49.4 ± 7.3	52.3 ± 6.9
Total lignan intake, median (Q25–Q75), µg/d	172.1 (151.1–188.3)	269.8 (258.4–281.5)	428.8 (389.9–500.6)	151.1 (134.1–163.2)	151.1 (134.1–163.2)	151.1 (134.1–163.2)	223.2 (214.7–231.7)	335.6 (308.7–384.1)	151.1 (134.1–163.2)	335.6 (308.7–384.1)
Matairesinol, µg/d	5.0 (4.1–6.1)	6.7 (5.5–8.4)	8.6 (6.2–13.1)	4.2 (3.5–5.1)	4.2 (3.5–5.1)	4.2 (3.5–5.1)	5.7 (4.8–6.8)	7.2 (5.6–10.0)	4.2 (3.5–5.1)	7.2 (5.6–10.0)
Secoisolariciresinol, µg/d	56.8 (45.8–68.5)	85.0 (71.5–99.4)	111.8 (91.9–136.0)	53.2 (42.7–63.5)	53.2 (42.7–63.5)	53.2 (42.7–63.5)	80.1 (68.9–91.9)	106.3 (89.1–126.1)	53.2 (42.7–63.5)	106.3 (89.1–126.1)
Pinoresinol, µg/d	34.5 (28.1–41.7)	60.3 (50.2–72.4)	110.9 (87.3–151.8)	30.0 (24.6–35.8)	30.0 (24.6–35.8)	30.0 (24.6–35.8)	46.9 (39.9–55.3)	79.3 (65.0–100.7)	30.0 (24.6–35.8)	79.3 (65.0–100.7)
Lariciresinol, µg/d	68.2 (57.7–79.0)	112.8 (100.7–126.1)	189.7 (162.0–226.4)	58.1 (49.5–66.3)	58.1 (49.5–66.3)	58.1 (49.5–66.3)	88.0 (78.7–97.9)	141.8 (121.1–168.8)	58.1 (49.5–66.3)	141.8 (121.1–168.8)
White race, %	94.7	95.2	94.9	97.2	97.2	97.2	98.0	97.9	97.2	97.9
Physical activity, median (Q25–Q75), MET-h/wk	8.0 (2.6–21.7)	12.3 (4.5–27.4)	16.9 (5.9–36.1)	4.6 (1.9–13.7)	4.6 (1.9–13.7)	4.6 (1.9–13.7)	7.7 (2.9–18.4)	10.3 (3.5–23.7)	4.6 (1.9–13.7)	10.3 (3.5–23.7)
Body mass index, mean ± SD	25.6 ± 3.4	25.4 ± 3.1	25.1 ± 3.3	25.5 ± 5.3	25.5 ± 5.3	25.5 ± 5.3	24.9 ± 4.5	24.5 ± 4.2	25.5 ± 5.3	24.5 ± 4.2
History of hypertension, %	20.2	19.4	20.0	8.6	8.6	8.6	7.8	8.0	8.6	8.0
History of renal failure, %	0.1	0.1	0.1	–	–	–	–	–	–	–
Diuretic use, %	9.4	9.1	8.6	12.3	12.3	12.3	12.4	12.3	12.3	12.3
Diet quality score, mean ± SD	45.0 ± 9.8	53.2 ± 9.8	59.3 ± 12.2	41.7 ± 9.3	41.7 ± 9.3	41.7 ± 9.3	48.0 ± 9.1	55.5 ± 11.2	41.7 ± 9.3	55.5 ± 11.2
Total energy intake, mean ± SD, kcal/d	2,000 ± 641	1,996 ± 610	1,979 ± 619	1,733 ± 539	1,733 ± 539	1,733 ± 539	1,754 ± 523	1,726 ± 542	1,733 ± 539	1,726 ± 542
Total vitamin C intake, mean ± SD, mg/d	330 ± 402	424 ± 468	562 ± 557	269 ± 347	269 ± 347	269 ± 347	322 ± 359	442 ± 447	269 ± 347	442 ± 447
Alcohol intake, g/d	1.8 (0–7.6)	6.0 (1.0–14.0)	11.8 (2.8–29.0)	1.0 (0–4.7)	1.0 (0–4.7)	1.0 (0–4.7)	2.4 (0–8.8)	3.9 (0.9–13.1)	1.0 (0–4.7)	3.9 (0.9–13.1)
Postmenopausal, %	–	–	–	48.1	48.1	48.1	48.0	49.3	48.1	49.3
Oral contraceptive use, %	–	–	–	47.2	47.2	47.2	48.2	49.0	47.2	49.0

* Variables are standardized to the age distribution of the study population. Diet quality at baseline was assessed using the Alternative Healthy Eating Index. HPFS, Health Professionals Follow-up Study; MET-h, metabolic equivalent of task (hours/week); NHS, Nurses' Health Study; Q, quintile; SD, standard deviation.

substantial contributor of both pinoreesinol and lariciresinol intake, we further adjusted for beer consumption (<1 serving per month, 1 per month to 1 per week, 2–4 per week, 5 per week to 1 per day, >1 per day) in a separate model. Among women, the model was further adjusted for oral contraceptive use, menopausal status, and postmenopausal hormone use (premenopausal, postmenopausal never, current, or past users, or missing). We evaluated the proportional hazards assumption by testing the significance of the interaction term between our exposure of interest and age using a likelihood ratio test; no violation of this assumption was observed (all *P* for interaction > 0.05). In our analysis of lignan intake, we also conducted a sensitivity analysis to further control for residual confounding by beer consumption by restricting our study population to infrequent beer drinkers, which we defined as up to one drink per month, as has been done previously among men in this cohort.¹²

Next, to examine the relation between whole grain foods and gout, we adjusted for energy intake, BMI, history of hypertension, history of renal failure (men only), diuretic use, physical activity, total vitamin C intake, beer intake, coffee intake (0, <1, 1–3, 4+ cups per day), and both diet quality indices. Among women, we again further adjusted for oral contraceptive use, menopausal status, and postmenopausal hormone use.

Finally, we conducted analyses stratified by adiposity (BMI <25 vs ≥25), hypertension status (yes vs no), physical activity level (above vs below median), total fiber intake (above vs below median), and bowel movement frequency (more than once per day vs once a day or less). We tested for potential effect modification by these variables by including cross-product terms in our models.

All analyses were conducted separately within each cohort, and cohort-specific hazard ratios (HRs) were pooled using a fixed-effects meta-analysis model. We used the Cochran Q statistic to assess potential heterogeneity across the cohorts. As a sensitivity analysis, we reanalyzed the pooled HRs by using a random-effects meta-analysis model. All statistical tests were two-sided with a significance level of 0.05. All analyses were conducted using SAS version 9.4 for UNIX (SAS Institute Inc). The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital, Harvard T. H. Chan School of Public Health, and Massachusetts General Hospital.

RESULTS

Baseline characteristics and patterns of lignan intake. Participant characteristics according to total lignan intake at baseline are shown in Table 1. Participants with higher total lignan intake tended to be older and had higher levels of physical activity, a lower BMI, and higher diet quality. Alcohol intake was greatest among those in the highest quintile of total lignan intake, although men consumed more alcohol than women

(median intake 11.8 g per day among men vs 3.9 g per day among women in the extreme quintiles).

In both cohorts, lignan intake increased during the follow-up, although the trends among covariates were unchanged. Participant characteristics at the median follow-up are shown in Supplemental Table 1. Food contributors to lignan intake were largely stable over the follow-up except for secoisolariciresinol, for which flaxseed drove the majority of intake after it was added to the FFQ beginning in 2006. Beer intake contributed to ~7% to 12% of pinoreesinol intake among women in the early follow-up period and ~11% to 30% of pinoreesinol intake over the follow-up among men. In both cohorts, the proportion of lignan intake obtained from beer declined over the study period. In both cohorts, intakes of all four lignans were highly correlated with each other (Supplemental Figure 2). During follow-up, the age-adjusted Spearman correlations ranged from 0.36 (*P* < 0.0001) between matairesinol and secoisolariciresinol in the NHS to 0.75 (*P* < 0.0001) between pinoreesinol and lariciresinol in the HPFS. Matairesinol was the most highly correlated with oatmeal and bran added to food. Pinoreesinol and lariciresinol were both also correlated with oatmeal and added bran, as well as total vitamin C intake. Pinoreesinol was also highly correlated with beer intake, particularly among men.

Lignan intake and incident gout. Over 2,704,899 person-years of follow-up, we documented 2,709 cases of incident gout. In the fully adjusted multivariable models, higher matairesinol and secoisolariciresinol intake were both associated with significantly lower risk of gout, although the association between secoisolariciresinol was only apparent among women (*P* for heterogeneity = 0.0003). Neither pinoreesinol nor lariciresinol was associated with gout in either cohort (Table 2). Among men, before further adjustment for beer consumption, we initially observed significant positive associations between both pinoreesinol and lariciresinol intake and incident gout. These associations were no longer significantly associated with gout after further adjustment for beer intake. Therefore, in the final multivariable model that adjusted for beer intake, comparing extreme quintiles, the pooled HRs were 0.78 (95% confidence interval [CI], 0.69–0.90) for matairesinol (*P* trend = 0.002), 0.78 (95% CI, 0.68–0.89) for secoisolariciresinol (*P* trend = 0.002), 0.91 (95% CI, 0.78–1.06) for pinoreesinol (*P* trend = 0.22), and 0.94 (95% CI, 0.80–1.10) for lariciresinol (*P* trend = 0.38) (Table 2).

To further control for residual confounding by beer intake, we repeated our analysis of lignan intake by restricting to those who reported infrequent beer consumption (defined as up to one drink per month) for each FFQ cycle. Our results were consistent with the main analysis, with higher intakes of matairesinol (HR for extreme quintile = 0.78; 95% CI, 0.66–0.92; *P* trend = 0.03) and secoisolariciresinol (HR, 0.76; 95% CI, 0.64–0.90; *P* trend = 0.001) both significantly associated with a lower risk of gout, whereas pinoreesinol and lariciresinol were not associated with

Table 2. Cohort-specific and pooled associations between lignan intake and gout risk in the Health Professionals Follow-up Study (1986–2012) and Nurses' Health Study (1984–2010)*

	Q1	Q2	Q3	Q4	Q5	P for trend ^a
Total lignans						
HPFS						
Gout cases/person-years	299/176,522	355/176,872	348/177,071	332/177,273	373/177,609	–
Age-adjusted model	1.0	1.17 (1.00–1.36)	1.13 (0.97–1.32)	1.07 (0.92–1.26)	1.20 (1.03–1.40)	0.09
Multivariable model ^b	1.0	1.19 (1.02–1.40)	1.20 (1.02–1.42)	1.18 (0.99–1.40)	1.47 (1.22–1.76)	0.0002
Multivariable model + beer ^c	1.0	1.09 (0.93–1.27)	1.02 (0.86–1.21)	0.94 (0.78–1.12)	1.04 (0.85–1.27)	0.95
NHS						
Gout cases/person-years	230/363,427	245/363,739	186/363,926	184/363,977	157/364,484	–
Age-adjusted model	1.0	1.02 (0.85–1.23)	0.75 (0.61–0.91)	0.72 (0.59–0.87)	0.59 (0.48–0.73)	<0.0001
Multivariable model ^b	1.0	1.02 (0.84–1.23)	0.76 (0.61–0.94)	0.76 (0.61–0.95)	0.70 (0.55–0.91)	0.001
Multivariable model + beer ^c	1.0	1.00 (0.83–1.21)	0.74 (0.59–0.91)	0.73 (0.58–0.91)	0.66 (0.51–0.86)	0.0002
Pooled (fixed effects)						
Age-adjusted model	1.0	1.10 (0.98–1.24)	0.96 (0.85–1.09) ^d	0.92 (0.81–1.04) ^d	0.93 (0.83–1.05) ^d	0.22 ^d
Fully adjusted model ^c	1.0	1.05 (0.93–1.19)	0.90 (0.79–1.03) ^d	0.85 (0.73–0.98)	0.88 (0.75–1.03) ^d	0.08 ^d
Matairesinol						
HPFS						
Gout cases/person-years	376/175,675	316/176,597	373/177,311	341/177,669	301/178,094	–
Age-adjusted model	1.0	0.83 (0.71–0.96)	0.96 (0.83–1.11)	0.86 (0.75–1.00)	0.76 (0.65–0.88)	0.002
Multivariable model ^b	1.0	0.79 (0.68–0.91)	0.90 (0.78–1.05)	0.82 (0.70–0.95)	0.77 (0.66–0.91)	0.02
Multivariable model + beer ^c	1.0	0.80 (0.68–0.93)	0.92 (0.80–1.07)	0.85 (0.72–0.99)	0.81 (0.69–0.96)	0.07
NHS						
Gout cases/person-years	214/362,724	240/363,141	202/364,454	182/364,505	164/364,730	–
Age-adjusted model	1.0	1.08 (0.89–1.29)	0.89 (0.73–1.08)	0.76 (0.62–0.93)	0.64 (0.52–0.79)	<0.0001
Multivariable model ^b	1.0	1.04 (0.86–1.25)	0.86 (0.70–1.05)	0.76 (0.61–0.94)	0.73 (0.58–0.92)	0.0006
Multivariable model + beer ^c	1.0	1.04 (0.86–1.25)	0.86 (0.70–1.06)	0.76 (0.62–0.94)	0.73 (0.58–0.92)	0.0007
Pooled (fixed effects)						
Age-adjusted model	1.0	0.92 (0.82–1.03) ^d	0.93 (0.83–1.05)	0.83 (0.73–0.93)	0.71 (0.63–0.81)	<0.0001 ^d
Fully adjusted model ^c	1.0	0.88 (0.78–0.99) ^d	0.90 (0.80–1.02)	0.82 (0.72–0.92)	0.78 (0.69–0.90)	0.002 ^d
Secoisolariciresinol						
HPFS						
Gout cases/person-years	337/176,375	320/176,908	371/177,072	336/177,322	343/177,669	–
Age-adjusted model	1.0	0.93 (0.80–1.08)	1.07 (0.92–1.24)	0.96 (0.82–1.11)	0.97 (0.83–1.13)	0.72
Multivariable model ^b	1.0	0.92 (0.79–1.08)	1.06 (0.91–1.24)	0.96 (0.82–1.13)	1.02 (0.87–1.20)	0.74
Multivariable model + beer ^c	1.0	0.87 (0.74–1.02)	0.98 (0.84–1.15)	0.88 (0.75–1.03)	0.93 (0.79–1.10)	0.53
NHS						
Gout cases/person-years	274/363,589	217/363,763	205/363,958	174/364,103	132/364,141	–
Age-adjusted model	1.0	0.75 (0.63–0.89)	0.68 (0.57–0.82)	0.56 (0.46–0.68)	0.41 (0.34–0.51)	<0.0001
Multivariable model ^b	1.0	0.77 (0.64–0.92)	0.75 (0.62–0.91)	0.66 (0.54–0.81)	0.56 (0.44–0.71)	<0.0001
Multivariable model + beer ^c	1.0	0.76 (0.63–0.92)	0.75 (0.62–0.90)	0.65 (0.53–0.80)	0.55 (0.44–0.70)	<0.0001
Pooled (fixed effects)						
Age-adjusted model	1.0	0.85 (0.75–0.95)	0.89 (0.80–1.00) ^d	0.78 (0.69–0.88) ^d	0.72 (0.64–0.82) ^d	<0.0001 ^d
Fully adjusted model ^c	1.0	0.82 (0.73–0.93)	0.88 (0.78–0.99) ^d	0.78 (0.69–0.89) ^d	0.78 (0.68–0.89) ^d	0.002 ^d
Pinoresinol						
HPFS						
Gout cases/person-years	294/176,545	338/177,014	345/177,078	356/177,375	374/177,334	–
Age-adjusted model	1.0	1.14 (0.98–1.34)	1.16 (0.99–1.35)	1.19 (1.02–1.38)	1.25 (1.07–1.46)	0.007
Multivariable model ^b	1.0	1.15 (0.98–1.35)	1.20 (1.02–1.41)	1.27 (1.08–1.50)	1.48 (1.25–1.74)	<0.0001
Multivariable model + beer ^c	1.0	1.06 (0.90–1.25)	1.05 (0.88–1.24)	1.03 (0.86–1.23)	0.98 (0.80–1.20)	0.68

(Continued)

Table 2. (Cont'd)

	Q1	Q2	Q3	Q4	Q5	P for trend ^a
NHS						
Gout cases/person-years	217/363,142	223/363,706	199/363,984	195/364,037	168/364,685	–
Age-adjusted model	1.0	1.01 (0.84–1.22)	0.89 (0.73–1.08)	0.83 (0.68–1.01)	0.69 (0.57–0.85)	<0.0001
Multivariable model ^b	1.0	1.01 (0.83–1.22)	0.93 (0.76–1.14)	0.92 (0.75–1.14)	0.88 (0.70–1.11)	0.18
Multivariable model + beer ^c	1.0	1.00 (0.82–1.21)	0.91 (0.74–1.12)	0.90 (0.72–1.11)	0.82 (0.64–1.04)	0.06
Pooled (fixed effects)						
Age-adjusted model	1.0	1.09 (0.96–1.23)	1.04 (0.92–1.18) ^d	1.03 (0.92–1.17) ^d	1.01 (0.89–1.14) ^d	0.46 ^d
Fully adjusted model ^c	1.0	1.03 (0.91–1.17)	0.99 (0.87–1.13)	0.97 (0.85–1.12)	0.91 (0.78–1.06)	0.22
Lariciresinol						
HPFS						
Gout cases/person-years	293/176,735	359/176,948	330/177,142	398/177,207	327/177,314	–
Age-adjusted model	1.0	1.21 (1.04–1.41)	1.10 (0.94–1.29)	1.33 (1.14–1.54)	1.08 (0.92–1.26)	0.39
Multivariable model ^b	1.0	1.25 (1.07–1.47)	1.18 (0.99–1.40)	1.47 (1.24–1.75)	1.30 (1.07–1.59)	0.008
Multivariable model + beer ^c	1.0	1.15 (0.98–1.35)	1.02 (0.86–1.22)	1.21 (1.02–1.45)	1.02 (0.83–1.25)	0.996
NHS						
Gout cases/person-years	214/363,624	222/363,773	202/364,034	187/363,992	177/364,130	–
Age-adjusted model	1.0	1.00 (0.83–1.21)	0.90 (0.74–1.09)	0.80 (0.66–0.97)	0.75 (0.61–0.91)	0.0004
Multivariable model ^b	1.0	0.99 (0.82–1.21)	0.90 (0.73–1.11)	0.82 (0.65–1.03)	0.84 (0.65–1.08)	0.09
Multivariable model + beer ^c	1.0	0.98 (0.81–1.20)	0.88 (0.71–1.09)	0.80 (0.63–1.01)	0.81 (0.62–1.06)	0.06
Pooled (fixed effects)						
Age-adjusted model	1.0	1.12 (1.00–1.27)	1.02 (0.90–1.15)	1.10 (0.98–1.24) ^d	0.94 (0.83–1.06) ^d	0.38 ^d
Fully adjusted model ^c	1.0	1.08 (0.95–1.22)	0.97 (0.84–1.10)	1.04 (0.90–1.20) ^d	0.94 (0.80–1.10)	0.38

* Values are the hazard ratio (95% confidence interval) unless otherwise indicated. HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; Q, quintile.

^a P value when we assigned the median value to each quintile and entered this as a continuous variable in the model.

^b Models were age and calendar time stratified and adjusted for energy intake, body mass index, history of hypertension, history of renal failure (men only), diuretic use, physical activity, total vitamin C intake, and both diet quality indices free of the top 10 dietary lignan contributors. Among women, the model was additionally adjusted for oral contraceptive use and menopausal status/postmenopausal hormone use.

^c Model was additionally adjusted for beer intake.

^d P value for Q-statistic < 0.05, indicating statistically significant heterogeneity between the two cohorts.

gout (Table 3). Our results did not change materially when we pooled estimates from both cohorts using a random-effects meta-analysis model as a further sensitivity analysis.

Subgroup analyses. We further examined the association of individual lignan intake with incident gout in stratified analyses. After adjusting for the same covariates as in the main analysis, the inverse association between matairesinol intake and gout was stronger among those who had lower fiber intake (*P* for interaction = 0.007). We found no other significant effect modification between individual lignans and adiposity, hypertension, physical activity, total fiber intake, or bowel movement frequency (all *P* for interaction > 0.05) (Table 4).

Whole grain foods and incident gout. Table 5 shows the associations between consumption of whole grain foods and the risk of gout. The pooled multivariable HRs comparing consumption of one or more servings a day with those consuming less than one serving a month were 0.97 (95% CI, 0.82–1.14) for dark breads and 0.62 (95% CI, 0.53–0.73) for whole grain cold

breakfast cereal. For the other foods with lower intake levels, the pooled HRs comparing participants consuming two or more servings a week with less than one serving a month were 0.78 (95% CI, 0.70–0.86) for cooked oatmeal or oat bran, 0.92 (95% CI, 0.77–1.09) for other cooked breakfast cereals, and 0.84 (95% CI, 0.74–0.95) for bran added to food.

DISCUSSION

In this large prospective cohort study of 122,680 men and women, we found that higher intakes of matairesinol and secoisolariciresinol, but not pinoreesinol or lariciresinol, were significantly associated with a lower risk of incident gout. These inverse associations were independent of known and potential risk factors for gout, including age, BMI, hypertension, diuretic use, and diet quality. Further analysis of these associations after restricting to participants with infrequent beer consumption were consistent with these findings. Our analysis of whole grain food items that are rich in lignans additionally revealed that higher intakes of

Table 3. Cohort-specific and pooled associations between lignan intake and gout risk among infrequent beer drinkers in the Health Professionals Follow-up Study (1986–2012) and Nurses' Health Study (1984–2010)*

	Q1	Q2	Q3	Q4	Q5	P for trend ^a
Total lignans						
HPFS						
Gout cases/person-years	191/123,087	174/97,123	162/85,824	126/79,388	122/78,712	–
Age-adjusted model	1.0	1.13 (0.92–1.39)	1.18 (0.96–1.46)	0.99 (0.79–1.24)	0.96 (0.76–1.21)	0.45
Multivariable model ^b	1.0	1.10 (0.89–1.37)	1.13 (0.90–1.42)	0.93 (0.72–1.20)	0.99 (0.75–1.31)	0.61
NHS						
Gout cases/person-years	214/331,393	215/310,384	159/298,347	147/288,146	137/280,901	–
Age-adjusted model	1.0	1.02 (0.85–1.24)	0.74 (0.61–0.92)	0.69 (0.56–0.85)	0.63 (0.51–0.78)	<0.0001
Multivariable model ^b	1.0	1.01 (0.83–1.24)	0.77 (0.61–0.96)	0.74 (0.58–0.94)	0.75 (0.57–0.99)	0.008
Pooled (fixed effects)						
Age-adjusted model	1.0	1.07 (0.93–1.23)	0.94 (0.81–1.08) ^c	0.81 (0.70–0.95) ^c	0.77 (0.66–0.90) ^c	0.0003 ^c
Multivariable model ^b	1.0	1.05 (0.91–1.22)	0.93 (0.79–1.09) ^c	0.83 (0.69–0.99)	0.86 (0.70–1.04)	0.06
Matairesinol						
HPFS						
Gout cases/person-years	197/102,400	130/90,797	142/85,921	160/88,556	146/96,460	–
Age-adjusted model	1.0	0.75 (0.60–0.93)	0.85 (0.69–1.06)	0.93 (0.75–1.15)	0.77 (0.62–0.96)	0.31
Multivariable model ^b	1.0	0.70 (0.56–0.88)	0.79 (0.63–0.99)	0.86 (0.69–1.07)	0.79 (0.62–1.00)	0.64
NHS						
Gout cases/person-years	185/303,608	207/298,364	175/297,136	155/299,847	150/310,216	–
Age-adjusted model	1.0	1.09 (0.89–1.33)	0.91 (0.74–1.11)	0.77 (0.62–0.95)	0.67 (0.54–0.83)	<0.0001
Multivariable model ^b	1.0	1.06 (0.87–1.31)	0.89 (0.72–1.11)	0.78 (0.62–0.98)	0.77 (0.60–0.98)	0.002
Pooled (fixed effects)						
Age-adjusted model	1.0	0.92 (0.79–1.06) ^c	0.88 (0.76–1.02)	0.85 (0.73–0.98)	0.72 (0.62–0.84)	0.0003 ^c
Multivariable model ^b	1.0	0.88 (0.76–1.02) ^c	0.84 (0.72–0.98)	0.82 (0.70–0.96)	0.78 (0.66–0.92)	0.03 ^c
Secoisolariciresinol						
HPFS						
Gout cases/person-years	197/114,755	151/92,769	160/86,691	119/83,510	148/86,408	–
Age-adjusted model	1.0	0.94 (0.76–1.16)	1.06 (0.86–1.31)	0.81 (0.65–1.02)	0.98 (0.79–1.21)	0.55
Multivariable model ^b	1.0	0.91 (0.73–1.13)	1.00 (0.80–1.25)	0.77 (0.60–0.98)	0.95 (0.75–1.21)	0.48
NHS						
Gout cases/person-years	249/323,487	187/304,270	172/295,184	148/290,917	116/295,314	–
Age-adjusted model	1.0	0.74 (0.61–0.90)	0.68 (0.55–0.82)	0.57 (0.47–0.71)	0.43 (0.35–0.54)	<0.0001
Multivariable model ^b	1.0	0.77 (0.63–0.93)	0.75 (0.61–0.92)	0.68 (0.55–0.85)	0.59 (0.46–0.75)	<0.0001
Pooled (fixed effects)						
Age-adjusted model	1.0	0.83 (0.72–0.95)	0.83 (0.72–0.96) ^c	0.67 (0.58–0.78) ^c	0.66 (0.56–0.77) ^c	<0.0001 ^c
Multivariable model ^b	1.0	0.83 (0.71–0.96)	0.86 (0.74–1.00)	0.72 (0.61–0.85)	0.76 (0.64–0.90) ^c	0.001 ^c
Pinoresinol						
HPFS						
Gout cases/person-years	209/133,795	196/103,364	131/87,955	148/75,280	91/63,740	–
Age-adjusted model	1.0	1.21 (0.99–1.47)	0.94 (0.75–1.17)	1.22 (0.99–1.51)	0.88 (0.69–1.13)	0.40
Multivariable model ^b	1.0	1.17 (0.96–1.43)	0.90 (0.72–1.14)	1.20 (0.95–1.51)	0.97 (0.74–1.27)	0.89
NHS						
Gout cases/person-years	206/337,116	189/316,161	182/301,630	162/289,659	133/264,606	–
Age-adjusted model	1.0	0.95 (0.78–1.16)	0.94 (0.77–1.15)	0.82 (0.66–1.00)	0.70 (0.56–0.87)	0.0003
Multivariable model ^b	1.0	0.95 (0.77–1.17)	0.98 (0.79–1.22)	0.90 (0.72–1.13)	0.86 (0.67–1.11)	0.22
Pooled (fixed effects)						
Age-adjusted model	1.0	1.07 (0.93–1.23)	0.94 (0.81–1.09)	0.99 (0.86–1.15) ^c	0.77 (0.65–0.91)	0.006 ^c
Multivariable model ^b	1.0	1.06 (0.91–1.22)	0.95 (0.81–1.11)	1.04 (0.88–1.22)	0.91 (0.76–1.10)	0.42
Lariciresinol						
HPFS						
Gout cases/person-years	165/114,558	175/92,506	136/85,083	178/82,770	121/89,217	–
Age-adjusted model	1.0	1.30 (1.05–1.60)	1.08 (0.86–1.36)	1.45 (1.18–1.80)	0.91 (0.72–1.15)	0.54
Multivariable model ^b	1.0	1.26 (1.01–1.57)	1.05 (0.82–1.34)	1.40 (1.10–1.80)	0.90 (0.67–1.21)	0.48
NHS						
Gout cases/person-years	197/325,574	189/305,787	175/295,892	155/289,894	156/292,025	–
Age-adjusted model	1.0	0.98 (0.80–1.20)	0.92 (0.75–1.13)	0.79 (0.64–0.97)	0.78 (0.63–0.96)	0.004
Multivariable model ^b	1.0	0.98 (0.79–1.21)	0.93 (0.74–1.16)	0.82 (0.64–1.06)	0.89 (0.67–1.17)	0.27
Pooled (fixed effects)						
Age-adjusted model	1.0	1.12 (0.97–1.29)	0.99 (0.85–1.15)	1.07 (0.92–1.24) ^c	0.83 (0.71–0.97)	0.03 ^c
Multivariable model ^b	1.0	1.10 (0.95–1.28)	0.98 (0.83–1.16)	1.07 (0.90–1.28) ^c	0.89 (0.73–1.09)	0.23

* Values are the hazard ratio (95% confidence interval) unless otherwise indicated. Infrequent beer drinkers were defined as those who consumed up to one beer per month. HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; Q, quintile.

^a P value when we assigned the median value to each quintile and entered this as a continuous variable in the model.

^b Models were age and calendar time stratified and adjusted for energy intake, body mass index, history of hypertension, history of renal failure (men only), diuretic use, physical activity, total vitamin C intake, and both diet quality indices free of the top 10 dietary lignan contributors. Among women, the model was additionally adjusted for oral contraceptive use and menopausal status/postmenopausal hormone use.

^c P value for Q-statistic < 0.05, indicating statistically significant heterogeneity between the two cohorts.

Table 4. Pooled associations between lignan intake and gout risk stratified by selected characteristics*

	Per standard deviation of lignan intake			
	Matairesinol	Secoisolariciresinol	Pinoresinol	Lariciresinol
Adiposity				
Normal weight	0.97 (0.90–1.05)	0.92 (0.83–1.02) ^a	1.03 (0.99–1.08) ^a	0.91 (0.82–1.01)
Overweight or obese	0.90 (0.85–0.96)	0.93 (0.86–0.99)	1.00 (0.95–1.07)	0.97 (0.91–1.03)
<i>P</i> for interaction ^b	0.12	0.66	0.74	0.47
Bowel movement frequency				
>1 per d	0.96 (0.87–1.06)	0.95 (0.85–1.06) ^a	0.97 (0.87–1.09)	0.99 (0.88–1.10)
≤1 per d	0.91 (0.86–0.96)	0.93 (0.87–1.00)	1.05 (1.02–1.09) ^a	0.94 (0.88–1.00)
<i>P</i> for interaction ^c	0.78	0.51 ^a	0.08	0.56
Total fiber intake				
Below median	0.84 (0.76–0.93)	0.88 (0.80–0.97)	0.99 (0.91–1.07)	1.00 (0.90–1.10)
Above median	0.97 (0.92–1.02)	0.97 (0.92–1.03) ^a	1.05 (1.02–1.09) ^a	0.96 (0.90–1.03)
<i>P</i> for interaction ^d	0.007	0.22	0.34	0.69
Physical activity				
Below median	0.91 (0.85–0.98)	0.94 (0.87–1.01) ^a	1.05 (1.01–1.09) ^a	0.93 (0.86–1.01) ^a
Above median	0.92 (0.86–0.99)	0.93 (0.85–1.01)	1.00 (0.92–1.08)	0.96 (0.88–1.04)
<i>P</i> for interaction ^d	0.30	0.61	0.82	0.23
Hypertension status				
No	1.00 (0.92–1.08)	0.96 (0.89–1.05) ^a	1.06 (0.98–1.14)	1.01 (0.92–1.11)
Yes	0.98 (0.92–1.04) ^a	0.92 (0.85–0.99)	1.02 (0.98–1.06) ^a	0.92 (0.86–0.99)
<i>P</i> for interaction ^e	0.18	0.97	0.13	0.48

* Values are the hazard ratio (95% confidence interval) unless otherwise indicated. All models were adjusted for the same covariates as in the main analysis except for the stratifying variables.

^a *P* value for *Q*-statistic < 0.05, indicating statistically significant heterogeneity between the two cohorts.

^b *P* for interaction comparing overweight/obese with normal weight.

^c *P* for interaction comparing less frequent with more frequent bowel movements.

^d *P* for interaction comparing above median with below median.

^e *P* for interaction comparing those without hypertension to those with hypertension.

cooked oatmeal or oat bran, whole grain cold breakfast cereal, and bran added to food were also all independently associated with a lower risk of incident gout. Conversely, dark bread and other cooked breakfast cereals were not significantly associated with gout. These inverse associations largely persisted among subgroups defined by various anthropometric, lifestyle, or dietary factors.

It is well established that diet is associated with the risk of developing gout.³¹ Prior work has shown that many healthful diets that emphasize the intake of certain plant-based foods, including the Dietary Approaches to Hypertension and Mediterranean diets, are associated with a lower risk of incident gout among both men and women.^{32,33} Moreover, a recent study reported that a healthy plant-based diet pattern is inversely associated with gout risk among men and women.¹⁵ However, less attention has been paid to the potentially beneficial constituents of these plant-rich diets. Two smaller human studies have examined lignan intake in relation to SU and hyperuricemia, but not gout. One study among ~2,500 middle-aged and elderly Chinese participants found inverse associations between baseline measures of matairesinol, secoisolariciresinol, and pinoresinol (but not lariciresinol) and development of hyperuricemia over 10 years.³⁴ A cross-sectional study using baseline data from ~6,300 participants enrolled in the PREDIMED-Plus trial found a modest positive association between lignan intake and SU among women but not men, although this study did not

distinguish between lignan types.³⁵ The mechanism underlying this observed sex difference is unknown; one possibility is the underlying differences in gout risk due to sex hormones, as the bioactive form of lignans (enterolignans) become capable of acting as weak estrogens and bind with low affinity to ERs.^{18–20} Such differences in gout risk may also arise in part due to distinct, sex-specific inflammatory responses.³⁶ Indeed, a dietary pattern predictive of circulating inflammatory biomarkers was shown to more strongly predict female gout versus male gout,³⁷ which is consistent with studies reporting on the anti-inflammatory potential of dietary lignans.³⁸ Among animal studies, one study examined the effect of flaxseed meal (the primary food source of secoisolariciresinol) on SU among rats and found that the group of rats fed flaxseed ad libitum had a lower SU level compared with those fed a soy-based chow.³⁹ In another study, three plant lignans (phyllanthin, hypophyllanthin, and phytetralin) found in *Phyllanthus niruri* were shown to increase uricosuric action among rats.^{40,41} The biosynthetic pathway to form phyllanthin and hypophyllanthin remains under investigation, but evidence suggests that they are derived from secoisolariciresinol.^{42,43} As lignans bear a structural similarity to E2,¹⁷ they may mimic the uricosuric properties of endogenous estrogen⁶ by suppressing urate reabsorptive transporters⁴⁴ and promoting the expression of urate efflux transporters.⁴⁵

Lignans may also potentially modulate gout risk indirectly through weight control. Evidence from cross-sectional studies

Table 5. Cohort-specific and pooled associations between lignan-rich food sources and gout risk in the Health Professionals Follow-up Study (1986–2012) and Nurses' Health Study (1984–2010)*

	Consumption level				<i>P</i> for trend ^a
	Never or <1 serving per mo	1 serving per mo to 1 serving per wk	>1 serving per wk to 4–6 servings per wk	≥1 serving per d	
Dark bread					
HPFS					
Gout cases/person-years	127/74,843	286/132,971	719/344,072	575/333,459	–
Age-adjusted model	1.0	1.27 (1.03–1.57)	1.17 (0.97–1.42)	0.98 (0.80–1.18)	0.002
Multivariable model ^b	1.0	1.25 (1.01–1.54)	1.14 (0.94–1.39)	1.04 (0.85–1.27)	0.38
NHS					
Gout cases/person-years	66/134,404	105/259,877	487/801,714	344/623,559	–
Age-adjusted model	1.0	0.81 (0.59–1.10)	0.84 (0.65–1.09)	0.76 (0.59–1.00)	0.005
Multivariable model ^b	1.0	0.81 (0.59–1.11)	0.87 (0.66–1.14)	0.83 (0.63–1.11)	0.11
Pooled (fixed effects)					
Age-adjusted model	1.0	1.10 (0.93–1.31) ^c	1.04 (0.89–1.22) ^c	0.90 (0.77–1.05)	<0.0001
Multivariable model ^b	1.0	1.09 (0.92–1.30) ^c	1.04 (0.89–1.22)	0.97 (0.82–1.14)	0.12
Whole grain cold breakfast cereal					
HPFS					
Gout cases/person-years	510/211,082	277/142,716	720/376,446	200/155,101	–
Age-adjusted model	1.0	0.81 (0.70–0.93)	0.76 (0.67–0.85)	0.53 (0.45–0.62)	<0.0001
Multivariable model ^b	1.0	0.79 (0.69–0.92)	0.77 (0.68–0.87)	0.62 (0.52–0.74)	<0.0001
NHS					
Gout cases/person-years	458/853,741	177/293,114	349/606,287	18/66,411	–
Age-adjusted model	1.0	0.86 (0.72–1.03)	0.76 (0.66–0.88)	0.48 (0.30–0.77)	<0.0001
Multivariable model ^b	1.0	0.84 (0.70–1.00)	0.84 (0.73–0.98)	0.65 (0.40–1.05)	0.0008
Pooled (fixed effects)					
Age-adjusted model	1.0	0.83 (0.74–0.93)	0.76 (0.69–0.83)	0.52 (0.45–0.61)	<0.0001
Multivariable model ^b	1.0	0.81 (0.73–0.91)	0.80 (0.73–0.88)	0.62 (0.53–0.73)	<0.0001
Oatmeal or cooked oat bran					
HPFS					
Gout cases/person-years	814/384,625	512/276,157	381/224,564	–	–
Age-adjusted model	1.0	0.87 (0.78–0.97)	0.75 (0.66–0.85)	–	0.0001
Multivariable model ^b	1.0	0.90 (0.80–1.00)	0.81 (0.71–0.92)	–	0.06
NHS					
Gout cases/person-years	456/820,703	336/624,441	210/374,409	–	–
Age-adjusted model	1.0	0.82 (0.71–0.95)	0.66 (0.56–0.78)	–	<0.0001
Multivariable model ^b	1.0	0.80 (0.69–0.93)	0.72 (0.60–0.85)	–	0.003
Pooled (fixed effects)					
Age-adjusted model	1.0	0.85 (0.78–0.93)	0.72 (0.65–0.79)	–	<0.0001 ^c
Multivariable model ^b	1.0	0.86 (0.79–0.94)	0.78 (0.70–0.86)	–	0.003
Other cooked breakfast cereal					
HPFS					
Gout cases/person-years	1,308/667,498	297/158,877	102/58,971	–	–
Age-adjusted model	1.0	0.96 (0.84–1.08)	0.86 (0.70–1.06)	–	0.14
Multivariable model ^b	1.0	1.01 (0.89–1.14)	1.00 (0.81–1.22)	–	0.96
NHS					
Gout cases/person-years	795/1,382,930	167/344,726	40/91,897	–	–
Age-adjusted model	1.0	0.84 (0.71–1.00)	0.67 (0.49–0.92)	–	0.004
Multivariable model ^b	1.0	0.87 (0.73–1.03)	0.74 (0.54–1.03)	–	0.03
Pooled (fixed effects)					
Age-adjusted model	1.0	0.91 (0.83–1.01)	0.80 (0.68–0.95)	–	0.01 ^c
Multivariable model ^b	1.0	0.95 (0.86–1.06)	0.92 (0.77–1.09)	–	0.44 ^c
Bran added to food					
HPFS					
Gout cases/person-years	1,214/602,223	247/130,195	246/152,928	–	–
Age-adjusted model	1.0	0.94 (0.82–1.07)	0.77 (0.67–0.89)	–	<0.0001
Multivariable model ^b	1.0	0.98 (0.85–1.13)	0.88 (0.77–1.02)	–	0.02
NHS					
Gout cases/person-years	800/1,331,798	103/236,983	99/250,772	–	–
Age-adjusted model	1.0	0.69 (0.56–0.84)	0.56 (0.46, 0.69)	–	<0.0001
Multivariable model ^b	1.0	0.79 (0.64–0.98)	0.75 (0.60, 0.93)	–	0.01

(Continued)

Table 5. (Cont'd)

	Consumption level				<i>P</i> for trend ^a
	Never or <1 serving per mo	1 serving per mo to 1 serving per wk	>1 serving per wk to 4–6 servings per wk	≥1 serving per d	
Pooled (fixed effects)					
Age-adjusted model	1.0	0.85 (0.76–0.95) ^c	0.70 (0.63–0.79) ^c	–	<0.0001 ^c
Multivariable model ^b	1.0	0.92 (0.82–1.03)	0.84 (0.74–0.95)	–	0.002

* Values are the hazard ratio (95% confidence interval) unless otherwise indicated. HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.

^a Calculated with continuous exposure variables.

^b Models were age and calendar time stratified and adjusted for energy intake, body mass index, history of hypertension, history of renal failure (men only), diuretic use, physical activity, total vitamin C intake, beer intake, coffee intake, and both diet quality indices free of the top 10 dietary lignan contributors. Among women, the model was additionally adjusted for oral contraceptive use and menopausal status/postmenopausal hormone use.

^c *P* value for *Q*-statistic < 0.05, indicating statistically significant heterogeneity between the two cohorts.

have found that individuals with greater lignan intake tend to have lower adiposity measures.^{46,47} These data are consistent with a prospective study that found that greater urinary excretion of lignan metabolites (particularly enterodiol) is associated with slower weight gain.⁴⁸ This is particularly relevant as long-term observational studies have consistently shown that adiposity is a key strong modifiable risk factor for gout.^{49,50} In addition, a secondary analysis of the Dietary Intervention Randomized Controlled Trial showed a urate-lowering effect of three different weight-loss diets (ie, a Mediterranean diet, low-carbohydrate diet, and low-fat diet) over 24 months in parallel with participants' weight loss over the follow-up.⁵¹

Interestingly, we did not observe statistically significant associations between gout and either pinoretinol or lariciresinol. In our cohorts, beer was a substantial contributor of both lignans and is also a strong risk factor for gout. Accordingly, we observed that beer intake confounded the associations of interest for pinoretinol and lariciresinol, and after adjusting for beer intake or restricting the analyses to less frequent beer drinkers, these two lignans were no longer associated with gout in either direction. Potential explanations for the differential associations between individual lignans and gout risk are unknown, although further studies are warranted to understand whether this may be due to differential production of bioactive enterolignans through human gut microbiota. Future work ought to replicate the current findings in other epidemiologic studies that examine lignan intake and enterolignan concentrations.

Our analysis of commonly consumed whole grain foods that are rich in lignans also deserves comment. We found that higher intakes of cooked oatmeal or oat bran, whole grain cold breakfast cereal, and added bran (but not dark bread or other cooked breakfast cereals) were each independently associated with a lower risk of gout. A recent investigation found that whole grain foods are collectively associated with a lower risk of gout,¹⁵ although prior studies of individual whole grain food items and gout are limited. A small study among 20 healthy adults found

no change from baseline SU after consuming a whole grain diet (consisting primarily of fiber-rich breads) for three weeks.⁵² These data are consistent with our finding that dark bread is not associated with the clinical endpoint of gout, although the study by Foerster and colleagues is limited by a small sample size and short follow-up duration. An earlier prospective study among men in the HPFS examined the association of a combination of high-purine plant-based foods, including oatmeal, and found no association with incident gout, although oatmeal was not examined separately.¹⁰ Oatmeal, which contains a moderate amount of purines,⁵³ was a significant contributor to matairesinol intake (up to ~57%), which we also observed as inversely associated with gout in the current study.

