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Myositis

Brepocitinib shows promise for dermatomyositis

Data from the phase III VALOR trial indicate that the TYK2–JAK1 inhibitor brepocitinib could improve muscle and skin symptoms and reduce glucocorticoid use in patients with dermatomyositis. The clinical benefits of the treatment were apparent as early as week 4 and were sustained over the 52-week double-blind trial period.

"Brepocitinib is a first-in-class, selective TYK2–JAK1 inhibitor, a mechanistic profile that maps closely to pathways strongly implicated in dermatomyositis biology," explains Ruth Ann Vleugels, co-corresponding author of the paper reporting the results. By inhibiting TYK2 and JAK1, brepocitinib targets the signalling pathways of several cytokines linked to the immunopathogenesis of dermatomyositis, including type I and II interferons, IL-6, IL-12 and IL-23.

The multicentre VALOR trial enrolled adults with dermatomyositis resistant to at least one previous therapy. The study population was representative of patients with dermatomyositis, and 81.3% had moderate-to-severe disease activity. Participants received oral brepocitinib (15 mg or 30 mg once daily) or placebo, in addition to standard therapy. "Importantly, the protocol incorporated a mandatory steroid taper, ensuring that efficacy could be evaluated in the context of reducing steroid exposure," says Vleugels.

Total Improvement Score, a composite measure of disease improvement, at week 52 was significantly higher in the brepocitinib 30 mg group, but not in the brepocitinib 15 mg group, than in the placebo group. In addition to this primary end point, brepocitinib 30 mg was superior to placebo across all nine key secondary end points. "The key secondary outcomes spanned skin disease, muscle disease, physical function, rapidity of impact, and systemic glucocorticoid sparing, which speaks to both the breadth and depth of response," notes co-corresponding author Julie Paik.

Among the participants who were receiving glucocorticoids at baseline, 62% of those in the brepocitinib 30 mg group tapered to the equivalent of ≤2.5 mg prednisone daily by week 52, and 42% discontinued glucocorticoids altogether; by contrast, 31% of those in the brepocitinib 15 mg group and 23% of those in the placebo group discontinued glucocorticoids by week 52.

The incidence of adverse events was similar across the three treatment groups. The rate of serious infections was higher in the brepocitinib 30 mg group, but these infections resolved with medical management, and most of the affected patients were able to continue treatment with brepocitinib.

The longer-term safety and efficacy of brepocitinib are being evaluated in a 52-week open-label extension trial, but the available findings of the VALOR trial indicate that this TYK2–JAK1 inhibitor shows promise as a targeted, disease-modifying therapy for dermatomyositis.

Sarah Onuora

Original article: Vleugels, R. A. et al. A phase 3 trial of brepocitinib in dermatomyositis. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2503531 (2026)

Lupus nephritis

T cells mediate tissue damage in lupus nephritis

Although loss of B cell tolerance and autoantibody production are key features of lupus nephritis, $CD8^+$ T cell kidney infiltration is a strong indicator of a poor outcome. Now, findings published in *Immunity* provide insights into how $CD8^+$ T cells cause kidney damage in lupus nephritis.

Al Souz et al showed that $CD8^+$ T cells in the kidneys of lupus-prone MRL/*lpr* mice had a cytotoxic (granzyme B) phenotype, expressed exhaustion markers (PD-1 and TIM3) despite retaining their effector functions, and were associated with worsening disease. Depletion of these cells stabilized disease. Further research revealed that these cells arise from stem-like $CD8^+$ T cell precursors in kidney-draining lymph nodes, where they undergo clonal expansion, migrate to the kidneys and differentiate into effector $CD8^+$ T cells. The authors show that this process is antigen dependent rather than being a result of bystander activation.

Adoptive transfer of these cells either alone or in combination with $CD4^+$ T cells into T cell-deficient MRL/*lpr* mice showed that help from $CD4^+$ T cells is essential for $CD8^+$ T cell-mediated damage in mice with lupus-like disease, because although $CD8^+$ T cells migrated to the kidneys after transfer, kidney damage occurred only when $CD4^+$ T cells were also transferred. Notably, this T cell-differentiation trajectory is also observed in cancer and in chronic infection; however, in these indications, $CD8^+$ T cells do not retain their effector function.