The strengths of our study deserve comment. To our knowledge, this is the first prospective evaluation of long-term dietary lignan intake among humans. Our cohorts had a large sample size and high number of confirmed gout cases, which has previously been shown to have high concordance with a medical record review by two board-certified rheumatologists. To that end, although the current study focused on incident gout (primary prevention), many risk factors for new-onset gout are also risk factors for recurrent gout (secondary prevention in a clinical setting).⁵⁴ We prospectively collected repeated measures of usual diet using a validated questionnaire before the diagnosis of gout, minimizing potential recall bias. Moreover, we used a comprehensive assessment of lignans by leveraging our existing large nutrient composition database. Nevertheless, our study is not without its limitations. Flaxseeds, the dominant contributor to secoisolariciresinol intake, were not assessed in the FFQ until later in the follow-up. Therefore, the total level of secoisolariciresinol is likely to be underestimated during the early follow-up years. However, flaxseed consumption was low in both cohorts, making it unlikely that this would have altered our findings. As in all studies of dietary intakes, measurement error remains a possibility. However, this measurement error is likely to be nondifferential with respect to gout and therefore would likely attenuate the observed

associations toward the null. Moreover, our use of repeated measures and cumulatively averaged intake further reduces random measurement error and within-subject variation. Next, our study population predominantly consisted of White US-based health professionals, and therefore our findings are most readily generalized to Americans of similar ancestral and socioeconomic backgrounds who share similar distributions of dietary lignan intake and absolute rates of gout. Therefore, it is imperative that future prospective studies aim to replicate our findings among more diverse populations. Finally, we did not investigate whether the reported associations were mediated by enterolignans, the bioactive end metabolites of ingested lignans. As there is considerable intra- and interindividual variability in the formation of enterolignans by the microbiota, future research in this area may help to elucidate the specific mechanisms through which lignans may contribute to gout prevention.

In conclusion, in these two large prospective cohorts of US men and women, higher intakes of matairesinol and secoisolariciresinol—but not pinoreosinol or lariciresinol—were associated with a significantly lower risk of incident gout. These inverse associations were independent of known and potential risk factors for gout, including age, BMI, hypertension, diuretic use, and broader diet quality. Higher intakes of cooked oatmeal or oat bran, whole grain cold breakfast cereal, and added bran were also all independently associated with a lower risk of incident gout. These findings support adherence to a healthful plant-based diet for gout prevention and highlight the potential role of the gut microbiome in gout pathogenesis.

ACKNOWLEDGMENTS

We thank the participants and staff of the Nurses' Health Study and the Health Professionals Follow-up Study for their valuable contributions.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Drs Rai and Sun confirm that all authors have provided the final approval of the version to be published and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW ARTICLE

Adverse Pregnancy Outcomes in Adult Patients With Idiopathic Inflammatory Myopathy: A Systematic Review and Meta-Analysis

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Objective. Studies of the impact of idiopathic inflammatory myopathy (IIM) and its pregnancy complications have yielded controversial results. The purpose of this study was to perform a systematic literature review and meta-analysis to evaluate the association between IIM and adverse pregnancy outcomes.

Methods. PubMed, Embase, and Web of Science databases were searched to identify reports of interest. The databases were searched from establishment to May 15, 2025. Two investigators independently screened literature and extracted data according to inclusion and exclusion criteria. The Newcastle-Ottawa Scale was used for quality assessment. A random-effects model with inverse-variance weighting was selected to estimate the pooled odds ratio (OR) and 95% confidence interval (CI). Data analysis was performed using Review Manager 5.3.

Results. This analysis included five population-based retrospective cohorts, predominantly comprising patients with dermatomyositis or polymyositis; thus, the pooled estimates primarily reflect these subtypes. Compared to pregnant patients without IIM, patients with IIM had significantly higher risks of hypertensive disorders of pregnancy (OR 2.73 [95% CI 1.76–4.23]; $I^2 = 70\%$, Cochran's $Q P = 0.01$, overall effect $P < 0.00001$) and cesarean section (OR 2.03 [95% CI 1.37–3.00]; $I^2 = 79\%$, Cochran's $Q P = 0.002$, overall effect $P = 0.004$). Infants born to birthing parents with IIM also had notably higher rates of being born preterm (OR 3.71 [95% CI 2.35–5.85]; $I^2 = 60\%$, Cochran's $Q P = 0.06$, overall effect $P < 0.00001$) and being small for gestational age or having intrauterine growth restriction (OR 1.90 [95% CI 1.03–3.51]; $I^2 = 43\%$, Cochran's $Q P = 0.15$, overall effect $P = 0.04$).

Conclusion. Our meta-analysis showed IIM to be associated with increased risk of hypertensive disorders of pregnancy, cesarean section, preterm birth, and infants who are small for gestational age or had intrauterine growth restriction, although residual confounding by disease activity and treatment may contribute.

INTRODUCTION

Idiopathic inflammatory myopathy (IIM), also known as myositis, is a group of rare, heterogeneous systemic autoimmune disorders that can manifest in multiple parts of the body such as the skin, muscles, and lungs. According to the latest and most accepted classification, IIM is further subdivided into dermatomyositis (DM), juvenile DM, clinically amyopathic DM, polymyositis (PM), inclusion body myositis, immune-mediated necrotizing myopathy, and antisynthetase syndrome.¹

All IIM subtypes except immune-mediated necrotizing myopathy are more common in female patients. Achieving full sexual health and reproduction requires the cooperation of multiple organs and systems. For birthing patients, normal ovarian function is crucial for producing eggs with reproductive potential, which is an essential step in reproduction. The fact that IIM can affect patients of childbearing age has raised concerns about the impact of this inflammatory autoimmune disease on ovarian reserve,² future fertility,³ and pregnancy outcomes. Accumulating data suggest systemic autoimmunity can affect the progress of

Supported by the Guangxi Zhuang Autonomous Region Health Commission, Guangxi Medical and Health Appropriate Technology Development and Promotion Application Project (grant S2024008).

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Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80048>.

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Submitted for publication August 23, 2025; accepted in revised form March 17, 2026.

SIGNIFICANCE & INNOVATIONS

- Our meta-analysis revealed idiopathic inflammatory myopathy (IIM) to be associated with increased risk of hypertensive disorders of pregnancy, cesarean section, preterm birth, and infants who are small for gestational age or have intrauterine growth restriction, although residual confounding by disease activity and treatment may contribute.
- The reason for this finding remains unclear, but it may be associated with a higher baseline risk of adverse pregnancies, disease activity, endothelial dysfunction, and impaired autoimmunity in IIM.
- Our study reemphasizes the importance of providing preconception counseling to IIM patients.
- The study also pointed out that there are deficiencies in the data, particularly regarding the incidence of other important adverse pregnancy outcomes and the pathophysiologic mechanisms of adverse pregnancy.

pregnancy, leading to complications including spontaneous abortion, stillbirth, and preterm birth.⁴ However, in contrast to other rheumatic autoimmune diseases, like systemic lupus erythematosus and rheumatoid arthritis, the pregnancy outcomes of patients with IIM have not been comprehensively investigated. The research that has been conducted related to IIM and pregnancy has shown inconsistent findings.^{5–10}

There is increased evidence on the importance of preconception counseling.¹¹ Planning pregnancy is a significant aspect of reproductive health management for patients with rheumatic diseases because timing pregnancy to coincide with both disease quiescence and pregnancy-compatible medications increases the likelihood of pregnancy success.¹² However, because of the paucity of systematic studies, it is difficult for rheumatologists and obstetricians to counsel patients with IIM. Thus, the aim of this study was to perform a systematic review and meta-analysis to evaluate the association between IIM and adverse pregnancy outcomes.

MATERIALS AND METHODS

This current systematic review and meta-analysis was elaborated according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The review protocol was registered in the Prospero database (CRD42024545411). Because this study is a systematic review of the literature, it did not require a review by an institutional ethics committee.

Inclusion and exclusion criteria. Studies included in our meta-analysis met the following criteria: (1) case-control or cohort design, (2) adult patients with diagnosed IIM, (3) pregnancy outcomes occurring after IIM diagnosis as the outcome of interest,

and (4) reported odds ratio (OR) or relative risk (RR) of adverse pregnancy outcomes (patients with IIM vs those without IIM) with 95% confidence intervals (CIs). For cohorts reported in multiple studies, only those with the most detailed information or largest sample size were included. Reviews, case reports or series, unpublished or nonhuman studies, and those lacking sufficient published or original data were excluded.

Literature search. YY and RXH independently searched published articles indexed in databases on PubMed, Embase, and Web of Science from their inception to May 15, 2025, using the medical subject headings (MeSH) terms “myositis” or “idiopathic inflammatory myopathy” and “pregnancy outcome” or “pregnancy.” The search terms included indexed terms from Emtree in Embase, MeSH in PubMed, and free-text terms. A manual search of the references of selected studies was also conducted. No language restrictions were applied during the literature search.

Study selection. YY and RXH independently screened titles and abstracts of all retrieved studies, excluding those clearly not meeting inclusion criteria to retain potentially relevant full texts. Eligibility was independently assessed by investigators, with conflicts resolved by discussion and consensus.

Data extraction and assessment of study quality.

For each included study, extracted data covered title, author, patient enrollment year, study country, design, sample size, population, IIM subtypes, birthing parent age at delivery, comorbidities (eg, hypertension, diabetes, obesity, and smoking), covariates (matched or multivariable-adjusted), and adjusted OR (aOR) or adjusted RR (aRR) with 95% CIs. For studies that reported several multivariable aORs or aRRs, the effect estimate that was most fully adjusted for potential confounders was selected.

YY and RXH independently assessed included studies' methodologic quality using the Newcastle-Ottawa Scale (NOS)¹³ (eight items across three dimensions: selection, comparability, and exposure), stratified by study type. Maximum NOS score was 9; studies were categorized as good (7–9), moderate (3–6), or low quality (0–2).

Statistical analysis. We examined the association between IIM and adverse pregnancy outcome risk using aORs or aRRs and their 95% CIs from each study. All calculations and graphs were performed using Review Manager 5.3 (Cochrane Collaboration). Point estimates and SEs were extracted from each study for meta-analysis using the generic inverse-variance method under a DerSimonian and Laird random-effects model.¹⁴ Given rare IIM cases, sparse data, and heterogeneous effect reporting, we pooled adjusted log-effects using the generic inverse-variance approach, incorporating multiple estimates per study to maximize available information while interpreting findings

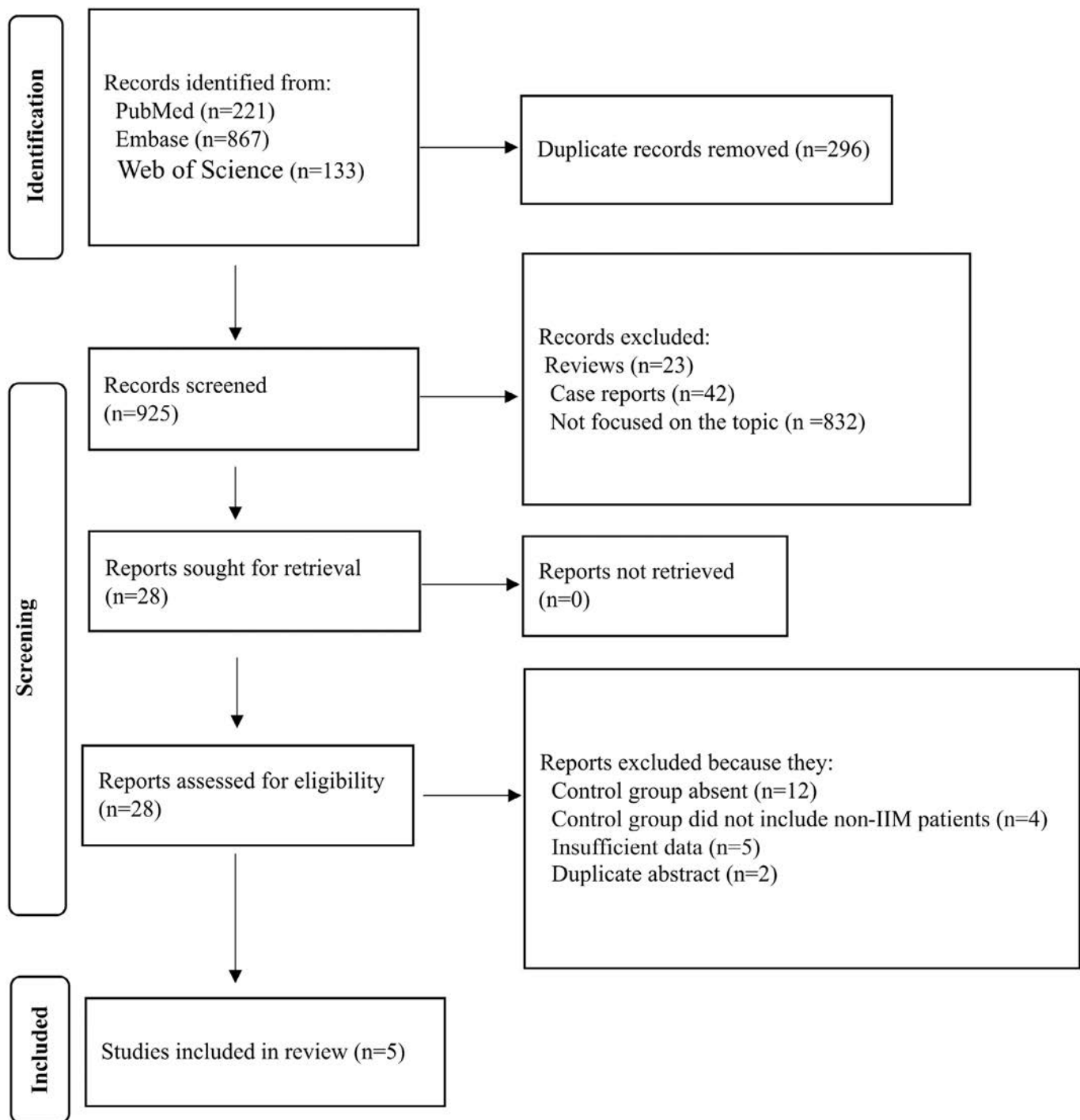


Figure 1. Flow diagram of study selection.

cautiously. Cochran's Q test and I^2 statistic evaluated interstudy heterogeneity; $I^2 = 76\%$ to 100% , 51% to 75% , 26% to 50% , and 0% to 25% represented high, moderate, low, and insignificant heterogeneity, respectively.¹⁵ For each outcome, the P value reported alongside I^2 corresponds to Cochran's Q test for heterogeneity; statistical significance of the pooled association is evaluated with a Z-test. If necessary, the possible causes

of heterogeneity were explored through subgroup analysis. Sensitivity analysis was performed by removing single study sequentially.

Data availability statement. Data are available on request from the corresponding author.

RESULTS

Literature search and study characteristics. Up to May 15, 2025, the literature search identified 1,221 articles (PubMed: 221, Embase: 867, Web of Science: 133). In total, 28 full-text articles were assessed for eligibility. Twelve were excluded for lacking a comparison group,^{16–27} four for lacking a control group without IIM,^{7,8,28,29} five abstracts for having insufficient information,^{30–34} and two abstracts for overlapping with full-text articles.^{35,36} Finally, five eligible studies were included, involving 830 births to patients with IIM and 17,362,323 births to birthing parents without IIM.^{5,6,9,10,37} The process of study identification and exclusion are summarized in Figure 1.

Included studies' basic characteristics are in Table 1: all compared patients with IIM versus controls without IIM were high quality (NOS 7–8) and were retrospective population-based (enrollment 1993–2016). Birthing parent characteristics of groups with and without IIM are in Table 2. According to Table 2, the majority of patients were diagnosed with DM and PM. Kolstad et al⁶ reported that patients in the group with IIM were more likely to have diabetes and were older compared to controls ($P < 0.001$). However, the remaining studies did not find or report significant differences in the basic characteristics between the group with IIM and the controls.

Adverse pregnancy outcomes occurring after IIM diagnosis. Adverse pregnancy outcomes analyzed in the meta-analysis are summarized in Table 3. Across included cohorts, DM and PM comprised the vast majority of IIM cases (Table 2); therefore, the pooled estimates primarily reflect DM and PM.

Our meta-analysis indicated significantly increased risks of hypertensive disorders of pregnancy and cesarean section in patients with IIM (OR 2.73 [95% CI 1.76–4.23]; $I^2 = 70\%$, Cochran's $Q P = 0.01$, overall effect $P < 0.00001$) versus those without IIM (OR = 2.03 [95% CI 1.37–3.00]; $I^2 = 79\%$, Cochran's $Q P = 0.002$, overall effect $P = 0.004$) (Figure 2). Additionally, patients with IIM had higher risks of premature birth (OR 3.71 [95% CI 2.35–5.85]; $I^2 = 60\%$, Cochran's $Q P = 0.06$, overall effect $P < 0.00001$) and delivering infants who were small for gestational age or had intrauterine growth restriction (OR 1.90 [95% CI 1.03–3.51]; $I^2 = 43\%$, Cochran's $Q P = 0.15$, overall effect $P = 0.04$).

Sensitivity analysis. To confirm the robustness and reliability of the results, jackknife sensitivity analysis was performed by excluding one study from the pooled analysis at a time. The sensitivity analysis results were basically consistent. For example, the pooled effect estimates for sensitivity analysis of hypertensive disorders of pregnancy ranged from 2.17 to 3.16 and were statistically significant. Leave-one-out analyses were consistent; however, it is important to note that several studies contributed

multiple related estimates, which were treated as independent in this analysis.

DISCUSSION

In DM- and PM-predominant cohorts, pregnancies were associated with increased risks of hypertensive disorders of pregnancy, preterm birth, small for gestational age or intrauterine growth restriction infants, and cesarean section compared with comparators without IIM; evidence remains insufficient to infer risks for other IIM subtypes. To our knowledge, this is the first meta-analysis comparing pregnancy outcomes between patients with and without IIM. Although prior systematic reviews exist,^{38,39} our meta-analysis provides additional evidence-based support for these reviews.

DM and PM correlated with higher hypertensive disorders of pregnancy risk versus controls in Kolstad et al⁶ (OR 2.90 [95% CI 2.00–4.22]) and Chen et al⁹ (OR 2.94 [95% CI 1.31–6.58]). Conversely, Tuccinardi et al¹⁰ reported no increased gestational hypertension risk (OR 1.58 [95% CI 0.95–2.62]). They observed a significant risk of preeclampsia in pregnancies of patients with IIM (OR 2.08 [95% CI 1.46–2.98]), attributing it to a higher frequency of preeclampsia risk factors in this population—a finding corroborated by other research.³⁷ Due to few outcomes, our meta-analysis of composite hypertensive disorders revealed a 2.7-fold higher risk in pregnancies of patients with IIM, a finding that requires validation in future prospective cohorts. All studies, including our meta-analysis, indicated an increased risk of preterm birth in pregnancies of patients with IIM. Kolstad et al³⁷ further demonstrated that patients with DM and PM were at markedly elevated risk for both early (aRR 10.0 [95% CI 3.2–31.1]) and late (aRR 5.2 [95% CI 2.9–9.4]) preterm birth compared to the general obstetric population. Evidence regarding the risk of infants who are small for gestational age or have intrauterine growth restriction in pregnancies of patients with IIM is conflicting, with earlier studies showing no significant difference but a recent report indicating increased risk.¹⁰ Our findings align with this recent evidence. An association between IIM and increased cesarean section rates was observed in our study and most prior research. Contributing factors likely include a higher burden of pregnancy complications and inter-regional differences in health care protocols.

Little is currently known about the pathophysiologic basis of the association between IIM and adverse pregnancy outcomes. Hypertensive disorders of pregnancy risk factors have been extensively studied,^{40,41} including chronic hypertension, pregestational diabetes, obesity, and advanced birthing parent age. Kolstad et al⁶ observed that the pregnant patients in the IIM group were more likely to have diabetes and were older compared to healthy controls ($P < 0.001$). Besides, four of these studies focused on a North American population, so results may also be related to genetic background, ethnicity, and lifestyle habits. In

Table 1. Basic characteristics of included studies*

Study	Year of patients' enrollment	Country	Study design	Number of births, IIM/control	Control group	Adjusted factors	Quality score
Chen et al ⁹	2001–2011	Australia	Retrospective cohort	17/991,292	General population without a diagnosis of rare autoimmune diseases selected from the same database	Birthing parent age, country of birth, socioeconomic status, birthing parent residence, chronic hypertension, pregestational diabetes, smoking during pregnancy, parity, and multiple births	8
Kolstad et al ⁶	1993–1999	United States	Retrospective cohort	399/101,123	Birth year–matched patients randomly selected from the same database	Birthing parent age, race, and diabetes mellitus	7
Che et al ⁵	1998–2016	Sweden	Retrospective cohort	68 ^a /242	Birth year– and residential area–matched patients randomly selected from another Sweden database	Residential area, birthing parent age at delivery, parity, delivery year, smoking status and body mass index	8
Tuccinardi et al ¹⁰	1999–2015	United States	Retrospective cohort	308/13,792,236	Population selected from the same database	Age, race, income quartile, insurance type, hospital type, comorbidities, obstetric history, and smoking status	8
Kolstad et al ³⁷	2007–2011	United States	Retrospective cohort	38/2,477,430 ^b	The general obstetric population without a diagnosis of IIM and others such as DLE and UCTD selected from the same database	Age, race/ethnicity, and smoking status	8

* DLE, discoid lupus erythematosus; IIM, idiopathic inflammatory myopathy; UCTD, unspecified connective tissue disease.

^a Births that occurred in patients after or up to a year before IIM diagnosis.

^b Births born to birthing parents without IIM.

the past decade, most of the epidemiologic investigations also showed advanced birthing parent age was often associated with many types of adverse pregnancy outcomes and birth defects, like preterm birth, small for gestational age infants, intrauterine growth restriction, stillbirth, lower birth weight, etc. The occurrence of these results may be related to molecular genetic changes caused by aging, eg, epigenetic dysregulation and gene mutations.⁴² It is well established that a pregnancy complicated by hypertensive disorders of hypertension/preeclampsia increases the risk of delivery of a small for gestational age infant.^{43–46} The most common pathophysiologic mechanism of small for gestational age status is decreased uteroplacental blood perfusion. High blood pressure during pregnancy is characterized

by both endothelial dysfunction and decreased placental perfusion.⁴⁷ Besides, elevated blood pressure may influence the development of the placental villous tree, resulting in decreased placental function, which can lead to reduced fetal growth and lower birth weight.⁴⁸

Studies not included in this meta-analysis—eg, case reports or case series, in which data were collected based on treating physicians' clinical observations—also offer useful information. A previous study displayed that active IIM during pregnancy significantly increased the risk of stillbirth or neonatal death (12% vs 1%, $P = 0.005$) and preterm birth (34.7% vs 11%, $P < 0.001$) compared to inactive IIM.³⁸ In addition, the incidence of other adverse pregnancy outcomes (total embryonic or fetal loss, low

Table 2. Baseline features of the patients included in the study*

Study	IIM subtypes	Birth parent age at delivery, IIM/control, years	Preexisting hypertension, IIM/control, %	Diabetes, IIM/control, %	Smoking, IIM/control, %	Obesity, IIM/control, %
Chen et al ⁹	DM+PM	NA	NA	NA	NA	NA
Kolstad et al ⁶	DM+PM	28.8/27.7	NA	4.1/0.9	NA	NA
Che et al ⁵	IIM	30/28	NA	NA	4.41/9.50	8.82/8.68
Tuccinardi et al ¹⁰	DM+PM	NA	10.39/1.59	NA	4.22/5.15	3.25/1.81
Kolstad et al ³⁷	DM+PM	31.0/28.2 ^a	5.3/1.4 ^a	2.6/0.9 ^a	0/3.8 ^a	18.4/18.7 ^a

* DM, dermatomyositis; IIM, idiopathic inflammatory myopathy; PM, polymyositis; NA, not applicable.

^a All patients, including patients with IIM and controls without IIM.

birth weight, and intrauterine growth restriction) was also increased in pregnancies with active disease, although not statistically significant. Patients with good control were more likely to give birth to a healthy child (67.2% vs 31.4%, $P < 0.001$). Other scholars have reported similar results too. A systemic review of 78 pregnancies among 59 female patients with adult-onset IIM or juvenile IIM revealed that active disease state and disease onset in early pregnancy were especially related to pregnancy complications.⁴⁹ Zhong et al⁷ found a greater risk of spontaneous abortion and preterm birth in post-IIM diagnosis pregnancies with active disease (aOR 435.35, $P = 0.007$). Akiyama et al⁵⁰ discovered active IIM negatively affected offspring outcomes. In their study, nine pregnancies occurring after IIM diagnosis ended in fetal death or abortion in active disease (9 of 21, 42.9%), whereas fetal death in inactive disease was observed only in one pregnancy (1 of 15, 6.7%), which was significantly lower than that in active disease ($P = 0.02$). For pregnant patients with active IIM, some physicians recommend cesarean section to avoid birthing parent exhaustion and to decrease the risk of rhabdomyolysis and myoglobinuria as Kolstad et al⁶ and Silva et al¹⁸ mentioned. Delay in commencing treatment among pregnant patients with IIM was reported to significantly influence fetal death and abortion ($P = 0.035$).⁵⁰ Notably, the studies mentioned in our review were

conducted before the “targeted therapy” era in rheumatology practice; thus, treating physicians primarily used glucocorticoids and some disease-modifying antirheumatic drugs, with intravenous Ig administered less frequently than it is today. Long-term use of medium or high doses of glucocorticoids during pregnancy increases the risk of gestational diabetes, hypertension, infections, and premature rupture of membranes.¹⁸ Other factors (IIM-specific autoantibodies, lung involvement, muscle symptoms, and elevated muscle enzymes) have also been linked to adverse pregnancy complications.⁵⁰ These align with proposed mechanisms: autoimmune impairment-induced endothelial dysfunction leads to placental dysfunction and subsequent pregnancy complications.

It is increasingly recognized that the risks of pregnancy associated with rheumatic disorders can be minimized if conception is planned and conducted during a period of minimally active disease.¹¹ On the basis of above findings, in our opinion, similar to other rheumatic diseases, pregnancy planning (preconception counseling) is also recommended in patients with IIM, which may be critical to reduce the incidence of adverse pregnancy outcomes. The pregnancy interests of a patient with IIM should be discussed often to ensure that pregnancy planning can begin several months to years before conception. Prior pregnancy

Table 3. Outcomes reported*

Study	Diagnosis of pregnancy outcomes	Selective birthing parent outcomes	Selective fetal outcomes
Chen et al ⁹	ICD-10 Australian Modification codes	Hypertensive disorders of pregnancy (gestational hypertension or preeclampsia), cesarean section (any)	Preterm birth (<37 weeks of gestation) or small for gestational age (birth weight <10th percentile for age and sex)
Kolstad et al ⁶	ICD-9 Clinical Modification codes	Hypertensive disorders of pregnancy (gestational hypertension, preexisting hypertension, preeclampsia, and eclampsia) or cesarean section	Intrauterine growth restriction
Che et al ⁵	ICD-10 codes	Hypertensive disorders of pregnancy (preeclampsia, eclampsia, or gestational hypertension) or cesarean section (elective or acute)	Preterm birth (<37 weeks of gestation) or small for gestational age (birth weight <10th percentile for age and sex)
Tuccinardi et al ¹⁰	ICD-9 and ICD-10 codes	Gestational hypertension, preeclampsia, or cesarean section	Preterm birth (<37 weeks of gestation) or small for gestational age (birth weight <10th percentile for age and sex)
Kolstad et al ³⁷	ICD-9 codes	Preeclampsia or eclampsia	Preterm birth (20–37 weeks of gestation)

* ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

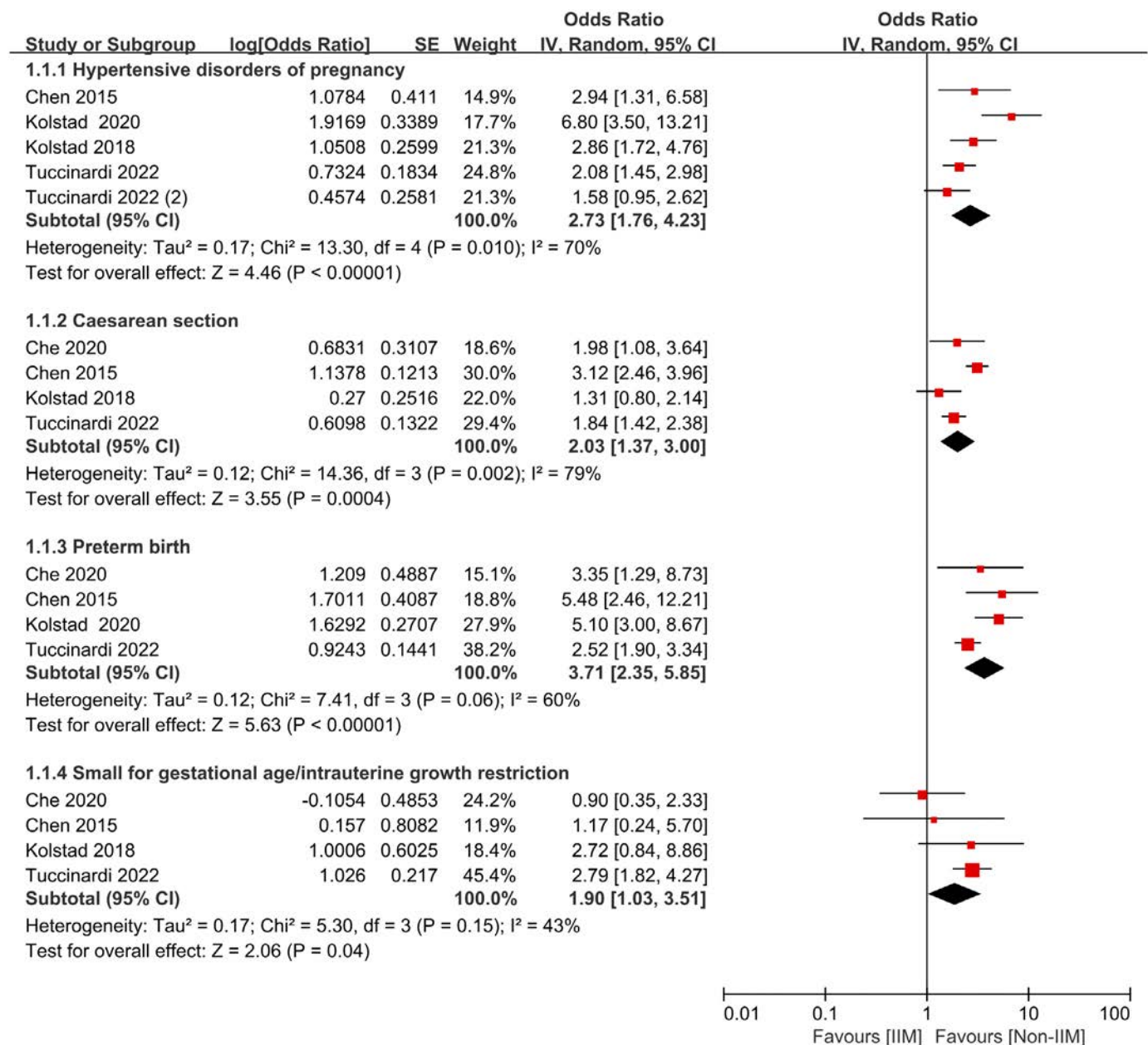


Figure 2. Adverse pregnancy outcomes that were observed in pregnant patients with IIM versus those without IIM. CI, confidence interval; IIM, idiopathic inflammatory myopathy; IV, inverse variance.

status, comorbidities, organ involvement, disease activity, and immunosuppressant medication use should be fully understood before conception. Conditions such as active or severe interstitial lung disease, liver insufficiency, acute renal failure, and pulmonary hypertension are regarded as contraindications for pregnancy of patients with IIM. For patients with active IIM, experts strongly recommend postponing pregnancy, treating to control disease activity, and reassessing at quiescent or low disease activity.¹¹ Female patients with active disease may be advised that at least several months of inactive disease is desirable before conception. Then, transitioning from medication that is incompatible with pregnancy,

like cyclophosphamide and mycophenolate mofetil, is strongly recommended before conception. Several studies suggested the efficacy and safety of intravenous Ig in the treatment of pregnant patients with IIM.^{7,29,51} For decades, numerous trials have evaluated the possible benefit of low-dose aspirin (50–150 mg daily) in pregnancy to minimize the risk of hypertensive disorders of pregnancy.⁵² The synthesis of these research studies has resulted in low-dose aspirin being recommended for the prevention or delay of hypertensive disorders of pregnancy in high-risk populations by various professional society guidelines, such as the US Preventive Services Task Force.⁵³ Current guidelines from

the National Institute for Health and Care Excellence suggest administering aspirin for patients with one high-risk factor (eg, autoimmune diseases, diabetes, and chronic hypertension) or two moderate risk factors for preeclampsia.⁵⁴ Thus, based on our and other scholars' findings, treatment with low-dose aspirin during pregnancy to prevent or delay the onset of hypertensive disorders of pregnancy is recommended for those with IIM because of their increased risk. Readers could obtain more information on the reproductive health management of patients with IIM from the guidelines provided by the American College of Rheumatology,¹¹ EULAR,⁵⁵ and the British Society for Rheumatology.^{56,57}

Some potential limitations in our study should be taken into consideration when interpreting the results. First, the retrospective design may cause enrollment bias in which the failure to enroll patients at positive pregnancy tests leads to substantial underestimation of early losses that are unrecorded in medical records. Second, meta-analysis cannot resolve confounding inherent to the original studies. Although most included studies adjusted for key potential confounders, residual or unknown confounding cannot be fully excluded. The lack of granular clinical data (disease activity, organ involvement, and immunosuppressants) across cohorts precluded stratification by these determinants. Third, the number of the studies included in the meta-analysis is small, given the rarity of the disease at baseline and the majority of cases occurring after childbearing years.^{18,58} As a result, many adverse outcomes (eg, placenta abruption, premature rupture of membranes, spontaneous abortion, and stillbirth) were not assessed in this meta-analysis because too few studies included these variables as outcomes. Fourthly, another limitation pertains to our statistical methodology. With only four to five studies per endpoint and I^2 up to 79%, DerSimonian-Laird CIs may be anticonservative. We did not compute Hartung-Knapp small-sample adjustments or 95% prediction intervals, and mixing ORs and RRs may bias magnitude for common outcomes (eg, cesarean section). Although the underreporting of prediction intervals is a common issue in meta-analyses, and our primary conclusions are based on standard practices in the field, readers should still exercise appropriate caution when interpreting the findings, particularly the CIs. Fifthly, including multiple related estimates from the same study without modeling within-study dependence may underestimate SEs and overstate precision. However, this is a widespread problem affecting ~95% of meta-analyses.⁵⁹ Finally, due to the limited number of included studies, we did not assess publication bias using funnel plots consistent with Cochrane guidelines, nor did we perform extensive subgroup analyses. It should be noted that each IIM subtype has distinct characteristics, with potential differences in pregnancy outcomes across subtypes. Consequently, our findings should not be generalized to these subtypes without caution. Prospective, well-designed research (which should encompass data on IIM subtypes, pregnancy planning, disease activity, medication use, detailed pregnancy outcomes, etc) are still warranted.

To summarize, we found that IIM is associated with higher odds of hypertensive disorders of pregnancy, preterm birth, infants who are small for gestational age or have intrauterine growth restriction, and cesarean section; unmeasured disease activity and treatment may contribute. Therefore, attention should be given not only before but also during pregnancy. Further, large high-level research is urgently needed to confirm our findings.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Lin confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW ARTICLE

Building a Framework for Sexual and Reproductive Health Care in the Rheumatology Context: Content and Approaches

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People with systemic autoimmune and rheumatic diseases (SARDs) are at higher risk than the general population of experiencing adverse pregnancy and perinatal outcomes such as preeclampsia, intrauterine growth restriction, and maternal and/or fetal death. The immune system undergoes changes during pregnancy that can precipitate adverse health outcomes among people with immunologic dysfunction at baseline—particularly those people who have active inflammatory disease at the time of and/or during pregnancy. However, in this commentary, we challenge the notion that immunologic and disease-centric aspects of pregnancy are the only drivers of adverse pregnancy and perinatal outcomes among people with SARDs. A focus on disease may have limited focus on other factors that could enhance reproductive health outcomes among people with SARDs, for example, the provision of high-quality sexual and reproductive health (SRH) care in the rheumatology context. Identification of such upstream factors can reveal approaches that enhance downstream reproductive outcomes for all women with rheumatic diseases, thereby enhancing person centeredness, holistic care, and SRH equity in rheumatology care. Herein, we also describe emerging approaches to SRH that provide a potential framework for high-quality SRH care in the rheumatology context.

Introduction

Sexual and reproductive health (SRH) is an important aspect of overall health for individuals with systemic autoimmune and rheumatic diseases (SARDs).¹ The majority of people with autoimmune conditions are female.² The hormonal and immunologic changes of pregnancy can accelerate disease progression and contribute to adverse maternal and fetal outcomes among people with SARDs, particularly in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).^{3–5} One to two percent of pregnancies among women with Ro antibody positivity will be complicated by fetal cardiac conduction abnormalities that may lead to fetal death or require lifelong cardiac pacing.⁶ Even pregnancies among women with rheumatoid arthritis (RA)—a condition that may symptomatically improve during pregnancy—are associated with higher risk of preeclampsia and fetal growth restriction compared to the general population.⁷ In general, active disease at the time of pregnancy and/or during pregnancy is a key risk factor for adverse pregnancy

and perinatal outcomes such as mortality and severe maternal morbidity.⁸

The disease-modifying antirheumatic drugs (DMARDs) used to control SARDs may also threaten healthy pregnancies. Although some treatments are safe for use during pregnancy and lactation, many others have unknown safety profiles, and several treatments have teratogenic potential. In a study of the American College of Rheumatology (ACR) Rheumatology Informatics System for Effectiveness registry, which captures clinical data from approximately one-third of US rheumatology practices, 44.5% of nonpregnant young females with RA and 29.5% with SLE were prescribed at least one teratogen; descriptive data confirm that some people become pregnant while prescribed these drugs.^{9,10} Many teratogens cause irreversible anomalies in the first trimester of pregnancy—a point at which some women are unaware that they are pregnant.¹¹ Contraception usage among women with SARDs appears to be lower than that of the general population—even when teratogens are prescribed—possibly due to concerns about the safety of exogenous hormones in this population.¹²

Supported by the NIH (grants U54-HD-113030 [EMBRACE Maternal Health Research Center of Excellence principal investigators (PIs): Mendez, Simhan, and Birru Talabi], R01-HD-118690 [PIs: Birru Talabi and Jarlenski], R33-HD-113515 [PI: Birru Talabi], and R01-MD-011678 [PIs: Borrero and Switzer]).

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80049>.

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Submitted for publication September 10, 2025; accepted in revised form February 25, 2026.

However, adverse reproductive outcomes are not inevitable across the SARDs; many women with SARDs experience healthy pregnancies and reproductive lives. Across disease states, a key predictor of healthy SRH outcomes is well-controlled disease for at least three to six months before pregnancy.^{13–15} As advances in treatment are leading to reductions in disease burden and organ damage, individuals with SARDs may increasingly enter pregnancy with better baseline health that can facilitate favorable downstream pregnancy outcomes.

However, immunologic factors provide an incomplete explanation for why some women experience healthy or unhealthy pregnancy outcomes (Figure 1). For example, social determinants of health, including income, education, health insurance, and transportation, affect people’s access to health care during the perinatal period.¹⁶ Clinical outcomes such as severe maternal morbidity and mortality among people with SARDs are rarely reported in the context of state- or federal-level reproductive health policies; however, such policies affect access to preventive and therapeutic SRH services (eg, prenatal care, pregnancy and antepartum care, contraception, abortion care).¹⁷

An oft-overlooked factor that also influences reproductive outcomes for people with SARDs is the quality and availability of SRH care.¹⁸ SRH care encompasses a range of services that help people to safely attain their desired number of children (if any), determine the spacing and timing of pregnancies, learn about and obtain contraception if needed, and obtain relevant preventive services (eg, cervical cancer screening). Rheumatologists who assess patients’ pregnancy preferences can help to prepare people for a desired pregnancy, mitigate risk factors for adverse pregnancy outcomes, prescribe pregnancy-compatible medications, and refer to primary

care providers (PCPs), obstetrician–gynecologists (OB/GYNs), reproductive endocrinologists, and potentially other specialists to optimize prepregnancy health. Rheumatologists can also counsel peripartum patients about pregnancy-compatible treatments in lactation and manage postpartum disease activity. Moreover, rheumatologists can help people who wish to avoid or delay pregnancy to identify safe contraceptive methods, thus preventing pregnancies that are undesired and potentially high risk.

Given a rheumatology workforce shortage and widespread burnout,¹⁹ some rheumatologists might argue that SRH care for patients with SARDs should largely be delegated to PCPs or OB/GYNs—currently a dominant model of care. A counterargument is that by diverting most SRH care and counseling to nonexperts in the SARDs, our field misses a critical chance to improve reproductive outcomes for patients at the core of our professional mission. Rheumatologists with specialized experience and interest in SRH (ie, “reproductive rheumatologists”) contribute to research, education, and patient care at the intersection of rheumatology and SRH. However, SRH care should not be a niche competency in rheumatology. To ensure that all patients with SARDs equitably receive high-quality SRH care and thus have the opportunity to experience their healthiest reproductive lives, practical and robust standards for the provision of this care must be developed in rheumatology.