The authors then provided further mechanistic insights by showing that IL-15 and IL-21 signalling is required for this $CD8^+$ T cell-induced damage. Both *Il15r* and *Il21r* were upregulated in kidney-infiltrating $CD8^+$ T cells. Stimulating stem-like $CD8^+$ T cells with IL-15 and IL-21 in vitro induced granzyme B expression and cytotoxicity. Blocking either IL-21 or IL-15 signalling in vivo in lupus-prone MRL/*lpr* mice inhibited the differentiation of stem-like $CD8^+$ T cells and mitigated tissue damage.

Single-cell RNA sequencing of kidney biopsies from 156 people with lupus nephritis and 30 healthy individuals revealed a similar stem-like $CD8^+$ T cell-differentiation trajectory in people with lupus nephritis. Disease chronicity was associated with an increased frequency of stem-like $CD8^+$ T cells and a reduction in $CD8^+$ cytotoxic T cells, indicative of a self-perpetuating damage loop. These analyses and in vitro experiments showed that both IL-15 and IL-21 can promote cytotoxicity in T cells from people with lupus nephritis, but not in those from healthy individuals.

When discussing the therapeutic implications of these findings, corresponding author Joseph Craft notes "We and others have shown that B cells, and $CD4^+$ T cells, activate $CD8^+$ T cell effector function in cancer and upon pathogen challenge. It will be important to determine if similar pathways are operative in lupus nephritis, and if so, this provides an argument for the use of bispecific T cell engagers as therapeutic options alongside B cell depleting therapies."

Holly Webster

Original article: Al Souz, J. et al. Organ injury in systemic autoimmunity is mediated by stem-like $CD8^+$ T cells arising from tissue-draining lymph nodes. *Immunity* https://doi.org/10.1016/j.immuni.2026.03.022 (2026)

Degenerative disc disease

Senotherapeutics suppress disc degeneration

Cellular senescence is increasingly implicated in age-related tissue degeneration and is emerging as a promising therapeutic target. New findings support senescence as an important contributor to intervertebral disc degeneration independently of ageing and demonstrate that systemically targeting senescence can preserve disc structure and cellular identity.

To separate the effects of ageing from disease mechanisms, the researchers used an SM/J mouse model, which develops spontaneous, early-onset disc degeneration. As early as 4 weeks of age, these mice showed increased expression of senescence markers and senescence-associated transcriptomic signatures in disc tissue, preceding structural degeneration.

Targeting a proposed early therapeutic window, the authors initiated early systemic treatment with a senotherapeutic combination of dasatinib and quercetin. This approach — unlike treatment with the alternative senolytic drug navitoclax — attenuated disc degeneration, reducing local senescence markers and selected senescence-associated secretory phenotype (SASP) factors, preserving disc architecture, and maintaining nucleus pulposus cell identity and viability.

"Our approach differs from prior studies by targeting disc degeneration proactively, at the earliest stages of degenerative change, rather than after structural damage is already well established," says corresponding author Makarand Risbud. "By showing that senolytic treatment can delay early-onset disc degeneration, this work expands the conceptual framework of disc disease and positions senescence as a therapeutic target even in non-aged contexts."

Transcriptomic analyses revealed transcriptional reprogramming in the discs following treatment, predominantly involving suppression of inflammatory, apoptotic and cell-cycle arrest pathways.

Cross-model comparisons with ageing C57BL/6 N mice identified JUN–JNK signalling as a shared mechanistic axis. Indeed, in vitro pharmacological inhibition of JUN in human cervical nucleus pulposus cells isolated from discs with advanced degeneration recapitulated the effects of dasatinib and quercetin treatment, reducing senescence markers and SASP gene expression.

"Dasatinib plus quercetin has successfully completed phase I and II clinical trials targeting senescence-related skeletal conditions, including osteoporosis," explains Risbud. "In this study, we validated our murine findings in human disc cells, opening the possibility of assessing disc health outcomes in patient populations where this serotherapeutic approach is already being tested."