A new opportunity to reconceptualize SRH care in rheumatology

Now is a particularly opportune time to reconceptualize how SRH can be meaningfully addressed in rheumatology care. Other subspecialties are similarly deliberating the minimum

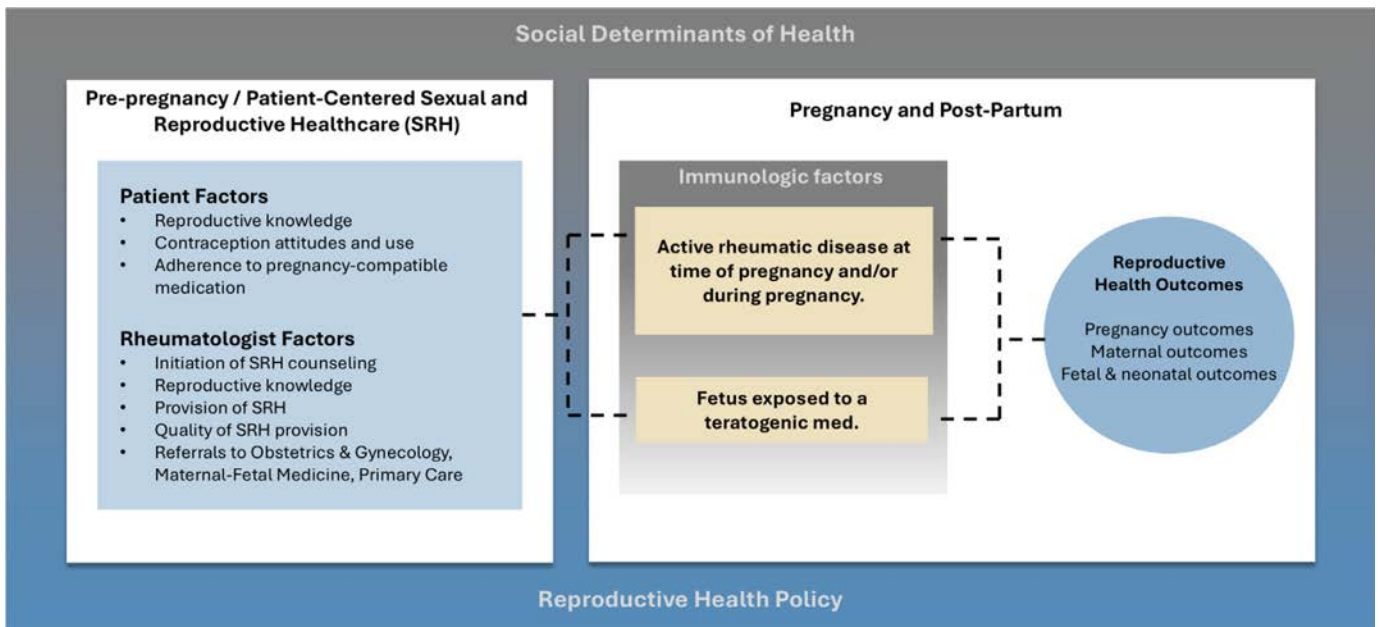


Figure 1. Novel conceptual model describing factors that contribute to sexual and reproductive health outcomes among individuals with systemic autoimmune and rheumatic diseases.

competencies that clinicians should have in SRH care provision²⁰; for example, cardiologists are advancing “cardio-obstetric” training and multidisciplinary care models to ameliorate the cardiovascular disease burden that underlies most maternal deaths.²¹ Broadly, the US crisis of maternal morbidity and mortality has led experts to interrogate the health care system and challenge long-standing models of SRH care.²² For example, the once ubiquitous paradigm of “family planning” has increasingly fallen out of favor, as described in the following:

- A high proportion of pregnancies in the United States remain unintended, despite a century of public health approaches to promote pregnancy planning.²³
- Family planning praxis was developed in the backdrop of the eugenics movement, and forced sterilization and contraception policies directed against racial and ethnic minority groups, poor people, and individuals with disabilities have caused long-standing harms and, understandably, medical distrust in some communities.²⁴
- Planning for a family may personally resonate for clinicians,²⁵ but may not reflect the lived realities of other people.
- Metrics around unintended pregnancy are shifting toward those that evaluate an individual’s acceptance of a pregnancy, as an unintended but welcomed pregnancy can still motivate healthy behaviors and lead to positive clinical outcomes.²⁶
- Many women have fluctuating, ambivalent, conflicted, or fatalistic attitudes around pregnancy; clinical approaches that require these individuals to report a discrete pregnancy decision may inaccurately assess their potential for pregnancy.²⁷
- Public health measures to reduce unintended pregnancy may have inadvertently led to clinical approaches that guide or pressure people to align their reproductive behaviors with public health objectives.²⁷

In contrast, emerging health care approaches are centering personalized, holistic, autonomy-supportive SRH care—framed, for example, by the praxis of reproductive justice, which indicates that people have a “(human) right to have a child, not to have a child, and to have safe and healthy conditions under which their children may be raised.”²⁴ Through person-centered approaches, clinicians tailor their counseling to individuals based on their priorities and life circumstances—meeting people where they are—rather than requiring or attempting to persuade an individual to tailor their needs toward a specific approach (eg, planning for pregnancy) or outcome (eg, pregnancy avoidance).²⁸ Person-centered SRH care in rheumatology may appear to conflict with data indicating that advance planning for pregnancy helps to ensure disease control while taking pregnancy-safe medications. Indeed, although pregnancy planning is reasonable for patients with serious chronic illnesses that can impact pregnancy

outcomes and will even be appealing to some patients, unplanned pregnancies, by active or passive choice, will remain a reality for some patients.²⁸ A model of SRH care is needed in rheumatology that addresses all patients’ SRH needs, including individuals whose preferences and actions do not align with planning paradigms or medical advice.

Recent federal guidance provides a patient-centered SRH care model for consideration for patients with SARDs. In 2024, the US Office of Population Affairs updated its Quality Family Planning (QFP) Services guidelines, a series of expert- and evidence-driven recommendations to ensure that all people of reproductive age receive high-quality SRH services.²⁹ The updated QFP provides guidance for any clinician who sees patients with SRH care needs, including those who are the primary providers of SRH services (eg, OB/GYNs, PCPs) and those who are not; rheumatology and other subspecialties are explicitly mentioned in this context. The QFP asserts that these clinicians should “screen for the need and desire for SRH services, share the limits of their practice, and refer or connect patients to other settings where they can obtain quality services.” The QFP aligns with the 2020 ACR “Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases” (colloquially called the “Reproductive Health Guideline” or RHG), which recommends that SRH conversations between the rheumatologist and patient occur early and often, “at an initial or early visit and periodically thereafter, and always when initiating treatment with potentially teratogenic medications.”¹

In the following sections, we build from QFP and ACR guidance to propose core competencies and approaches for a basic standard of SRH care in rheumatology (Box 1). Our recommendations are not definitive or comprehensive and are meant to stimulate discussion about ways that SRH care can be meaningfully integrated into rheumatology practice. Recommendations reflect the authors’ opinions and do not reflect the official policy or positions of the ACR.

SRH care in rheumatology: Core competencies for the rheumatologist

Although all rheumatologists should have at least a basic understanding of SRH care in the rheumatology context, the degree of requisite education and training will vary by the rheumatologist’s interests, prior experience and training, patient population, and scope of practice. Herein and in Figure 2, we suggest core SRH competencies and knowledge domains for the practicing rheumatologist. Box 1 presents the following: (1) ways to potentially build these core competencies and (2) opportunities for rheumatologists who seek advanced clinical training, scholarship, and/or professional demonstration of SRH competency.

Assessment of pregnancy preferences.

Rheumatologists should feel comfortable with initiating conversations about SRH with patients. Screening for reproductive

Box 1. Suggestions for how to build sexual and reproductive health (SRH) care competencies in rheumatology care**Build core competencies in SRH for all rheumatologists**

- Use resources from the American College of Rheumatology (ACR),¹ EULAR,^{13,47} and other professional societies that provide comprehensive recommendations for management of the patient with SRH needs.
- Rheumatology, obstetrics and gynecology, and/or maternal-fetal medicine professional organizations should codevelop continuing medical education tailored to rheumatology clinicians.
- SRH didactics should be available at regional and national rheumatology meetings, ideally scheduled at times to optimize participation.
- Rheumatologists should build competency in prescribing or recommending over-the-counter progestin-only pills and/or emergency contraception to people who desire contraception and have an urgent need (eg, at initiation of a teratogenic medication).
- Rheumatologists should be aware of freely available educational resources around SRH for clinicians and patients:
 - Mother to Baby, which provides online and phone-based resources in English and Spanish for medication safety in pregnancy and lactation (www.mothersbaby.org)
 - The Healthy Outcomes in Pregnancy with SLE Through Education of Providers (HOP-STEP) Program, which provides SRH information for patients with systemic lupus erythematosus (SLE) and other systemic autoimmune and rheumatic diseases (SARDs) (www.lupuspregnancy.org)
 - LactMed, an online resource providing information about medication safety in lactation⁷⁶

Build advanced expertise in SRH among interested rheumatologists

- A formalized certification program in “reproductive rheumatology” could build a cadre of rheumatology professionals with SRH knowledge and expertise.
 - A formalized certification program in reproductive rheumatology could include professional education materials, digital lectures, an online certification examination and use study materials from existing textbooks and guidelines from ACR, EULAR, and British Society for Rheumatology.^{77–79}
- Develop pregnancy registries and SRH-focused rheumatology research registries to generate data advancing SRH care.
- National meetings of experts in rheumatology and trainees/early-stage investigators interested in reproductive rheumatology to discuss emerging findings in the field and challenging cases and build cross-institutional collaborations.
 - Examples include the Reproductive Rheumatology National Lab Meeting monthly teleconference funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (Duke University, Principal Investigator: Megan E.B. Clowse, MD MPH).
- International SRH-focused rheumatology meetings, such as the International Conference on Reproduction, Pregnancy, and Rheumatic Diseases (“Rheumapreg”), highlight multidisciplinary SRH care models for patients with SARDs.

preferences increases the frequency of counseling as well as patient satisfaction.^{30,31} Around the time of diagnosis, we recommend that rheumatologists explain to patients that reproductive health is integral to overall health in the SARDs and encourage patients to raise SRH concerns or questions during and/or between visits. Although there is no consensus on the frequency with which pregnancy preferences should be assessed, at a minimum, we recommend doing so annually and, as per the ACR RHG, when teratogenic medications are considered or prescribed.¹ The QFP further suggests that clinicians should ask patients to openly communicate their reproductive goals, preferences, and priorities.²⁹ The clinician next should, without judgment, share personalized and general information about these goals and preferences and then, together with the patient, tailor the care plan to help to ensure that the patient’s needs are met as safely as possible.³² The QFP also indicates that the clinician should “confirm understanding” about information conveyed, as some people may not recall or understand the information that is offered during the clinic visit.²⁹

Simple and open-ended questions can provide a respectful foundation for SRH conversations. One Key Question (OKQ) could be used to elicit patients’ pregnancy preferences: “Would you like to become pregnant in the next year?” When tested in rheumatology clinics as a quality improvement (QI) initiative, OKQ appeared to increase referrals for OB/GYN care, although

it had poor uptake into clinical practice.³³ Critiques of OKQ include that it does not capture patients’ attitudes around pregnancy prevention and focuses on a limited time frame (ie, one year). In contrast, the Pregnancy Attitudes, Timing, and How Important Is Prevention (PATH) questions help to elicit patients’ orientations around pregnancy and contraception through three questions: (1) “Do you think you might like to have (more) children at some point?” (2) “When do you think that might be?” and (3) “How important is it to you to prevent pregnancy (until then)?”²⁷ These questions guided appropriate SRH referrals in the general population.³⁴ For patients with SARDs, we recommend additional language to gauge a patient’s understanding of their health risks in the SRH context: (1) “I hear your reproductive goal is (x). Did I get that right? I want to help you to meet your goals as safely as possible.” (2) “What is your understanding of how your (disease) might impact your (reproductive goal or preference)?” (3) “Can I share with you what I know about your (disease/medications) and how it might affect your (reproductive goal or preference)?”¹⁸

As rheumatologists engage in SRH care, we advocate for an approach framed by cultural humility, in which the clinician respectfully considers social, historical, and/or lived experiences that might affect an individual’s preferences and priorities apart from disease control.³⁵ Such contexts might include a person’s religious beliefs, cultural preferences, and/or an acknowledgment

Pregnancy preferences assessment
Contraceptive counseling, including method types, safety in the context of systemic autoimmune and rheumatic diseases (SARDs), relative efficacy, and common side effects Awareness of over-the-counter contraceptive methods, such as progestin-only pills and oral emergency contraception, are safe for all patients with SARDs
Safety and compatibility of medications in states of pre-pregnancy, pregnancy, and lactation
Management of SARDs during pregnancy, including recognition of how immunologic changes of pregnancy may affect disease monitoring and laboratory values, and checking blood pressure for signs of hypertensive disorders of pregnancy
Provision of timely referrals to primary women's and reproductive health providers - Primary care providers - Obstetrician-gynecologists and associated specialties: -Maternal-fetal medicine experts -Reproductive endocrinologists -Complex family planning/contraception
Management of SARDs during fertility procedures, including an understanding of how exogenous hormones may affect disease activity
Important SRH topics for additional consideration:
Management of SARDs during menopause transition, including an understanding of how endogenous hormone changes and hormone replacement therapy might affect disease activity and quality of life
Provision of referrals for cervical cancer screening, particularly among patients with SLE and/or individuals who are immunosuppressed— some of whom may require annual screening
Familiarity with menstrual-associated disease flares and querying about menstrual arthritis in context of cyclical disease flares among individuals who menstruate
Screening for sexual health and function among all adult patients with rheumatic diseases

Figure 2. Recommended sexual and reproductive health (SRH) competencies for rheumatologists by topic area. SLE, systemic lupus erythematosus. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80049/abstract>.

of health care traumas perpetuated on historically marginalized populations.

Pregnancy and fertility care. Once rheumatologists have assessed people's preferences for pregnancy, rheumatologists may advise women who desire pregnancy to take a prenatal vitamin and/or folic acid—particularly if they have used a

medication that can reduce folic acid stores (eg, methotrexate, sulfasalazine). Disease activity and medication safety and compatibility in pregnancy should ideally be assessed before pregnancy. Rheumatologists should strongly consider prescribing hydroxychloroquine to patients with SLE and with high-titer Ro/SS-A antibodies to prevent neonatal lupus and fetal heart block.¹ During pregnancy, the ACR RHG recommends that

disease activity laboratory tests are checked at least once a trimester.¹ Rheumatologists should be aware that the biologic changes of pregnancy can affect the assessment of disease activity. For example, during normal pregnancy, complement levels rise by 10% to 50%, physiologic proteinuria of less than 300 mg/day is common, the erythrocyte sedimentation rate can increase by 30% to 70%, and increases in intravascular volume can lead to mild anemia and thrombocytopenia.³⁶ Rheumatologists should also be aware that as compared to the general population, some patients with SARDs—particularly SLE and APS—are at higher risk for potentially life-altering hypertensive disorders of pregnancy (eg, preeclampsia, HELLP [hemolysis, elevated liver enzymes, and low platelets] syndrome).³⁷ Low-dose aspirin (LDASA), started by the end of the first trimester, may modestly reduce the risk of preeclampsia among individuals with SLE, antiphospholipid antibodies (aPLs)/APS, and other risk factors for preeclampsia (eg, chronic hypertension, history of preeclampsia); whereas OB/GYNs usually initiate LDASA as part of their practice, rheumatologists can also safely do so.^{1,38,39} Rheumatologists who see pregnant patients whose blood pressures meet or exceed systolic and diastolic pressures of 140 mm Hg and/or 90 mm Hg, respectively, should directly communicate with OB/GYN colleagues, as urgent treatment and monitoring may be required.

Fertility is generally preserved in the SARDs; however, some patients may experience subfertility or infertility related to cyclophosphamide exposure, uncontrolled RA, or advanced maternal age.¹ Rheumatologists should promptly refer patients with suspected infertility to reproductive endocrinology for evaluation and consideration of assisted reproductive technologies (ART).⁴⁰ Patients with stable or quiescent diseases, including SLE, can safely undergo ART; however, during ovarian stimulation, low molecular weight heparin should be considered for individuals with aPLs and provided to individuals with obstetric or thrombotic APS.¹ To preserve reproductive potential for women using intravenous cyclophosphamide, reproductive endocrinologists can facilitate oocyte preservation before therapy, and rheumatologists or OB/GYNs may consider prescribing gonadotropin-releasing hormone agonist therapy for ovarian protection (eg, leuprolide acetate). With the exception of cyclophosphamide, all other immunosuppressive therapies—including those with teratogenic risk—can be continued during ovarian stimulation for oocyte/embryo cryopreservation; teratogens, however, must be discontinued in advance of implantation and during pregnancy.¹

Medication safety during pregnancy and lactation.

DMARDs are often required before, during, and after pregnancy to control SARDs disease activity and thus may be essential for optimizing downstream reproductive outcomes.⁴¹ However, despite revisions to the Federal Policy for the Protection of Human Subjects—the “Common Rule”—which declassified pregnant women as a protected class in research in 2019, many drug and

vaccine trials continue to exclude pregnant women. Rather than enhancing safety in this group, this approach to research has undermined the generation of evidence needed to inform safe prescribing decisions during pregnancy and lactation.^{41,42} Among newer drugs approved by the US Food and Drug Administration (FDA), 90% present limited or no human data on pregnancy safety.⁴³ More research is urgently needed to investigate the safety of medications in the pregnancy and lactation context and to determine how potential risks can be clearly communicated to clinicians and patients.

All rheumatologists should be aware of evolving guidance around medication safety in pregnancy and lactation. The ACR RHG and EULAR indicate that certain medications are not safe to use in pregnancy, including cyclophosphamide (in the first trimester), methotrexate, and mycophenolate/mycophenolic acid.^{1,13} Although azathioprine is safe to use throughout pregnancy, the FDA has issued a warning around a rare association of thiopurines with intrahepatic cholestasis of pregnancy (ICP). One study of SLE reported a 4.7% risk of ICP in thiopurine-exposed pregnancies versus 1.9% in unexposed pregnancies. This complication resolves with drug discontinuation and may potentially be mitigated by twice-daily dosing.^{44,45} The FDA has also advised against use of nonsteroidal anti-inflammatory drugs beginning around 20 weeks’ gestation due to risk of fetal oligohydramnios and at around 30 weeks’ gestation due to risk of premature closure of the fetal ductus arteriosus.⁴⁶ Other medications, such as hydroxychloroquine, sulfasalazine, colchicine, tumor necrosis factor inhibitors, and low-dose steroids, are safe to use at all stages of pregnancy.^{1,13}

EULAR also asserts that rheumatologists may also consider treating patients with biologic drugs with molecular properties that render them unlikely to cross the placenta during early fetal development.¹³ For example, monoclonal antibodies of IgG (eg, belimumab, canakinumab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab, rituximab) have high affinity to neonatal Fc receptor (FcRn) but are unlikely to cross the placenta until after 16 weeks’ gestation, a point after which fetal organogenesis has concluded and risk of teratogenesis is low. The FcRn has weak binding affinity to the Fc fusion proteins of certain biologics (eg, etanercept, abatacept), and neonatal drug levels are low. Fc-free drugs and biologic drugs without Ig structures (eg, certolizumab, anakinra) do not enter the fetal circulation.¹³ This guidance significantly broadens the therapeutic armamentarium for people who require treatment during pregnancy and thus may positively impact pregnancy outcomes in the SARDs.

Following a case of disseminated tuberculosis in an infliximab-exposed infant who received the live BCG vaccine, a number of studies examined the health risks associated with fetal exposure to biologics and have not found an increased risk of major infections among these children in their first year of life.⁴⁷ ACR and EULAR indicate that nonlive vaccines are safe to give

on schedule to biologic-exposed infants, and the live rotavirus vaccine can be given on schedule to infants exposed to some biologics (eg, tumor necrosis factor inhibitors). At present, guidelines conditionally recommend delay of the rotavirus vaccination until six months of age for infants exposed in utero to anti-B cell agents (eg, rituximab, belimumab) and potentially other biologics that are less well studied.^{13,48} All guidelines indicate that risks of neonatal immunosuppression with in utero exposure to DMARDs must be balanced with the potential consequences of uncontrolled disease activity on the patient and fetus.^{1,13,49}

Contraception. All people with SARDs can use at least one method of contraception safely; however, OB/GYNs and PCPs may be less familiar with safety issues related to the SARDs. We therefore believe that basic contraception counseling and care is important for rheumatologists to build into their clinical practice. Clear contraception safety guidance is available from the ACR RHG and the Medical Eligibility Criteria from the Centers for Disease Control and Prevention.^{1,50} Methods that appear to be safe for nearly all patients, including those with SLE and moderate- or high-titer aPLs/APS, are the intrauterine device (IUD), emergency contraception (including over-the-counter oral tablets or the copper IUD, which is hormone free), and the progestin-only pill (POP).^{1,51–53}

Underscoring the safety of POPs, an FDA-approved POP, norgestrel, has been available for purchase over the counter since 2023.⁵⁴ Rheumatologists should feel comfortable recommending this option to patients, particularly those with an urgent contraceptive need and with appropriate referrals to OB/GYN or contraception specialists for follow-up care. Importantly, norgestrel currently costs around \$20 for a one-month supply, which will be cost-prohibitive to some patients; rheumatologists ideally would feel comfortable prescribing POPs, which are low-cost or even free with certain insurance plans.

Menstruation, menopause, and sexual function. The rheumatologist should be generally aware of how menstruation and menopause may affect SARDs activity and quality of life. Although understudied, menstrual arthritis—disease flares occurring around the time of menstruation—can be debilitating and, if not explicitly screened for among menstruating people, can be misconstrued as treatment-resistant disease activity. In up to half of cases, contraception and/or nonsteroidal anti-inflammatory drugs may ameliorate these symptoms without the need for DMARD escalation.⁵⁵ The menopause transition is associated with emergence of SARDs such as RA and Sjögren disease and can be difficult to differentiate from the recently characterized “musculoskeletal syndrome of menopause,” which includes perimenopausal/menopausal arthralgia, osteoarthritis, adhesive capsulitis, tendinitis, osteoporosis, sarcopenia, and/or diffuse musculoskeletal pain.^{56,57} During menopause, sexual dysfunction becomes more prevalent among women with vasomotor and

genitourinary symptoms, the latter of which may be particularly challenging for women with pre-existing vaginal dryness from SARDs (eg, Sjögren disease).⁵⁸

Vasomotor, genitourinary, and potentially even musculoskeletal symptoms may improve with systemic or topical estrogens and/or progesterone, ie, menopausal hormone therapy (MHT), previously called hormone replacement therapy. Recently reinterpreted clinical data suggest that MHT is safer than previously recognized for many women younger than 60 years and/or within 10 years of menstrual cessation⁵⁹; midlife patients may increasingly ask their rheumatologists about the safety of MHT in the context of their SARDs. Of note, MHT formulations have lower estrogen content than estrogen-containing contraceptives.⁶⁰ The ACR RHG indicates MHT—particularly transdermal options (eg, patch), which have less of a thrombotic risk than oral options—can be safely considered for individuals with SLE and other SARDs. MHT currently is not recommended for individuals with APS or conditionally for individuals with persistently positive aPLs, as the acceptably safe dose of exogenous estrogens in this group is unknown.¹ Individuals with genitourinary symptoms who are not candidates for MHT can use vaginal estrogen, which has minimal systemic absorption. For vasomotor symptoms, these individuals can consider FDA-approved paroxetine, a selective serotonin reuptake inhibitor (SSRI), or the expensive but effective neurokinin receptor antagonists (NK1/3, NK3), which modulate thermoregulatory zones in the hypothalamus. Nonhormonal, off-label options for vasomotor symptoms include nonparoxetine SSRIs, serotonin–norepinephrine reuptake inhibitors, gabapentin or pregabalin, oxybutynin, and cognitive behavioral therapy.⁶⁰

Building structural resources that enhance SRH care for patients with SARDs

A challenge for the rheumatologist is how to operationalize SRH competencies within existing clinical care models. Qualitative findings and QI projects provide guidance for the integration of SRH into practice.^{33,61–63} However, the creation of an implementable SRH framework in rheumatology will also require multidisciplinary clinical collaboration, trainee education, and patient information resources, as described in Box 2 and the following sections:

1. Build bridges with primary care and obstetrics and gynecology. Although patients need PCPs and OB/GYNs to address SRH needs such as pregnancy care and contraception, OB/GYN shortages, particularly in rural areas and states with abortion restrictions, are undermining access to SRH care.^{64,65} Among nearly 2,500 reproductive-aged women with SARDs who received regular rheumatology care in a large health care system, only one-third and two-thirds saw a gynecologist or PCP, respectively, over a two-year time frame.⁶⁶ Some patients report that no provider takes ownership of their SRH needs or that

Box 2. Building structural resources that enhance sexual and reproductive health (SRH) care for patients with systemic autoimmune and rheumatic diseases (SARDs)

Build collaborative care models between rheumatologists, reproductive rheumatologists, and obstetrician–gynecologists (OB/GYNs)/maternal–fetal medicine (MFM)

- Identify an OB/GYN practice or OB/GYN with whom to collaborate on SRH care.
- Develop multidisciplinary case conferences at academic centers that highlight clinical pearls.
- Use the electronic health record to do the following:
 - Create easy referral pathways between OB/GYN and rheumatology.
 - Collect local data about SRH outcomes; gaps in care could be prioritized for quality improvement.
- Develop virtual or electronic cross-institutional consultation systems between reproductive rheumatologists and community-based rheumatology providers for challenging SRH cases.⁸⁰
- Develop easy referral pathways between rheumatology and complex contraception specialists—OB/GYN clinicians who provide contraception for people with medical complexity.
- Develop collaborative clinical care models between OB/GYN and rheumatology, such as the following:
 - Reproductive rheumatology clinics that provide guidelines-concordant SRH care and coordinate care with OB/GYN and OB/GYN specialists
 - Current examples include the University of Pittsburgh/University of Pittsburgh Medical Center, Duke University, Hospital for Special Surgery, and University of Chicago.
 - Rheumatology–obstetric clinics that integrate rheumatology and OB/GYN care
 - US example includes Women & Infants Hospital in Providence, Rhode Island⁸¹; multiple clinics internationally offer this care in a single, combined clinic.⁸²
 - As 30% of maternal deaths occur 42 days after delivery until one year post partum, Interconception Care (ICC) and Fourth Trimester (4TM) care models engage primary care clinicians and subspecialists in management of maternal health immediately after and between pregnancies to enhance postpartum and future pregnancy outcomes.^{83,84}
- Develop large-scale research centers that integrate SRH and rheumatology/chronic disease management and advance the evidence base for SRH care for individuals with SARDs:
 - U.S. examples include University of Pittsburgh,⁸³ Duke University, Hospital for Special Surgery, and New York University.

Build SRH education for rheumatology trainees

National or regional level

- Perform an updated needs assessment around SRH education in rheumatology.⁷⁰
 - Include rheumatology advanced practice providers.
- Develop standards for SRH education in rheumatology fellowship, developed by content experts in reproductive rheumatology, medical education, and women's health specialties.
- Increase representation of SRH topics on the rheumatology initial certification examination.
- Increase awareness of and access to educational opportunities to build SRH knowledge:
 - Expand access to up-to-date lectures (eg, American College of Rheumatology [ACR] Virtual Rheumatology Program for Fellows in Training); provide pre- and post-tests to assess knowledge acquisition.
 - Require continuing medical education on SRH topics.
- The Objective Structured Clinical Examination can assess competency in counseling around contraception or pregnancy planning and can be proctored virtually or in person by content experts in reproductive rheumatology or OB/GYN/women's health.⁸⁵
- A certification program in rheumatology and SRH could build expertise in reproductive rheumatology.
- Increase research opportunities for interested fellows in topics related to SRH.
 - Cross-institutional collaborations may be needed if local expertise is not available.
- Foundation- and industry-funded one-year fellowships at reproductive rheumatology centers could advance a cadre of highly trained rheumatologists in SRH (eg, UCB Women's Health Fellowship in Rheumatology).

Institutional level

- Develop local SRH curricula and training opportunities (eg, clinic rotations) with faculty from OB/GYN/MFM, reproductive endocrinology, and complex contraception.
- Invite conference speakers with clinical and research expertise in SRH (ie, reproductive rheumatologists) to lecture to trainees and faculty.
- Implement multidisciplinary case-based conferences for training programs that lack access to patients who have SRH/obstetric needs based on population demographics with OB/GYN/MFM experts to review clinical scenarios that they may face in practice.
- Routinely observe and evaluate fellows while providing an aspect of SRH care and counseling to patients.
- Encourage trainees to develop and implement quality improvement projects focused on SRH, which have measurable outcomes and can augment SRH education and quality of care within a single rheumatology division.

Develop patient-directed resources focused on SRH and SARDs

- ACR, Arthritis Foundation, Lupus Foundation of America, Vasculitis Foundation, Mother to Baby (www.mothersbaby.org), HOP-STEP (www.lupuspregnancy.org), and Bedsider (www.bedsider.org), among others, offer person-centered SRH materials online.
- SRH materials in the SARDs context must be accessible to individuals with limited health literacy and numeracy skills.

Continued

Box 2 Building structural resources that enhance sexual and reproductive health (SRH) care for patients with systemic autoimmune and rheumatic diseases (SARDs)—cont'd

- Digital resources can offer SRH information directly to patients:
 - Digital resources have been developed for patients with SARDs.
 - MyVoice:Rheum is a digital decision aid that may build reproductive knowledge among women with SARDs.⁷⁴
- Trained doulas, community health workers, and/or peer support groups, in addition to clinicians, may support information needs, as well as emotional and physical needs related to pregnancy, parenting, pregnancy loss, adoption/surrogacy, or other areas of SRH.

their rheumatologists and OB/GYNs provide conflicting advice, particularly around contraception safety or medication safety during pregnancy and lactation.¹⁰ Moreover, some rheumatologists report that they lack professional relationships with OB/GYNs.⁶⁷

Rheumatologists can no longer safely assume that patients have an SRH provider. Ideally, every rheumatology practice should be able to identify at least one OB/GYN provider or practice to whom they can place referrals for urgent patient care. We believe it is particularly important that rheumatologists and maternal-fetal medicine (MFM) experts—obstetric specialists who care for patients with chronic and complex medical conditions—work collaboratively and provide clinical care from a common evidence base. To better meet the SRH needs of individuals with SARDs, structural changes are urgently needed to break silos and improve communication, collaboration, and guidelines-concordant care between rheumatologists and OB/GYNs/MFM.

2. Build rheumatology fellowship training in SRH.

Rheumatologists' knowledge and comfort level around SRH care may reflect their exposure to SRH in the training pathway. It is unclear how many rheumatology fellowship programs currently integrate SRH into their curricula. SARDs-specific aspects of women's and SRH care are not explicitly featured in the Accreditation Council for Graduate Medical Education program requirements for rheumatology fellowship training.⁶⁸ The rheumatology certification examination includes content areas such as "lupus pregnancy," "neonatal lupus," and "antiphospholipid antibody syndrome in pregnancy."⁶⁹ However, important aspects of peripartum care across other SARDs, pharmacologic management in pregnancy and lactation, and contraception care do not appear to be featured in the primary content of the examination. It is therefore conceivable that some rheumatologists enter independent practice without having received formal SRH education or demonstrated SRH knowledge. Even less is known about SRH training for advanced practice providers (APPs), who are increasingly providing rheumatology care in the United States.

To build a foundation of SRH in rheumatology, SRH education must be integrated into rheumatology fellowship and APP training; fellows have greater bandwidth to learn about SRH than practicing rheumatologists, and a prior study indicated that they are eager to expand their SRH knowledge using summary sheets, question banks, didactics, and online modules.⁷⁰ To enhance accountability, rheumatology in-training and certification

examinations should cover a broader range of SRH topics. Fellows in training and APPs should also learn how to routinely assess people's reproductive goals and preferences as part of the standard clinical encounter.

3. Build evidence-based educational resources for patients with SARDs.

Patient knowledge may be an important driver of downstream SRH outcomes. Some patients lack basic and SARDs-specific SRH knowledge, such as the effectiveness and safety of contraception in the context of SARDs. Such knowledge gaps might lead some patients to inadvertently choose low-efficacy methods of contraception, increasing the risk for pregnancies that are undesired and may be high risk.^{31,71,72} In addition, some patients discontinue effective, pregnancy-compatible medications during pregnancy and lactation due to uncertainty about medication safety, which can lead to suboptimal clinical outcomes.¹⁰

Patients need trustworthy, accurate, and accessible information about SRH. Rheumatologists and/or support staff (eg, nurses) should be prepared to share educational materials about SRH. As SRH decisions are often nuanced, complex, and preference sensitive, individuals need time to reflect on their own priorities and sometimes seek opinions of their partners or family members; they also need ways to communicate their questions to their rheumatologists. Resources are available to educate patients and help to build their SRH knowledge and clarify and communicate their information needs, such as videos, websites and printable fact sheets,⁷³ decision aids,^{41,74} SRH knowledge assessments for in-clinic and research use,^{72,75} and educational interventions.⁷⁵

Conclusions

An important opportunity exists to enhance the SRH of individuals with SARDs through proactive care provided in the rheumatology context. We highlight potential targets for intervention before and during pregnancy that may help to support healthy reproductive outcomes that align with people's preferences and priorities. We offer ideas about how existing SRH-related resources from the QFP, ACR, and EULAR can be integrated into rheumatology care.

We acknowledge that our recommendations have limitations. First, we focus on female patients with SARDs; however,

adolescents, male patients, and LGBTQIA individuals also need and deserve high-quality SRH services and should be the focus of future deliberation. Furthermore, our recommendations are not exhaustive; for example, although not addressed in depth in the current article, referrals for cervical cancer screening and assessments for sexual dysfunction and postpartum depression are important in certain populations. Finally, additional brainstorming is needed to feasibly advance SRH delivery in rheumatology clinics with high patient volumes and/or abbreviated visit times.

However, by building a stronger foundation of SRH care in rheumatology, we can reconceptualize the adverse reproductive outcomes that can occur in rheumatology as being intervenable and not inevitable; this can provide reassurance and hope for patients with SARDs. Moving forward as a field, we must respectfully and proactively deliberate how best to integrate SRH care in rheumatology in ways in which rheumatologists will support and invest and that best meet the needs of individuals with SARDs.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Birru Talabi confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Formal and Informal Social Care in People With Rheumatic and Musculoskeletal Diseases: A Cross-Sectional Multicenter Survey

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Objective. Rheumatic and musculoskeletal diseases (RMDs) are leading causes of physical disability, necessitating support with activities of daily living. This study describes social care received by patients with RMDs in two disparate regions of England: Salford (urban) and Norfolk (rural).

Methods. A cross-sectional survey identified how many patients received care and who provided it as well as care type (formal/informal), frequency, and duration. Participants included (1) patients attending rheumatology outpatient facilities at Salford Royal Hospital and (2) participants with inflammatory polyarthritis enrolled in the Norfolk Arthritis Register (NOAR). Descriptive statistics compared the care received, and a logistic regression model investigated factors associated with receiving help.

Results. The Salford cohort was younger and had a wider range of RMDs compared with NOAR. A significant number of participants in the Salford (85%) and NOAR (38%) groups required help with daily activities. Of those needing help, 61% and 73% received care in Salford and NOAR, respectively, predominantly informally from family and friends. Local authorities delivered social care to just 0.5% of Salford and 1.4% of NOAR participants. Daily care was provided to 43% of Salford and 53% of NOAR participants. Weekly care duration varied: 21% of Salford and 31% of NOAR responders received ≤ 4 hours, and 19% of Salford and 10% of NOAR responders received > 20 hours. Having multiple conditions increased the likelihood of receiving care: Salford odds ratio 1.93 (95% confidence interval [CI] 1.18–3.18) and NOAR odds ratio 3.30 (95% CI 1.45–7.60).

Conclusion. The survey highlights a lack of formal care for patients with RMDs, who mostly rely on undocumented informal care. Patients with multiple conditions often require daily living assistance; rheumatology services should consider incorporating social care reviews as part of routine practice.

INTRODUCTION

Rheumatic and musculoskeletal diseases (RMDs) encompass a diverse range of more than 200 conditions that affect the joints, bones, muscles, and tendons and includes both inflammatory and noninflammatory diseases, often resulting in pain, stiffness, and decreased mobility.¹ The World Health Organization

Global Burden of Disease study has highlighted RMDs as a leading cause of disability worldwide, ranking them as the second most prevalent contributor to total years lived with disability.² Within RMDs, rheumatoid arthritis (RA) is a debilitating, multisystem, chronic inflammatory condition and is the most common inflammatory diagnosis within RMDs.³ RA has been shown to have a considerable impact on the physical, social, and mental

The views expressed are those of the authors and not necessarily the funders (visit <http://www.nuffieldfoundation.org> and <http://www.versusarthritis.org>).

Assembling the Data Jigsaw (Salford study) has been supported by the Nuffield Foundation's Oliver Bird Fund and Versus Arthritis. The Norfolk Arthritis Register is supported by Versus Arthritis (grant reference numbers 20380, 20385, and 21229). Work for this current project was supported by University of East Anglia Health and Social Care Partners (grant number UHP14SOCRA).

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80031>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80031>.

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Submitted for publication July 24, 2025; accepted in revised form January 12, 2026.

SIGNIFICANCE & INNOVATIONS

- This study is the first to examine the association between rheumatic and musculoskeletal diseases and social care. Three in five patients received regular care, mostly unpaid from family or friends, revealing a substantial hidden economic burden on patients, caregivers, and society.
- Further, we found that one in three people with these conditions require help with basic activities of daily living such as washing, dressing, and household chores. For 7 of 10 of those receiving this social care, it was on at least a daily basis and often for several hours.
- Importantly, our findings were broadly consistent across two differing regions of the United Kingdom. Norfolk is largely classified by the Office for National Statistics as “majority rural”; by contrast Salford is an urban population. This suggests that these patterns of care do not change based on rurality.

health of patients.¹ In a recent meta-analysis, up to 50% of people diagnosed with RA had to stop working because of the disease, leading to a significant decrease in the quality of life, and most are of working age at the time of diagnosis.⁴ Although there has been extensive research into medication to treat active disease, reduce disability, and improve the quality of life for people with RA, despite these advances, many patients still experience significant impairment, known as the disability gap.⁵

RA and other RMDs lead to substantial economic burdens both directly and indirectly with contributions from both formal and informal care.⁶ Formal caregiving refers to professional health services provided by individuals or agencies that are paid for their care, which can include medical practitioners, in-home nursing and personal care, and institutional care facilities. In the United Kingdom, health care is provided free at the point of access, through the NHS. In contrast, formal social care is only provided through local authorities on a means-tested basis; it may also be accessed through self-funding, charities, and other third-sector organizations. Informal caregiving, on the other hand, involves unpaid support by family members, friends, or volunteers who provide assistance with daily activities and medical needs. These two types of care contribute to the direct and indirect costs associated with RA and other RMDs. Direct costs encompass medical treatments such as hospital stays, clinic visits, medications, laboratory tests, and imaging procedures, as well as costs for physical therapy and adaptive equipment, which might include alterations to living spaces. These direct expenses are generally well documented.⁷ Indirect costs, on the other hand, stem from decreased work productivity, job-related disability, and, notably, the necessity for nonprofessional or informal caregiving services. These costs are often more difficult to capture and are typically

not well documented in health records.⁸ Support provided by family and friends to those with conditions such as RA and other RMDs is not frequently recognized or recorded as caregiving, making it challenging to assess its economic value. This informal care, although often essential, is difficult to quantify monetarily because of its private and unstructured nature.

Further, caregiving can extend past activities of daily living (ADLs) to include help with mobility, household chores, medication management, and transport. The indirect costs relating to supporting individuals, which can be defined as social care support, have largely been unexplored in people with RMDs and are crucial in determining the true disease burden they pose to individuals. This is in part because this information is not captured routinely and needs to be asked about directly. This study aimed to characterize and quantify both formal (provided by local authorities and other paid care providers) and informal (provided by friends, family, and others) social care in people with RMDs in two distinct regions of the United Kingdom, one rural and one urban.

PATIENTS AND METHODS

Population. Two different groups of patients with RMDs were sent an online cross-sectional survey to identify and characterize formal and informal social care use (details below). The first were unselected adult patients attending Salford Royal Hospital Rheumatology outpatient clinics as part of a wider study nested within the “Data Jigsaw” program of research (<https://thedatajigsaw.co.uk/>). The survey was distributed via QR codes and text messages, and informed electronic consent was gained. Text message invites were sent to patients who had attended these clinics between October 2022 and September 2023 via the DrDoctor messaging service. Patients were also recruited directly from rheumatology clinics between November 2022 and March 2023. Rheumatology patients at Salford Royal Hospital were eligible to participate if they were adults with a musculoskeletal condition under the hospital’s care, had internet access, and could understand English with or without help from a caregiver. Eligibility included adults older than 18 years with a musculoskeletal diagnosis who had seen a rheumatologist at Salford Royal and were under active follow-up with the rheumatology department.

The second group were current participants of the Norfolk Arthritis Register (NOAR). NOAR has been described in detail elsewhere⁹; briefly, since 1990, NOAR has recruited adults older than age 16 years from Norfolk with recent swelling in two or more joints for at least 4 weeks. Participants who were actively enrolled in NOAR (n = 1,085), had consented to contact, and had provided an email address were sent an email invitation to take part in the social care survey between March 27 and 31, 2023. Reminders were subsequently sent to those who had yet to complete the survey between April 17 and May 12, 2023.

Survey development and refinement. The survey was originally adapted from an existing social care interview survey developed as part of a project funded by the Nuffield Foundation and the Department of Health¹⁰ and has been used by our team previously.¹¹ It was further refined with input from a patient advisory group to develop a web-based survey to enhance patient usability and reduce burden using Qualtrics software. The patient advisory group was made up of four patient partners living with RMDs based in Salford who took part in a Patient and Public Involvement workshop in January 2022 that explored this and other aspects of the Data Jigsaw program. They also provided feedback specifically on the survey in a postworkshop questionnaire. The workshop and feedback did not recommend major changes to the survey.

The survey collected data on participant demographics, whether help was required with ADLs (for example washing, dressing, or grocery shopping), which activities these were, who provided it, and the frequency and duration of the help provided. This captured both formal and informal help. Details of demographics, comorbid conditions, and partial postcodes were recorded to allow calculation of the Townsend Deprivation Index. Quintiles were created by setting 0 as the threshold for the Townsend Deprivation level to allow comparison with the national average Townsend Deprivation score.¹² Additional questions were asked in the NOAR survey pertaining to work (see Supplementary Exhibit 1). The Salford study received ethics approval from the UK Health Research Authority (REC ref 22/WA/0056, IRAS number 306827). NOAR received ethics approval from East of England – Cambridgeshire and Hertfordshire Research Ethics Committee (REC reference 15/EE/0076; IRAS 166048 substantial amendment No. 6, amendment date November 8, 2022).

Analysis. Data from the Qualtrics survey data were exported to R (version 4.2.1) for analysis and visualization. Detailed descriptive and summary statistics were performed. Data from each cohort were analyzed in parallel because of the differences in recruitment approaches and underlying population differences. To examine representativeness, the demographics of each cohort were compared with its background population (rheumatology outpatients for Salford and the NOAR 2020 population for NOAR).

The type, frequency, and duration of care were quantified in both cohorts, and descriptive comparisons were made between the two cohorts. Logistic regression analysis was conducted to identify factors associated with requiring help. Variables included in the model were age, sex, multiple long-term condition count (defined as a person who has no underlying health conditions or one, two, or more than three comorbidities), and the Townsend Index as a continuous variable. The data used for the survey are not publicly available without the completion of specific training requirements and information governance checks mandated by the data owners.

RESULTS

Demographics. A total of 805 people interacted with the Salford survey. Of these, 502 consented to take part, and 439 completed the survey. The majority, 326 (74%), were female, with a median age of 58 years, and an age range spanning from 21 to 94 years (Table 1). Osteoarthritis was self-reported by 154 participants (35%) and RA by 136 (31%) (see Table 1). Two hundred eighty-two (64%) participants reported multiple long-term health conditions (MLTCs).

In NOAR, a total of 1,085 personalized invitation emails were sent between March 27 and March 31, 2023, with 210 individuals taking part. Of these, 183 consented and completed the survey. The majority, 128 (69%), were female, with a median age of 63 years and an age range spanning from 27 to 84 years (Table 1). Because of the population of NOAR, a high proportion of NOAR respondents had a diagnosis of RA ($n = 135$, 73%). Osteoarthritis was reported by 38 of the participants (20%) (see Table 1). Eighty-eight participants (48%) reported MLTCs. Thirty-nine percent of the respondents were in paid employment, 51% were retired, 3% were looking for work, and 7% were unable to work.

The demographics of the Salford survey respondents were similar to those of the hospital population, and the NOAR respondents were similar to the NOAR cohort. This comparison included age, sex, Index of Multiple Deprivation, and ethnicity. The average age for both populations was similar, with a higher proportion of women, and most of the population was of a White British background. Reporting of other ethnicities was not possible because of low counts and the resultant risk of participant re-identification.

ADLs. People who reported living with an RMD often required assistance with ADLs, with 85% (374 of 439) of the Salford cohort and 38% (71 of 183) of the NOAR cohort stating they required help. These ADLs included carrying out household chores, grocery shopping, and managing to get in and out of bed. Specifically, nearly half of the Salford individuals and more than 80% of the NOAR participants who reported receiving help did so for routine household tasks, whereas approximately two-fifths of the Salford individuals and two-thirds of the NOAR participants reporting receiving help did so for grocery shopping. The next most common reported activity with those receiving help was getting in and out of bed. Moreover, approximately one-third of the Salford participants and almost half the NOAR participants reporting receiving assistance did so for dressing and undressing, approximately one-third of both cohorts for leaving their homes, and roughly one-sixth for help with medication (see Figure 1).

Providers of social care. For both groups, most participants who received assistance with ADLs received help informally from family and friends (Figure 2A and B): 61% (226 of 374) in Salford and 73% (52 of 71) in NOAR. Approximately 16% (63 of 374)

Table 1. Participant demographics*

	Salford			NOAR		
	Social care		Overall (N = 439)	Social care		Overall (N = 183)
	No (n = 65)	Yes (n = 374)		No (n = 112)	Yes (n = 71)	
Age, y						
Median [min–max]	59.0 [21.0–87.0]	57.5 [21.0–94.0]	58.0 [21.0–94.0]	63.0 [27.0–84.0]	63.0 [27.0–84.0]	63.0 [27.0–84.0]
Sex, n (%)						
Female	50 (76.9)	276 (73.8)	326 (74.3)	72 (64.3)	55 (77.5)	128 (69.6)
Male	13 (20.0)	96 (25.7)	109 (24.8)	40 (35.7)	15 (21.1)	55 (29.9)
Missing	2 (3.1)	2 (0.5)	4 (0.9)	0 (0)	1 (1.4)	1 (0.5)
Diagnosis reported, n (%) ^a						
Rheumatoid arthritis	21 (32.3)	115 (30.7)	136 (31.0)	82 (73.2)	53 (74.6)	135 (73.4)
Osteoarthritis	27 (41.5)	127 (34.0)	154 (35.1)	18 (16.1)	20 (28.2)	38 (20.7)
Psoriatic arthritis	7 (10.8)	48 (12.8)	55 (12.5)	16 (14.3)	5 (7.0)	21 (11.4)
Axial spondyloarthropathy	6 (9.2)	28 (7.5)	34 (7.7)	0 (0)	2 (2.8)	2 (1.1)
Other inflammatory condition	5 (7.7)	32 (8.6)	37 (8.4)	8 (7.1)	7 (9.9)	15 (8.2)
Sjögren disease	5 (7.7)	32 (8.6)	37 (8.4)	40 (35.7)	48 (67.6)	88 (48.1)
Systemic sclerosis	7 (10.8)	38 (10.2)	45 (10.3)	–	–	–
Osteoporosis	10 (15.4)	42 (11.2)	52 (11.8)	9 (8.0)	6 (8.5)	15 (8.2)
Fibromyalgia	19 (29.2)	99 (26.5)	118 (26.9)	15 (13.4)	14 (19.7)	29 (15.8)
Other	15 (23.1)	96 (25.7)	111 (25.3)	54 (48.2)	28 (39.4)	82 (44.8)
Multiple long-term conditions, n (%) ^b	11 (16)	271 (72)	282 (64)	17 (15.2)	8 (11.3)	25 (13.7)
Townsend Deprivation Index category						
1 (<−3.80), n (%)	7 (10.8)	70 (18.7)	77 (17.5)	17 (15.2)	14 (19.7)	31 (16.9)
2 (−3.79 to −2.92), n (%)	4 (6.2)	18 (4.8)	22 (5.0)	63.0 [27.0–84.0]	63.0 [27.0–84.0]	63.0 [27.0–84.0]
and median [min–max]						
3 (−2.91 to −2.09), n (%)	11 (16.9)	45 (12.0)	56 (12.8)	72 (64.3)	55 (77.5)	128 (69.6)
4 (−2.08 to −0.55), n (%)	20 (30.8)	88 (23.5)	108 (24.6)	40 (35.7)	15 (21.1)	55 (29.9)
5 (>−0.54), n (%)	23 (35.4)	152 (40.6)	175 (39.9)	0 (0)	1 (1.4)	1 (0.5)

* Max, maximum; min, minimum; NOAR, Norfolk Arthritis Register.

^a Some participants reported more than one diagnosis for their pain.

^b Includes the musculoskeletal disorders above and the following chronic diseases listed in the questionnaire: angina, heart attack, heart disease, anxiety, gastrointestinal disease, stroke, chronic obstructive pulmonary disease, diabetes, cancer, multiple sclerosis, depression, and other.

of Salford participants and 23% (17 of 71) of NOAR participants arranged and paid for assistance themselves without involvement from local authorities or social care organizations. Notably, only a small percentage in both surveys (0.5% or 2 of 374 for Salford and 1.4% or 1 of 71 for NOAR) had their services paid for by the local authority. There were also a few participants (2.4% [9 of 373] for Salford and 8.4% [6 of 71] for NOAR) who received support from homecare assistants, occupational therapists, and voluntary helpers (Figure 2A and B). Overall, 10% of the Salford cohort reported “other,” and the other included a variety of examples such as “gardener,” “hospital staff,” and “supermarket delivery.” A small number of participants received help from more than one group, for example, family and friends as well as paid services: in Salford, this was two individuals, and for NOAR this was 18 people. A total of 16% (63 of 374) also received help with leisure activities, such as hobbies, socializing, or meeting up with friends in the last month.

Duration and frequency. The amount of time that assistance was received per week varied among the participants, with the largest group receiving care for 4 hours or less per week (46% [80 of 171] of respondents in Salford and 30% [22 of 71] in NOAR cohorts). However, a notable minority (19% [n = 74] in Salford and 25% [n = 18] in NOAR) required more than 10 hours of care per week (Figures 3A and 4A). Approximately 7 in 10 people (72% [n = 123] in Salford and 68% [n = 45] in NOAR) received assistance on a daily basis (Figure 3B and C; Figure 4B and C). Participants who required daily care also tended to require more weekly hours of support (Figures 3C and 4C) compared with those who received care less frequently. There was a significant number of participants in the Salford cohort who did not answer these two questions, with 201 nonresponders. Across both cohorts, the frequency and duration of support was similar between those receiving formal and informal care (Supplementary Figure 1A–D). In those receiving very

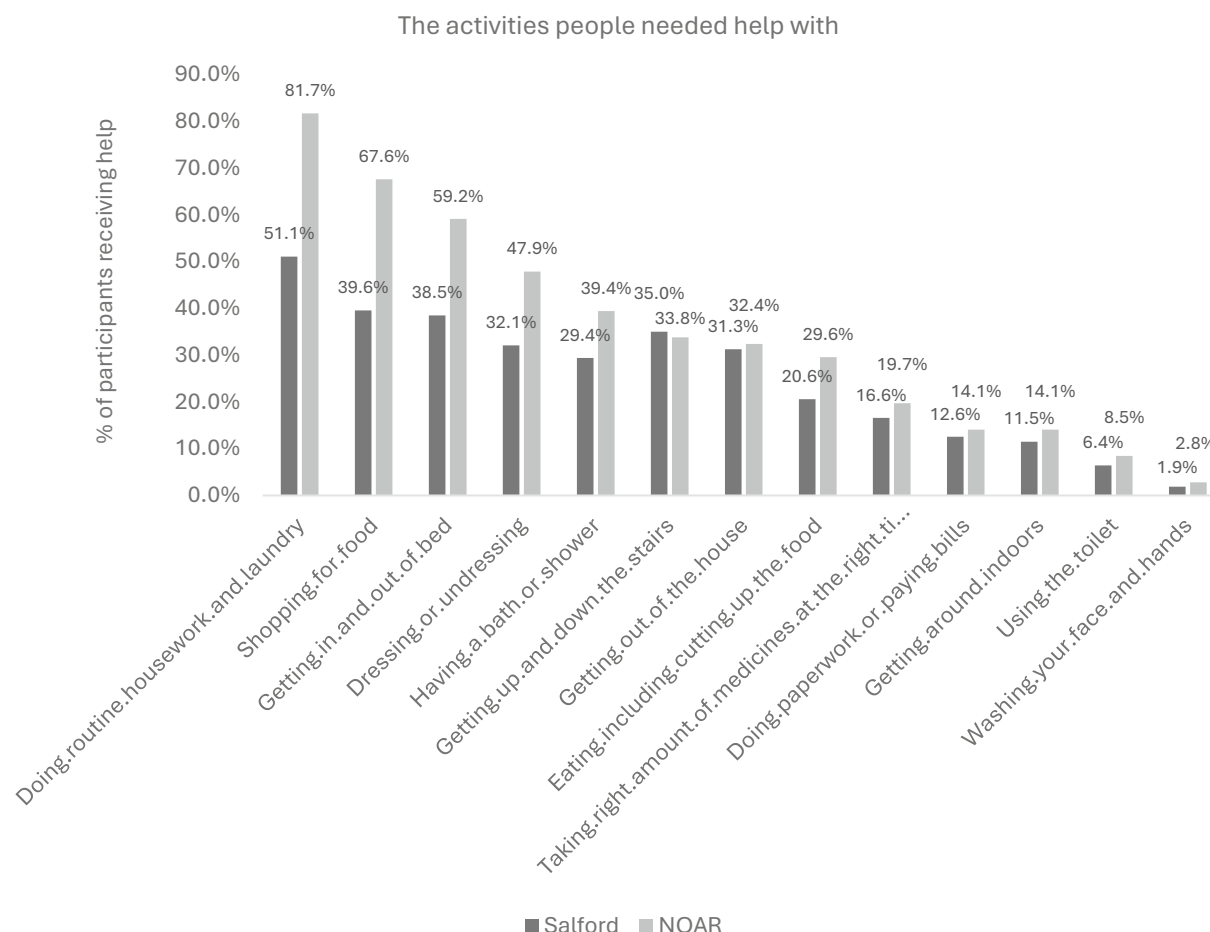


Figure 1. Activities of daily living requiring social care. NOAR, Norfolk Arthritis Register.

infrequent or occasional help (once per month or less), it was predominantly provided formally.

Factors associated with receiving social care. In the two multivariable models (Table 2), similar patterns were identified across both cohorts. Unexpectedly, younger people were found to be more likely to receive help with ADLs in Salford, with an odds ratio (OR) of 0.97 for age (95% confidence interval [CI] 0.96–0.99). However, in the NOAR population, age was not associated with receiving help, with an OR of 0.99 (95% CI 0.97–1.02). Participants who had MLTCs (defined as reporting at least one additional long-term condition to their index RMD) were found to be more likely to receive help across both cohorts, with one additional long-term condition OR of 1.93 (95% CI 1.18–3.18) and 3.30 (95% CI 1.45–7.60) in Salford and NOAR, respectively.

DISCUSSION

In this survey of people with RMDs in two sites across the United Kingdom, three to four of every five people who received help did so informally without financial remuneration from family and friends. We have shown approximately one in three people with these

conditions need help with basic ADLs, such as shopping, household chores, and personal care activities. This help is needed frequent and for several hours daily. In addition, people with MLTCs were more likely to need help. Despite the differences in the demographics between the two regions investigated, and in particular rural versus urban settings, the results were broadly similar across the cohorts.

To our knowledge, this is the first study to investigate the relationship between RMDs and social care use. It is an important outcome to describe for people with RMDs because RMDs are the most common cause of chronic physical disability. As a group, they are likely to require support with ADLs at some point during their lifetime. Previously, we have investigated these rates in people with chronic pain and also found high levels of informal social care provision.¹¹ According to the Office for National Statistics (ONS), there are approximately five million unpaid carers across England and Wales, representing a significant economic burden.¹³ Understanding which diseases drive the need for care is therefore important. RMDs are often present in people with MLTCs and contribute significantly to function disability in this context.^{14,15} We have demonstrated here that this is also an important factor in driving the social care burden. Further work remains to understand the relative social care burden of RMDs

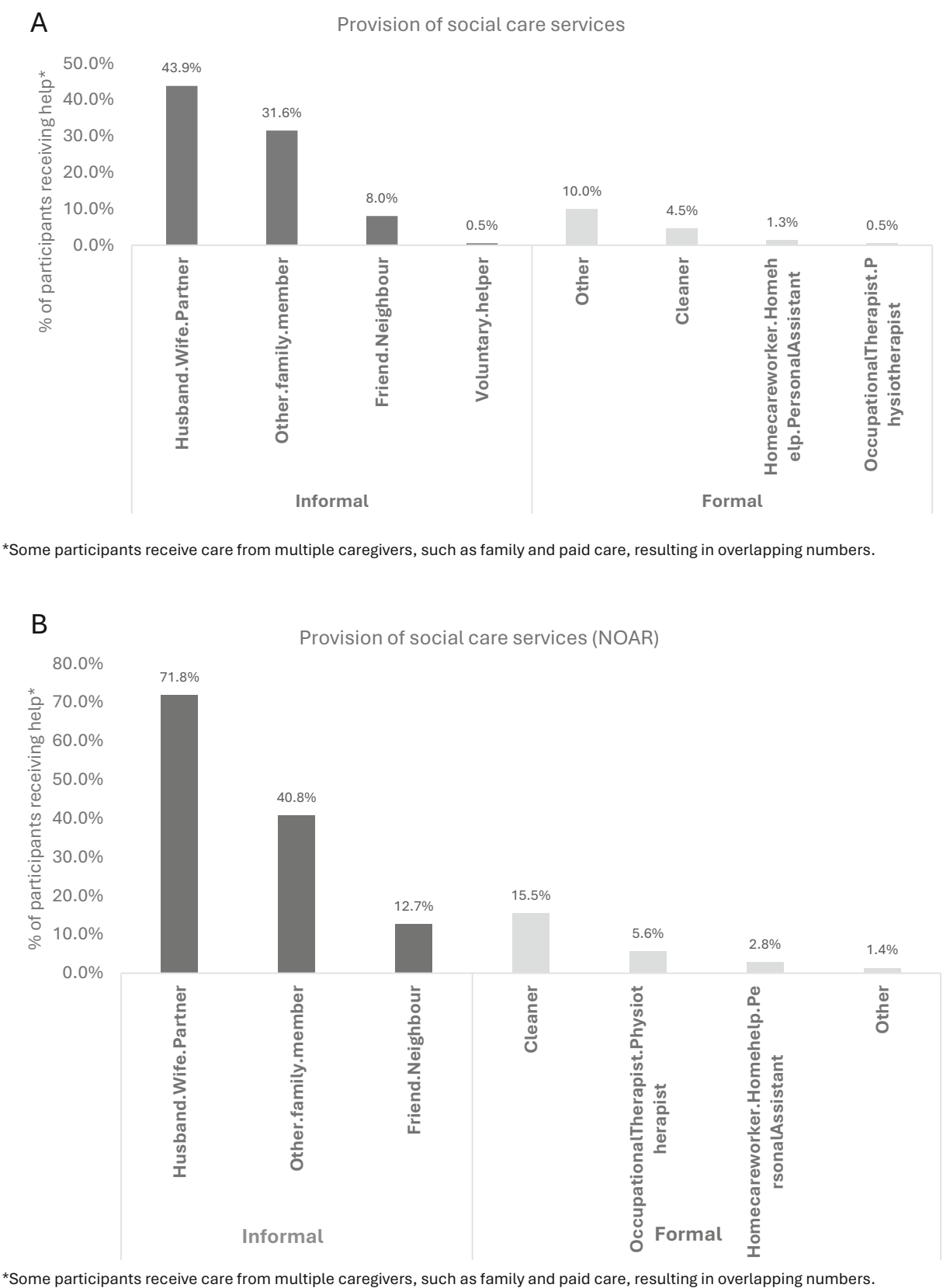


Figure 2. (A) Provision of social care services (Salford). (B) Provision of social care services (NOAR). *Some participants receive care from multiple caregivers, such as family and paid care, resulting in overlapping numbers. NOAR, Norfolk Arthritis Register.

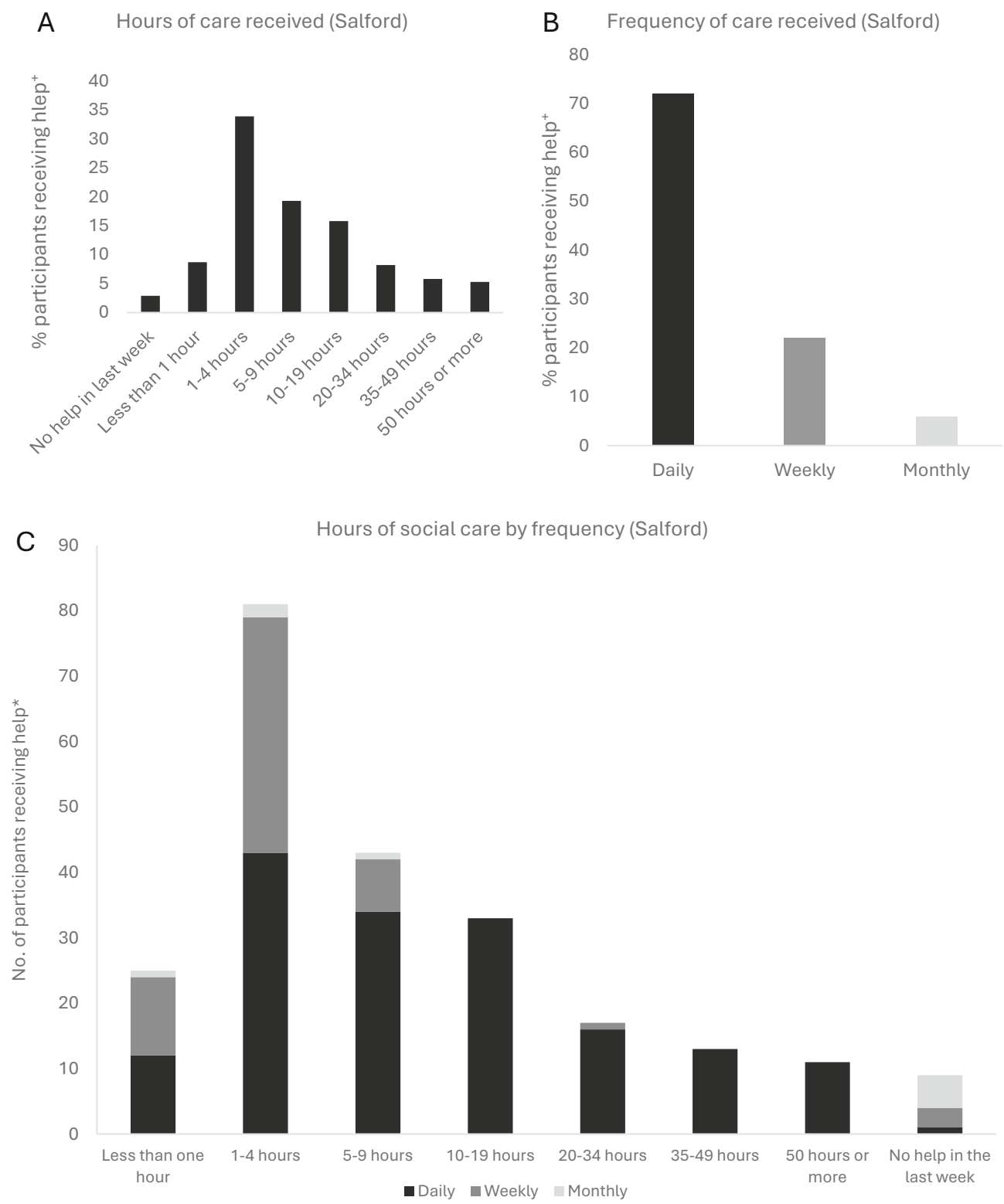


Figure 3. (A) Hours of social care received per week H (Salford). (B) Frequency of social care services received (Salford). (C) Hours of social care by frequency (Salford). +Presented as the percentage of nonmissing data. *Some participants receive care from multiple caregivers, such as family and paid care, resulting in overlapping numbers.

compared with other long-term conditions. We have also provided some insight into which activities these patients need help with that may be important for patient charities and support groups. The care

provided is often highly personal, and, therefore, it may be the informal care that is being required, falling heavily on very close friends and family when professional support is not accessible or available.

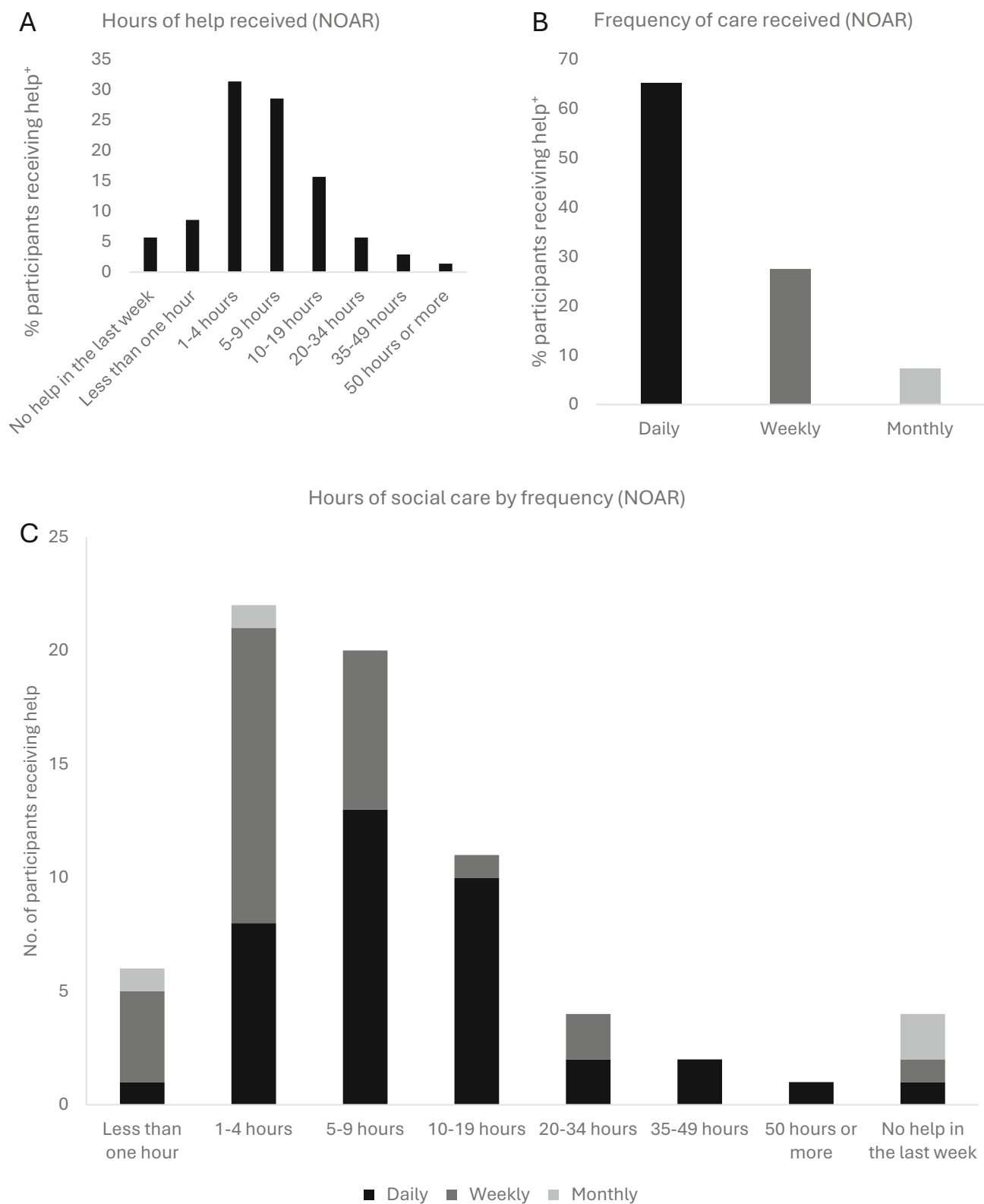


Figure 4. (A) Hours of social care received per week (NOAR). (B) Frequency of social care services received (NOAR). (C) Hours of social care by frequency (NOAR). +Presented as the percentage of nonmissing data. NOAR, Norfolk Arthritis Register.

Table 2. Factors associated with social care received in the last month*

	Salford			<i>P</i>	NOAR			<i>P</i>
	aOR	95% CI			aOR	95% CI		
Age	0.97	0.96	0.99	<0.001	0.99	0.97	1.02	0.57
Sex								
Female	Ref	Ref	Ref		Ref	Ref	Ref	
Male	0.31	0.19	0.51	<0.001	0.42	0.19	0.88	0.035
Townsend Deprivation Index	1.02	0.93	1.13	0.61	1.04	0.82	1.30	0.76
Additional long-term conditions								
0	Ref	Ref	Ref		Ref	Ref	Ref	
1	1.93	1.18	3.18	<0.001	3.3	1.45	7.60	<0.001
2	3.76	2.08	6.95	<0.001	5.87	2.53	14.2	<0.001
≥3	2.92	1.55	2.89	<0.001	2.14	1.40	9.89	<0.001

* Multivariate logistic regression, adjusting for all variables presented in the table. aOR, adjusted odds ratio; CI, confidence interval; NOAR, Norfolk Arthritis Register; Ref, reference.

Answering “yes” to the question “Have you received help with activities of daily living in the last month?”

In the United Kingdom, government-funded social care comes under the Care Act 2014 and is provided through local authorities (councils).¹⁶ This law states eligibility for formal social care has been assessed on the basis of an individual's care needs and is not dependent on other informal care that may be provided. Our study demonstrates that rates of council-funded or paid-for care are low in people with RMDs, with less than 2% reporting this in our survey. These low levels of formal care provision suggest that people with RMDs either do not meet the eligibility criteria for formal care or do not seek out formal care support. Nevertheless, significant amounts of unpaid informal care are being provided, demonstrating a large “care gap.” Informal carers are filling this gap with implications for society and the economy. For example, older carers themselves may have their own health needs that are left unattended, or for younger carers there may be significant impact on their education and/or employment. These costs should be considered for inclusion in the health economic analysis of the disease burden from RMDs.

These data provide a snapshot of care use in people with RMDs. The strengths of this study include a large survey of two regions of the United Kingdom across a spectrum of different socioeconomic positions and rurality. Salford is classified by the UK ONS within its most urban regional category. In contrast, Norfolk has a mixed profile: approximately 25% of its population lives in the urban center of Norwich, and the rest falls under rural classifications ranging from “intermediate rural” to “majority rural,” with the latter being the most rural category defined by the ONS.¹⁰ The population of Salford is younger, with a median age of 34 years; in comparison, the North Norfolk local authority has the highest median age in England at 54 years. Both regions have a higher proportion of population of White ethnicity compared with England and Wales as a whole.¹⁷ Salford has high levels of deprivation and is in the top 5% of the most deprived local authorities in England.¹⁸ By contrast Norfolk is in the bottom 50% of the least deprived regions.¹⁹

Importantly, the study measured both formal and informal care, allowing for the quantification of the hidden burden of

informal care in this patient group. However, there are some limitations. We remain unsure of the prevalence of social care use at a population level because of response rates and possible selection bias in who responded to the survey. The NOAR survey recruited people from a pre-existing study of patients with inflammatory arthritis. We have compared the demographics in both the rheumatology outpatient population in Salford and the overall population in NOAR (data not shown), and these appear similar. However, we cannot rule out unmeasured differences between those who responded to the survey and those who did not. We identified an association between younger age and receiving help among Salford respondents; this somewhat surprising finding may also be because of a response or selection bias, as younger people with more significant needs may have been more likely to take part in the survey.

It is possible that people invited but not responding to the study were either more or less likely to require help. This could be because rates of digital literacy are associated with markers of deprivation, and therefore, those not responding may have been in need. Although the participants represented an economically diverse group, the study population had little ethnic diversity, with an underrepresentation of non-White participants compared with the UK population in general. This is in keeping with the demographics of the two regions recruited from (Salford and Norfolk), which limits the applicability of our findings to other ethnic groups, which may access and provide care differently. Furthermore, a cross-sectional study is not suited to address whether these arrangements have changed over time. Differential selection bias may be present because of the distinct characteristics of the Salford social care survey respondents compared with the NOAR research cohort. The Salford respondents, having actively participated in a survey focused on social care, might exhibit different response tendencies or perspectives compared with the NOAR cohort accustomed to a broader range of survey topics. This potential disparity in response behaviors could introduce bias, influencing the generalizability of findings from either group to the broader population.

In conclusion, there is a large care gap among this population of patients, which has significant ramifications for future care policy. With increasing rates of RMDs, this care gap will affect larger proportions of the population with consequences for the health and productivity of informal caregivers. By capturing informal care use by patients living with RMDs, this study highlights and quantifies this problem. This is crucial as these data are currently not captured by administrative organizations. Requiring assistance with ADLs was associated with MLTCs and those of younger age. Policymakers and care providers, as well as clinicians providing care to patients with RMDs, should consider these results in their policymaking and practice and be aware of the high unmeasured burden of informal care in this population. It might be possible to consider incorporating an annual assessment of formal and informal care provision for patients within routine rheumatology services, supported by the full multidisciplinary team. This could allow signposting to available support and services as well as providing an opportunity for more detailed data collection to better define need and refine care provision in this population.

ACKNOWLEDGMENTS

We would like to thank all the participants of the survey. We would also like to thank Dr Paul Clarkson for his contribution and advice.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Humphreys confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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REVIEW ARTICLE

Risk of Retinopathy Associated with Long-Term Use of Hydroxychloroquine in Patients with Rheumatic Diseases: A Systematic Review and Meta-Analysis

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and J. Antonio Avina-Zubieta, MD, PhD^{1,2} 

Objective. We aimed to estimate the prevalence and cumulative incidence of hydroxychloroquine retinopathy (HCQ-R) and its risk factors among patients receiving long-term HCQ with rheumatic diseases through a systematic review and meta-analysis of observational studies that used spectral-domain optical coherence tomography (SD-OCT) for screening.

Methods. A systematic search of PubMed, Scopus, Ovid EMBASE, and World Health Organization databases (inception–December 31, 2025) identified observational studies meeting the following criteria: 1) adults with rheumatic diseases on HCQ for at least one year, 2) SD-OCT used for HCQ-R screening, 3) reported HCQ-R prevalence or cumulative incidence or calculable data, 4) reported HCQ-R risk factors as hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and 5) English full text. Study quality was assessed using the Newcastle–Ottawa Scale. Random-effects meta-analysis estimated pooled prevalence, cumulative incidence, and risk-factor associations.

Results. We screened 827 studies from which an overall 19 met inclusion criteria (18 cohort and 1 case-control). Pooled HCQ-R prevalence from 2008 to 2023 was 5.1% (95% CI 3.9–6.5). Pooled cumulative incidence was 0.1% (95% CI 0.0–0.5) at 5 years, 2.6% (95% CI 1.6–4.1) at 10 years, and 5.6% (95% CI 3.2–9.6) at 15 years. Risk factors measured as HR (95% CI) included daily dose >5 mg/kg actual body weight (4.32 [2.80–6.65]), chronic kidney disease (CKD) (1.94 [1.27–2.96]), female sex (3.78 [1.90–7.48]), and Asian vs White ethnicity (1.67 [1.07–2.62]).

Conclusion. HCQ-R risk increases with duration and is dose-dependent, reaching 5.6% by 15 years. Findings support dose optimization with intensified screening for higher-risk patients, including those with CKD or those who are female and/or Asian.

INTRODUCTION

Hydroxychloroquine (HCQ) is a generally well-tolerated anti-rheumatic medication that is widely used for systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and other rheumatic diseases, including during pregnancy.^{1–3} HCQ improves patient survival^{4–6} and reduces disease-related complications.^{7–9} However, it carries a risk of irreversible vision loss due to HCQ retinopathy (HCQ-R).¹ Earlier screening studies relying on visual field

tests and/or clinical examination (eg, bull's-eye maculopathy) estimated HCQ-R risk at 0.1% to 0.5% among patients receiving long-term HCQ.^{10,11} With the introduction of advanced retinal imaging, particularly macular spectral-domain optical coherence tomography (SD-OCT) in 2006, reported HCQ-R frequency increased, largely because SD-OCT detects early outer retinal structural changes before typical visual field defects.^{12–14}

In 2011, the American Academy of Ophthalmology (AAO) recommended macular SD-OCT for chloroquine/HCQ-R

Supported by the Canadian Institutes for Health Research (CIHR) (grant number: PJT-162133). Dr Daftarian is a recipient of a CIHR Doctoral Research Award (number: 494089). Dr Avina-Zubieta is the BC Lupus Society Research Scholar and the Walter and Marilyn Booth Research Scholar.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80033>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80033>.

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Submitted for publication October 22, 2025; accepted in revised form February 20, 2026.

SIGNIFICANCE & INNOVATIONS

- This is the first meta-analysis to estimate pooled prevalence, cumulative incidence, and risk factors of hydroxychloroquine retinopathy (HCQ-R) from studies that used spectral-domain optical coherence tomography for screening.
- The weighted pooled prevalence of HCQ-R was 5% between 2008 and 2023, indicating the overall burden among different screened populations and reflecting both existing and newly detected cases.
- Pooled cumulative incidence was 0.1%, 2.6%, and 5.6% at 5, 10, and 15 years, respectively. These results show that risk for HCQ-R rises over time, which supports the need for continued screening while on HCQ.
- Pooled prevalence of 5% mirrored the 15-year pooled cumulative incidence of 5.6%, which is consistent with the mostly irreversible course of HCQ-R that cases accumulate instead of recovering over time.
- Risk factors for HCQ-R include patients with an HCQ dose >5 mg/kg/day of actual body weight (ABW), who had a four-fold higher risk of HCQ-R compared with those on ≤5 mg/kg/day (ABW). Additional risk factors associated with an increased HCQ-R risk include chronic kidney disease, female sex, and Asian ethnicity.

screening and in 2016 updated its guidance to designate SD-OCT and automated visual field (VF) as the primary screening tests.¹⁵ In the updated AAO recommendation, SD-OCT is a primary screening test, with wide-field fundus autofluorescence when available. VF and multifocal electroretinogram (mf-ERG) are used as confirmatory tests rather than primary screening modalities.¹⁶ Since the adoption of SD-OCT-based screening recommendations, reported HCQ-R prevalence has ranged from ~1% to ~15%.^{13,17–27} This variation likely reflects differences in populations, study design, screening practices, and follow-up. Because HCQ-R is uncommon and typically late-onset, robust estimates require large cohorts with long-term follow-up; many studies are underpowered to provide precise risks or risk-factor effect sizes. These evidence gaps may limit patient counseling and optimization of long-term HCQ monitoring.²⁸

To address these gaps, we conducted a systematic review and meta-analysis of observational studies to estimate pooled prevalence and cumulative incidence of HCQ-R, focusing on studies that used macular SD-OCT as an objective screening tool. Additionally, we quantified pooled effect sizes for key HCQ-R risk factors using data from eligible studies.

MATERIALS AND METHODS

This systematic review and the meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) guidelines²⁹ (Supplementary Material 1). We synthesized data from published reports and involved no human participants or identifiable data; therefore, institutional ethics approval was not required for our study. We have registered our systematic review and meta-analysis on PROSPERO with the registration number CRD42024532847, dated April 19, 2024.

Search strategies. With assistance from a biomedical librarian, ND, and CY searched PubMed, Scopus, EMBASE (Ovid), and the World Health Organization (WHO) Global Index Medicus from inception to December 31, 2025. We used controlled vocabulary (MeSH/Emtree) and free-text terms for hydroxychloroquine/Plaquenil, retinopathy/retinal toxicity, incidence/prevalence/risk, rheumatic diseases (SLE/lupus, RA), and risk factors. We also hand-searched reference lists of included full texts and relevant textbooks for additional studies. Search strategies are provided in Supplementary Material 2.

Study selection. We included studies that met the following inclusion criteria: 1) adults on long-term (≥1 year) HCQ therapy for a rheumatic disease; 2) use of macular SD-OCT (an objective assessment) with or without another test, such as VF or mf-ERG (functional test) for HCQ-R screening, or HCQ-R identified through guideline-concordant screenings with clinician-confirmed diagnoses documented from ophthalmology records during the SD-OCT era (2006 onward, encompassing early adoption and the 2011 AAO guideline); 3) studies that reported HCQ-R prevalence during their study period (period prevalence) or data to calculate it; 4) studies that reported cumulative incidence of HCQ-R since HCQ initiation or data to calculate it; 5) studies on purported risk factors for HCQ-R, including daily dose, cumulative dose, duration of use, sex, race/ethnicity, chronic kidney disease (CKD), older age or tamoxifen use, which reported their effect sizes as hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) estimates or data to calculate them; and 6) full text in English. Based on our inclusion criteria, cross-sectional studies, surveys, case-series, and case-report study designs were not included. We imposed no restrictions on participant demographics or other study characteristics beyond those prespecified. Two reviewers (ND, CY) independently screened titles/abstracts and full texts, documented exclusion reasons, and resolved disagreements by consensus; unresolved conflicts were adjudicated by a third reviewer (JAAZ).

Data extraction. For studies meeting the eligibility criteria, we extracted the following: 1) study characteristics (authors' names, year of publication, country of study, cohort type [retrospective vs prospective], study setting [community vs clinic-based], start and end date of study [study period], follow-up length [if available], source of information [medical records vs registry vs audit vs health data]; 2) study sample (sample size, number of HCQ-R detected events [prevalent cases vs incident

cases], distribution of age, sex, race/ethnicity, geographic region, and type of rheumatic disease); 3) primary outcome (reported HCQ-R prevalence, HCQ-R cumulative incidence at 5, 10, 15, and ≥ 20 years post-HCQ initiation), 4) risk factors for HCQ-R and their effect size with point estimates of HR or OR with (95% CI) or data to calculate them. Information on biologic sex and/or gender were collected when available. Information on race or ethnicity as a purported risk factor for HCQ-R was categorized per National Institute of Health terminology.³⁰ ND and CY independently extracted data; discrepancies were resolved by consensus or, if needed, adjudicated by JAAZ.

Risk-of-bias (quality) assessment. Two authors (ND, CY) independently applied the Newcastle–Ottawa Scale (NOS), a 10-point tool for cohort and case-control studies. Discrepancies were resolved by consensus. Each study was scored on eight items (six scored 0/1; two scored 0/1/2). Scores of 7 to 10 indicated low risk of bias (good), 4 to 6 intermediate risk (fair), and under 4 high risk (poor) quality. For cohort studies, items and scoring were the following: cohort representativeness/setting (community vs clinic), exposure ascertainment/source (medical records/registries vs self-report), confirmation that HCQ-R was absent at baseline, selection of participants from the same underlying source population, comparability through confounding control (major and additional covariates), outcome ascertainment during follow-up (expert confirmation/medical records/*International Classification of Diseases* codes), adequacy of follow-up duration (>5 years), and completeness of follow-up (loss to follow-up $<20\%$). Full operational definitions and case-control-specific NOS items are provided in Supplementary Material 3.

Statistical analysis. Period prevalence of HCQ-R was defined as the proportion of detected HCQ-R cases during the study period, calculated as the number of existing cases divided by the total number of patients screened within that period. Cumulative incidence of HCQ-R was the probability that patients free of HCQ-R at baseline experience HCQ-R event by time “t” after HCQ initiation, which was defined relative to the baseline at-risk cohort and estimated as event probability accounting for right censoring and, when applicable, competing risks.^{31,32}

We used a random-effects model to estimate weighted pooled period prevalence, weighted pooled cumulative incidence, and weighted pooled effect sizes (OR or HR) of the association of risk factors with HCQ-R. Weighting was based on the study sample size, and pooled estimations were reported as point estimates with 95% CI. With only two studies, we used a fixed-effects model because between-study variance is unreliable to estimate for random-effects.³³

Heterogeneity was assessed using the Q-test ($P \leq 0.05$) and the I^2 statistic.³⁴ To explore potential sources of heterogeneity, we initially conducted subgroup analyses by stratifying on the key methodologic study-level variables. These included study setting

(community vs clinic-based), cohort type (retrospective vs prospective), study quality (high [≥ 7] vs low [<7]), publication year (before vs after 2016), follow-up length (>5 years vs ≤ 5 years), and geographic region (Europe and North America versus Asia). Although subgroup analyses provided some insight into variation across studies, they were limited in their ability to quantify and adjust for overlapping or confounding effects between variables. Therefore, we proceeded with univariate meta-regression analysis to further assess the extent to which these methodologic variables contributed to between-study heterogeneity in logit-transformed prevalence or cumulative-incidence estimates. When a methodologic variable demonstrated a significant but partial effect in subgroup analysis, we used multivariable meta-regression to adjust for the influence of a potential confounding variable and better isolate its independent association.³⁵

Additionally, we assessed whether study-level demographics and HCQ exposure variables explained heterogeneity in logit-transformed prevalence estimates. We tested mean participant age, mean HCQ exposure duration, mean cumulative HCQ dose, and mean daily HCQ dose. Because of the limited number of studies and to avoid overfitting and collinearity, we performed univariate meta-regression.^{35,36}

To evaluate the robustness of results, leave-one-out sensitivity analysis was performed by sequentially removing individual studies and comparing the results with baseline. Our analyses were conducted using Comprehensive Meta-Analysis Version 4 (Biostat, Englewood, NJ) software.

Publication bias. Publication bias was assessed using funnel plots (SE on the y-axis and log effect on the x-axis). In the absence of small-study effects, studies should be symmetrically distributed around the pooled estimate, with larger studies clustering near the top. Funnel plot asymmetry was further evaluated using Egger’s regression test (p value).

Certainty of evidence for outcomes. We assessed the certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Certainty was rated separately for each of the outcomes. Because all included studies were observational, evidence started at low certainty and was rated down as appropriate for inconsistency (between-study heterogeneity), indirectness (differences in population, setting, data source), imprecision (width of CI), and publication bias (Egger’s test). Final certainty was categorized as low or very low.

RESULTS

Search results. A total of 1,596 records were identified through database searches (Scopus, PubMed, Ovid EMBASE, WHO) and citation tracking. After removing 769 duplicates, 827 records were screened by title and abstract, of which

753 were excluded by consensus for not meeting eligibility criteria. The remaining 74 articles underwent full-text review. Of these, 55 were excluded for an ineligible study design (ie, cross-sectional, case-series, survey) ($n = 9$), lack of SD-OCT for screening throughout follow-up ($n = 17$), no reported outcome measures or data to calculate ($n = 20$), ineligible population (nonrheumatic diseases, <1-year exposure) ($n = 6$), or non-English full text ($n = 3$). Nineteen studies met the inclusion criteria and were included in the risk-of-bias assessment and data extraction (Supplementary Figure 1 PRISMA flowchart).