Jessica McHugh

Original article: Novais, E. J. et al. Dasatinib and quercetin senolytic treatment delays early onset intervertebral disc degeneration in SM/J mice. *Bone Res.* **14**, 42 (2026)

Vasculitis

Adjunctive glucocorticoids in Kawasaki disease

In children with Kawasaki disease, treatment with intravenous immunoglobulin (IVIG) and aspirin reduces the development of coronary artery lesions but does not fully prevent this complication in all patients. Current guidelines recommend adding glucocorticoids to this standard primary treatment for children at high risk of resistance to IVIG treatment (a known risk factor for coronary artery lesions); however, whether this approach benefits unselected patients remains controversial. The results of a phase III, open-label, randomized trial in China now suggest that adjunctive prednisolone does not reduce the incidence of coronary artery lesions within 1 month of disease onset in unselected patients.

The trial included 3,208 children with newly diagnosed Kawasaki disease from 28 sites across China, irrespective of risk of IVIG resistance or coronary artery status. Participants were randomly allocated to receive either standard treatment (IVIG and oral aspirin) or standard treatment plus prednisolone.

At 1 month, coronary artery lesions were detected in 13.8% of those who received standard treatment alone and 16.0% of those who received standard treatment plus prednisolone. The occurrence of coronary artery lesions at 3 months was 10.5% and 12.6% in the two groups, respectively.

The proportion of participants with progression of coronary artery lesions and the incidence of medium-to-giant coronary-artery aneurysms were similar in both treatment groups. Rescue therapy for participants deemed to have resistance to IVIG therapy was received by 4.6% of those in the prednisolone group and 10.1% of those in the standard treatment group. The two groups were similar with respect to duration of fever and reductions in C-reactive protein levels.

Together, the results indicate that the addition of glucocorticoids to standard therapy does not improve clinical outcomes in unselected patients with Kawasaki disease at 1 month, although further studies are needed to assess longer-term outcomes.

Sarah Onuora

Original article: Lin, S. et al. Randomized trial of adjunctive prednisolone for Kawasaki disease. *N. Engl. J. Med.* **394**, 1480–1490 (2026)

Osteoarthritis

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Small but relevant effects of exercise therapy in osteoarthritis

Sita Bierma-Zeinstra & Jos Runhaar

Evidence for the effectiveness of exercise in osteoarthritis, particularly the long-term benefit, remains unclear. Now, a review of current evidence suggests that the benefits could be negligible. This finding raises an important question: should exercise therapy continue to be recommended as a first-line treatment for osteoarthritis?

Refers to Schleimer, T. et al. Effectiveness of exercise therapy for osteoarthritis: an overview of systematic reviews and randomised controlled trials. *RMD Open* **12**, e006275 (2026).

In 2026, Schleimer et al.[1] published a report synthesizing systematic reviews and randomized controlled trials (RCTs) on the effectiveness of exercise therapy for osteoarthritis (OA). The main conclusion was that the evidence for exercise remains largely inconclusive, showing negligible or only short-term small effects, which are comparable to – or even less effective than – other treatments. The report focused on comparators that are clinically relevant, such as placebo, sham, attention control, no intervention or other OA treatments. Fifty-five reviews were initially eligible for inclusion, five of which were then selected by the authors. The reviews collectively reported on 100 RCTs covering knee, hip, hand and ankle OA and 'mixed OA', with minimal overlap between the trials (0.2%). An additional 28 RCTs were included to address gaps and/or limitations in the selected reviews (for example, no meta-analysis for a specific OA type or relevant comparator).

Based on evidence from the placebo-controlled trials included, the authors reported small, short-term effects of exercise therapy. This finding might mislead readers into thinking that the placebo effect has been ruled out. However, the placebo conditions used were for other types of interventions (that is, inactive ultrasound, inactive topical cream or intra-articular saline injection), meaning the placebo effects associated with those interventions remain present. In these instances, exercise is compared with the contextual and placebo effects of that intervention. These placebo effects are substantial in OA (average effect size ≈0.51) and vary depending on the intervention type and quality of blinding[2,3]. Small benefits of exercise still occur when compared with placebo interventions, which means that exercise is effective, if the contextual effects of the placebo interventions are larger than or equal to those associated with exercise. Currently, the placebo effect of exercise remains unknown and is probably dependent on the context in which exercise is delivered.