Study characteristics. The main characteristics of the 19 studies included in the systematic review and meta-analysis are shown in Table 1. The 19 included studies were conducted across diverse geographic regions: 7 from Asia,^{17,19,21–23,26,37} 6 from North America,^{13,25,38–41} 5 from Europe,^{18,20,24,27,42} and 1 multinational.⁴³ The majority were retrospective cohorts (14 studies),^{13,17,19,21–23,25,27,37,41} and almost all used electronic or medical records as data sources. A total of 14 studies were clinic-based,^{17–27,37,41,42} whereas 5 were community or

population-based,^{13,38–40,43} reflecting a mix of real-world practice settings. From the community-based studies, only one reported prevalence.¹³

Among the 12 studies reporting prevalence,^{13,17–27} female participants comprised 90% of the population. Regarding rheumatic disease types, 59%, 27%, and 14% had SLE, RA, and others, respectively. The mean duration of HCQ use among them was 11.25 ± 3.35 years.

Among studies that reported cumulative incidence in at-risk patients for HCQ-R,^{37,38,40,41,43} 86% were female, 60% were diagnosed with SLE, 24% were diagnosed with RA, and the remaining 16% were diagnosed with other rheumatic diseases. The average duration of HCQ exposure was 10 ± 4.33 years.

Weighted pooled estimations. *Period prevalence.* A total of 12 studies reported the prevalence of HCQ-R, including 3 prospective cohort studies^{18,20,24} and 9 retrospective cohort studies.^{13,17,19,21–23,25–27} The pooled sample consisted of 9,321 at-risk individuals, including 519 prevalent HCQ-R cases identified across seven countries. The weighted pooled period

Table 1. Characteristics of the 19 studies included in the systematic review and meta-analysis*

Author (country)	Design, data/setting, period, FU	Sample (N/n), female (%)	Prev; (Y [#]) or CumI; (at Y*)	Quality (ROB score)
Ahn 2024 (SKR) ¹⁷	Retro cohort, EMR/clinic, 2008–2023, FU ≥ 5 y	2,635/92, 94.6	Prev 3.5%; (15.4 $\pm$ 6.8)	Good (7)
Alieldin 2023 (UK) ¹⁸	Pros cohort, audit/clinic, 2018–2020, FU <5 y	566/10, 86	Prev 1.76%; (9.0 $\pm$ 5.0)	Good (7)
Almeida-Brasil 2022 (multi) ⁴³	Pros cohort (SLICC), RT- MR/community, 1999–2019, FU ≥ 5 y	1,460/11, 89	CumI <1%; (10)	Good (8)
Dabit 2022 (US) ³⁸	Retro cohort, health data (REP)/community, 2010–2019, FU ≥ 5 y	634/11, 79	CumI 0% (5); 3.9% (10)	Good (8)
Eo 2017 (SKR) ¹⁹	Retro cohort, MR/clinic, 2011–2014, FU <5 y	310/9, 92.3	Prev 2.9%; (6.0 $\pm$ 3.36)	Fair (6)
Gobbett 2021 (UK) ²⁰	Pros cohort, RT-MR/clinic, 2017–2019, FU <5 y	333/2, 85	Prev 0.6%; (N/A)	Good (7)
Jorge 2024 (US) ³⁹	Retro cohort, health data (KPNC)/community, 2004–2020, FU ≥ 5 y	4,677/125, 82.9	N/A	Good (9)
Kao 2022 (TW) ²¹	Retro cohort, MR/clinic, 2017–2020, FU <5 y	92/10, N/A	Prev 10.9%; (11.09 $\pm$ 2.44)	Fair (6)
Kim 2017 (SKR) ²²	Retro cohort, MR/clinic, 2015–2016, FU <5 y	123/17, 96	Prev 13.8%; (10.03 $\pm$ 5.08)	Fair (6)
Lee 2015 (SKR) ²³	Retro cohort, MR/clinic, 2011–2015, FU ≥ 5 y	218/9, 87.6	Prev 4.12%; (8.37 $\pm$ 3.8)	Good (7)
Lenfant 2020 (FR) ⁴²	Retro CC, MR/clinic, ^a 2007–2010, FU N/A	• Cases: 570/23, 96 • Controls: 547/ N/A, 92	N/A	Good (8)
Marshall 2021 (UK) ²⁴	Pros cohort, audit/clinic, 2017–2019, FU <5 y	869/14, 91	Prev 1.6%; (11.25 $\pm$ 5.87)	Good (7)
Melles 2014 (US) ¹³	Retro cohort (CC analysis), health data (KPNC)/community, 2009–2013, FU ≥ 5 y	2,361/177, 83.1	Prev 7.5%; (12.24 $\pm$ 5.04)	Good (9)
Melles 2023 (US) ⁴⁰	Retrospective, health data (KPNC)/Community, 2004–2020, FU ≥ 5 y	3,325/81, 82.7	CumI 0% (5), 2.5% (10), 8.6% (15)	Good (9)
Mukwikwi 2020 (CA) ²⁵	Retro cohort (CC analysis), registry and MR/clinic, 2016–2019, FU ≥ 5 y	326/18, 92	Prev 5.5%; (17.55 $\pm$ 1.62)	Good (7)
Petri 2020 (US) ⁴¹	Retro cohort, MR/clinic, 2013–2020, FU ≥ 5 y	537/23, 92	Interval risk ^b	Good (8)
Roy 2021 (IN) ²⁶	Retro cohort, MR/clinic, 2017–2019, FU N/A	984/133, 85.8	Prev 13.5%; (N/A)	Fair (6)
Spinelli 2018 (IT) ²⁷	Retro cohort, MR/clinic, 2008–2016, FU ≥ 5 y	504/28, 89.8	Prev 5.5%; (12.5 $\pm$ 6.4)	Good (7)
Tangtavorn 2016 (TH) ³⁷	Retro cohort, MR/clinic, 2004–2014, FU ≥ 5 y	61/2, N/A	CumI 3.28%; (10)	Fair (6)

* Y# is mean $\pm$ SD of HCQ exposure duration in years; at Y* is years since HCQ initiation. CA, Canada; CC, case-control; ctrl/s, controls; CumI, cumulative incidence; EMR, electronic medical records; FR, France; FU, follow-up; HCQ, hydroxychloroquine; IN, India; IT, Italy; KPNC, Kaiser Permanente Northern California; MR, medical records; Multi, multinational; n, HCQ retinopathy cases; N, total at-risk; N/A, not available; Prev, prevalence; Pros cohort, prospective cohort; REP, Rochester Epidemiology Project; Retro cohort, retrospective cohort; ROB, risk-of-bias; RT-MR, real-time MR; SKR, South Korea; SLICC, Systemic Lupus International Collaborating Clinics; TH, Thailand; TW, Taiwan; UK, United Kingdom; US, United States; Y, year.

^a Multicentral study, controls were taken from PLUS study: randomized, double-blind, placebo-controlled, multicentre trial;

^b Data used to calculate cumulative incidence at to 5, 10, and 15 years post-HCQ initiation by conducting actuarial survival table method.³² Interval risk: 1% (≤ 5), 1.8% (6–10), 3.3% (11–15), 11.5% (16–20), 8% (>20).

prevalence from 2008 to 2023 was 5.1% (95% CI 3.9–6.5), based on a random-effects model (Figure 1). Given substantial heterogeneity ($Q = 197.44$, $P < 0.0001$; $I^2 = 94.4\%$), we explored potential sources by stratifying studies according to methodologic study-level variables (Figure 1).

Subgroup analysis showed that cohort type (prospective vs retrospective) was the only methodologic variable that explained part of the heterogeneity ($P < 0.001$). To assess confounding, multivariable meta-regression showed that retrospective cohorts reported higher prevalence than prospective cohorts after adjusting for follow-up length ($\beta = 1.72$; 95% CI 1.04–2.40; $P < 0.001$) or publication year ($\beta = 1.69$; 95% CI 0.52–2.85; $P = 0.0045$).

Although higher-quality studies (≥ 7) showed a lower pooled prevalence than lower-quality (< 7) studies, the between-subgroup difference was not statistically significant and did not explain heterogeneity. Likewise, stratification by follow-up length (< 5 vs ≥ 5 years), publication year (2016 and after vs before 2016), and geographic region (Europe/North America vs Asia)

did not materially reduce heterogeneity. Because only one study was community-based, we did not stratify by setting.

Among demographic/HQ variables, univariate meta-regression indicated that only mean daily HCQ dose ($\beta = 0.53$; 95% CI 0.14–0.92; $z = 2.67$; $P = 0.007$; $R^2 = 0.57$) significantly explained between-study heterogeneity in prevalence. However, this estimation should be interpreted cautiously because only six studies reported dose metrics, precluding multivariable adjustment.

Cumulative incidence. Four cohort studies reported cumulative incidence of HCQ-R at 5 years,^{38,40} and five reported it at 10 years after HCQ initiation^{37,38,40} or data to calculate it,^{41,43} with three of them additionally providing data at 15 years^{40,41,43} (Figure 2). Weighted pooled cumulative-incidence estimates were calculated at each time point. The pooled sample comprised 6,017 long-term HCQ patients from 10 countries, among whom 128 HCQ-R cases were identified through screening.

Weighted pooled cumulative incidence of HCQ-R was 0.1% (95% CI 0–0.5) at 5 years, 2.6% (95% CI 1.6–4.1) at 10 years, and 5.6% (95% CI 3.2–9.6) at 15 years after HCQ initiation

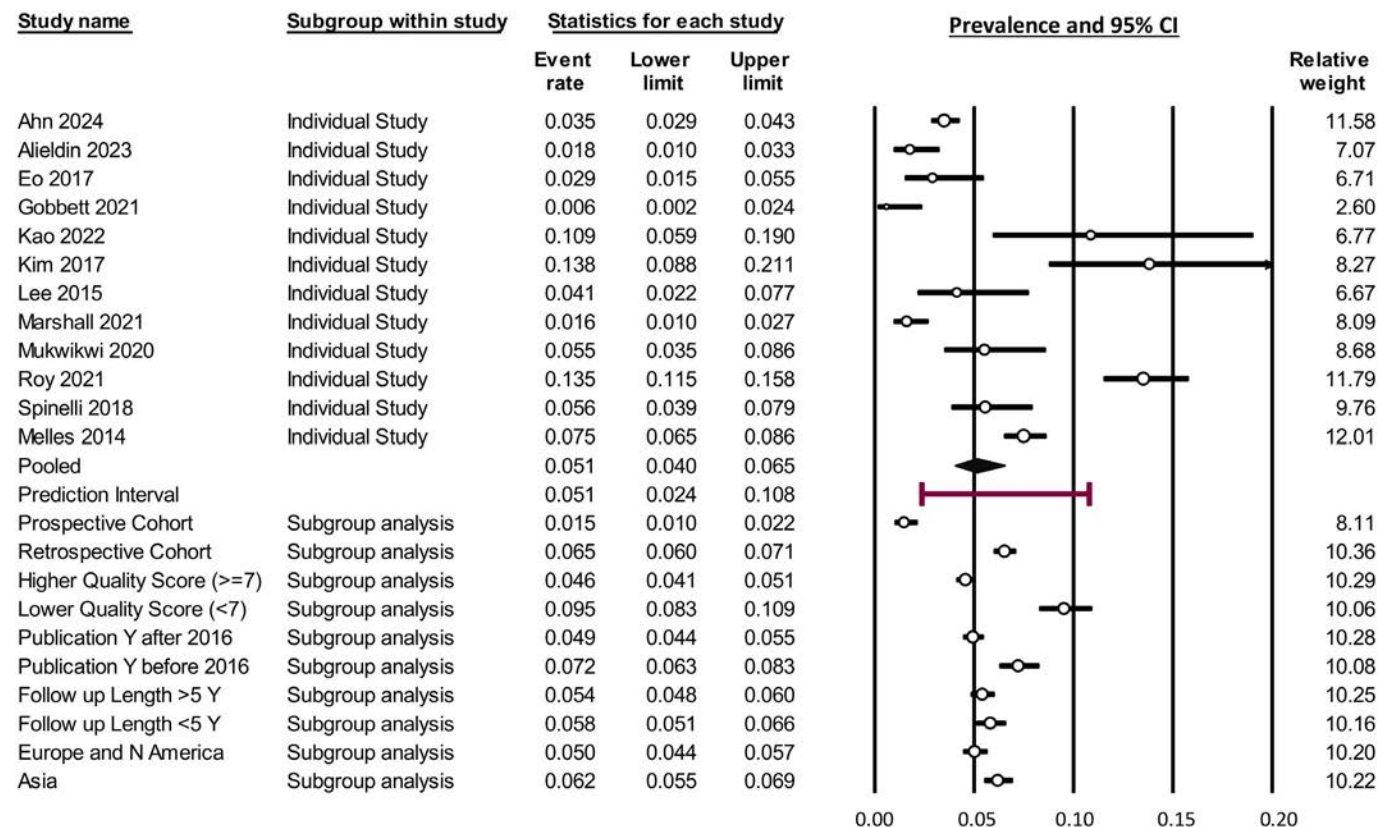


Figure 1. Forest plot showing period-prevalence point estimates of HCQ retinopathy for individual studies (open circles; circle size proportional to inverse-variance weight) and 95% CIs (lines) for individual studies, with the random-effects pooled prevalence (diamond) per 1,000 population (horizontal bracket denotes the prediction interval). Because heterogeneity was substantial, results were stratified by methodologic variables, including cohort type; prospective vs retrospective; quality score (≥ 7 vs < 7 ; HQ vs LQ); Pub Y (2016 and later vs before 2016); FU duration (≥ 5 years vs < 5 years); and geographic region (Europe and N America vs Asia). CI, confidence interval; FU, follow-up; HCQ, hydroxychloroquine; HQ, higher quality; LQ, lower quality; N America, North America; Pub Y, publication year.

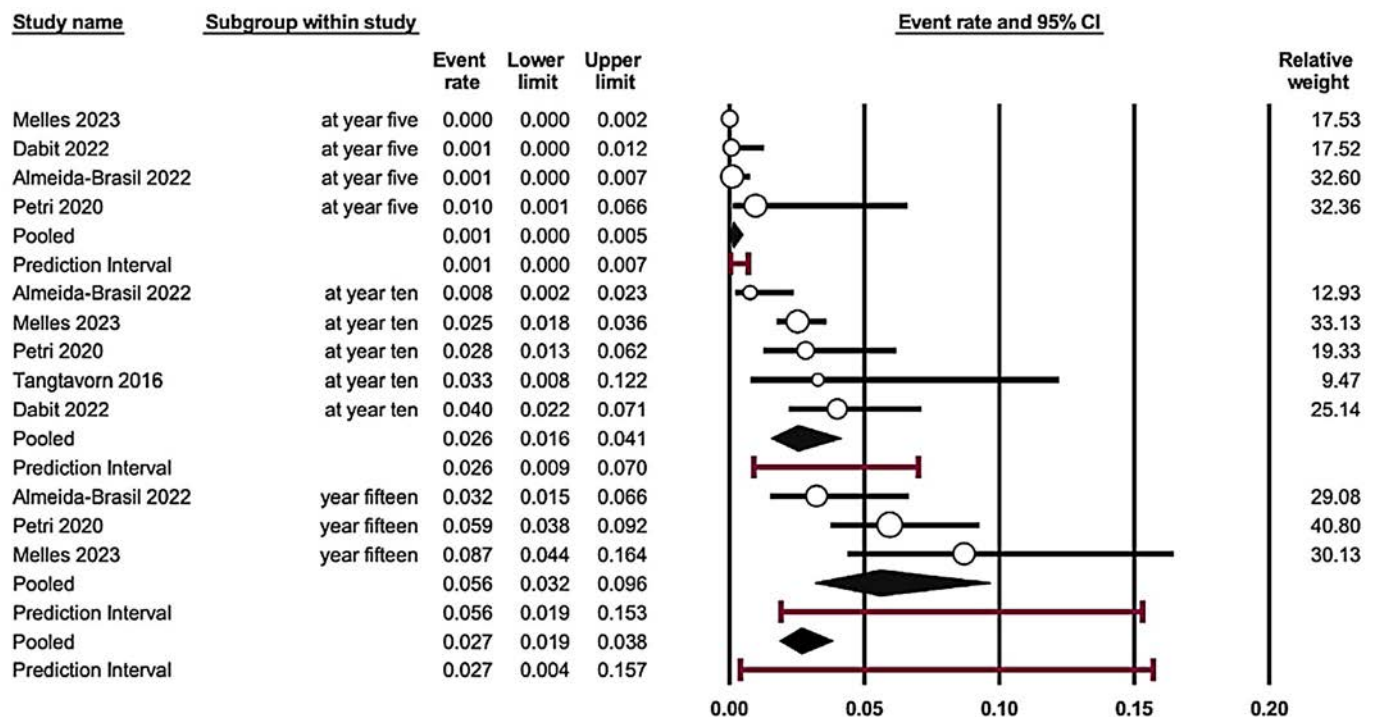


Figure 2. Forest plot of HCQ retinopathy cumulative incidence (per 1,000) at 5, 10, and 15 years after HCQ initiation. Open circles show study-specific estimates with 95% CIs (horizontal lines); circle size is proportional to inverse-variance weight. Diamonds indicate random-effects pooled estimates (5 years: 0.1%; 10 years: 2.6%; 15 years: 5.6%). Horizontal brackets denote prediction intervals. CI, confidence interval; HCQ, hydroxychloroquine. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80033/abstract>.

(Figure 2). Heterogeneity among studies within each five-year interval was nonsignificant (Q -test = 6.47 for ≤ 5 , 6.85 for 5 to 10, and 3.94 for 10 to 15 years, respectively; $P > 0.05$). However, I^2 values of 53.6%, 41.5%, and 49.2%, respectively, suggested a moderate inconsistency among them.³⁴

Cumulative incidence of HCQ-R grouped by daily dosage. Using a random-effects model, the estimated weighted pooled cumulative incidence of HCQ-R for daily dose at five years was 0% (95% CI 0–0.3) for doses ≤ 5 mg/kg actual body weight (ABW) per day compared with 0.1% (95% CI 0–0.7) for doses > 5 mg/kg (ABW) per day. At 10 years, the weighted pooled cumulative incidence was 1.1% (95% CI 0.6–2.0) vs 3.7% (95% CI 1.9–7.2), and at 15 years it was 2.7% (95% CI 0.8–8.8) vs 13.8% (95% CI 6.2–28.1), respectively.^{40,43}

Daily dose (HR). The weighted pooled HR point estimate for HCQ daily dose > 5 mg/kg (ABW) vs ≤ 5 mg/kg (ABW) was 4.32 using the random-effects model.^{38,39,43}

Other covariates (HR). Pooled HRs for cumulative HCQ dose, CKD, sex, and race/ethnicity are summarized in Table 2. Data on older age at HCQ initiation were inconsistent across the two available studies,^{39,43} preventing pooled HR estimation (Table 3). Evidence on the risk of HCQ-R for concurrent use of tamoxifen with HCQ was limited to a single study.³⁹

Duration of HCQ use (OR). Two studies provided sufficient data to estimate the association between HCQ duration of use

and HCQ-R prevalence. Using a random-effects model, the pooled OR per five-year increase in HCQ use was 2.83 (95% CI 1.26–6.35) (Table 3).^{13,22}

Other covariates (OR). Three studies provided information to estimate the weighted pooled OR for the risk of HCQ-R associated with chronic kidney disease (CKD). Using a random-effects model, the weighted pooled OR of HCQ-R was 1.87 (95% CI,

Table 2. Weighted pooled estimation for risk factors of HCQ retinopathy*

Risk factor	Weighted Pooled HR (95% CI)	Studies (references)
HCQ daily dose (> 5 mg/kg [#] /day) (reference: ≤ 5 mg/kg [ABW]/day)	4.32 (2.80–6.65)	Dabit et al. ³⁸ Jorge et al. ³⁹ Almeida-Brasil et al. ⁴³
Cumulative HCQ dose (per 100-gr increment)	1.63 (1.46–1.84)	Dabit et al. ³⁸ and Jorge et al. ³⁹
CKD (reference: no CKD)	1.94 (1.27–2.96)	Dabit et al. ³⁸ and Jorge et al. ³⁹
Female sex (reference: male)	3.78 (1.90–7.48)	Dabit et al. ³⁸ and Jorge et al. ³⁹
Race/ethnicity: Asian (reference: White)	1.67 (1.07–2.62)	Jorge et al. ³⁹ and Almeida-Brasil et al. ⁴³

* ABW, actual body weight; CI, confidence interval; CKD, chronic kidney disease; HCQ, hydroxychloroquine; HR, hazard ratio.

Table 3. Summary of significant findings on HCQ retinopathy associated risk factors*

First author and year	Study type	Statistics	Risk factor(s) significantly associated with HCQ-R risk: point estimates (95% CI)
Almeida-Brasil et al, 2022 ⁴³	Prospective inception cohort	Unadjusted HR	• Age at SLE diagnosis: 1.05 (1.01–1.09); • Asian (reference: White): 0.94 (0.19–4.65)
Dabit et al, 2022 ³⁸	Retrospective cohort	Unadjusted HR	• Cumulative dose per 100 g: 1.48 (1.03–2.14) • Daily dose >5 mg/kg (ABW) (vs ≤5 mg/kg): 3.59 (1.09–11.84)
Jorge et al, 2024 ³⁹	Retrospective cohort	Adjusted HR	• Older age (reference: <45 y): ◦ 45–54: 2.48 (95% CI 1.28–4.78) ◦ 55–64: 3.82 (95% CI 2.05–7.14) ◦ >65: 5.68 (95% CI 2.99–10.79) • Daily dose 5–6 mg/kg (ABW) (vs ≤5 mg/kg): 3.23 (1.90–5.50) • Daily dose >6 mg/kg (ABW) (vs ≤5 mg/kg): 5.30 (3.46–8.10) • Cumulative dose per 100 gr: 1.64 (1.44–1.87) • Female sex: 3.83 (1.86–7.89) • CKD: 1.95 (1.25–3.04) • Tamoxifen use: 3.43 (1.08–10.89) • Asian (reference: White): 1.76 (1.10–2.81)
Kao et al, 2022 ²¹	Retrospective cohort	Unadjusted OR	• Body weight: 0.88 (0.78–0.97)
Kim et al, 2017 ²²	Retrospective cohort	Adjusted OR	• Duration of use (in 5-year increments): 4.71 (2.18–10.15) • Daily dose (in 100-mg increment): 3.34 (1.03–10.80) • CKD: 8.56 (1.15–64.00)
Lenfant et al, 2020 ⁴²	Case-control	Adjusted OR	• Duration of use (per year): 1.13 (1.07–1.18) • Higher cumulative dose (per g): 1.001 (1.001–1.001) • Creatinine clearance: 0.95 (0.93–0.97) • Geographic origin: Sub-Saharan Africa (reference: Europe): 3.2 (1.37–7.77)
Melles et al, 2014 ¹³	Retrospective cohort (case-control analysis)	Adjusted OR	• Daily dose in 100-mg increments: 5.11 (3.83–6.83) • Duration of use in 5-year increments: 2.03 (1.72–2.40) • Tamoxifen use: 4.59 (2.05–10.27) • CKD: 2.08 (1.44–3.01) • Weight: 0.96 (0.95–0.97)

* ABW, actual body weight; CI, confidence interval; CKD, chronic kidney disease; g, gram; HCQ, hydroxychloroquine; HR, hazard ratio; kg, kilo-gram; mg, milligram; OR, odds ratio; SLE, systemic lupus erythematosus.

0.91–3.85) in those with CKD compared to those without CKD.^{13,22,42} Descriptive statistics regarding risk factors for HCQ-R from single studies are shown in Table 3.^{13,21,22,38,39,42,43}

Sensitivity analysis. Leave-one-out sensitivity analyses showed that pooled prevalence estimates remained stable when omitting each study in turn (Supplementary Figure 2). Pooled cumulative-incidence estimates were similarly robust across iterations (Supplementary Figure 3).

Publication bias. Separate funnel plots were generated for prevalence and cumulative incidence (Figure 3A–B). The prevalence funnel plot showed mild asymmetry with greater dispersion among smaller studies, but Egger's test was not significant ($P > 0.05$). The cumulative-incidence funnel plot was largely symmetric, and Egger's test was also nonsignificant ($P > 0.05$), suggesting limited evidence of small-study effects or publication bias.

Risk-of-bias (quality) assessment. We assessed risk of bias with the Newcastle–Ottawa Scale; summary scores are presented in Table 1, with item-level details in Supplementary Material 3.

Certainty of evidence for outcomes. Certainty of evidence (GRADE) was low for the 5- and 10-year cumulative-incidence estimates and for the effects of dose and CKD. It was very low

for period prevalence, 15-year cumulative incidence, sex, and ethnicity. Details are summarized in Supplementary Table 1.

DISCUSSION

This is the first meta-analysis to estimate the pooled prevalence, cumulative incidence, and risk factors of HCQ-R focusing on studies that used SD-OCT as an objective screening tool to diagnose HCQ-R. Across studies from 2008 to 2023, pooled prevalence was 5.1%. Pooled cumulative incidence (overall dosing) was 0.1% at 5 years, 2.6% at 10 years, and 5.6% at 15 years after HCQ initiation. Risk was higher with daily dose >5 vs ≤5 mg/kg/day (ABW) (~4-fold), CKD (~2-fold), and per 100-g higher cumulative dose (~1.6-fold), and was also higher in females (~4-fold) and Asian versus White patients (~1.7-fold).

Our pooled prevalence of 5.1% (2008–2023) was similar in magnitude to the pooled 15-year cumulative incidence of ~5.5%. This is broadly consistent with epidemiologic expectations for a chronic, nonfatal condition with long duration, in which cases accumulate over time and prevalence can approach long-term cumulative incidence.³¹ Prevalence varied widely across studies (ie, 0.6% to 13.8%).^{20,22} Cohort type appeared to

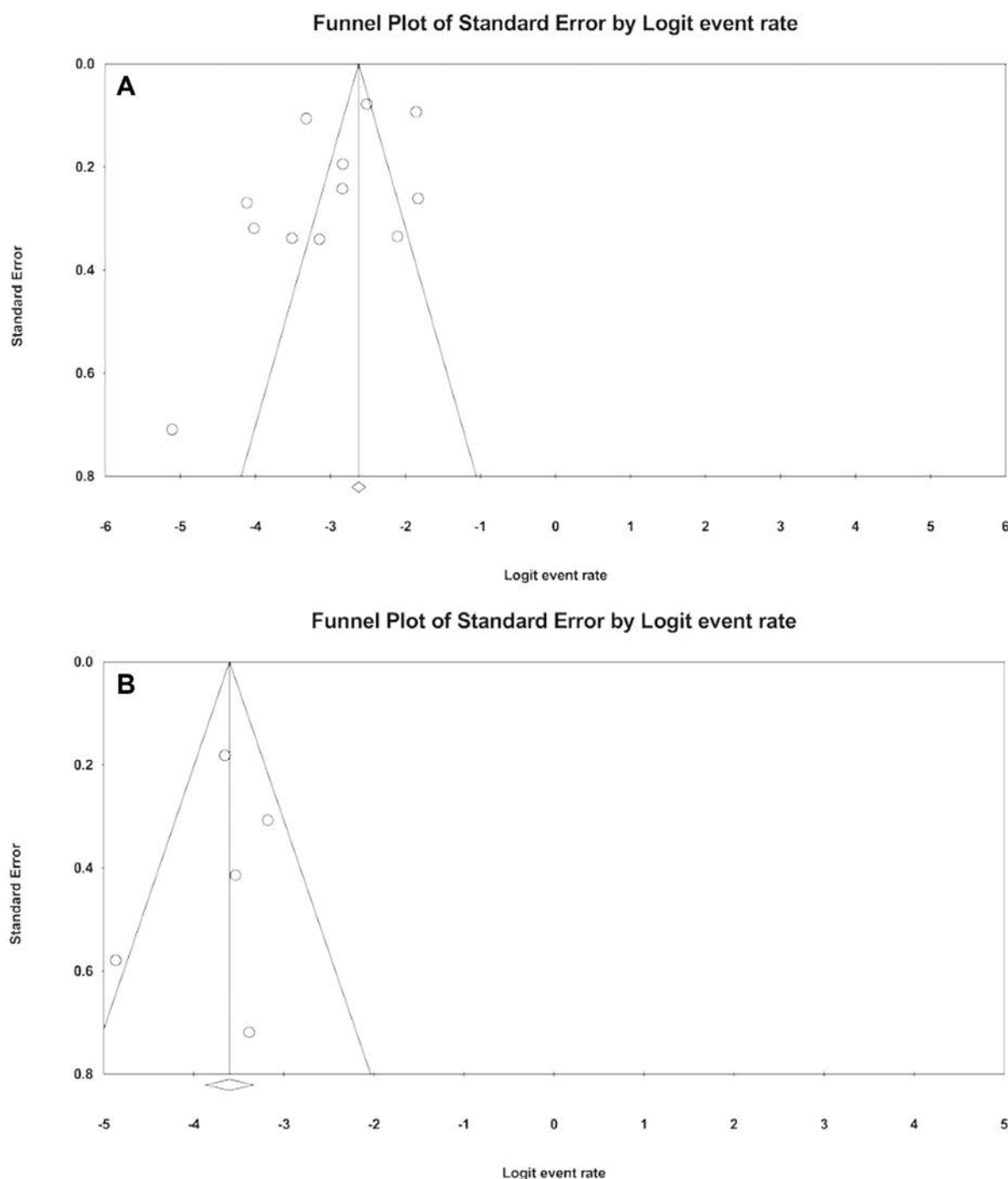


Figure 3. (A) Funnel plot of studies reporting HCQ-R period prevalence shows mild asymmetry to the left of the vertical line representing the logit of the weighted pooled prevalence; studies toward the bottom have larger standard errors and smaller sample sizes (Egger's regression test $P > 0.05$). (B) Funnel plot for cumulative incidence is largely symmetrical (Egger's regression test $P > 0.05$). HCQ-R, hydroxychloroquine retinopathy.

contribute to heterogeneity, with higher prevalence in retrospective studies, a difference that persisted after accounting for follow-up length and publication year, suggesting design-related ascertainment differences may partly explain variability. These differences may partly reflect variation in case ascertainment and

data completeness across study designs.⁴⁴ Definite HCQ-R requires two abnormal tests (SD-OCT and visual field), whereas probable HCQ-R is based on one abnormal test.¹⁵ Retrospective cohorts may misclassify probable as definite because of limited confirmatory testing and may undercount unaffected individuals

because of incomplete documentation. Additionally, unmeasured differences in screening frequency and SD-OCT interpretation thresholds for HCQ-R diagnosis across cohorts may also contribute to heterogeneity in the observed risk (prevalence or cumulative incidence).⁴⁵

Our pooled 10-year cumulative incidence estimate was similar to that reported in the large community-based cohort by Melles et al.⁴⁰ Differences at 15 years may partly reflect fewer patients remaining at risk in later follow-up in the single cohort, whereas our estimate is pooled across studies.

Similarly, pooled dose-stratified cumulative incidence was consistent with large cohorts.^{13,40} Among patients receiving ≤ 5 mg/kg/day (ABW), HCQ-R was rare in the first five years and remained low (1% at 10 years; 3% at 15 years), whereas >5 mg/kg/day was associated with around a four-fold higher risk (4% at 10 years; 14% at 15 years). These findings highlight the importance of accurate weight-based dosing, particularly in underweight patients given fixed 200-mg tablets. Therefore, weekly dose calculations with day-to-day tablet adjustments can help maintain recommended limits. In the United States, 100-mg HCQ tablets became available in 2022, allowing more precise weight-based dosing.⁴⁶

For cumulative incidence, Q-tests were nonsignificant, but I^2 values around 50% indicate moderate inconsistency across time points.³⁴ Most contributing studies were retrospective cohorts,^{37,38,40,41} and only one accounted for the competing risk of death.³⁸ The remaining study was a prospective multinational Systemic Lupus International Collaborating Clinics (SLICC) inception cohort⁴³ differing in design, population diversity, and potentially data quality. These clinical and methodologic differences likely contributed to the I^2 -based inconsistency despite nonsignificant Q-tests.

Two community-based studies^{38,39} suggested a ~ 1.6 -fold higher hazard of HCQ-R per 100-g increase in cumulative dose. However, high daily dosing over shorter periods may still pose substantial risk despite modest cumulative exposure; HCQ-R has been reported in graft-versus-host disease patients receiving very high mg/kg doses within months to a few years.⁴⁷ This information underscores considering daily dose and duration alongside cumulative dose in risk assessment.

Pooled estimates suggest approximately two-fold higher HCQ-R risk in patients with CKD,^{48,49} highlighting the importance of monitoring renal function in those receiving HCQ. For patients with diagnosed CKD, clinicians should consider adjusted weight-based dosing and initiating screening earlier than five years after HCQ start, with consistent annual screening thereafter. This aligns with the AAO's 2016 recommendations and the recent 2026 revised recommendations for higher-risk patients.¹⁵

Our pooled estimate suggested that female sex is associated with a higher risk of HCQ-R (~ 4 -fold). Because this evidence is limited to two studies with unadjusted³⁸ versus adjusted³⁹ analysis, we have to consider that this association may also reflect

residual confounding and ascertainment bias rather than intrinsic susceptibility. Biologic sex differences in body size, composition, and fat/lean mass proportions could bias exposure estimates. Fixed tablet dosing can overexpose underweight patients when weight is unmeasured (compromising mg/kg dosing), whereas dosing based on actual body weight in overweight patients may overestimate exposure.⁵⁰ Other potential sex-related contributors include differences in drug metabolism (hormone-influenced),⁵¹ ocular vascular/structural parameters,^{52–54} and differences in medication adherence or screening uptake⁵⁵; these mechanisms remain plausible but unproven.

Regarding race/ethnicity, studies reported mixed associations for Asian versus White patients,^{39,43} whereas our pooled estimate suggested higher risk in patients who were Asian and receiving HCQ long-term. Differential ascertainment may contribute because Asian patients more often have pericentral HCQ-R that is better detected with wide-field macular SD-OCT (12 $\times$ 12 mm) or 24-2/30-2 VF testing; thus, guideline-concordant screening may yield higher observed hazards, whereas underuse may underestimate risk. Biologic differences (eg, retinal melanin content, binding, or structural differences) remain plausible but unproven.⁵⁶

Tamoxifen, although not co-prescribed with HCQ, has been associated with retinopathy (tamoxifen retinopathy), particularly with higher doses and long-term use.⁵⁷ Two large cohorts reported higher HCQ-R risk with concurrent tamoxifen and HCQ, supporting guideline recommendations to consider tamoxifen as a co-risk factor.^{13,39} However, whether tamoxifen or other endocrine therapies (eg, aromatase inhibitors) modify HCQ retinal toxicity remains unclear.⁵⁸ Future studies should capture HCQ and endocrine co-therapies, test effect modification across HCQ exposure metrics, and use guideline-concordant multimodal outcome ascertainment.

Our study has several limitations. Given substantial heterogeneity in prevalence, we could not conduct multivariable meta-regression for key study-level factors because too few studies reported the necessary data. For example, mean daily HCQ dose partly explained heterogeneity in univariate analysis, but dosing data were available in only six studies. As a result, potential confounding among study variables could not be evaluated, and the sources of heterogeneity could not be fully elucidated.

Also, this meta-analysis evaluated dose using the most commonly reported threshold (>5 vs ≤ 5 mg/kg/day) and therefore could not examine a graded dose-response across finer weight-based categories (eg, <4 , 4–5, 5–6, ≥ 6 mg/kg/day) as suggested in large cohort studies.^{13,40} We also could not assess HCQ blood levels as a predictor because these data were rarely reported. Given limited reporting of alternative dose cut points and HCQ blood levels despite their importance as potential predictors, future studies are needed to evaluate graded dose-response relationships and HCQ blood levels in relation to HCQ-R risk.

Unmeasured heterogeneity, including variation in screening coverage and HCQ adherence, could not be evaluated because of limited reporting.^{59,60} For example, screening uptake among those receiving long-term HCQ in England was reported to be only 1.9% to 3.8%, which could underestimate risk.⁶¹ Reported nonadherence to HCQ in SLE ranges widely (3%–75%) depending on assessment method, which may further bias estimates toward under-ascertainment.⁶²

In addition, evidence for age at HCQ initiation was limited or inconsistent across studies, with lack of covariate adjustment in most regression analyses. Methodologic heterogeneity further complicates interpretation.

On the other hand, notable strengths of this study include the large, pooled sample size across multiple studies, enhancing the statistical power and generalizability of the findings. Furthermore, the absence of significant publication bias and the stability of results in sensitivity analyses support the robustness of the pooled estimates.

GRADE assessments were largely low to very low, reflecting that the evidence was from observational studies. Certainty was lowest for period prevalence and 15-year cumulative incidence because of the heterogeneity and wide CI, respectively. Estimates for female sex and race/ethnicity were very low because of sparse data and wide CIs. Associations with 5- and 10-year cumulative incidence, dose, and CKD were rated low certainty.

In summary, this systematic review and meta-analysis estimated a pooled HCQ-R prevalence of 5.1%, which is comparable with the 15-year pooled cumulative incidence (5.6%). Risk increased over time (0.1% at 5 years, 2.6% at 10 years, 5.6% at 15 years) and was strongly dose-dependent: >5 mg/kg/day (ABW) was associated with almost four-fold higher hazard and 15-year incidence of 14% versus 3% at ≤5 mg/kg/day. CKD was a consistent risk factor, with higher risk also observed for female sex and Asian ethnicity among those receiving HCQ long-term. These findings provide a robust approximation of long-term risk and underscore the importance of appropriate dosing and adherence to established screening guidelines.

ACKNOWLEDGMENTS

We thank Dean Giustini, an experienced biomedical librarian at the University of British Columbia, who assisted authors through our systematic literature search. We thank Dr Mahyar Etminan, PharmD, MSc, an experienced pharmacoepidemiologist, for his constructive comments and guidance throughout the study.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Avina-Zubieta confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration

by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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High Health Care Utilization Preceding Diagnosis With Juvenile Idiopathic Arthritis

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Objective. Although early diagnosis improves long-term outcomes, patients with juvenile idiopathic arthritis (JIA) often experience prolonged, circuitous paths to diagnosis. To inform diagnostic improvement, we sought to characterize health care utilization in the year preceding diagnosis.

Methods. We identified 10,021 patients with an incident diagnosis of JIA and 20,042 age- and sex-matched healthy controls in the Merative MarketScan administrative datasets (2014–2022). Using negative binomial or hurdle models, we calculated incidence rate ratios (IRRs) comparing outpatient, inpatient, and emergency department or urgent care (ED/UC) utilization between patients with JIA and controls.

Results. In the year before diagnosis, patients with JIA had significantly increased health care utilization compared to controls (IRR 2.55 [95% confidence interval (CI) 2.49–2.62], $P < 0.001$). Accounting for sex, age, and insurance, utilization was increased across care settings: outpatient (IRR 2.56 [95% CI 2.49–2.62], $P < 0.001$), inpatient (IRR 2.00 [95% CI 1.48–2.71], $P < 0.001$), and ED/UC encounters (IRR 1.76 [95% CI 1.67–1.86], $P < 0.001$). The most common visits by patients with JIA preceding diagnosis were to a general practitioner (91.8%), ED/UC (47.0%), and orthopedist (22.9%). Health care utilization increased as the index date approached. In patients insured by Medicaid, ED/UC care was more frequent (odds ratio 2.05 [95% CI 1.89–2.23]) and orthopedic care less frequent (odds ratio 0.27 [95% CI 0.24–0.34]) than in patients with commercial insurance.

Conclusion. In the year before diagnosis, children with JIA have significantly higher health care utilization compared to healthy peers. There are differences in the patterns of utilization in patients with Medicaid versus commercial insurance. There may be opportunities for earlier identification of JIA in primary care, orthopedics, and ED/UC.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) can cause destructive joint damage, blindness from uveitis, and long-lasting pain and disability.¹ However, there is a growing therapeutic arsenal for managing JIA, including numerous safe medications that can halt disease progression.² These medications are most effective when started early in the disease course,³ and early diagnosis and therapy have been shown to improve long-term outcomes and increase the likelihood of preserved remission.^{4–7} As such, timely recognition of the condition and timely initiation of rheumatologic care are crucial to enabling optimal outcomes for patients with JIA.

Despite this diagnostic imperative, in practice, it is common to diagnose JIA in a patient who already has irreversible complications of longstanding disease, such as ocular scarring, leg length discrepancy, erosive joint damage, micrognathia, and joint contractures.⁸ Characterizing the health care utilization patterns that precede diagnosis is a critical step in identifying opportunities for earlier recognition in the diagnostic process and, ultimately, designing interventions to improve timely diagnosis. The existing literature is largely derived from international cohorts and utilizes retrospective chart review or prospective single-center or multi-center surveys to capture health care utilization patterns.^{9–16} These data are limited in their generalizability to US health care and its ability to account for care delivered across health care

Dr Costello's work was supported by the Childhood Arthritis and Rheumatology Research/Arthritis Foundation and AcademyHealth/the Betty and Gordon Moore Foundation. Dr Rasooly's work was supported by the Agency for Healthcare Research and Quality (grant K08-HS-028682). Dr Weiss's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K24-AR-078950); the Patient-Centered Outcomes Research Institute; and the Spondylitis Association of America.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80037>).

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80037>.

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Submitted for publication November 12, 2025; accepted in revised form March 3, 2026.

SIGNIFICANCE & INNOVATIONS

- Patients with juvenile idiopathic arthritis (JIA) have high health care utilization for at least a year preceding diagnosis, suggesting missed opportunities for an earlier diagnosis.
- Patients with JIA most often seek care from primary care physicians, emergency departments or urgent care centers, and orthopedic providers preceding diagnosis.
- There are differential health care utilization patterns between patients with Medicaid and those with commercial insurance, with increased utilization of emergency departments or urgent care centers and lower utilization of orthopedic care among patients with Medicaid.

systems and settings. Thus, our study aim was to describe and quantify the health care utilization of children with JIA from the United States in the year preceding diagnosis, compared to a population of healthy controls, in a large, population-based administrative dataset that includes patients with both commercial insurance and Medicaid.

MATERIALS AND METHODS

Study design. Retrospective cohort study comparing the health care utilization of children with an incident diagnosis of JIA to age- and sex-matched health controls.

Ethics. This study was deemed exempt from review by the Children's Hospital of Philadelphia Institutional Review Board (IRB 24-022056).

Data source. This study utilized deidentified data from the Merative MarketScan commercial and Medicaid databases from 2014 to 2022.¹⁷ The Merative MarketScan databases contain de-identified patient-level data, including diagnoses (*International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes), inpatient and outpatient encounters, and pharmacy data (outpatient national drug codes, days' supply, strength, and route of administration). The commercial and Medicaid databases are distinct patient samples, with the commercial database containing data for dependents covered by private health insurance plans throughout the United States and the Medicaid database presenting data for Medicaid enrollees from select states. Certain variables differ in availability, with race and ethnicity recorded only in the Medicaid dataset and geographic region recorded only in the commercial dataset.

Participants. We identified patients ages 1 to 18 years with an incident diagnosis of JIA. Patients diagnosed between 16 and

18 years old were included in the study per the provisional Pediatric Rheumatology International Trials Organization criteria for JIA.¹⁸ The diagnosis of JIA was defined according to previously published algorithms^{19–22} with the one or more of the following criteria:

1. Two or more JIA codes (Supplemental Tables 1 and 2) separated by ≥ 14 days and within 183 days.
2. One or more JIA codes by any provider plus one or more of the following:
 - a. Medication code for intra-articular glucocorticoids injection only (Supplementary Table 3) in the 183 days following the JIA code,
 - b. Intra-articular injection procedure code (Supplementary Table 3) in the 183 days following the JIA code, and
 - c. Claim for a disease-modifying antirheumatic drug or biologic in the 183 days following the JIA code (Supplementary Table 4).
3. One or more codes indicating JIA by a rheumatologist.

To ensure cases represented incident diagnoses only, patients were excluded if they had less than one year of continuous enrollment before the index date or if they had a claim for a JIA diagnostic code during that period. The index date for patients was defined as the date of the first JIA code assignment. Age- and sex-matched controls were identified at a 2:1 ratio within each insurance type (commercial or Medicaid). Healthy controls were excluded if (1) they did not have 12 months of continuous enrollment before their inclusion or (2) they had a diagnosis any of the complex chronic condition (CCCs) at cohort inclusion.^{23,24} The index date for healthy controls was defined as the date of an outpatient visit occurring within two months of the index date of the matched JIA patient.

Outcomes. The primary outcome was health care utilization as count data, which was defined as any inpatient admission, emergency department or urgent care (ED/UC) visit, or outpatient claim for a billing visit with any physician or advanced practice provider. Secondary outcomes included provider specialty type (generalist, orthopedist, rheumatologist, ophthalmologist, dermatologist, or other medical subspecialist) with specific analysis of orthopedic and generalist utilization for outpatient visits. Visits with a general practitioner were defined as any visit with a provider code from a pediatrician, family medicine provider, internal medicine provider, or general acute care provider as well as codes from medical doctors, nurse practitioners, and physicians' assistants not elsewhere classified. ED/UC visits were defined as visits with a provider code from an emergency medicine provider or site code consistent with a care delivery in an ED/UC. Orthopedic visits were defined as any visit with a provider code from an orthopedist, a pediatric orthopedist, or a sports medicine physician.

Covariates. Potential predictors for health care utilization included sex (male or female), age (continuous), and insurance type (commercial vs Medicaid). The geographic region was only available for those in the commercial insurance dataset and is categorized based on the patient's state of residence into the following categories: Northeast, Midwest, South, and West. Race and ethnicity (Black, Hispanic, White, other, or missing) were available for patients in the Medicaid database. Because these variables were not consistently available across groups, they were excluded from the primary adjusted models (which included patients from both the commercial and the Medicaid databases). There was no missingness of any of the covariates included in the primary adjusted models. All demographic factors were defined at time of the index or diagnosis date.

Statistical analysis. All analyses were performed using R Studio version 12.0 (Posit). Descriptive statistics were used to summarize cohort characteristics and specialty utilization. Medians and interquartile ranges (IQRs) were calculated for total health care, outpatient, inpatient, and ED/UC visits, with limited medians also computed for patients with one or more visits to account for excess zeros.

Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were calculated to compare health care utilization between patients with JIA and healthy controls in the 12 months before the index date. For outcomes without zero inflation, Poisson and negative binomial (NB) models were considered, whereas for outcomes with excess zeros, hurdle models and zero-inflated NB models were considered.²⁵ Models were compared with Akaike's information criterion, Bayesian information criterion, and Vuong tests, and the best-fitting, most parsimonious approach was selected. Ultimately, NB modeling was used for outcomes without zero inflation including total health care, outpatient, and generalist utilization, whereas hurdle modeling was used for outcomes with zero inflation including ED/UC, inpatient, and orthopedic utilization. Two types of modeling were used because outcomes with substantial zero inflation may reflect two distinct processes: the likelihood of any utilization of that type and the degree of utilization among those who access that type of care. For these outcomes, modeling that does not account for zero inflation would be challenging to interpret. Hurdle modeling is a two-step process in which logistic regression is used to model a binary outcome of utilization versus no utilization (the decision to seek care), and, for those with some utilization, an NB regression is then performed to model visit counts among utilizers (degree of utilization). Odds ratios (ORs) were reported for the binary component, and IRRs for the count component in a hurdle model.²⁵ All models were adjusted for sex, age at diagnosis, and insurance type. To better understand how utilization differed by insurance type, we conducted a subgroup analysis including only patients with JIA to compare the utilization between patients in the commercial versus Medicaid databases.

Sensitivity analyses. To ensure utilization among patients with JIA was not driven up by preexisting chronic conditions, patients with any of the CCCs^{23,24} were excluded from the analysis. The analyses were repeated using this adjusted cohort. Additionally, we examined the impact of race and ethnicity in the Medicaid cohort and geographic region in the commercial cohort. Finally, because multiple model types were used, IRR estimates were compared across model specifications to assess robustness. Because the study period included the COVID-19 pandemic, an additional analysis was performed replicating Figure 1 for patients diagnosed in the prepandemic period (2014–2019), the pandemic period (2020–2021), and the postpandemic period (2022) (Supplemental Figure 1).

RESULTS

Cohort characteristics. We identified 10,021 children with an incident diagnosis of JIA and 20,042 age- and sex-matched healthy controls. The cohort was 35.4% male with a median age at index date of 13 years (IQR 8–15). A majority of the population (59%) was commercially insured. Among patients with JIA, 93.7% had no CCCs before JIA diagnosis (Table 1).

Overall health care utilization. Among the 10,021 children with JIA, there were 134,650 total visits composed of 118,103 outpatient provider visits, 15,384 ED/UC visits, and 1,163 inpatient hospitalizations in the year before diagnosis. Patients with JIA had a median of 10 total health care encounters (IQR 6–18), whereas controls had a median of four visits (IQR 2–8) (Table 2). Increased utilization was most pronounced in the outpatient setting in which patients with JIA had a median of nine visits (IQR 5–16) for patients with JIA compared with four visits (IQR 2–7) for healthy controls. Only 376 patients with JIA (3.8%) had no utilization preceding diagnosis, whereas 3,695 controls (18.4%) had no utilization. In the year preceding the index date, total health care utilization was significantly higher for patients with JIA versus healthy controls (IRR 2.55 [95% CI 2.49–2.62], $P < 0.001$), with increased utilization consistent across all settings after accounting for sex, age, and insurance type: outpatient (IRR 2.56 [95% CI 2.49–2.62], $P < 0.001$), inpatient (IRR 2.00 [95% CI 1.48–2.71], $P < 0.001$), and ED/UC encounters (IRR 1.76 [95% CI 1.67–1.86], $P < 0.001$) (Table 2). For zero-inflated data, ORs of utilization versus no utilization were also calculated. Patients with JIA had significantly higher odds of inpatient utilization (OR 4.16 [95% CI 3.56–4.87]) and ED utilization (OR 2.36 [95% CI 2.24–2.49]) than the healthy controls. There was no statistically significant difference in total utilization among patients with JIA by age, insurance type, or sex. Interaction terms between case status and insurance status were added to the model to assess for potential effect modification. However, they were not statistically significant, and therefore, they were not included in the final parsimonious multivariable models.

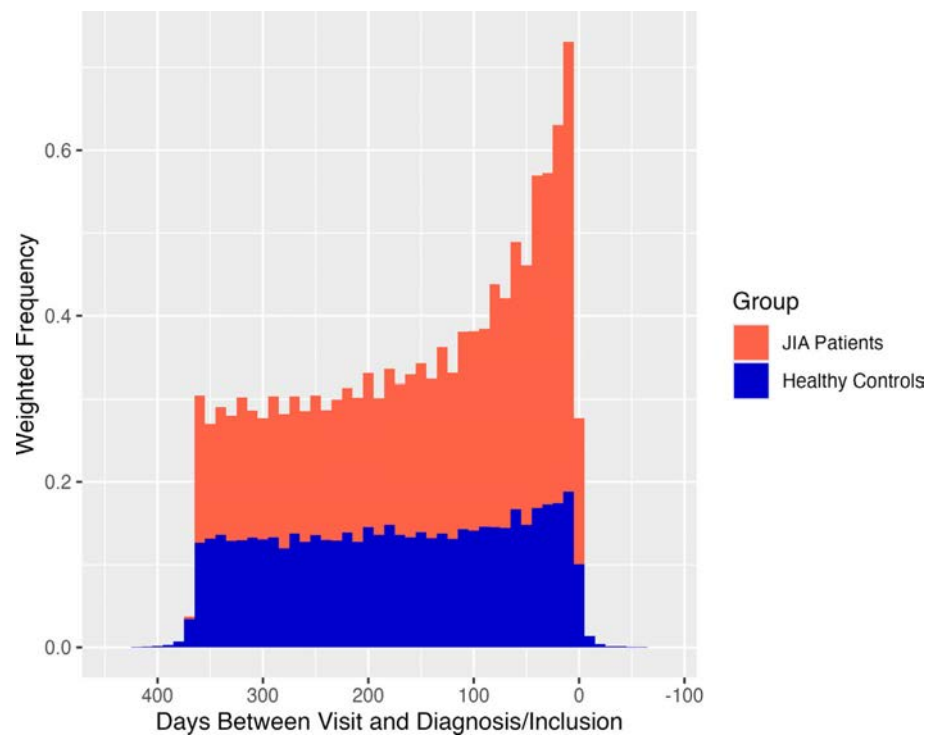


Figure 1. Time between visits and diagnosis/inclusion. This figure demonstrates the frequency of health care utilization in the outpatient, inpatient, or emergency department settings as patients approach the date of diagnosis (day 0) for patients with JIA or inclusion in the cohort for healthy controls. The visit frequencies are weighted to account for the number of patients versus controls. JIA, juvenile idiopathic arthritis.

Table 1. Cohort demographics*

	Patients with JIA (n = 10,021)	Healthy controls (n = 20,042)
Demographics		
Male, n (%)	3,552 (35.4)	7,104 (35.4)
Age at diagnosis, median (IQR)	13 (8–15)	13 (8–15)
Insurance type, n (%)		
Commercial	5,914 (59.0)	11,828 (59.0)
Medicaid	4,107 (41.0)	8,214 (41.0)
Geographic region of residence, ^a n (%)		
Northeast	1,070 (18.1)	1,213 (10.3)
North central	1,380 (23.3)	2,676 (22.6)
South	2,275 (38.5)	7,093 (59.9)
West	1,131 (19.1)	830 (7.0)
Missing or unknown	58 (1.0)	16 (0.1)
Race, ^b n (%)		
Black	792 (19.3)	2,714 (33.0)
Hispanic	317 (7.7)	756 (9.2)
White	2,431 (59.2)	3,942 (48.0)
Other	159 (3.9)	431 (5.3)
Missing	408 (9.9)	379 (4.6)
Number of complex chronic conditions, n (%)		
0	9,392 (93.7)	20,042 (100)
1	580 (5.8)	0 (0)
2+	49 (0.4)	0 (0)

* *International Classification of Diseases, Ninth Revision* (696.0, 714.x, 720.0, 720.81, 720.89, and 720.9) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (M05.00, M06.xx, M08.xx, M45.x, M46.0x, M46.8x, M46.9x, and L40.5x) codes were used to determine cohort inclusion. IQR, interquartile range; JIA, juvenile idiopathic arthritis.

^a Region only available for patients with commercial insurance.

^b Race is only available for patients with Medicaid insurance.

Table 2. Health care utilization 12 months before index date*

	JIA cohort (n = 10,021), median ^a (IQR) [range]	Healthy controls (n = 20,042), median ^a (IQR) [range]	Odds ratio ^b (95% CI)	Incidence rate ratio ^c (95% CI)
Total health care utilization	10 (6–18) [0–376]	4 (2–8) [0–365]	–	2.55 (2.49–2.62)
Outpatient visits	9 (5–16) [0–376]	4 (2–7) [0–365]	–	2.56 (2.49–2.63)
ED/urgent care visits	2 (1–4) [0–69]	2 (1–3) [0–26]	2.36 (2.24–2.49)	1.76 (1.67–1.86)
Inpatient hospitalizations	1 (1–2) [0–18]	1 (1–1) [0–8]	4.16 (3.68–4.70)	2.00

* Visit numbers presented as median, IQR, and total range. Negative binomial models were utilized for total and outpatient health care utilization, and hurdle models were utilized for ED and inpatient utilization. CI, confidence interval; ED, emergency department; IQR, interquartile range; JIA, juvenile idiopathic arthritis.

^a Median and IQR calculated for only those patients with some health care utilization.

^b Odds ratios calculated for utilization vs no utilization in zero-inflated outcomes.

^c Incidence rate ratios were adjusted for age, sex, and insurance type.

Timing of utilization. Elevated levels of health care utilization among patients with JIA were observed from 12 months before JIA diagnosis, with an escalation in utilization starting around three months before diagnosis (Figure 1). This figure was replicated for the prepandemic, during-pandemic, and postpandemic period (Supplementary Figure 1), which demonstrated that the utilization differences between patients with JIA and controls persisted despite the pandemic. All types of health care utilization became more frequent as the JIA diagnosis approached. Health care utilization remained stable over time in the healthy control population.

Utilization by insurance type in patients with JIA.

Although overall health care utilization did not differ between patients with JIA with Medicaid versus commercial insurance (IRR 1.03 [95% CI 0.99–1.07]), utilization patterns differed (Table 3). Patients with Medicaid coverage utilized ED care more frequently (OR 2.05 [95% CI 1.89–2.23]) and orthopedic care much less frequently (OR 0.27 [95% CI 0.24–0.34]). Utilization of outpatient providers was overall slightly lower (IRR 0.94 [95% CI 0.90–0.98]) in the population with Medicaid, but general practitioner utilization was higher (IRR 1.31 [95% CI 1.26–1.36]).

Table 3. Health care utilization for patients with JIA with Medicaid compared to those with commercial insurance*

	Odds ratio ^a (95% CI)	Adjusted incidence rate ratio ^b (95% CI)
Total health care utilization	–	1.03 (0.99–1.07)
Outpatient visits	–	0.94 (0.90–0.98)
General practitioner visits	–	1.31 (1.26–1.36)
Orthopedic visits	0.27 (0.24–0.34)	0.91 (0.78–1.06)
ED/urgent care visits	2.05 (1.89–2.23)	1.75 (1.62–1.88)
Inpatient hospitalizations	1.19 (1.03–1.38)	0.99 (0.731–1.36)

* Odds ratios and incidence rate ratios for health care utilization of patients with Medicaid vs those with commercial insurance. Negative binomial models were utilized for total, outpatient, and generalist health care utilization, and hurdle models were utilized for ED, inpatient, and orthopedic utilization. CI, confidence interval; ED, emergency department; JIA, juvenile idiopathic arthritis.

^a Odds ratios were calculated for utilization vs no utilization in zero-inflated outcomes.

^b Incidence rate ratios were adjusted for age and sex.

Utilization by specialty. JIA outpatient encounters were most frequent with generalists (84,507 visits; 71.6% of total outpatient visits) and orthopedists (5,743; 4.9%) in the prediagnosis period. Patients with JIA were also seen more frequently than healthy controls in the prediagnosis period by rheumatologists, ophthalmologists, dermatologists, and other medical subspecialists (Table 4). In the year preceding diagnosis, 91.8% (n = 9,203), 47.0% (n = 4,714), and 22.9% (n = 2,906) of children with JIA were seen by a general practitioner, ED/UC, or orthopedist, respectively.

Sensitivity analyses. In a sensitivity analysis that removed patients with CCCs from the JIA cohort (n = 629), JIA cases continued to have excess health care utilization across all settings in the year preceding diagnosis when compared to controls. The OR and IRR of inpatient utilization decreased from 4.16 (95% CI 3.56–4.87) and 2.00 (95% CI 1.48–2.71) to 3.42 (95% CI 3.03–3.91) and 1.89 (95% CI 1.38–2.60), respectively, with the exclusion of patients with CCCs, but this outcome remains statistically significant. In subgroup analyses, inclusion of geographic region in models restricted to commercially insured patients and inclusion of race in models restricted to Medicaid patients did not substantially alter the observed differences in health care utilization between patients with JIA and controls.

DISCUSSION

This study quantifies and describes health care utilization in a large, population-based cohort of US patients with an incident

Table 4. Frequency of visit to provider types in the year preceding diagnosis*

Provider type	Patient with JIA (visits per person-year)	Healthy control (visits per person-year)
General provider	8.4	3.52
Orthopedic provider	0.57	0.15
Rheumatology	0.31	<0.001
Ophthalmology	0.18	0.02
Dermatology	0.24	0.12
Other medical subspecialty	0.46	0.06

* Frequency of utilization by provider type in the year preceding diagnosis presented as visits per person-year. JIA, juvenile idiopathic arthritis.

diagnosis of JIA and demonstrates that patients with JIA consistently utilize more health care in the year preceding diagnosis when compared to healthy controls, across all health care settings. Utilization among these patients is elevated from the time of cohort inclusion and escalates closer to the time of diagnosis, demonstrating that many patients are frequently seeking care for their symptoms, for at least a year before JIA diagnosis. In this cohort, patients sought care from generalists, orthopedists, and ED/UC centers before diagnosis. Interestingly, patients insured by Medicaid were more likely to seek emergency care, whereas commercially insured patients were more likely to seek orthopedic care. A better understanding of these trajectories of health care utilization preceding JIA diagnosis is a critical first step to designing interventions to improve time to diagnosis and targeted treatment.

Several findings from this study are worth exploring further. Surprisingly, patients with JIA in this cohort had more than a two-fold higher level of health care utilization from time of cohort inclusion. In designing the current study, the duration of one year preceding diagnosis was selected based on prior data that suggested a median time to diagnosis of three to four months for patients with JIA.^{26,27} However, the utilization patterns in the cohort demonstrated that patients have almost twice the utilization of healthy controls a year before diagnosis, which suggests that the diagnostic process may start earlier and take longer than prior studies have suggested. Although a stepwise diagnostic evaluation for a cause of joint pain may be expected to take weeks to months, as reflected in the acute rise in health care utilization of patients with JIA just before diagnosis, it is unlikely to explain high health care utilization spanning a year. This utilization suggests that there are multiple visits with health care professionals at which an earlier JIA diagnosis may be possible or that there are subtle early symptoms of JIA that are being missed in the clinical setting. This is consistent with prior qualitative studies of patients with JIA that have characterized the diagnostic journey as “turbulent,” requiring multiple interactions with the health care system and significant parental persistence for a diagnosis to ultimately be made.^{28,29} High health care utilization before diagnosis has also been documented in other pediatric rheumatic diseases including systemic lupus erythematosus³⁰ and inflammatory bowel disease (IBD).³¹ In pediatric IBD, elevated levels of health care utilization were noted for up to four years before diagnosis, implying the existence of a preclinical symptomatic period or of prolonged diagnostic delay.³¹ Studies of time to diagnosis in adult inflammatory arthritis have yielded results with diagnostic delays lasting up to a decade in some patients.^{32,33} It is important to note that, although the diagnostic intervals presented within for children with JIA are shorter than those for equivalent adult conditions, active arthritis in childhood comes with unique risks for acquired deformities during periods of active growth, such as leg length discrepancy and negative developmental effects.¹

Although this study does not elucidate the reasons for diagnostic delay in JIA, many factors make JIA a diagnostically complex condition, including its subtle and heterogenous clinical presentation, the overlap of symptoms with more common pediatric conditions, and the lack of a single, true diagnostic test. As such, the initial clinicians interacting with these patients may be poorly equipped to recognize it, and the development of screening tools and management guidance for these providers may be necessary to accelerate appropriate referral. The workforce shortage and geographic limitation of the pediatric rheumatology workforce in the United States^{34,35} may contribute to diagnostic delays and heightens the importance that nonrheumatologic providers can recognize and appropriately refer patients with inflammatory arthritis. In developing interventions to improve the diagnostic process, it is important to understand the settings in which patients are receiving care. In the presented cohort, utilization was most frequent with general practitioners, orthopedists, and ED/UC providers. The vast majority of patients with JIA (91.8%) were seen by a general practitioner in the year preceding diagnosis, nearly half (47.0%) were seen in an ED/UC, and 22.9% were seen by orthopedists. These clinical settings may be the highest yield targets for interventions to encourage early referral for pediatric rheumatology assessment in appropriate patients.

Beyond general patterns of utilization, our analysis also highlights differential health care utilization between patients in the commercial and Medicaid databases. There was increased utilization of ED/UC centers and lower utilization of orthopedic care among patients in the Medicaid-insured database. This is consistent with data from studies across multiple disease processes that demonstrate that Medicaid patients seek more care from the ED and less from subspecialists.^{36–38} With MarketScan data, we are unable to determine the etiology of these differential utilization patterns between insurance types and whether other demographic factors, such as socioeconomic status, geographic region, or race and ethnicity, are the drivers of the differences. Although this differential utilization is likely multifactorial, the pattern makes it clear that multiple, setting-specific interventions will be needed to improve diagnosis equitably for children with all insurance types.

The strengths of this study include the use of a national administrative database, which has generated a large cohort and enabled the capture of interactions across multiple health care systems. Capturing data across health systems is particularly important in studies related to diagnostic delay/error because prior studies have demonstrated that patients are more likely to seek care across systems when an error occurs or a diagnosis is not received.³⁹ This study also has several limitations. Although utilizing both the commercial and Medicaid databases improves the generalizability of the presented study, it is important to note that geographic location is only available for patients with commercial insurance and race and ethnicity data are only available for those with Medicaid insurance, which limited the subgroup

analyses that could be performed based on demographic factors. However, a sensitivity analysis was performed to ensure that correction for these factors did not alter the point estimate or statistical significance of differences between cases and controls. As with any administrative database study, misclassification is also possible, and there is no validated method for identifying incident cases of JIA. By leveraging previously published JIA identification algorithms,^{19–22} we aimed to minimize any misclassification.

In summary, this study leveraged administrative data to characterize the frequency, patterns, and types of health care utilization before diagnosis of JIA, which is essential to identifying system issues and practice patterns preceding JIA diagnosis. This study demonstrated that patients with JIA utilize significantly more health care in the year preceding diagnosis, particularly from generalists, orthopedists, and emergency care providers, and that this high utilization starts at least a year before diagnosis. These utilization patterns indicate that the diagnostic journey for patients with JIA may be more prolonged and nuanced than previously believed and that there may be opportunities for earlier recognition of key symptoms and referral to rheumatology care.

ACKNOWLEDGMENTS

The authors wish to acknowledge the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the ongoing Arthritis Foundation financial support of CARRA. ChatGPT was used to check the spelling and grammar of the abstract and methods of the article.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Costello confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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Cumulative Social Disadvantage and Disease Activity in Juvenile Idiopathic Arthritis: A Childhood Arthritis and Rheumatology Research Alliance Registry Study

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Objective. Social determinants of health (SDOH) contribute to juvenile idiopathic arthritis (JIA) disparities, but most studies have assessed SDOH independently rather than cumulatively across individual, family, and neighborhood levels. Using a socioecological framework, we investigated the relationship among cumulative social disadvantage, neighborhood disadvantage, and JIA disease activity.

Methods. We conducted a retrospective cohort study using the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry (2015–2022). Individual- and family-level SDOH were combined into a cumulative social disadvantage score (range: 0–3), with one point each for public or no insurance, family income less than \$50,000 per year, and guardian education of high school level or less. Neighborhood disadvantage was measured using Area Deprivation Index (quartiles). The primary outcome was active disease by clinical Juvenile Arthritis Disease Activity-10 (cJADAS-10). Mixed effects models were generated to assess associations adjusted for demographic and clinical covariates, and causal mediation analysis evaluated whether cumulative social disadvantage mediated the relationship between neighborhood disadvantage and disease activity.

Results. Among 9,609 children with JIA with a median follow-up time of 2.1 (interquartile range 0.3–5.8) years, 39.1% had a cumulative social disadvantage score greater than 0 with higher scores correlating with greater neighborhood disadvantage. In adjusted analysis, cumulative social disadvantage was associated with higher odds of active disease (adjusted odds ratio 2.10, 95% confidence interval [CI] 1.73–2.53 for a score of 3 vs 0). A total of 87% (95% CI 38–100) of the effect of neighborhood disadvantage was mediated through cumulative social disadvantage.

Conclusion. Cumulative social disadvantage is strongly associated with active JIA and mediates much of the effect of neighborhood disadvantage. Interventions addressing multilevel SDOH will be essential to reducing JIA health disparities.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease affecting children, with an estimated incidence between 1.6 and 23 cases per 100,000 children per year globally.¹ Poorly treated JIA can lead to permanent joint deformities and predispose those with this condition to a lifetime of chronic

pain with a significant loss in function.^{2,3} Improvements in therapies, including biologic disease modifying anti-rheumatic drugs (bDMARD), have led to significant improvements in long-term outcomes for children living with JIA.⁴

However, multiple health disparities have been demonstrated in children with JIA, including higher disease activity among individuals who are economically disadvantaged^{5–9} and

This study used data collected in the CARRA Registry. The views expressed are the authors' and do not necessarily represent the view of CARRA or the National Institutes of Health (NIH).

Supported by the National Center for Advancing Translational Sciences, NIH, through University of California, San Francisco (UCSF)-Clinical and Translational Science Institute grant UL1-TR-001872. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Dr Soulsby's work was supported by an Arthritis Foundation Diversity, Equity, and Inclusion Research in Health Outcomes award and is currently supported by a CARRA-Arthritis Foundation Career Development Award and UCSF Society of Hellman Fellows award. Dr Knight's work was

supported by a Canadian Research Chair in Mental Health and Chronic Disease of Childhood and a Lupus Research Alliance Career Development Award. Dr Horton's work was supported by funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (R01-AR-074436), Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01-HD-109335), National Center for Advancing Translational Sciences (UL1-TR-003017, UM1-TR-004789), CARRA, and the Arthritis Foundation. Dr von Scheven's work receives support from CARRA.

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SIGNIFICANCE & INNOVATIONS

- This is the first study in juvenile idiopathic arthritis (JIA) to evaluate social determinants of health (SDOH) across multiple socioecological levels (ie, individual, family, and community level) using a single analytic framework.
- In a large US cohort of children with JIA, cumulative social disadvantage (measuring income, insurance, and education) was strongly associated with active JIA.
- We identified that the effect of neighborhood-level deprivation (as measured by Area Deprivation Index) is largely mediated by more proximal individual- and family-level SDOH.
- This work provides new evidence to guide the development of multilevel interventions aimed at reducing health disparities in JIA.

delays in treatment among those who are publicly insured.¹⁰ In most health disparities research in JIA, social determinants of health (SDOH) are studied as independent risk factors. This has yielded inconsistent relationships between SDOH and JIA outcomes. However, SDOH more likely work together to influence patient outcomes; therefore, the presence of multiple risk factors associated with social disadvantage portends worse outcomes as compared with a single risk factor.^{11,12} The socioecological model is a framework that acknowledges multiple levels of social influence, including individual, family, community, and societal levels, which converge and interact to create and perpetuate health disparities.¹³ An analytic approach that acknowledges this multilevel complexity is needed to further elucidate causes of health disparities in JIA that can inform intervention strategies. We previously used such an approach to investigate cumulative social disadvantage in childhood arthritis in a nationally representative data set (the National Survey of Children's Health).¹⁴ In that study, successive exposure to cumulative social disadvantage, comprised of individual- and family-level SDOH, was associated with higher odds of an arthritis diagnosis and higher disease activity. However, childhood arthritis diagnoses and disease severity in this data set were guardian-reported, limiting conclusions with respect to JIA specifically.

Therefore, we aimed to assess individual, family, and community-level SDOH and their associations with disease activity among a cohort of patients with JIA in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. We

generated a cumulative social disadvantage score comprising household (including individual- and family-level) SDOH and separately analyzed Area Deprivation Index (ADI) at the community level. We hypothesized that, among children with JIA, those with higher exposure to cumulative social disadvantage and higher neighborhood disadvantage (ADI) would have higher disease activity across long-term follow-up. Informed by associations demonstrated among the cumulative social disadvantage score, neighborhood disadvantage, and disease activity, we subsequently performed causal mediation analysis to investigate neighborhood disadvantage as a mediator of the effect of the cumulative social disadvantage score on active disease.

METHODS

Study design and setting. We performed a retrospective cohort study using data from the CARRA Registry, a prospective, North American multicenter registry for children with rheumatic diseases, including JIA.¹⁵ We queried the registry for all patients with JIA and analyzed deidentified demographic and clinical data. See Appendix A for the CARRA Registry Site Principal Investigators, Sub-Investigators, and Research Coordinator.

Analytic sample. The sample population includes all eligible children with JIA enrolled in the CARRA Registry between July 2015 and January 2022 who reside in the United States. Registry eligibility requires a diagnosis of JIA by a pediatric rheumatologist according to the International League of Associations for Rheumatology (ILAR) classification criteria.¹⁶ Patients enrolled in the registry represent a convenience sample of patients treated at registry sites. Each patient in the CARRA Registry completes an enrollment visit followed by follow-up visits every six months. Additional inclusion criteria for our study included at least one visit with a complete clinical Juvenile Arthritis Disease Activity-10 (cJADAS-10) score (see section "Primary Outcome"). All available registry visits per participant were included for longitudinal analyses.

Primary exposures. Our aim was to study SDOH available in the CARRA Registry that represented different social strata as conceptualized by our socioecological model (Figure 1A). We conceptualized individual- and family-level risk factors as operating on the same strata (eg, household) given that traditional individual-level risk factors, such as insurance and income, are informed by family-level factors in a pediatric population (eg, parental income and insurance). One primary exposure

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80051>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80051>.

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Submitted for publication October 10, 2025; accepted in revised form March 17, 2026.

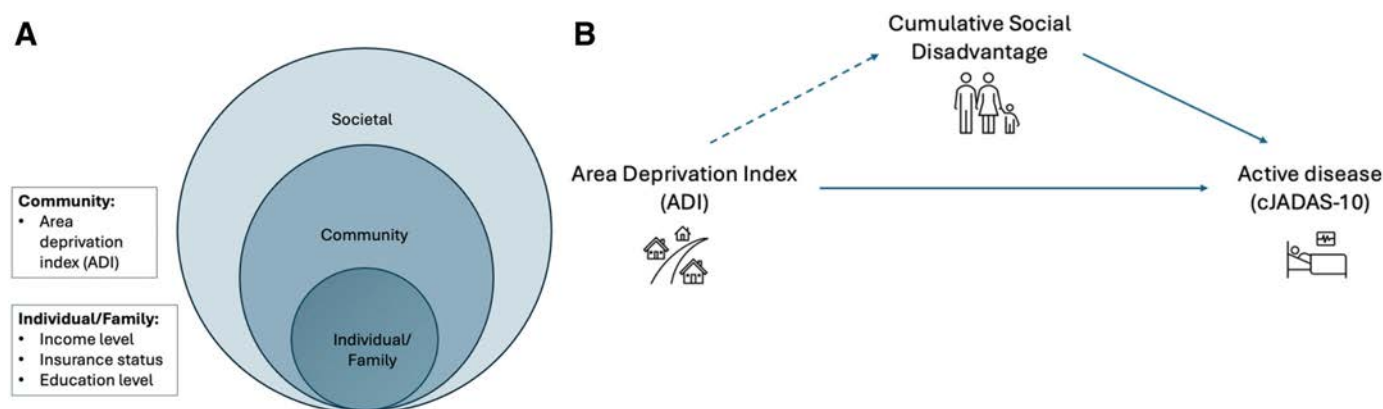


Figure 1. (Left) The socioecological model for SDOH applied to this study. Individual/family-level factors (income, insurance, education) were combined into a cumulative social disadvantage score; community-level factors were measured by the ADI, a composite measure of neighborhood-level deprivation encompassing domains including housing, education, employment, and income and geocoded to the census-tract level. Societal-level factors were not measured in this study. (Right) A DAG demonstrating proposed relationships between community-level SDOH (ADI) and individual/family-level SDOH (cumulative social disadvantage) and active JIA (cJADAS-10). The dashed line references the proposed mediating relationship under study. ADI, Area Deprivation Index; cJADAS-10, Clinical Juvenile Arthritis Disease Activity Score 10; DAG, directed acyclic graph; JIA, juvenile idiopathic arthritis; SDOH, social determinants of health. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80051/abstract>.

variable was the cumulative social disadvantage score (range 0–3) that comprised available individual- and family-level SDOH in the CARRA Registry, including insurance status (one point for public or no insurance), income level (one point for self-reported family income level of <\$50,000 per year), and guardian education (one point for high school level education or less). These three SDOH were chosen because of their availability in the registry and similarity to the parameters chosen in our previous work.¹⁴ Adverse childhood experiences (ACEs) were omitted from this iteration of the cumulative social disadvantage score because they were not available in the registry. Our other primary exposure variable was ADI, a composite measure of social and economic deprivation at the neighborhood (census tract) level,¹⁷ to represent neighborhood disadvantage. ADI was collected and grouped into quartiles to make comparisons between groups. This community-level SDOH has already been studied in previous pediatric¹⁸ and adult rheumatology¹⁹ populations. Societal-level factors, hypothesized to impact our outcomes, could not be measured. These exposures were assessed at the enrollment registry visit; therefore, changes in SDOH over time were not able to be assessed.

Primary outcome. Our primary outcome was the presence of active disease by the cJADAS-10,²⁰ a composite measure including Physician Global Assessment (PGA) (0–10), Parent or Patient Global Assessment (0–10), and active joint count (0–10). cJADAS-10 scores are collected at a per visit level in the CARRA Registry with study visits occurring every six months. Active disease by cJADAS-10 was defined as a score greater than 1 for oligoarticular JIA and greater than 2.5 for all other JIA subtypes.²¹ All available cJADAS-10 scores at

enrollment and follow-up visits were included in our analysis; visits in which cJADAS components were missing were not included.

Secondary outcome. The presence of functional disability at any point during follow-up was defined by a Child Health Assessment Questionnaire (CHAQ)²² score greater than 0. All available CHAQ scores at enrollment and follow-up visits were included in our analysis.

Study covariates. Demographic covariates assessed included age at enrollment into the registry, self-identified race and/or ethnicity (White, Black, Hispanic, Asian, other race, missing, or more than one race), and sex (female or male). Disease-related covariates included (1) JIA subtype (by ILAR criteria); (2) time from symptom onset to JIA diagnosis; (3) time from diagnosis; (4) year of diagnosis; (5) the presence of any secondary rheumatologic disease; (6) ever use of a conventional synthetic DMARD (csDMARD), bDMARD (biologic DMARD), or JAK inhibitors at enrollment or across follow-up; (7) any previous glucocorticoid use at enrollment or across follow-up; and (8) current glucocorticoid use.

Statistical analysis. Summary statistics were calculated, including median and interquartile range (IQR), to describe the demographic, disease-related, and SDOH variables of the cohort. Comparisons of these variables by the cumulative social disadvantage score were tested by chi-squared testing or Kruskal-Wallis testing, as appropriate. Univariable and multivariable (adjusting for all covariates—see section “Study Covariates”) mixed effects logistic regression models were generated to estimate the association of cumulative social disadvantage and neighborhood disadvantage with active disease as a binary

outcome across registry follow-up. Univariable models included fixed effects for the categorical cumulative social disadvantage score and a random effect for participant to account for intrasubject correlation across longitudinal measurements. Multivariable models additionally included fixed effects for all covariates, as specified previously (see section “Study Covariates”). All models were estimated with robust clustered SEs at the individual level to guard against model misspecification.²³ Similar models were generated to estimate the association of cumulative social disadvantage and neighborhood disadvantage with the presence of functional disability across registry follow-up. Because of significant missingness of individual components of the cumulative social disadvantage score (income 24.6%; guardian education: 15.7%; insurance: 0.2%) and ADI (17.2%), chained equation multiple imputation²⁴ was used (N = 50 cycles) with the cumulative social disadvantage score and all multivariable model covariates in the data set used to inform our imputation. Final models used imputed data. We tested for interaction between the cumulative social disadvantage score and race and between the cumulative social disadvantage score and neighborhood disadvantage and found no significant interactions; therefore no interaction terms were included in the final models. All analyses were conducted in STATA version 18.²⁵ The University of California, San Francisco’s institutional review board determined our study to be exempt from review (#22-36233).

Sensitivity analysis. As a sensitivity analysis, we generated similar univariable and multivariable mixed effects models estimating the association between cumulative social disadvantage and neighborhood disadvantage on active disease at different cJADAS-10 thresholds, including moderate disease activity or higher (oligoarticular JIA with cJADAS >4 and in all other JIA categories >5) and severe disease activity (oligoarticular JIA with cJADAS >12 and in all other JIA categories >16).²¹

Causal mediation analysis. Based on our theoretical framework of the relationships among cumulative social disadvantage, neighborhood disadvantage (ADI), and disease activity (Figure 1B), we performed a causal mediation analysis to investigate if there was a significant mediating relationship between the cumulative social disadvantage score (individual- and family-level SDOH) and neighborhood disadvantage (community-level SDOH) on disease activity. Therefore, we tested whether the cumulative social disadvantage score was a mediator of the effect of neighborhood disadvantage on disease activity. The average causal mediation effects, along with the total effects and the proportion of the effect via the proposed mediator, were estimated using linear probability models²⁶ with robust clustered SEs at the subject level. This causal mediation analysis adjusted for other demographic and disease-related covariates in our models. To understand if specific components of the cumulative social disadvantage score (eg, low income, underinsured status, or guardian education level) were individual mediators of the

relationship between neighborhood disadvantage and disease activity, analogous causal mediation analyses were performed that substituted these components as the proposed mediator and adjusted for the other components.

RESULTS

Demographic and clinical characteristics of the cohort. In total, 9,609 participants meeting inclusion criteria were identified (Table 1) among 10,225 who were eligible in the registry. Most of the cohort had a cumulative social disadvantage score of 0 (60.9%) with lower proportions for a score of 1, 2, and 3 (21.3%, 12.9%, and 4.9%, respectively). The median time from diagnosis was 2.1 years (IQR 0.3–5.8 years). The most common subtypes of arthritis represented were oligoarticular JIA (35.6%) closely followed by rheumatoid factor (RF) negative polyarticular JIA (29.5%). bDMARD and csDMARD use were common across the cohort (68.6% and 77.9%, respectively). Glucocorticoid use was uncommon overall but increased in frequency both at enrollment and at any point across follow-up among those reporting the highest cumulative social disadvantage score (use at enrollment 13.0% and at any time across follow-up 42.6% for a score of 3). Of the parameters of the cumulative social disadvantage score, having public or no insurance was the most common, with 26.3% of the cohort reporting, followed by low income (19.1%) and low guardian education (16.4%). Yearly household income had a high degree of missingness (24.6%) as did guardian education (15.7%), with little missingness in insurance status (0.2%). Those who had a higher cumulative social disadvantage score were more likely to live in an area of higher neighborhood disadvantage (51.6% of those with a score of 3 lived in the highest ADI quartile, as compared with only 11.7% of those with a score of 0). Participants identifying as Black or Hispanic were more likely to have higher cumulative social disadvantage scores (11.9% Black with a score of 3 vs 1.8% with a score of 0; 21.3% Hispanic with a score of 3 vs 3.4% with a score of 0).