When comparing exercise therapy to advanced-stage surgical interventions, such as total hip or knee replacement, surgery would be expected to outperform exercise. Surgery is the final step in the OA treatment pathway, and patients eligible for such surgery typically have already been offered exercise therapy in earlier stages. Moreover, the strong placebo effects associated with major surgery complicate any fair comparison. By contrast, comparisons with alternative interventions that are used across disease stages showed that exercise generally yielded similar effects. Notably, moderate evidence suggested that exercise was slightly superior to glucocorticoid injections and patient education. We argue that, given that all comparators were passive interventions, these comparable or slightly superior effects are sufficient reason to maintain exercise as a safe and active core treatment aimed at reducing physical inactivity and muscle atrophy, key mediators of disability in OA[4].

In the comparison of exercise with no treatment, the findings differed by OA type. In hand OA, evidence of moderate certainty indicated a small benefit of exercise. For hip OA, the effects of exercise treatment were below the threshold for a small effect. Based on 54 RCTs, the effect of exercise for knee OA fell between the small and moderate effect threshold and the 95% confidence interval for this pooled estimate did not include those effects that fell below the smallest effect threshold, underscoring the meaningfulness of these results. The certainty of the evidence, however, was rated very low, owing to methodological limitations, inconsistency and imprecision. Given the wide variation in exercise content, dosage, adherence and patient characteristics, inconsistency is difficult to avoid. Moreover, as expected, none of the exercise trials was blinded.

The authors decided post-hoc to change their prespecified threshold for sensitivity analyses. Initially, small studies (that is, <20 people per arm) were excluded, but they increased this threshold to <100 per arm as many trials met the original criterion. Trials with 100 people per arm are considered large within nonpharmacological research and, unsurprisingly, few studies met this stricter requirement. This result is not unexpected: the thresholds used for the magnitude of effect in the certainty assessment and the pooled standard deviation the authors refer to indicate that for a moderate effect, a superiority trial with 90% power and a 5% significance level would require only 63 people per arm. Thus, either the large trials anticipated small effect sizes, which must have been considered clinically relevant, as substantial funding for large trials would otherwise be unlikely, or prespecified subgroup analyses were incorporated into the study protocol. Therefore, larger sample sizes with more than 100 people per arm are not intrinsically superior in OA research.

Minimal long-term effects were observed across all comparisons. However, this observation is not unique to exercise; many OA treatments show limited sustained benefits. For example, pain medications do not produce long-lasting effects and NSAIDs are known to have no long-term benefit, even with continuous use[5]. Importantly, the assessed long-term outcomes (self-reported pain and function) might not capture the full impact of exercise. Muscle weakness is a known predictor of long-term disease progression[6], and preventing (further) muscle weakness is a key goal of exercise therapy. Therefore, one might

question whether concluding that exercise has no long-term effects when only pain and function are assessed is fair.

The authors suggest that future research should focus on identifying subgroups of patients who respond better to specific types of exercise, an aim with which we fully agree. Individual patient data meta-analyses have already shown that patients with early-stage knee OA respond substantially better to exercise than those with more advanced disease[7]. Also, individuals with more severe baseline pain tend to show greater improvements with exercise[8]; however, these findings might partly reflect a statistical issue: patients with very low pain levels simply have less room for improvement.

The authors also propose developing a true control condition for exercise to estimate its 'real' effect, but they acknowledge that this approach is challenging because the mechanisms by which exercise alleviates OA symptoms are still unclear. In our view, elucidating these underlying mechanisms is precisely the most important step for advancing the field[9]. A clearer understanding of how exercise works would enable us to determine optimal exercise regimes and identify those patients who will benefit the most from different exercise types, those for whom general physical activity is sufficient and those for whom targeted exercise therapy is needed.

Although this report is rigorous and transparent, the message conveyed in both the abstract and conclusion — in which the authors question the universal promotion of exercise as a first-line treatment for OA — comes across as somewhat overly mathematical, and potentially leads to an overly narrow interpretation of its clinical relevance, especially at a time when substantial effort is being invested in implementing exercise therapy, particularly for knee OA, in first-line care.

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Competing interests

The authors declare no competing interests.

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Review article

Check for updates

The gut–joint axis in osteoarthritis

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Abstract

Osteoarthritis (OA) is a complex condition driven by biomechanical, metabolic and inflammatory factors; however, effective disease-modifying treatments remain unavailable. Growing evidence suggests that gut microbiota dysbiosis has an important role in OA pathogenesis, giving rise to the emerging concept of a functional and targetable gut–joint axis. Gut microbiota dysbiosis can impair enteroendocrine signalling, intestinal immunity and gut barrier integrity, alter the secretion of hormones and cytokines and facilitate the translocation of gut microorganisms, pro-inflammatory molecules and metabolites into the circulation or joints. These processes can disrupt systemic and local homeostasis, promote metabolic dysregulation and obesity, trigger low-grade inflammation and contribute to both the onset and progression of OA. Although these insights open up new avenues for disease-modifying treatments and build on the long-standing paradigm in OA, which primarily focuses on pain relief rather than disease modification, evidence supporting therapeutic strategies that target the gut–joint axis remains limited. Further research is needed to translate this promising biology into clinical benefits, including deeper mechanistic elucidation through integrated multi-omics approaches, exploration of the interplay between host genetics, environmental factors and the gut microbiota and also multidimensional validation of the safety and efficacy of treatments that target this axis using complementary models (such as organoids and large animal models), clinical trials and real-world studies.

Sections

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Key points

- Growing evidence from human studies indicates that gut microbiota dysbiosis and alterations in microbial metabolites are associated with osteoarthritis (OA), supporting the emerging concept of a gut–joint axis.
- Preclinical studies indicate that gut dysbiosis promotes OA through endocrine, immune and barrier dysfunction, and also via altered microbial metabolites.
- The emergence of the gut–joint axis in OA has led to interest in targeted therapies, including probiotics and prebiotics, gut hormone or metabolite supplementation and dietary interventions.
- Future research should standardize methods, integrate a multi-omics approach and multicentre cohorts, investigate host–environment–microbiome interactions, develop next-generation biotics and validate therapies in preclinical and clinical settings.

Introduction

Osteoarthritis (OA) is the most common joint disease worldwide and a leading cause of disability, characterized by pain, functional limitation, reduced mobility, joint deformity, crepitus and muscle atrophy[1,2]. The 2021 Global Burden of Disease study estimated that 595 million people, 7.6% of the global population, were living with OA, imposing substantial social and economic burdens[3]. The prevalence of OA is projected to rise steadily through 2050, straining health care systems[3]. Although OA is recognized as a complex degenerative condition driven by biomechanical, metabolic, inflammatory and systemic factors, effective disease-modifying therapies for OA remain unavailable[4]; current treatments focus primarily on pain relief and functional improvement[5]. Therefore, identifying modifiable pathogenic pathways is essential for developing effective interventions.

The gut microbiota, the largest and most diverse microbial ecosystem in the body[6], has a central role in host physiology through the production of various bioactive components[7]. Growing evidence indicates that microbial dysbiosis contributes to diseases that affect distant organs, leading to the recognition of multiple gut–distant organ axes as potential therapeutic targets[8]. Evidence suggests that gut microbiota dysbiosis contributes to the onset and progression of OA by disrupting enteroendocrine signalling, altering intestinal immune responses and impairing gut barrier integrity[9–13]. Systemically, dysbiosis-driven changes in metabolic and inflammatory pathways, such as those associated with obesity, create an environment that might accelerate joint damage[14]. Locally, increased intestinal permeability enables gut microorganisms, pro-inflammatory molecules and microorganism-derived metabolites to enter the circulation and reach the joint, where they disturb homeostasis and promote OA progression[15].