Disease activity by cJADAS-10. The median cJADAS-10 score at enrollment was 4.0 (IQR 1.0–9.0), with 62% having active cJADAS-10 score at enrollment (Table 1). In unadjusted analyses of the effects of individual- and family-level SDOH, there was a successive increase in the odds of active disease across the registry follow-up (highest for a cumulative social disadvantage score of 3: odds ratio [OR] 2.15, 95% confidence interval [CI] 1.73–2.68) (Table 2). After adjustment for all covariates, the relationship among cumulative social disadvantage and disease activity remained strong (highest for a cumulative social disadvantage score of 3: adjusted odds ratio [aOR] 2.17, 95% CI 1.77–2.65). After adjustment for all covariates and neighborhood disadvantage, these associations were minimally changed (highest for a cumulative social disadvantage score of 3: aOR 2.10, 95% CI 1.73–2.53). In unadjusted analyses of the effects of community-level SDOH, there was a successive increase in the odds of active disease across

Table 1. Demographic and clinical characteristics of pediatric patients with JIA in the CARRA Registry (2015–2022)*

Demographic and clinical characteristics	Cumulative Social Disadvantage Score ^a					Test ^b
	0	1	2	3	Total	
Patients, N (%)	5,849 (60.9)	2,048 (21.3)	1,243 (12.9)	469 (4.9)	9,609 (100.0)	
Median age at enrollment (IQR), y	11.7 (7.3–15.1)	12.0 (7.6–15.4)	11.6 (7.2–15.1)	10.5 (6.1–14.2)	11.7 (7.3–15.1)	<0.001
Female, n (%)	4,117 (70.4)	1,433 (70.0)	850 (68.4)	317 (67.6)	6,717 (69.9)	0.360
Male, n (%)	1,732 (29.6)	615 (30.0)	393 (31.6)	152 (32.4)	2,892 (30.1)	
Race and/or ethnicity, n (%)						
White	4,783 (81.8)	1,442 (70.4)	726 (58.4)	246 (52.5)	7,197 (74.9)	<0.001
Hispanic	199 (3.4)	212 (10.4)	223 (17.9)	100 (21.3)	734 (7.6)	
Multiracial	340 (5.8)	138 (6.7)	108 (8.7)	39 (8.3)	625 (6.5)	
Black	108 (1.8)	105 (5.1)	109 (8.8)	56 (11.9)	378 (3.9)	
Asian	183 (3.1)	45 (2.2)	21 (1.7)	6 (1.3)	255 (2.7)	
Other	114 (1.9)	52 (2.5)	45 (3.6)	22 (4.7)	233 (2.4)	
Refuse/missing	122 (2.1)	54 (2.6)	11 (0.9)	0 (0.0)	187 (1.9)	
National ADI ^c quartiles, n (%)						
Q1 (lowest)	1,701 (29.1)	269 (13.1)	102 (8.2)	23 (4.9)	2,095 (21.8)	<0.001
Q2	1,334 (22.8)	411 (20.1)	183 (14.7)	61 (13.0)	1,989 (20.7)	
Q3	1,027 (17.6)	489 (23.9)	313 (25.2)	91 (19.4)	1,920 (20.0)	
Q4 (highest)	687 (11.7)	546 (26.7)	481 (38.7)	242 (51.6)	1,956 (20.4)	
Missing	1,100 (18.8)	333 (16.3)	164 (13.2)	52 (11.1)	1,649 (17.2)	
Median national ADI score (IQR)	29.0 (15.0–47.0)	46.0 (27.0–67.0)	57.0 (36.0–77.0)	66.0 (41.0–84.0)	37.0 (20.0–60.0)	<0.001
Family income level, n (%)						
<\$25,000	0 (0.0)	110 (5.4)	370 (29.8)	243 (51.8)	723 (7.5)	<0.001
\$25,000–49,999	0 (0.0)	354 (17.3)	531 (42.7)	226 (48.2)	1,111 (11.6)	
\$50,000–74,999	676 (11.6)	405 (19.8)	85 (6.8)	0 (0.0)	1,166 (12.1)	
\$75,000–99,999	790 (13.5)	238 (11.6)	33 (2.7)	0 (0.0)	1,061 (11.1)	
\$100,000–150,000	1,417 (24.3)	241 (11.8)	17 (1.4)	0 (0.0)	1,675 (17.4)	
Above \$150,000	1,378 (23.6)	113 (5.5)	5 (0.4)	0 (0.0)	1,496 (15.6)	
Prefer not to answer	789 (13.5)	305 (14.9)	99 (8.0)	0 (0.0)	1,193 (12.4)	
Unknown	792 (13.6)	280 (13.7)	103 (8.3)	0 (0.0)	1,175 (12.2)	
Insurance status, n (%)						
Private	5,056 (86.4)	900 (43.9)	191 (15.4)	20 (4.3)	6,167 (64.2)	<0.001
Public	0 (0.0)	859 (41.9)	952 (76.6)	437 (93.2)	2,248 (23.4)	
Other insurance	792 (13.5)	212 (10.4)	62 (5.0)	0 (0.0)	1,066 (11.1)	
Uninsured	0 (0.0)	64 (3.1)	35 (2.8)	12 (2.6)	111 (1.2)	
Missing/unknown	1 (0.0)	13 (0.6)	3 (0.2)	0 (0.0)	17 (0.2)	
Guardian education level, n (%)						
Elementary/middle school (grade 1 – 8)	0 (0.0)	41 (2.1)	47 (4.0)	42 (9.0)	130 (1.4)	<0.001
Some high school (grade 9–11)	0 (0.0)	40 (2.0)	72 (6.1)	65 (13.9)	177 (1.9)	
Graduated high school (grade 12 or GED)	0 (0.0)	489 (25.0)	420 (35.9)	362 (77.2)	1,271 (13.9)	
College (1–4 y college, junior college or technical school)	2,657 (48.0)	848 (43.3)	438 (37.4)	0 (0.0)	3,943 (43.2)	
Graduate school (eg, Masters, Doctorate, or professional degree)	1,889 (34.1)	234 (12.0)	51 (4.4)	0 (0.0)	2,174 (23.8)	
Prefer not to answer	986 (17.8)	305 (15.6)	143 (12.2)	0 (0.0)	1,434 (15.7)	
Components of the Cumulative Social Disadvantage Score, n (%)						
Income <\$50,000/year	0 (0.0)	464 (22.7)	901 (72.5)	469 (100.0)	1,834 (19.1)	<0.001
Guardian education ≤ high school	0 (0.0)	570 (27.8)	539 (43.4)	469 (100.0)	1,578 (16.4)	<0.001
Public or no insurance	0 (0.0)	1,014 (49.5)	1,046 (84.2)	469 (100.0)	2,529 (26.3)	<0.001
	2015 (2012–2018)	2016 (2012–2018)	2016 (2012–2018)	2016 (2013–2018)	2015 (2012–2018)	0.003

(Continued)

Table 1. (Cont'd)

Demographic and clinical characteristics	Cumulative Social Disadvantage Score ^a					Test ^b
	0	1	2	3	Total	
Median year of diagnosis (IQR)						
Median days from symptom onset to diagnosis (IQR)	137.0 (62.0–312.0)	150.0 (63.0–342.5)	157.0 (66.0–371.0)	132.0 (61.0–330.0)	143.0 (63.0–328.0)	0.526
Median years from diagnosis (IQR)	2.1 (0.3–5.9)	2.1 (0.3–5.9)	1.8 (0.2–5.4)	1.7 (0.2–5.1)	2.1 (0.3–5.8)	0.043
JIA subtype, n (%)						
Enthesitis related arthritis	661 (11.3)	209 (10.2)	111 (8.9)	30 (6.4)	1,011 (10.5)	<0.001
Oligoarthritis	2,214 (37.9)	692 (33.8)	362 (29.1)	148 (31.6)	3,416 (35.6)	
Polyarthritis (RF+)	302 (5.2)	144 (7.0)	115 (9.3)	49 (10.4)	610 (6.3)	
Polyarthritis (RF–)	1,679 (28.7)	587 (28.7)	404 (32.5)	160 (34.1)	2,830 (29.5)	
Psoriatic arthritis	441 (7.5)	161 (7.9)	84 (6.8)	17 (3.6)	703 (7.3)	
Systemic arthritis	386 (6.6)	179 (8.7)	123 (9.9)	57 (12.2)	745 (7.8)	
Undifferentiated arthritis	166 (2.8)	76 (3.7)	44 (3.5)	8 (1.7)	294 (3.1)	
Any secondary rheumatic disease	5,611 (95.9)	1,957 (95.6)	1,191 (95.8)	448 (95.5)	9,207 (95.8)	
Medication use, n (%)						
Any bDMARD use	3,895 (66.6)	1,448 (70.7)	902 (72.6)	349 (74.4)	6,594 (68.6)	<0.001
Any csDMARD use	4,517 (77.2)	1,585 (77.4)	1,007 (81.0)	381 (81.2)	7,490 (77.9)	0.008
Any JAK inhibitor use	250 (4.3)	83 (4.1)	37 (3.0)	20 (4.3)	390 (4.1)	0.214
Glucocorticoid use at enrollment visit	435 (7.4)	181 (8.8)	141 (11.3)	61 (13.0)	818 (8.5)	<0.001
Any glucocorticoid use during follow-up	1,874 (32.0)	712 (34.8)	482 (38.8)	200 (42.6)	3,268 (34.0)	<0.001
Components of the cJADAS-10						
Median Physician Global Assessment (IQR)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	2.0 (0.0–4.0)	1.5 (0.0–3.5)	1.0 (0.0–3.0)	<0.001
Median Patient/Parent Global Assessment (IQR)	1.0 (0.0–3.0)	1.0 (0.0–4.0)	2.0 (0.0–5.0)	2.0 (0.0–5.0)	1.0 (0.0–4.0)	<0.001
Active joint count (IQR)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	1.0 (0.0–4.0)	1.0 (0.0–3.0)	0.0 (0.0–2.0)	<0.001
Median cJADAS score at enrollment (IQR)	3.5 (0.5–8.0)	4.0 (1.0–9.0)	6.0 (1.5–12.0)	5.0 (1.5–12.0)	4.0 (1.0–9.0)	<0.001
Active disease by cJADAS at enrollment n (%)	3,460 (59.2)	1,293 (63.1)	883 (71.0)	325 (69.3)	5,961 (62.0)	<0.001
Median CHAQ score at enrollment (IQR)	0.0 (0.0–0.5)	0.2 (0.0–0.8)	0.4 (0.0–1.0)	0.4 (0.0–1.0)	0.1 (0.0–0.6)	<0.001
Functional disability by CHAQ at enrollment n (%)	2,772 (48.9)	1,166 (58.5)	819 (67.5)	312 (67.7)	5,069 (54.3)	<0.001

* ANOVA, analysis of variance; ADI, Area Deprivation Index; bDMARD, biologic disease modifying anti-rheumatic drug; CARRA, Childhood Arthritis and Rheumatology Research Alliance; csDMARD, conventional synthetic DMARD; CHAQ, Child Health Assessment Questionnaire; cJADAS-10, clinical Juvenile Arthritis Disease Activity-10; GED, General Education Development Test; IQR, interquartile range; JIA, juvenile idiopathic arthritis; Q, quartile; RF, rheumatoid factor.

^a Cumulative social disadvantage score (range 0–3) is calculated as follows: 1 point for self-reported family income level <\$50,000/year, 1 point for public or no insurance, and 1 point for guardian level education of high school or less.

^b Computed using descriptive statistics, such as chi-squared testing, one-way ANOVA, or Kruskal-Wallis testing, as appropriate.

^c ADI is a composite measure of neighborhood-level deprivation that comprises 17 indicators of neighborhood deprivation, including income, housing, employment, and education using US Census data and geocoded to the census-tract level.

registry follow-up with successive increases in neighborhood disadvantage that corresponded to increased neighborhood-level disadvantage (OR for ADI quartile 4: 1.45, 95% CI 1.18–1.77). After adjustment for all covariates, these associations were minimally changed (aOR for ADI quartile 4: 1.41, 95% CI 1.16–1.71). After adjustment for all covariates and the cumulative social disadvantage score, there was no longer a statistically significant relationship between neighborhood disadvantage and active disease (aOR for ADI quartile 4: 1.11, 95% CI 0.92–1.35).

To understand if specific components of the cumulative social disadvantage score were more strongly associated with persistent disease activity across registry follow-up, we generated univariable and multivariable models in which score components were individually assessed. In these multivariable models, low insurance (aOR 1.53, 95% CI 1.35–1.75), low guardian education (aOR 1.35, 95% CI 1.22–1.49), and low income (aOR 1.69, 95% CI 1.51–1.88) were associated with persistent disease activity (Table 3). Neighborhood disadvantage remained statistically

Table 2. Unadjusted and adjusted logistic regression models assessing the association between the cumulative social disadvantage score, race and/or ethnicity, and ADI and any disease activity (by cJADAS-10) across registry follow-up*

Social disadvantage, race/ethnicity, ADI, and disease activity	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)	Final adjusted ^b OR (95% CI)
Cumulative social disadvantage score			
0	Ref	Ref	Ref
1	1.34 (1.19–1.51)	1.32 (1.18–1.48)	1.30 (1.16–1.45)
2	1.81 (1.58–2.07)	1.84 (1.61–2.10)	1.79 (1.57–2.04)
3	2.15 (1.73–2.68)	2.17 (1.77–2.65)	2.10 (1.73–2.53)
ADI			
1 (lowest)	Ref	Ref	Ref
2	1.14 (1.00–1.31)	1.15 (1.01–1.32)	1.09 (0.95–1.24)
3	1.24 (1.05–1.46)	1.23 (1.04–1.45)	1.08 (0.91–1.28)
4 (highest)	1.45 (1.18–1.77)	1.41 (1.16–1.71)	1.11 (0.92–1.35)

* cJADAS-10 defined in participants with oligoarticular JIA as >1.1 and in all other JIA categories as >2.5. ADI, Area Deprivation Index; bDMARD, biologic disease modifying anti-rheumatic drug; CI, confidence interval; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score-10; csDMARD, conventional synthetic DMARD; JIA, juvenile idiopathic arthritis; OR, odds ratio; Ref, reference.

^a Adjusted for age at enrollment, time from symptom onset to diagnosis, year of diagnosis, sex, JIA category, presence of secondary rheumatic disease, medication use during follow-up (bDMARD, csDMARD, small molecule), current glucocorticoid use, any glucocorticoid use during follow-up.

^b Adjusted for the same covariates, including either the cumulative social disadvantage score or ADI.

significant in adjusted analysis in these multivariable models (aOR for ADI quartile 4: 1.41, 95% CI 1.16–1.71).

As a sensitivity analysis, similar multivariable regression models were generated to estimate the association of the cumulative social disadvantage score and neighborhood disadvantage with persistent disease activity using different disease activity cut-offs, including moderate disease activity or higher and severe disease activity or higher (Table 4). There remained a successive increase in the odds of the cumulative social disadvantage score and disease activity using these

Table 3. Unadjusted and adjusted logistic regression models assessing the association between the individual components of the cumulative social disadvantage score, race and/or ethnicity, and ADI and any active disease (by cJADAS-10) across registry follow-up*

Social disadvantage components, race/ethnicity, ADI, and disease activity	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Low insurance	1.62 (1.41–1.85)	1.53 (1.35–1.75)
Low guardian education	1.51 (1.33–1.70)	1.35 (1.22–1.49)
Low income	1.73 (1.53–1.96)	1.69 (1.51–1.88)
ADI		
1 (lowest)	Ref	Ref
2	1.14 (1.00–1.31)	1.15 (1.01–1.32)
3	1.24 (1.05–1.46)	1.23 (1.04–1.45)
4 (highest)	1.45 (1.18–1.77)	1.41 (1.16–1.71)

* cJADAS-10 defined in participants with oligoarticular JIA as >1.1 and in all other JIA categories as >2.5. ADI, Area Deprivation Index; bDMARD, biologic disease modifying anti-rheumatic drug; CI, confidence interval; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score-10; csDMARD, conventional synthetic DMARD; JIA, juvenile idiopathic arthritis; OR, odds ratio; Ref, reference.

^a Adjusted for age at enrollment, time from symptom onset to diagnosis, year of diagnosis, sex, JIA category, presence of secondary rheumatic disease, medication use during follow-up (bDMARD, csDMARD, small molecule), current glucocorticoid use, any glucocorticoid use during follow-up.

thresholds with no qualitative differences identified (for a score of 3, any disease activity: aOR 2.10, 95% CI 1.73–2.53; moderate disease activity or higher: aOR 2.16, 95% CI 1.82–2.56; severe disease activity or higher: aOR 2.09, 95% CI 1.61–2.72). The association between neighborhood disadvantage and disease activity was attenuated in multivariable analysis at every threshold (for ADI quartile 4, any disease activity: aOR 1.11, 95% CI 0.92–1.35; moderate disease activity or higher: aOR 1.03, 95% CI 0.88–1.20; severe disease activity or higher: aOR 1.07, 95% CI 0.83–1.38). As a separate sensitivity analysis, our univariable and multivariable primary models were generated using our final imputed data set versus complete case series analysis with no significant differences noted in our measures of association (Supplemental Table 1).

Causal mediation analysis. Comparing the most disadvantaged with least disadvantaged neighborhoods (ADI quartile 4 vs quartile 1), the total effect of neighborhood disadvantage on disease activity (4.8%, 95% CI 2.7–7.1) can be separated into a 0.7% (95% CI –1.9 to 3.2) direct effect and 4.2% (95% CI 3.0–5.4) indirect effect mediated through the cumulative social disadvantage score. Therefore, 87% (95% CI 38–100) of the effect of neighborhood disadvantage on disease activity is mediated through the cumulative social disadvantage score ($P < 0.001$) (Figure 2). When performing similar mediation analyses substituting the individual components of the score, we found that low income mediated 72% (95% CI 30–100) of the effect of neighborhood disadvantage on disease activity ($P = 0.001$), whereas public or no insurance mediated 52% (95% CI 21–83) of this relationship ($P = 0.001$),

Table 4. Adjusted logistic regression models assessing the association between the cumulative social disadvantage score, race and/or ethnicity, and ADI and disease activity (by varying cJADAS-10 cutoffs) across registry follow-up)*

Social disadvantage, race/ethnicity, ADI, and disease activity by cJADAS-10 Cutoffs	Any active disease, ^a N = 5,961, Adjusted OR (95% CI)	Moderate disease activity or higher, ^b N = 4,154, Adjusted OR (95% CI)	Severe disease activity or higher, ^c N = 1,026, Adjusted OR (95% CI)
Cumulative social disadvantage score			
0	Ref	Ref	Ref
1	1.30 (1.16–1.45)	1.33 (1.18–1.50)	1.33 (1.11–1.58)
2	1.79 (1.57–2.04)	1.91 (1.69–2.17)	1.83 (1.49–2.24)
3	2.10 (1.73–2.53)	2.16 (1.82–2.56)	2.09 (1.61–2.72)
ADI			
1 (lowest)	Ref	Ref	Ref
2	1.09 (0.95–1.24)	1.06 (0.93–1.22)	1.14 (0.93–1.40)
3	1.08 (0.91–1.28)	1.09 (0.94–1.26)	1.07 (0.87–1.33)
4 (highest)	1.11 (0.92–1.35)	1.03 (0.88–1.20)	1.07 (0.83–1.38)

* OR adjusted for age at enrollment, time from symptom onset to diagnosis, year of diagnosis, sex, JIA category, presence of secondary rheumatic disease, medication use during follow-up (bDMARD, csDMARD, small molecule), current glucocorticoid use, any glucocorticoid use during follow-up. ADI, Area Deprivation Index; bDMARD, biologic disease modifying anti-rheumatic drug; CI, confidence interval; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score-10; csDMARD, conventional synthetic DMARD; JIA, juvenile idiopathic arthritis; OR, odds ratio; Ref, reference.

^a Defined in participants with oligoarticular JIA as cJADAS >1.1 and in all other JIA categories as >2.5.

^b Defined in participants with oligoarticular JIA as cJADAS >4 and in all other JIA categories as >5

^c Defined in participants with oligoarticular JIA as cJADAS >12 and in all other JIA categories as >16

and guardian education mediated 27% (95% CI 5–48) of this relationship ($P = 0.016$).

Functional disability by CHAQ. Functional disability as defined by a CHAQ score greater than 0 was common at enrollment at 54.3% (Table 1). Across registry follow-up in both unadjusted and adjusted analyses, an increase in the

cumulative social disadvantage score was associated with a successive increase in the odds of functional disability (for a score of 3: aOR 2.86, 95% CI 2.14–3.81). In unadjusted analysis, a similar relationship was found between neighborhood disadvantage and persistent functional disability (for ADI quartile 4: aOR 2.32, 95% CI 1.74–3.10). This relationship was attenuated but remained statistically significant in adjusted

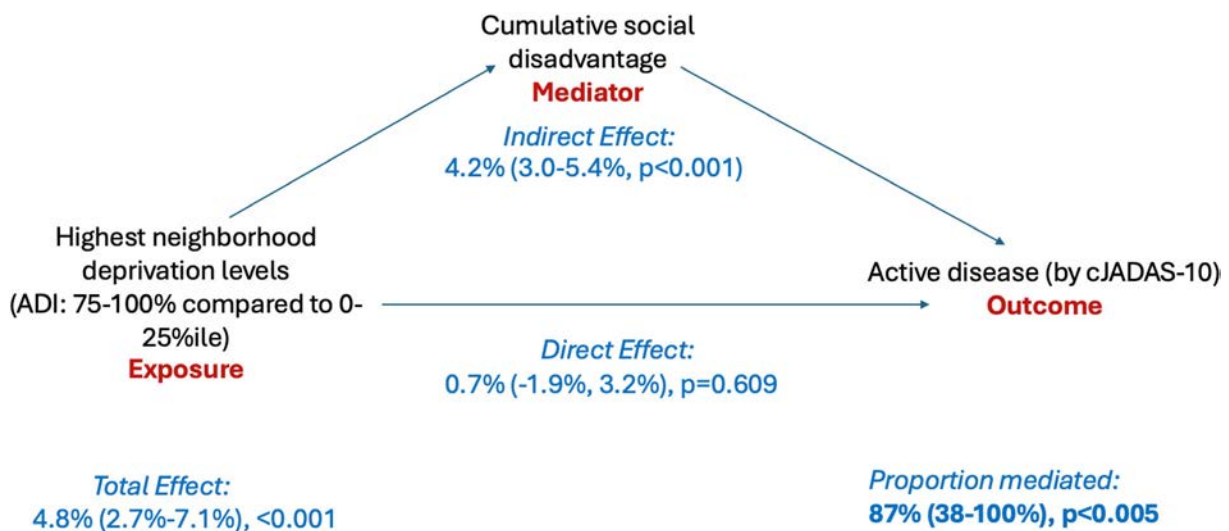


Figure 2. Causal mediation analysis to investigate the cumulative social disadvantage score as a mediator of the relationship between ADI and any disease activity throughout registry follow-up. Causal mediation analysis quantifies the total effect of a predictor (highest ADI quartile as compared to lowest) into its direct effect on an outcome (disease activity by cJADAS-10 score) and indirect effect mediated through a proposed mediator (cumulative social disadvantage score), from which the total proportion of the effect that is mediated can be calculated (proportion mediated). Age at enrollment, time from symptom onset to diagnosis, year of diagnosis, sex, JIA category, presence of secondary rheumatic disease, medication use during follow-up (bDMARD, csDMARD, small molecule), current glucocorticoid use, and any glucocorticoid use during follow-up were adjusted for in this analysis. ADI, area deprivation index; bDMARD, biologic disease-modifying antirheumatic drug; cJADAS-10, Clinical Juvenile Arthritis Disease Activity Score 10; csDMARD, conventional synthetic disease-modifying antirheumatic drug; JIA, juvenile idiopathic arthritis.

analysis (for ADI quartile 4: aOR 1.38, 95% CI 1.03–1.83) (Supplemental Table 2).

DISCUSSION

In the largest cohort study of US children with JIA to date focused on health disparities, we found that cumulative social disadvantage, a composite measure of individual- and family-level SDOH, was strongly and dose-dependently associated with persistent disease activity and functional disability across CARRA registry follow-up. This association persisted after adjustment for demographic and disease-related factors, suggesting that cumulative social disadvantage exerts an independent effect on JIA outcomes. Additionally, we identified neighborhood disadvantage as a statistically significant predictor of disease activity across registry follow-up, although most of the effect of this community-level SDOH on disease activity is mediated through more proximal individual- and family-level SDOH. These findings build on our previous work in a nationally representative data set¹⁴ by replicating this relationship in a large, rheumatologist-confirmed JIA cohort and confirm that cumulative social disadvantage is a clinically relevant construct for JIA risk stratification and intervention design.

SDOH rarely act in isolation. Social disadvantages, including poverty, underinsured status, and low education level, may accumulate and have been consistently linked to poorer childhood health, including having a chronic medical condition, and having functional limitations.¹¹ Previous studies had used combined scoring systems to investigate this concept of cumulative social disadvantage on health outcomes.²⁷ In a previous study, we created a cumulative social disadvantage score that comprised measures of childhood poverty, insurance status, low guardian education, and high ACE scores, and found an increase in the odds of a childhood arthritis diagnosis among a representative population of US children and higher reported disease severity.¹⁴ Limitations of this study were its cross-sectional nature, which could not assess if such disparities were sustained over time, as well as the self-reported nature of both arthritis diagnosis and severity, which could have been subject to misclassification bias. This study extends our understanding by demonstrating that social disadvantage appears to operate additively or synergistically over time, even within the context of subspecialty care. This underscores the need to address both individual-level and family-level risk factors and the overall burden of social disadvantage in pediatric rheumatology.

When considering potential targets for intervention, it is important to consider the ways in which cumulative social disadvantage may operate to worsen JIA health outcomes. Our mediation analysis provides important insight into potential mechanisms. Most of the effect (87%) of neighborhood disadvantage (as measured by ADI) on disease activity was mediated through more proximal individual and family-level factors. Of

these, low family income emerged as the strongest mediator, followed by public or no insurance and low guardian education. Although this suggests that addressing proximal needs may have the greatest impact and will be necessary to successful JIA interventions, it does not completely diminish the importance of community context. Community-level poverty, defined as 20% or more of the population of a geographic area living below the federal poverty limit, has been demonstrated to be associated with delays in time to first rheumatology appointment and persistent disease activity and functional disability among children with polyarticular JIA.^{28,29} We hypothesize that community-level determinants remain critical in shaping JIA outcomes. Pediatric rheumatology care in the United States is concentrated in urban academic centers,³⁰ often requiring families, especially those in rural and high-deprivation areas, to travel significant distances to specialty care.³¹ Such geographic and resource barriers may exacerbate delays in diagnosis,³² limit timely follow-up, and constrain access to health care and other ancillary services, such as physical therapy, mental health support, or social work. Moreover, neighborhood-level factors not captured by ADI, including availability of transportation, local health care infrastructure, community health literacy, and exposure to environmental stressors, may independently influence disease management and outcomes.³³ Future studies incorporating broader community-level metrics and health care access geography will be important to further assess the role between community and health disparities in JIA.

The findings of our study underscore the need for multilevel interventions extending beyond the clinic. At a systems level, potential strategies to mitigate the impact of social disadvantage include expanding telehealth infrastructure,³⁴ efforts to increase recruitment of pediatric rheumatologists to address workforce shortages,³⁵ establishing satellite clinics or mobile care units to reduce travel burden,³⁶ and embedding social care services into pediatric rheumatology practices.^{37,38} Presently among CARRA registry sites, only 31% of pediatric rheumatology clinics have a social worker or psychologist.³⁹ Patient navigator programs have been successful in diseases such as Type I diabetes⁴⁰ and piloted in adult rheumatoid arthritis^{41,42} and may provide both individualized support and stronger links between tertiary care centers and patients' home communities. Additionally, policy initiatives that improve insurance coverage (including expansion of Medicaid and the Children's Health Insurance Program⁴³), transportation assistance,⁴⁴ and broadband access^{45,46} may also help bridge the gap for families in high-deprivation areas. Building community partnerships with schools, primary care practices, and community-based organizations⁴⁷ could further reinforce disease management support where children live.

The persistence of disparities among patients receiving care at tertiary and quaternary centers (ie, CARRA Registry sites) highlights that access to specialty care alone is insufficient, and delays to diagnosis or pediatric rheumatology care do not fully explain

JIA health disparities. Routine SDOH screening in pediatric rheumatology should be a priority, with intervention models designed for scalability across diverse practice settings. The feasibility of SDOH screening in rheumatology clinics has already been demonstrated⁴⁸ but, to our knowledge, not yet applied to or studied in a pediatric rheumatology population. Our mediation results suggest that pairing community-level strategies with targeted individual and family support will be essential. Programs such as the Novel Interventions in Child Health model^{49,50} or patient navigation programs warrant further evaluation in JIA.

There are several limitations of this study to consider. We had a high degree of missingness of our predictor variables. However, we addressed this with multiple imputations and performed sensitivity analyses comparing complete case versus imputed data models with no substantive quantitative differences. SDOH variables and ADI were measured only once at the enrollment registry visit, preventing assessment of SDOH changes over time. Unmeasured confounding is possible, particularly from societal-level factors that are difficult to measure, including structural racism and policy environments. Although we chose cJADAS and CHAQ as our outcomes of interest, given their broad applicability to the JIA cohort at large and their use in other JIA trials, they may not fully capture patient experience. Future work will integrate more patient-reported outcomes. Finally, generalizability may be limited because the CARRA Registry is a convenience sample of patients with access to specialty care and who consent to registry participation and excludes those managed in adult rheumatology or primary care settings.

Despite these limitations, this is the largest North American cohort of patients with JIA analyzed longitudinally with validated measures of disease activity and function focusing on health disparities. Additionally, the CARRA Registry allowed for the analysis of individually reported household-level SDOH, including family income and guardian education, which are not routinely available in large data sets. Neighborhood-level proxies for household-level SDOH, such as ADI, may be more useful in data sets in which these SDOH are not available. Our application of the socioecological model, combined with causal mediation analysis, advances our understanding of how multilevel SDOH influence pediatric rheumatology outcomes. Even with limited heterogeneity in SDOH within this cohort, we identified a clear gradient effect of cumulative social disadvantage on JIA outcomes.

In conclusion, we identified cumulative social disadvantage, comprising individual- and family-level SDOH, as strongly associated with persistent disease activity among a large cohort of US children with JIA. We also identified a mediating relationship between neighborhood disadvantage and cumulative social disadvantage on disease activity. These findings demonstrate that although community-level SDOH are implicated in JIA health disparities, their influence is primarily mediated through more proximal SDOH and highlights the need for individual-level intervention to mitigate JIA health disparities. Future directions will

expand measurement of community-level determinants and leverage these findings to develop interventions targeting SDOH through patient navigation, care coordination, and community partnerships. We also plan to create and validate a JIA-specific social disadvantage screening tool for integration into routine clinical practice. Given the persistence of disparities in JIA despite therapeutic advances, it is imperative that interventions address the broader social context in which children live and receive care. Pediatric rheumatology should move toward integrated care models that recognize and mitigate social disadvantage to achieve equitable outcomes for all children with JIA.

ACKNOWLEDGMENTS

The authors wish to acknowledge CARRA and the ongoing Arthritis Foundation financial support of CARRA. This study used (data and/or biospecimens) collected in the CARRA Registry. The views expressed are the authors' and do not necessarily represent the view of CARRA. This work could not have been accomplished without the aid of the following organizations: The NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation. We would also like to thank all participants and hospital sites that recruited patients for the CARRA Registry. The authors thank the CARRA Registry site principal investigators, sub-investigators and research coordinators. Members are listed in Appendix A.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Soulsby confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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APPENDIX A: CARRA REGISTRY SITE PRINCIPAL INVESTIGATORS, SUB-INVESTIGATORS, AND RESEARCH COORDINATORS

The CARRA Registry site principal investigators, sub-investigators, and research coordinators are as follows: R. Amir, K. Abulaban, A. Adams, C. Aguiar Lapsia, H. Ahmed, S. Akoghlarian, A. AlBijadi, E. Allenspach, M. Alpizar, G. Amarilyo, M. Amoruso, S. Angeles-Han, S. Ardoin, S. Armendariz, N. Aviran Dagan, I. Balboni, S. Balevic, S. Ballinger, S. Baluta, L. Barillas-Arias, M. Basiaga, K. Baszis, M. Becker, A. Begezda, E. Beil, H. Bell-Brunson, H. Benham, S. Benseler, L. Bermudez-Santiago, W. Bernal, T. Bigley, C. Bingham, B. Binstadt, C. Black, B. Blackmon, M. Blakely, J. Bohnsack, A. Boneparth, H. Bradfield, J. Bridges, E. Brooks, M. Brothers, D. Brown, H. Brunner, L. Buckley, Mary Buckley, Meredith Buckley, H. Bukulmez, D. Bullock, A. Cancino, S. Canna, L. Cannon, S. Canny, V. Cartwright, E. Chalom, Johanna Chang, Joyce Chang, M. Chang, A. Chang-Hoffman, A. Chen, P. Chiraseveenupapund, K. Ciaglia, M. Cidon, D. Co, E. Cohen,

Trajectories of Physical Function in Canadian Children With Juvenile Idiopathic Arthritis

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Objective. We describe trajectories of physical function in children newly diagnosed with juvenile idiopathic arthritis (JIA) and identify trajectories with persisting functional impairments and associated baseline characteristics.

Methods. We included patients enrolled in the Canadian Alliance of Pediatric Rheumatology Investigators (CAPRI) Registry between 2017 and 2024 whose parents provided Kids Disability Screen (KDS) scores from at least two visits (from 0 = no disability to 10 = severe disability). Analyses included descriptive statistics, locally weighted scatterplot smoothing, Kaplan-Meier plots of time to KDS = 0, latent class trajectory analysis (LCTA), and classification trees to predict trajectories with persisting impairments.

Results. We included 940 patients providing 7,351 KDS scores starting at a median 6 days after diagnosis up to 7 years. Baseline KDS scores were highest for rheumatoid factor–positive polyarthritis (mean 4.9, SD 3.1) and lowest for psoriatic arthritis (mean 2.4, SD 2.5), and mean scores improved within the first year in all JIA categories. Median time to KDS = 0 was 36 weeks (from 13 weeks for systemic arthritis to 73 weeks for undifferentiated arthritis). LCTA identified five trajectories: one with little measurable impairment (38% of patients), two with impairments resolving in one to two years (24%), and two with persisting mild impairments (38%). A baseline KDS ≥ 1.5 had a sensitivity of 0.79 and specificity of 0.48 to detect persisting mild impairment trajectories. There were no trajectories with persisting moderate or severe impairments.

Conclusion. Most children with JIA in this cohort had mild to moderate functional impairments at diagnosis that resolved in one to two years, but one in three followed trajectories with mild persisting impairments.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood, with reported worldwide prevalence ranging from 4 to 400 cases per 100,000 children.¹ Children and adolescents with JIA often experience pain, joint

swelling, and functional impairments. Functional impairments can take many forms, including difficulties engaging in play or sports and in daily activities, such as getting dressed or writing. JIA is classified into seven categories according to the International League of Associations for Rheumatology (ILAR) criteria: oligoarthritis, rheumatoid factor (RF)–negative polyarthritis,

The CAPRI Registry was supported by grants from the Arthritis Society Canada (grants CAPRI-15-001 and SOG 18-0352) and the Canadian Institutes of Health Research (grant PJT-175235). This work was supported by a co-op studentship from the Division of Pediatric Rheumatology, British Columbia Children's Hospital and the University of British Columbia (to Ms Cunningham) and by a clinical investigator award from the British Columbia Children's Hospital Research Institute (to Dr Guzman).

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Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.80039>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80039>.

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Submitted for publication July 20, 2025; accepted in revised form March 3, 2026.

SIGNIFICANCE & INNOVATIONS

- In this Canadian longitudinal study of 940 children newly diagnosed with juvenile idiopathic arthritis (JIA) between 2017 and 2024, most had mild to moderate functional impairments at the time of diagnosis that improved quickly with a median time to optimal function of 36 weeks.
- At diagnosis, rheumatoid factor–positive polyarthritis had the largest functional impact, and psoriatic arthritis had the least, and patients with systemic arthritis and oligoarthritis attained optimal function earlier than patients in other JIA categories.
- In latent class trajectory analysis, 38% of patients were assigned to trajectories with persisting mild functional impairments, and a baseline Kids Disability Screen ≥ 1.5 was able to identify 79% of these patients.
- There were no functional trajectories with persisting moderate or severe impairments, but 8% of patients reported moderate to severe impairment at least once beyond two years after diagnosis.

RF-positive polyarthritis, and systemic, psoriatic, enthesitis-related, and undifferentiated arthritis.² JIA category significantly impacts a child's expected disease course and medical treatment.³

Early studies have reported that juvenile arthritis was frequently associated with lifelong disability. In a 1981 study, about half of patients followed for 10 to 22 years became handicapped or experienced some functional limitation, and 11.3% had severe limitations.⁴ With modern targeted treatment with conventional synthetic, targeted synthetic, and biologic disease-modifying antirheumatic drugs (DMARDs), it is anticipated that most children with JIA will quickly improve in function.

In Canada, achievement of clinically inactive disease within 70 weeks of JIA diagnosis has increased from 64% to 83% when comparing 2005 to 2010 and 2017 to 2021 inception cohorts.⁵ Despite these improvements in control of disease activity, it is known that some children still experience substantial functional impairments, but the characteristics of this patient population have not been systematically described.⁶ There is limited prospective data on physical function trajectories in patients on modern treatments, including how often impairments persist and which baseline factors predict them. A systematic review found that the few proposed predictors were not confirmed in other studies,⁷ and there is a dearth of information on long-term function of patients with disease onset in the biologic era.⁸

The World Health Organization (WHO) International Classification of Functioning, Disability, and Health (ICF) is the international framework for measuring health and disability in individuals and broader populations.⁹ In ICF, functioning refers to all body functions, activities, and participation, whereas disability refers to all impairments (significant deviations or loss of body functions),

activity limitations, and participation restrictions.⁹ Worse functional impairments are associated with poorer health-related quality of life,^{10,11} and better physical functioning is consistently associated with better overall pediatric quality of life scores.¹² In children and adolescents ages 8 to 16 years, a key period for development, functional impairments can cause delays in the optimization of gross motor skills and disrupt emotional and social development, ultimately affecting overall quality of life.¹²

In Canada, most children with JIA receive services to address function, such as physiotherapy and/or occupational therapy assessment and management. These interventions aim to reduce pain, improve range of motion in joints, increase strength, and improve participation in daily activities.^{13,14} By introducing these services closer to disease onset, patients may be more likely to improve physical function and well-being. Implementing preventive measures rather than treating established deficits is thought to have long-term positive effects on function.

This study aimed to describe modern longitudinal trajectories of physical function in children with different JIA categories and to identify data-driven trajectories of physical function that may lead to persisting functional impairments and the baseline characteristics that may predict these trajectories. Early identification of patients at high risk for long-term functional impairments would enable timely, targeted preventive interventions.

METHODS

Patients. Data collected between February 2017 and April 2024 from 20 academic and community pediatric rheumatology clinics across Canada participating in the Canadian Alliance of Pediatric Rheumatology Investigators (CAPRI) Registry were analyzed. (Members of the CAPRI Registry Investigators are included in Acknowledgements). The CAPRI Registry prospectively collects information on disease course, treatment, and outcomes among Canadian children diagnosed with JIA.¹⁵ Children and adolescents with disease onset before the age of 16 years are eligible to be enrolled within the first three months after their JIA diagnosis, if the family is able to complete questionnaires in English or French. Demographic and clinical characteristics of patients are reported by parents and physicians at enrollment and at every clinic visit until discharge from clinic or transfer to adult care. The CAPRI Registry study was approved by research ethics boards at all participating centers. Informed consent and appropriate assent were obtained from parents and participants, respectively. Central approval was provided by The University of British Columbia Children's & Women's Health Centre of British Columbia Research Ethics Board (H16-00309). For this study, registry participants whose parents had completed at least two functional assessment questionnaires by April 2024 were included; patients with missing recorded date of diagnosis or JIA category were excluded.

Measures. Physical function, our main outcome, was assessed using the Kids Disability Screen (KDS).¹⁶ KDS is the mean of numerical responses (from 0 to 10 in a 21-point scale) to two questions: “Does your child usually need help from you or another person because of arthritis?” and “Is it hard for your child to run and play because of arthritis?” The KDS score ranges from 0 = no disability to 10 = severe disability and has psychometric properties comparable to the 32-item Childhood Health Assessment Questionnaire (CHAQ) disability index.¹⁶ Based on their relationship with CHAQ scores, KDS scores >0 to 1.5 indicate mild disability, >1.5 to 4 mild to moderate disability, and >4 moderate to severe disability. In a validation cohort, the KDS had a standardized response mean of 0.67 compared with 0.62 for CHAQ, and it detected functional impairments in 44% of children with no impairment detected by CHAQ (CHAQ = 0).¹⁶ The answers to the two questions can also be combined with other patient characteristics to calculate an estimated CHAQ (eCHAQ) score. Concordance between eCHAQ and CHAQ was very good with a weighted kappa of 0.78.¹⁶ The parents of all registry participants were asked to complete the KDS at enrollment and at each subsequent clinic visit. At enrollment (and annually thereafter) parents were also asked to complete the CHAQ.

Selected variables collected at enrollment in the registry were examined as possible predictors of physical function trajectories. These included child’s age at diagnosis, sex, disease duration (length of time between the first symptom and diagnosis), number of active joints at enrollment, physician global assessment of disease activity (PGA; 0–10), acute phase reactants (highest erythrocyte sedimentation rate and highest C-reactive protein since onset), and pain intensity (0–10). Additionally, we examined baseline domain scores of the Juvenile Arthritis Quality of Life Questionnaire (JAQQ; gross motor function, fine motor function, psychosocial function, and systemic symptoms)¹⁷ and scores for fatigue and pain interference using Patient-Reported Outcome Measurement System (PROMIS) short parent-proxy questionnaires.^{18,19}

Analysis. Baseline characteristics of the cohort were described with numbers and percentages or medians and 25th and 75th percentiles, as appropriate for categorical, ordinal, and continuous variables. Trajectories of mean KDS scores for each JIA category following diagnosis were plotted with locally weighted scatterplot smoothing (LOWESS) with a bandwidth of 0.8 using STATA 15 software (StataCorp LLC). Kaplan–Meier survival analysis was used to estimate and display median time for children to attain optimal functioning (KDS = 0), for the overall cohort and by JIA category. Pairwise comparisons between JIA categories were done with log-rank tests with Bonferroni correction for multiple comparisons. As there were 21 comparisons, the Bonferroni threshold was $P < 0.002$. We calculated the frequency of visits with KDS scores >4 points after 2 years post diagnosis and examined their relationship with disease flares.

Flare was defined as an increase of one point or more in the PGA and starting or increasing antirheumatic medications.

Latent class trajectory analysis (LCTA) was used to identify groups of patients with similar trajectories of function irrespective of their JIA category,²⁰ starting at the time of diagnosis and for up to four years. This was done in a subset of participants who had at least four visits recorded in the registry and at least two valid KDS scores. After multiple imputation of missing scores and exclusion of the baseline score (because we were interested in examining the predictive value of baseline KDS scores), we explored LCTA models from one to six trajectories and selected the model with the best values of both the Akaike Information Criterion and the Bayesian Information Criterion.²¹ In secondary analyses, we also explored LCTA using eCHAQ scores. As age and sex are required for eCHAQ calculation, patients with missing recorded data on age or sex were excluded from this analysis.

Recursive partitioning was used to identify simple decision trees that could be used in clinic to detect patients assigned to latent classes with persisting impairments.²² Multiple imputation by chained equations was used to impute values in 5 data sets for the LCTA with averages taken as per Rubin’s rules²³ and in 20 data sets for the recursive partitioning analysis. Our recursive partitioning (decision tree) analyses focused on predicting patients who develop persisting impairments versus those with resolving or no impairments. Because our aim was to identify a simple decision tree that could be used at baseline to detect most patients likely to follow trajectories with persisting impairments, we focused on sensitivity calculations and assessed scenarios when a KDS was available, a CHAQ was available, or no patient reported measures were available. Because we had 20 imputed data sets and there are not established methods to combine 20 trees that may select different variables and cutoff values, we combined all 20 data sets first and then constructed 1 tree that was agreed to by the bulk of the data, with imputation uncertainty reflected by allowing proportional node assignments. We used the full stacked data set with 20 rows of imputed data per patient to build trees containing one to five splits (two to six terminal nodes). To objectively evaluate the predictive ability of each different tree size, we performed five-fold cross-validation on the stacked data, fitting classification trees to each of the five folds. The folds were created by randomly assigning each patient to a fold, ensuring that all 20 observations per patient were assigned to the same fold. Missing data imputation, LCTA, and recursive partitioning computations were done using R software packages “mice,” “lcm,” and “rpart,” respectively,²⁴ and they are described in detail in the online Supplementary Materials.

RESULTS

A total of 1,125 patients had been enrolled in the CAPRI Registry within three months of diagnosis by April 2024. After excluding patients with missing JIA category ($n = 10$) and those who had less

than two KDS scores ($n = 175$), a total of 940 patients were included in our study. Among 8,850 clinic visits recorded in the registry for these patients, there were 7,351 KDS scores available (83% of visits), 6,088 of them within three years of JIA diagnosis. Participant's median follow-up time was 787 days after diagnosis (25th, 75th centiles 383–1,350), and 333 patients (35.4%) were followed for more than three years. The median number of visits per patient was 5 (25th, 75th centiles 2–8) with a maximum of 37 visits. Patients included in the study were comparable to excluded patients (Table 1), except that excluded patients were more recently diagnosed and followed for a shorter period, a median of 70 days following diagnosis (25th, 75th centiles 0–265).

The demographic and clinical characteristics of participants at enrollment are summarized in Table 1. Participants were enrolled a median of six days after diagnosis (25th centile 0, 75th centile 52) at a median age of 9.1 years (25th centile 4.3, 75th

centile 13.2), and 63.2% were female. Most patients had oligoarthritis (45.3%), RF-negative polyarthritis (19.3%), or enthesitis-related arthritis (ERA; 14.4%). The median KDS score upon enrollment was 2.50 (25th centile 0.50, 75th centile 5.25), and the median CHAQ was 0.375 (25th centile 0, 75th centile 1.0). The mean KDS score at enrollment was 3.1 (SD 2.9), with children with RF-positive polyarthritis having the highest mean KDS at enrollment (4.9, SD 3.1) and children with psoriatic arthritis having the lowest (2.4, SD 2.5) (Table 1).

Trajectories of physical function by JIA category.

Figure 1 shows trajectories of mean KDS scores for each JIA category obtained with LOWESS and the dispersion in KDS scores. Trajectories varied across JIA categories. As stated in the previous paragraph, patients with RF-positive polyarthritis reported the highest KDS scores shortly after diagnosis, and patients with psoriatic arthritis reported the lowest scores. Mean KDS scores improved for all categories within the first year after diagnosis and then stabilized, with patients with ERA having somewhat higher mean KDS scores than the other categories up to four years. Because the number of patients followed for more than four years for infrequent JIA categories was small, LOWESS trajectories in Figure 1 should be interpreted with caution beyond this time. Although mean trajectories improved in the first year, 75 patients (8.0%) reported KDS >4 at least once beyond the initial two years after diagnosis (Figure 1B). There were 148 study visits with a KDS score >4 after two years of diagnosis in these 75 patients; 31 visits (20.9%) had a concomitant disease flare, 107 visits (72.3%) did not, and 10 visits (6.8%) did not have enough information to determine the presence of a flare. The median PGA value for these visits was 1 (25th, 75th centiles 0–3), with a KDS >4 reported in 50 visits with a PGA of 0.

Time to attain optimal function. A Kaplan–Meier survival analysis of the rate at which patients in different JIA categories attain an optimal KDS score of 0 showed substantial differences across JIA categories (Figure 2). The median time for the overall cohort to attain KDS = 0 was 36 weeks after diagnosis (25th, 75th centiles 15, 96). Patients with systemic arthritis attained a KDS score of 0 sooner, at a median of 13 weeks (25th, 75th centiles 7, 40), followed by patients with oligoarthritis at a median of 26 weeks (25th, 75th centiles 12, 61). Patients with undifferentiated arthritis took the longest at a median of 73 weeks (25th, 75th centiles 24, 104). Pairwise comparisons across JIA categories with log-rank tests showed that patients with systemic arthritis and oligoarthritis had significantly faster attainment of a KDS of 0, relative to patients with polyarthritis RF-negative and ERA ($P < 0.001$; Figure 2).

LCTA. LCTA included 727 patients with at least four recorded visits and two valid KDS scores. These patients attended 7,211 visits. The best fitting LCTA model identified five distinct data-driven trajectories of physical function (Figure 3). There was one trajectory with little measurable functional

Table 1. Baseline characteristics of the cohort at enrollment*

Characteristic	Included patients	Excluded patients
Number of patients	940	185
Age, y	9.1 (4.3, 13.2)	11.2 (7.0, 14.0)
Female, n (%)	587 (63.2)	101 (62.0)
Time since diagnosis, d	6 (0, 52)	0 (0, 42)
Time since disease onset, d	163 (90, 307)	152 (90, 381)
Follow-up time, d	787 (383, 1350)	70 (0, 265)
Visits per patient	5 (2, 8)	2 (1, 5)
JIA category, ^a n (%)		
Oligoarthritis	426 (45.3)	84 (46.9)
Polyarthritis RF-negative	181 (19.3)	30 (16.8)
Enthesitis-related arthritis	135 (14.4)	30 (16.8)
Psoriatic arthritis	52 (5.5)	14 (7.8)
Systemic arthritis	46 (4.9)	8 (4.5)
Polyarthritis RF-positive	37 (3.9)	2 (1.1)
Undifferentiated	63 (6.7)	11 (6.1)
Active joint count	2 (1, 6)	2 (1, 4)
Physician global assessment	4.0 (2.5, 6.0)	3.0 (1.5, 5.0)
Parent global assessment	2.0 (0.5, 5.0)	2.0 (1.0, 5.0)
Pain in last week	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)
CHAQ disability index	0.375 (0.0, 1.0)	0.375 (0.0, 1.0)
KDS	2.50 (0.50, 5.25)	2.625 (0.5, 5.5)
Whole cohort, mean (SD)	3.1 (2.9)	3.3 (2.9)
Oligoarthritis, mean (SD)	2.7 (2.9)	2.8 (2.7)
Polyarthritis RF-negative, mean (SD)	3.6 (2.9)	3.9 (3.2)
Enthesitis-related arthritis, mean (SD)	3.6 (2.6)	3.4 (2.6)
Psoriatic arthritis, mean (SD)	2.4 (2.5)	4.5 (3.1)
Systemic arthritis, mean (SD)	2.7 (3.3)	2.8 (3.3)
Polyarthritis RF-positive, mean (SD)	4.9 (3.1)	1.9 (1.6)
Undifferentiated, mean (SD)	3.2 (2.7)	4.5 (3.1)

* Numbers are median (25th, 75th centiles) unless otherwise specified. CHAQ, Childhood Health Assessment Questionnaire; JIA, juvenile idiopathic arthritis; KDS, Kids Disability Screen; RF, rheumatoid factor.

^a JIA category assigned by physician at diagnosis.

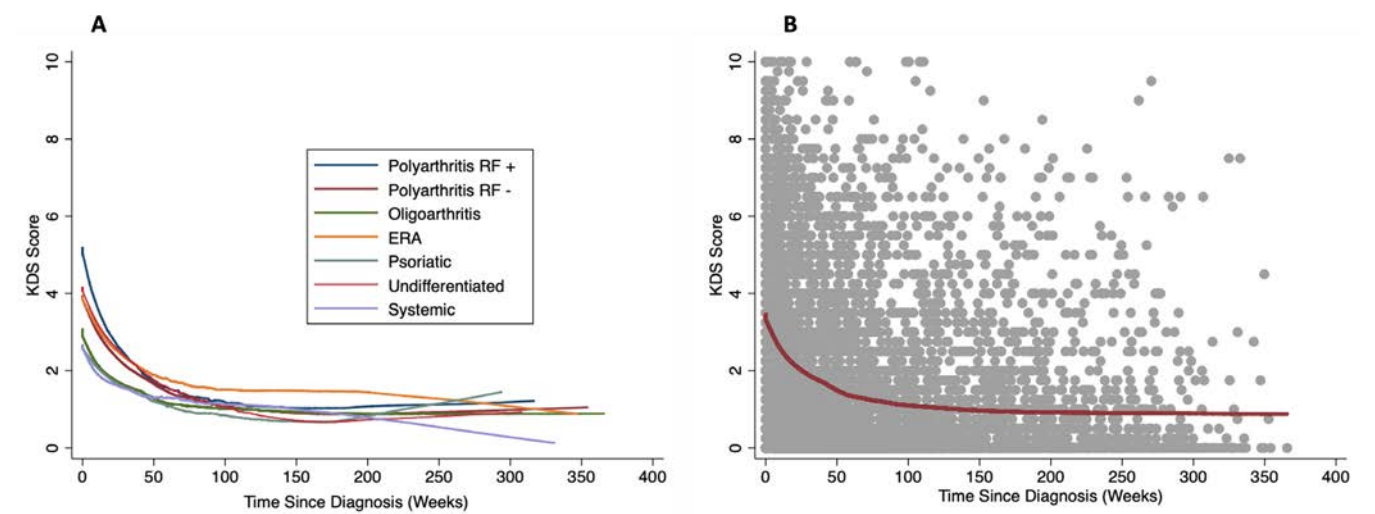


Figure 1. Trajectories of physical function by JIA category. Shown are (A) the trajectories of physical function by JIA category following diagnosis and (B) KDS score dispersion for the whole cohort. Trajectories were plotted using LOWESS with a bandwidth of 0.8. ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; KDS, Kids Disability Screen; LOWESS, locally weighted scatterplot smoothing; RF, rheumatoid factor.

impairment throughout four years of follow-up (class 5, 38% of patients), two trajectories with initial impairments that resolved during follow-up (class 1 with moderate impairment in 5% of patients and class 2 with mild to moderate impairment in 19% of patients), and two trajectories associated with persisting mild functional impairments (class 3 with initial mild to moderate impairment that improves but does not resolve in 24% of patients

and class 4 with persisting mild impairment throughout in 14% of patients). There were no trajectories with persisting moderate or severe impairments identified by LCTA.

LCTA looks at patterns within the data suggesting patient subgroups that share similar trajectories; then it calculates probabilities for each patient to belong to each of the identified classes/trajectories. The online Supplementary Materials report the

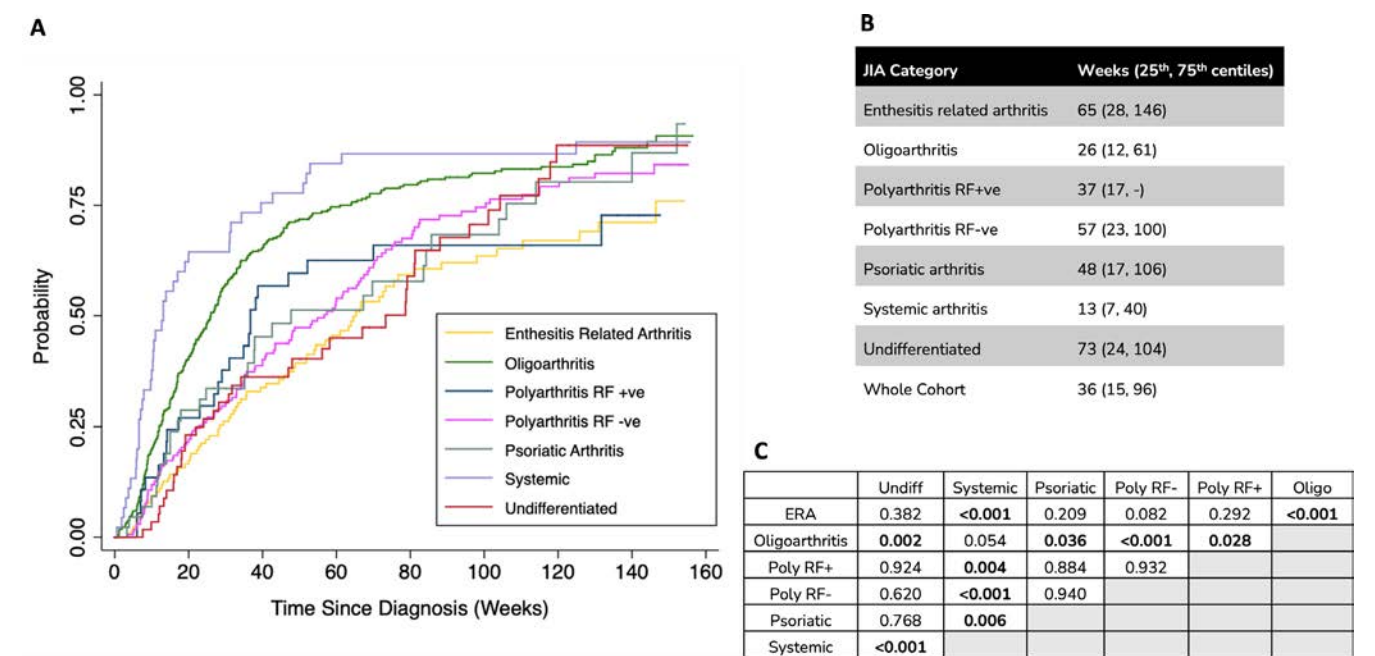


Figure 2. Time to first attainment of an optimal KDS score of 0. Shown is (A) the probability of attaining an optimal KDS score of 0 over 3 years after JIA diagnosis by JIA category. Shown is (B) the median (25th, 75th centiles) number of weeks to attain a KDS score of 0 for each JIA category and for the overall cohort. Shown is (C) *P* values for pairwise comparisons of JIA categories using the log-rank test. Comparisons with *P* < 0.05 are bolded. Considering the multiple pairwise comparisons in (C) (*n* = 21), values of *P* < 0.002 would correspond to the Bonferroni correction threshold. ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; KDS, Kids Disability Screen; RF, rheumatoid factor.

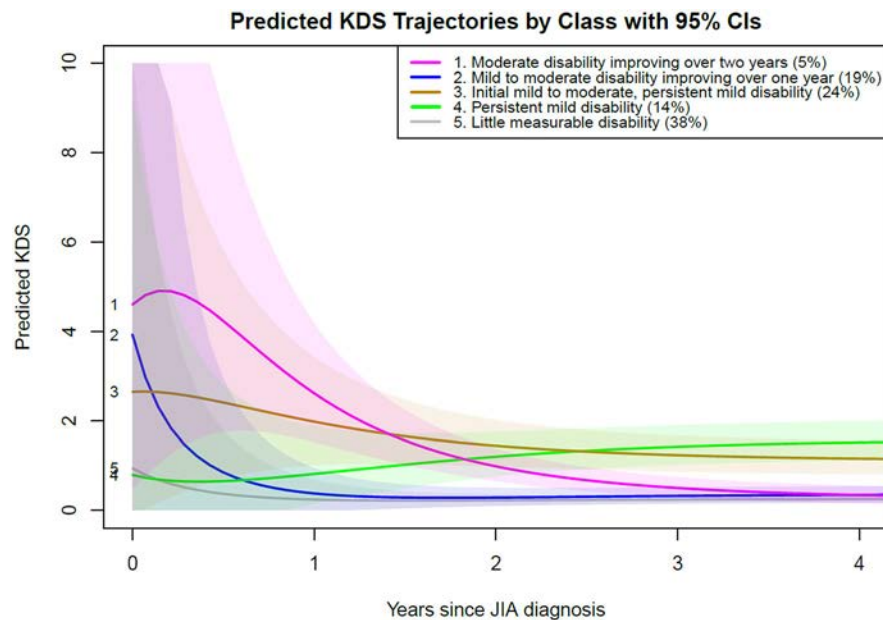


Figure 3. Predicted KDS trajectories of physical function by LCTA with 95% CIs. Shown are the data-driven trajectories of KDS scores over the 4 years after diagnosis, modeled using LCTA, and the proportion of patients predicted to follow each trajectory. CI, confidence interval; JIA, juvenile idiopathic arthritis; KDS, Kids Disability Screen; LCTA, latent class trajectory analysis.

diagnostic measures that led to choosing our five-trajectory model. We assigned each patient to the class with the highest probability. The mean posterior classification probabilities for patients to be assigned to classes 1 to 5 were 0.66, 0.62, 0.64, 0.71, and 0.82, with 42%, 34%, 32%, 50%, and 68% of assigned patients having a probability above 0.70, respectively. The best fitting LCTA model when using eCHAQ scores, instead of KDS scores, identified three trajectories, and none of them had persisting functional impairments (see Supplementary Materials).

Many baseline indicators of disease activity, symptoms, function, and quality of life were significantly different across the five physical function trajectories (Table 2). The proportion of patients with oligoarthritis ranged from 15.8% in patients with initial moderate impairment (class 1) to 53% in patients with little measurable impairment in class 5. The median number of affected joints was 5 (25th, 75th centiles 2, 10) in class 1, compared to 2 (25th, 75th centiles 1, 5) in class 5 ($P < 0.0001$ across trajectories). The median pain score was 4.5 in class 1 (25th, 75th centiles 3, 7.5), compared to 1.5 in class 5 (IQR 0, 3.5; $P < 0.001$). Other parent-reported outcomes followed a similar pattern with greater severity in class 1 and lesser severity in class 5, although class 3 had the highest levels of pain (median 5; 25th, 75th centiles 3, 7.5) and parent global assessment score (median 4; 25th, 75th centiles 2, 6). Joints important for ambulation, such as hip, foot, and ankle, showed a similar gradient, with more frequent involvement in class 1 (18.4% with hip and 60.5% with ankle involvement) and lesser involvement in class 5 (5.8% and 37.7%, respectively). In summary, the milder the disease presentation at baseline, the more likely patients would follow a trajectory with little measurable impairment.

Decision trees. When we analyzed scenarios in which baseline KDS scores were available, recursive partitioning selected KDS as the most discriminating first variable, and a cutoff of $KDS \geq 1.5$ detected 79% of patients in trajectories with persisting mild deficits (ie, sensitivity = 0.79), with a specificity of 0.48 (Figure 4). When we analyzed scenarios in which a baseline CHAQ (but not a KDS) was available, recursive partitioning selected a CHAQ score ≥ 0.5 as the most discriminating variable cutoff with sensitivity of 0.59 and specificity of 0.59. Adding additional baseline variables to decision trees that included KDS or CHAQ scores did not substantially improve detection of patients with persisting mild functional impairments. In scenarios in which no baseline patient-reported measures were available, age was the most discriminating variable and a cutoff of ≥ 9.5 years had a sensitivity of 0.54 and specificity of 0.60 for detecting patients with persisting mild functional impairments.

DISCUSSION

This study examined modern trajectories of physical function in a large Canadian JIA inception cohort with full representation of all JIA categories. We found that, shortly after JIA diagnosis, functional impairments measured with the KDS varied across JIA categories. Initial KDS scores were worse for patients with RF-positive polyarthritis and best for psoriatic arthritis. The mean KDS scores decreased during the first year after diagnosis for all JIA categories and then stabilized. A minority of children in each category reported significant impairments at visits beyond two years after diagnosis, and only one fifth of these visits were

Table 2. Baseline characteristics of patients in each of five physical function trajectories identified with latent class trajectory analysis*

Characteristic	Class 1: initial moderate impairment	Class 2: initial mild to moderate impairment	Class 3: initial mild-moderate, persisting mild	Class 4: persisting mild impairment	Class 5: little measurable impairment	P value
Patients, n (%)	38 (5)	137 (19)	176 (24)	100 (14)	276 (38)	
Age, y	8.4 (3.5, 11.8)	8.6 (3.8, 12.8)	10.7 (5.2, 13.8)	9.5 (4.2, 13.1)	7.1 (3.2, 12.0)	<0.001
Female, n (%)	23 (60.5)	84 (61.3)	120 (68.2)	64 (64.0)	171 (62.0)	0.665
Time to diagnosis, d	151 (73, 347)	104 (58, 213)	160 (78, 364)	139 (63, 364)	118 (61, 236)	0.049
JIA category, ^a n (%)						0.001
Oligoarthritis	6 (15.8)	47 (34.3)	72 (40.9)	50 (50)	148 (53.6)	
Polyarthritis RF-negative	11 (28.9)	34 (24.8)	35 (19.9)	16 (16)	49 (17.7)	
Enthesitis-related arthritis	5 (13.2)	23 (16.8)	31 (17.6)	13 (13)	22 (8.0)	
Psoriatic arthritis	3 (7.9)	11 (8.0)	9 (5.1)	3 (3.0)	15 (5.4)	
Systemic arthritis	2 (5.3)	6 (4.4)	8 (4.6)	6 (6.0)	18 (6.5)	
Polyarthritis RF-positive	2 (5.3)	7 (5.1)	9 (5.1)	6 (6.0)	9 (3.3)	
Undifferentiated	9 (23.7)	9 (6.6)	12 (6.8)	6 (6.0)	15 (5.4)	
Active joint count	5 (2, 10)	3 (2, 8)	3 (1, 6)	2 (1, 5)	2 (1, 5)	<0.001
Limited joint count	3 (1, 7)	3 (1, 5)	2 (1, 4)	1 (1, 3)	1 (1, 3)	<0.001
Hip involvement, n (%)	7 (18.4)	20 (14.6)	27 (15.3)	14 (14.0)	16 (5.8)	0.005
Foot or ankle involvement, n (%)	23 (60.5)	83 (60.6)	87 (49.4)	34 (34.0)	104 (37.7)	<0.001
Wrist involvement, n (%)	14 (36.8)	46 (33.6)	60 (34.1)	27 (27.0)	74 (26.8)	0.313
Presence of enthesitis, n (%)	5 (14.3)	14 (10.8)	22 (13.6)	9 (9.0)	10 (4.2)	0.013
Physician global assessment	4.2 (3, 7)	5 (3, 7)	4 (2.5, 6)	3.5 (2, 5)	3 (2, 5)	<0.001
Parent global assessment	3.7 (1.5, 7)	2.5 (1, 5)	4 (2, 6)	2 (0.5, 4)	0.5 (0, 2)	<0.001
Pain in last week (parent)	4.5 (3, 7.5)	3 (2, 7)	5 (3, 7.5)	3 (1.5, 5)	1.5 (0, 3.5)	<0.001
CHAQ disability index	1.1 (0.5, 1.2)	0.5 (0.1, 1.0)	0.7 (0.2, 1.4)	0.3 (0.1, 0.9)	0.1 (0, 0.5)	<0.001
KDS	5.6 (3.5, 7.7)	3.5 (1.2, 6.0)	5 (2.5, 7.0)	2 (0.7, 4.0)	0.5 (0, 2.5)	<0.001
ESR, mm/h	24 (14, 44)	25 (12, 41)	20 (9, 42)	18 (10, 44)	16 (7, 37)	0.062
CRP, mg/L	9 (4, 26)	11 (3, 31)	6 (1, 14)	5 (2, 15)	4 (1, 17)	<0.001
Pain interference score	70 (65, 74)	66 (60, 71)	69 (64, 74)	65 (56, 71)	57 (46, 65)	<0.001
Fatigue score	64 (60, 69)	60 (51, 67)	64 (58, 69)	60 (44, 66)	52 (43, 60)	<0.001
JAQQ total score	3.8 (2.9, 4.7)	3.0 (2.2, 4.4)	3.6 (2.7, 4.8)	2.7 (1.9, 3.7)	1.8 (1.4, 2.8)	<0.001

* Values are median (25th, 75th centiles) unless otherwise specified. P value calculated across the five trajectories with Kruskal-Wallis test or chi-square test, as appropriate. CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JAQQ, Juvenile Arthritis Quality of Life Questionnaire; JIA, juvenile idiopathic arthritis; KDS, Kids Disability Screen; RF, rheumatoid factor.

^a JIA category assigned by the pediatric rheumatologist at diagnosis.

associated with documented arthritis flares. Children with systemic arthritis and oligoarthritis attained an optimal KDS score of 0 earlier than those in other JIA categories.

LCTA found five data-driven physical function trajectories with one in three children following trajectories with persisting mild functional impairments. There were no trajectories with persisting moderate or severe functional impairments. Because patients were recruited between 2017 and 2024 and the length of follow-up varied with most patients having under four years of follow-up, the LCTA trajectories are presented for the first four years after diagnosis. Although multiple baseline characteristics differed across the five trajectories, in our decision tree analyses, an initial KDS ≥ 1.5 performed best and identified 79% of patients with persisting mild impairments. That said, our assignment of patients to the LCTA trajectory with greatest probability should be interpreted with caution because often the posterior probability of assignment was less than ideal (<70%).

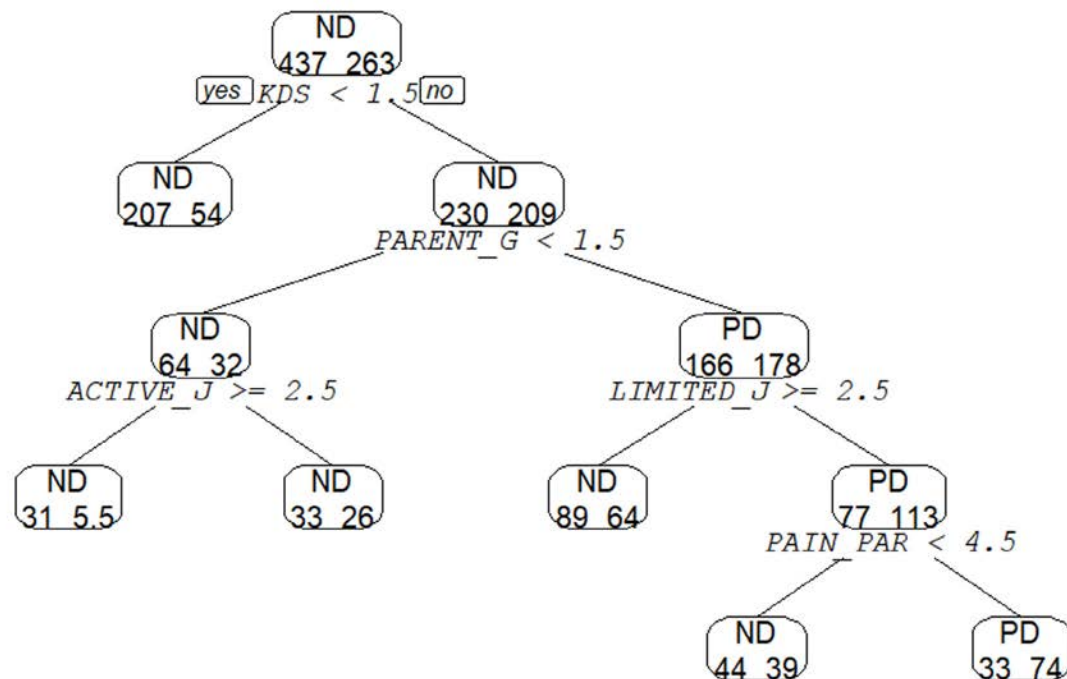
Although, to our knowledge, this is the first study to examine modern trajectories of physical function in children with JIA, multiple studies have examined trajectories of other disease

outcomes, including disease activity,^{25,26} pain,²⁷ and health-related quality of life.²⁸ Shoop-Worrall et al reported trajectories of active joint counts, PGA, and parent global assessment of well-being, identifying six trajectory clusters.²⁵ Balay-Dustrude et al assessed predictors of disease activity and found correlations across polyarticular RF-negative, psoriatic, and enthesitis-related JIA and worse disease activity at 12 and 24 months. Active disease at 3 months post diagnosis and older age were also associated with higher disease activity at 12 and 24 months.²⁶

Treatments were not specifically examined in our study; however, therapies used in the CAPRI Registry have been recently described, highlighting a step-up approach with escalation of treatment when there is an inadequate clinical response to prior therapy, consistent with current practice guidelines.^{5,29} Practices for discontinuing DMARDs in patients with inactive disease vary, although children with polyarticular arthritis typically remain on DMARDs for a longer duration.³

Our cohort, with patients newly diagnosed with JIA between 2017 and 2024, more accurately reflects current functional

A Analysis 1 | Pruned Tree, Nodes: 6



B

	Best cutoff	Sensitivity	Specificity
If KDS available	KDS≥1.5	0.79	0.48
If CHAQ, but no KDS	CHAQ≥0.5	0.59	0.59
If no PROS available	Age≥9.5y	0.54	0.60

Figure 4. Results of decision tree analyses. Shown is (A) the example of a 6-node decision tree when a KDS is available at baseline and (B) the variables and cut-offs that optimize detection of patients with trajectories of persisting mild impairments under different circumstances. ACTIVE_J, number of active joints; CHAQ, Childhood Health Assessment Questionnaire; KDS, Kids Disability Screen; LIMITED_J, number of joints with limited movement; ND, no persisting disability; PAIN_PAR, pain intensity in the last week reported by parent; PARENT_G, parent global assessment of well-being; PD, persisting disability; PROS, patient-reported outcomes. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.80039/abstract>.

trajectories, relative to studies in patients diagnosed before the widespread use of biologic DMARDs. These treatments have made significant impacts on the expectations of remission in children with JIA.³⁰ Oliveira Ramos et al highlighted that long-term longitudinal studies of JIA cohorts with disease onset in the biologic era are a necessary next step in JIA research.⁶ Joint damage is considered an important factor leading to physical disability, and with full control of disease activity with modern medications, it is expected that joint damage is mitigated or prevented.^{6,31}

The main strengths of this study are the large cohort of children with JIA that is representative of all JIA categories and the data collection at every clinic visit using a validated brief measure of physical function resulting in thousands of assessments. Other studies of function in JIA have studied “convenience” populations, in which they collect information from all patients who attend the clinic within a certain time frame. This may lead to overrepresentation of children with functional impairments because patients who are clinically worse tend to have more frequent visits

and, thus, a higher likelihood of being included in those studies. Collecting data from families across many locations in a country with a universal health care system and well-developed pediatric rheumatology services resulted in a demographic that closely represents the general population of children with JIA. Collecting data at every visit to the clinic provides closer monitoring and more accurate detail about the longitudinal trajectories of function than could be provided by periodic questionnaires completed once or twice a year.

Our study should be interpreted considering several limitations. First, 17% of recorded visits to clinic for the included patients had missing KDS scores. Although questionnaires are often missing simply because families forget to complete them, there may be an association between having inactive disease and not completing questionnaires. Families often report that they feel questionnaires are not necessary when they have “nothing to report.” In our study, missing data were addressed with multiple imputation before LCTA. That said, we acknowledge that other factors may influence KDS scores and there are limitations to the accuracy of imputation of patient-reported measures.

Second, there may be understandable hesitancy to directly compare results using the KDS to those obtained with the CHAQ, given the latter’s widespread use and rigorously verified metrics in multiple settings and languages. The KDS used in this study has been shown to be highly sensitive at detecting the presence of functional impairments in children with JIA and may have a lesser ceiling effect and greater responsiveness than the CHAQ disability index in this population.¹⁶ Interestingly, the use of the eCHAQ scores in LCTA in our cohort failed to detect the trajectories with mild persisting impairments detected using KDS scores. Being a short index with only two items makes it feasible to collect KDS scores at every clinic visit, relative to the 30+ item CHAQ. When designing the CAPRI Registry, it was felt that sustaining ongoing reliable completion of the CHAQ questionnaire at every visit to the clinic across all centers was not feasible, and feasibility was also the reason why Canadian pediatric rheumatologists were hesitant to include functional assessment at every visit as a key performance indicator in JIA.³²

Third, our inability to detect trajectories with persisting moderate or severe functional impairments does not mean that no Canadian children with JIA experience substantial ongoing impairments. Despite modern treatments, many pediatric rheumatologists can recall at least one patient who developed significant disability despite best efforts. The number of such patients may be too small for LCTA to detect their trajectories, or they may come from marginalized communities with limited participation in the CAPRI Registry. Additionally, because most patients were followed for less than four years and the posterior probabilities of assignment to a trajectory were often below 0.7, caution should be exercised in interpreting LCTA results.

In conclusion, this longitudinal assessment of trajectories of physical function in children with JIA in Canada diagnosed in

2017 to 2024 show that shortly after diagnosis, patients have different levels of functional impairment related to their JIA category and they improve in function during the first year and subsequently stabilize. We identified five JIA data-driven physical function trajectories with about one in three children having mild persisting impairments and no trajectories with persisting moderate or severe impairments. At baseline, multiple characteristics differed across the five trajectories, with patients with more involved joints and more severe symptoms having less favorable trajectories. If the KDS is available at baseline, a KDS score ≥ 1.5 would identify both children with current significant impairments and about 79% of children who subsequently develop persisting mild functional impairments. This KDS cutoff may help identify patients who may benefit from early, intensive targeted rehabilitation intervention.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Guzman confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ACKNOWLEDGEMENTS

The following Investigators participated in the design of the CAPRI JIA registry: David A. Cabral, Gaëlle Chédeville, Ciarán M. Duffy, Kerstin Gerhold, Jaime Guzman, Linda Hiraki, Adam M. Huber, Heinrike Schmeling, Natalie J. Shiff, and Lori B. Tucker. The following Investigators provided data that were analyzed in this study: Julie Barsalou, Daniah Basodan, Michelle Batthish, Roberta A. Berard, Nicholas Blanchette, Gilles Boire, Roxana Bolaria, Alessandra Bruns, David A. Cabral, Sarah Campillo, Tania Cellucci, Mercedes Chan, Gaëlle Chédeville, Amieleena Chhabra, Julie Couture, Paul Dancey, Jean-Jacques De Bruycker, Erkan Demirkaya, Muhammed Dhalla, Ciaran M. Duffy, Talal El Tal, Tommy Gerschman, Jaime Guzman, Liane Heale, Julie Herrington, Kristin M. Houghton, Adan M. Huber, Andrea Human, Nicole Johnson, Roman Jurencak, Bianca Lang, Claire LeBlanc, Lillian Lim, Lily S. H. Lim, Nadia Luca, Jeanine McColl, Tara McGrath, Tamara McMillan, Megan McPherson, Paivi Miettinen, Kimberly Morishita, Honyan Ng, Jonathan Park, Jean-Philippe Proulx-Gauthier, Johannes Roth, Evelyn Rozenblyum, Dax G. Rumsey, Heinrike Schmeling, Rosie Scuccimari, Gordon Soon, Rebeka Stevenson, Elizabeth Stringer, Herman Tam, Lori B. Tucker, Marinka Twilt, Ruud H. J. Verstegen, and Karen Watanabe Duffy.

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LETTER

DOI 10.1002/acr.80062

Limitations of ultrasonography in the assessment of aortic involvement in giant cell arteritis: comment on the article by Bull Haaversen et al

To the Editor:

We read with interest the article entitled “Ultrasonography compared with computed tomography in identifying thoracic aortic aneurysms in patients with giant cell arteritis” by Bull Haaversen et al.¹ We congratulate the authors on addressing an important and clinically challenging question in the care of patients with giant cell arteritis (GCA). The study demonstrates a correlation between ultrasonography and computed tomography (CT) measurements of ascending aortic diameter, leading the authors to conclude that ultrasonography can be used for screening and monitoring of aortic aneurysms in GCA. Although we commend this contribution, we raise considerations regarding the interpretation and broader clinical implications of these conclusions.

Thoracic aortic aneurysms are generally late-term complications of GCA, and their incidence increases over time.² Emerging radiologic and histopathological evidence support the concept that aortic aneurysm formation is driven by aortic inflammation.^{3–5} Furthermore, radiologic evidence of active disease in large arteries, including the aorta, has been linked to clinical relapse and future development of aortic aneurysms.^{3,6–8} Although ultrasonography might be a reasonable modality for assessing the diameter of the ascending aorta, it has important limitations in detecting and monitoring active inflammatory disease within the aortic wall as well as in evaluating disease involvement beyond the ascending aorta. CT angiography (CTA), magnetic resonance angiography (MRA), and positron emission tomography–CT offer the advantage of assessing disease activity in the whole aorta by revealing signs of wall thickening, contrast enhancement, wall gadolinium uptake, wall edema, and wall hypermetabolism.⁹ In the cross-sectional portion of this study, Bull Haaversen et al identified six patients with descending thoracic aortic aneurysms, five of whom also had concomitant aneurysms in the ascending aorta. This observation led the authors to conclude that isolated descending thoracic aortic aneurysms in GCA are rare and that ultrasonography is sufficient for aortic aneurysm assessment in GCA despite its limited ability to visualize the descending aorta.

Estimates of the frequency and distribution of aortic aneurysms in GCA vary across studies, partly due to differences in study design, imaging modalities, and definitions of aneurysm. We agree that the ascending aorta is a common site of aortic aneurysm in GCA; however, isolated descending thoracic aortic involvement, including aneurysm and dissection, also

occurs.^{2,3} In a prospective study in GCA, Moreel et al identified 23 patients with aortic aneurysms, of whom 18 had involvement of the descending thoracic aorta and 6 of the ascending aorta.³ Furthermore, descending thoracic aortic involvement at diagnosis has been identified as a risk factor for future vascular events.¹⁰ The limitation of ultrasonography to visualize the descending thoracic aorta is particularly important because advocating for primary reliance on ultrasonography to assess large-vessel disease in GCA risks missing potentially life-threatening aortic involvement. Ultrasonography may play an important role in longitudinal monitoring of known ascending aortic aneurysms in GCA as a noninvasive and accessible follow-up tool. However, it is our opinion that CTA or MRA should remain the standard modality in screening for large-vessel involvement in patients with GCA.

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80062>.

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Reply

To the Editor:

We thank the authors for their thoughtful comments and the opportunity to clarify the aims and implications of our study.¹ First, we would like to emphasize that the main objective of our study was not to assess disease activity or whole-aorta involvement, or to monitor inflammatory burden, but rather to compare ultrasonographic measurements of ascending aortic diameter with those from computed tomography (CT) to assess structural damage, such as aneurysms. Thus, the authors' comment that involvement of the descending thoracic aorta at diagnosis is a risk factor for future vascular events, although beyond the primary aim of our study, highlights an important limitation of ultrasonography in assessing the full extent of aortic disease rather than contradicting our findings.²

We would also like to address the concept of "radiologic evidence of active disease." At present, there is no consensus definition across imaging modalities, and the relationship between imaging findings (eg, wall thickening, contrast enhancement, or metabolic activity) and clinically meaningful outcomes such as relapse remain uncertain.^{3–7} This is reflected in current clinical practice, in which imaging is not routinely recommended for the follow-up of patients with giant cell arteritis (GCA).^{8,9}

Although thoracic aortic aneurysms are often assumed to be late-onset complications in GCA, the temporal relationship between inflammation and aneurysm formation remains incompletely understood. The finding in our study that 20% of patients already had aneurysms at diagnosis underscores the burden of preexisting structural vascular damage in GCA. This observation reinforces the need for accurate and reproducible methods to assess aortic dimensions, which was the specific focus of our study. Studies suggest that aneurysm development may reflect cumulative vascular damage, but it is

unclear to what extent this is driven by ongoing inflammation versus other factors such as age-related or degenerative changes. Furthermore, although vascular damage may occur at sites of prior inflammation, the predictive value of such findings is limited, with most vascular territories demonstrating imaging evidence of inflammation not progressing to structural damage over time.¹⁰

We agree that ultrasonography has limitations, particularly in assessing the descending thoracic aorta. However, this limitation does not negate the value of ultrasound for assessment of the ascending aorta, where agreement with CT was high. There is an unmet need for cost-effective strategies that are readily accessible to screen patients with GCA for long-term structural damage like aneurysms. Multiple studies indicate that the risk of aneurysm formation in GCA is primarily confined to the ascending thoracic aorta, which can be assessed with ultrasonography and echocardiography.¹¹ In the study by Moreel et al, in which aneurysms were reported predominantly in the descending thoracic aorta, the prevalence of concomitant ascending aortic aneurysms was not specified. In addition, different diameter thresholds were applied, with ≥ 35 mm used for the descending aorta and ≥ 45 mm for the ascending aorta.¹² According to European Society of Cardiology guidelines, follow-up of thoracic aortic dilatation is generally based on comparable diameter thresholds (≥ 40 mm), and thus, the results in the study by Moreel et al may be of limited relevance for clinical follow-up and surveillance decisions.¹³

The authors state, "[CT angiography] or [magnetic resonance angiography] should remain the standard modality in screening for large-vessel involvement in patients with GCA," and we respectfully disagree. Although cross-sectional imaging is necessary for comprehensive assessment of the entire aorta, current recommendations support ultrasonography as a first-line modality in GCA.⁸ We recognize the limitations in our sample size and study duration and that a cross-sectional design has inherent constraints. Importantly, our study does not argue for exclusive reliance on ultrasonography; rather, it highlights its utility as one of several complementary imaging modalities for evaluating large-vessel disease in GCA. These questions warrant further investigation. Nevertheless, our study demonstrates that, within its anatomic limits, ultrasonography provides reliable measurements of ascending aortic diameter, supporting its role as a complementary tool in clinical practice.

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Paper retraction and reviewer constraints: comment on the article by Vettori and Iudici

To the Editor:

The article by Vettori and Iudici¹ is highly significant. They comprehensively analyzed retracted papers in rheumatology, and papers from a specific country accounted for approximately half of them. The most common reasons for retraction involved misconduct, including peer review issues. The authors emphasized adherence to publication ethics, strengthening institutional oversight, and enhancing journals' vigilance. I fully agree with their view. However, they could further emphasize the reviewers' role. I wish to describe an additional issue, largely unexplored in this context, which may complement their findings: practical constraints faced by reviewers.

Many experienced reviewers have likely encountered instances of suspected misconduct during peer review. I have had such experiences. When the review process is single blind, reviewers may check authors' names in PubMed to determine whether they have prior retraction notices and to assess their publication record. A history of retraction does not in itself indicate misconduct; however, such contextual information may appropriately heighten vigilance, particularly when prior misconduct has been documented.

In practice, reviewers may encounter difficulties in accurately identifying authors. In several populations worldwide, surname concentration is high, and author names are often presented in abbreviated formats (eg, family name plus initial), rendering multiple individuals indistinguishable. Although affiliations may help clarify identity, they frequently change. These factors can make it difficult to determine whether an author has previously been associated with a retraction due to misconduct. Certain abbreviated names may recall prior retractions encountered in journals or databases; however, when surname concentration is high, recognizing that the current author is the same individual may not be straightforward.

Although discussed here from a reviewer's perspective, these challenges likely extend to editors and journals as well. I therefore hope that systems enabling more reliable author identification can be consistently and widely implemented. The use of persistent digital identifiers (eg, ORCID) in a user-friendly and mandatory manner may strengthen traceability, thereby improving transparency and accountability. As Vettori and Iudici noted, emerging technologies including artificial intelligence may further facilitate such efforts.

Reviewers remain an important safeguard against misconduct, preventing flawed or unethical work from entering the literature. As Allen² emphasized in her accompanying editorial, the ultimate purpose of medical publication is to improve

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Reviewers remain an important safeguard against misconduct, preventing flawed or unethical work from entering the literature. As Allen² emphasized in her accompanying editorial, the ultimate purpose of medical publication is to improve

patient care; thus, safeguarding integrity is inseparable from protecting patients. Strengthening reviewers' ability to perform this role becomes increasingly important given the rising number of retractions. Although discussed here in the context of rheumatology, these practical constraints are likely not unique to this field.

Two additional considerations merit attention. First, in settings of high surname concentration, structural ambiguity may unintentionally weaken the deterrent effect that retractions are expected to exert. Improved traceability may reduce this unintended effect and strengthen accountability. Second, a retraction does not always indicate misconduct. Some retractions are initiated by authors who identify serious errors that cannot be corrected through reanalysis or replication. As previously reported,³ author-initiated retractions accounted for approximately 5% of all retractions. These considerations should inform the design of any enhanced traceability system.

ACKNOWLEDGMENT

ChatGPT-5 (OpenAI) was used solely for English grammar and language editing. The author takes full responsibility for the content of the manuscript.

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80043>.

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DOI 10.1002/acr.80047

Reply

To the Editor:

We read with great interest the letter by Matsubara regarding our article.¹ The author raises an important point concerning the

role of reviewers in identifying possible causes of misconduct and the obstacles related to tracking the publication history of submitting authors. In particular, it can be difficult to check for prior retraction notices when the full first name is not available, particularly in contexts of surname clustering, and when a digital author identifier is not provided.

We agree with our colleague that ensuring transparency and limiting cases of misconduct is a challenging task that should involve multiple stakeholders, including readers, reviewers, editors, and publishers. Reviewers can contribute to maintaining research integrity at several levels: avoiding accepting peer review assignments when conflicts of interest exist, assessing key transparency issues such as prospective trial registration and concordance between registered and reported methodology, verifying compliance with ethical regulations, evaluating methodologic rigor, and ensuring transparency regarding funding sources and author contributions. Equally important is the commitment to reproducibility, which includes requiring thorough reporting of methodologies and encouraging data sharing.

We believe that the task of reviewers has become more demanding in recent years due to the need to identify forms of misconduct that may be difficult to detect and often require more sophisticated tools, such as data fabrication, duplication, figure manipulation, or plagiarism. Moreover, the number of submitted papers and reviewer invitations is increasing in a context in which researchers face busy schedules and limited time available for peer review activities. We agree with Matsubara that implementing reliable tools to identify authors and screen their scientific production would represent an important step toward improving the quality of peer review and that further efforts should be made to provide such tools to reviewers.

More broadly, improving peer review represents a difficult task, and the best strategies to implement remain the subject of ongoing debate.² Progress will likely require a combination of complementary approaches aimed at improving reviewer accountability, increasing awareness of their role in safeguarding public health, strengthening methodologic expertise, promoting diversity, fostering more open and transparent processes, and providing appropriate recognition for peer review activities. Addressing these different dimensions simultaneously may help reinforce the trustworthiness and sustainability of peer review in an increasingly complex scholarly publishing landscape.

ACKNOWLEDGMENTS

ChatGPT-5 (OpenAI) was used solely for English grammar and language editing. The author takes full responsibility for the content of the manuscript.

Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80047>.

patient care; thus, safeguarding integrity is inseparable from protecting patients. Strengthening reviewers' ability to perform this role becomes increasingly important given the rising number of retractions. Although discussed here in the context of rheumatology, these practical constraints are likely not unique to this field.

Two additional considerations merit attention. First, in settings of high surname concentration, structural ambiguity may unintentionally weaken the deterrent effect that retractions are expected to exert. Improved traceability may reduce this unintended effect and strengthen accountability. Second, a retraction does not always indicate misconduct. Some retractions are initiated by authors who identify serious errors that cannot be corrected through reanalysis or replication. As previously reported,³ author-initiated retractions accounted for approximately 5% of all retractions. These considerations should inform the design of any enhanced traceability system.

ACKNOWLEDGMENT

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/acr.80043>.

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DOI 10.1002/acr.80047

Reply

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