In this Review, we synthesize current evidence on the gut–joint axis in OA and highlight mechanistic pathways that link gut dysbiosis to joint degeneration. We further propose and prioritize candidate biological pathways and therapeutic targets to guide future investigations aimed at developing gut-focused disease-modifying strategies for OA.

Gut microbiota dysbiosis and disturbed microbial metabolites

Gut microbiota dysbiosis and disturbed microbial metabolites have been increasingly implicated in OA, with evidence linking them to both disease susceptibility and symptom severity across different joints. However, findings are heterogeneous, highlighting the need for standardized, joint-specific studies to better elucidate the gut–joint axis and identify reproducible microbial taxa and metabolites relevant to OA.

Gut microbiota dysbiosis

Emerging evidence from human studies highlights a potentially pivotal role of gut microbiota in OA across different joint sites and pain phenotypes (Table 1). Global diversity metrics, including α-diversity and β-diversity, provide an overview of gut microbial composition in OA. Findings regarding these metrics have been inconsistent: some studies report altered α-diversity in individuals with OA[9,16–20], whereas others show no statistically significant differences compared with people without OA[21–27]. Similarly, β-diversity analyses show variable results across cohorts[9,17–27].

Although global diversity provides community-level snapshots, taxon-specific analyses are essential to identify microbial features relevant to OA pathogenesis. Four case–control studies reported overlapping but not identical sets of altered genera in individuals with knee OA, including *Bacteroides*, *Peptococcus*, *Prevotella*, *Ruminococcus*, *Roseburia*, *Lactobacillus*, and *Clostridium*[16,17,21,22]. Most early studies relied on 16S rRNA gene sequencing, which provides limited species-level resolution owing to short read lengths[28]. By contrast, shotgun metagenomic sequencing enables higher resolution profiling[29]. Using shotgun metagenomic sequencing data from 221 individuals with symptomatic knee OA and 760 individuals without OA in the Xiangya OA study, researchers found that gut microbiota alterations, especially a lower relative abundance of *Clostridium bolteae*, were positively associated with prevalent symptomatic knee OA[9].

Previous studies have largely focused on knee OA, even though its underlying mechanisms might differ from OA at other joint sites, such as the hands. Only a small number of studies have examined the association between gut microbiota and hand OA. Initial findings from the Xiangya OA study using 16S rRNA gene sequencing indicated that symptomatic hand OA was associated with a lower relative abundance of *Roseburia*, and higher relative abundance of *Bilophila* and *Desulfovibrio*[23]. Subsequent shotgun metagenomic sequencing in the same cohort revealed that individuals with symptomatic hand OA had higher relative abundance of *Bilophila wadsworthia*, *Lactobacillus mucosae*, *Citrobacter koseri* and *Hungatella hathewayi* but lower relative abundance of *Roseburia intestinalis*, *Bacteroides* spp. and *Haemophilus* spp.[18]. Several alterations in these taxa, including reduced *Roseburia* members and increased *Bilophila* and *Desulfovibrio* members, have been reported to modulate host inflammatory responses[30–32]. Functional profiling based on shotgun metagenomics further indicated a depletion of Kyoto Encyclopedia of Genes and Genomes (KEGG) modules involved in amino acid metabolism (for example, tryptophan biosynthesis), alongside enrichment of pathways related to carbohydrate metabolism (such as pyruvate and butanoate metabolism) and lipid metabolism (such as fatty acid degradation) in individuals with symptomatic hand OA[18]. Additionally, within the same cohort, individuals with erosive hand OA (a severe, rapidly progressing inflammatory subtype) exhibited higher relative abundance of *Alistipes senegalensis* and *Fournierella massiliensis*[19].

Several studies have also examined gut microbiota in relation to polyarticular OA or unspecified OA phenotypes. One case–control

study identified five enterotypes. Compared with individuals without OA, three enterotypes dominated by genera *Akkermansia*, *Bacteroides*, *Ruminococcus* and *Phascolarctobacterium* were inversely associated with OA[11]. The Johnston County Health study reported higher abundance of *Eubacterium siraeum* and *Akkermansia* but lower levels of *Faecalibacterium* and *Coprococcus* in people with radiographic polyarticular OA, and associations for specific taxa such as lower Christensenellaceae R-7 group and higher *Lachnoclostridium*[25]. Findings from the UK Twins Project revealed reduced levels of *Bifidobacterium longum* and *Faecalibacterium prausnitzii*, but increased *Clostridium* spp. in individuals with OA[20]. Similarly, reduced abundance of *Bacteroides plebeius* and *Faecalibacterium prausnitzii* has been observed in individuals with OA[26]. Additional species-level alterations have been reported in OA, particularly within the genera *Bacteroides* and *Blautia*[27,33]. Given the heterogeneous clinical presentations and distinct pathophysiological mechanisms across joint sites, joint-specific microbial signatures might be obscured when OA is studied as a combined or unspecified condition. Future microbiome research will probably benefit from joint-specific analyses to enhance biological interpretability and facilitate the identification of mechanism-relevant microbial markers within the gut–joint axis.

In addition to disease susceptibility, several studies have examined the relationship between gut microbiota and OA-related pain. Data from the Rotterdam study demonstrated that a higher abundance of *Streptococcus* spp. was associated with increased knee pain in OA, a finding replicated in the Lifelines-DEEP study[34]. Notably, this association seems to be mediated by local inflammation[34]. The Johnston County Health study further reported that a lower abundance of Christensenellaceae, but a higher abundance of *Lachnoclostridium* was associated with pain severity[24]. Collectively, these findings indicate that the gut microbiome might contribute not only to OA susceptibility but also to variation in symptom severity.

Some broadly consistent microbial patterns are observed across different cohorts and OA joints. For example, reduced abundance of anti-inflammatory taxa has been observed in different joints — including members of the *Bacteroides* genus (such as *Bacteroides uniformis*) in knee, hand and unspecified OA; and the *Faecalibacterium* genus (such as *Faecalibacterium prausnitzii*) in polyarticular OA and studies without joint-site specification[16,18,20,26,27]. In addition, increased abundance of potentially pro-inflammatory taxa, including certain *Clostridium* spp., have been noted across knee and unspecified OA[9,17,20,27]. However, these patterns are not consistently joint-specific and current evidence remains insufficient to determine whether shared gut microbiome features directly contribute to common pathological processes across joints affected by OA. One possible explanation is that the gut microbiota might differentially influence distinct systemic pathways and pathogenic mechanisms, leading to site-specific microbial signatures. For instance, knee OA, a weight-bearing condition, might be driven predominantly by obesity-related mechanical–metabolic interactions[35], whereas hand OA, a non-weight-bearing phenotype, seems to be more strongly linked to systemic immune-mediated inflammatory processes[36].

Notably, microbiome-related studies in OA are highly sensitive to potential confounding factors. The gut microbiome and its associated features are strongly influenced by obesity, metabolic status and dietary patterns[37], which are also closely linked to OA. For example, ultra-processed foods are known to alter gut microbial composition[38], and evidence indicates that higher consumption of these foods is associated with worse knee OA-related imaging and clinical outcomes[39], suggesting a potential link between diet, gut dysbiosis and OA pathogenesis. In addition, heterogeneity across studies can arise from differences in disease stage (such as early versus late OA), the affected joint site (such as knee, hand or hip), sample size, cohort characteristics and analysis methodologies. The ability to fully control for these factors has remained limited in many studies, which might partly explain inconsistencies in reported microbiome-associated features. Therefore, findings from any single study should be interpreted cautiously and validated across diverse populations. Future research should prioritize larger cohorts, standardized methodologies and careful adjustment for key confounders to improve reproducibility.

Microbial metabolite disturbances

One key molecular pathway that links the microbiome and OA involves gut microbiota-derived metabolites, which modulate host physiology through diverse biochemical effects[40]. Observational studies have demonstrated widespread disturbances in microbial metabolites among individuals with OA (Table 1). Using untargeted metabolomics across multiple biospecimens, considerable perturbations have been identified in amino acids, short-chain fatty acids (SCFAs), indoles and phenolic compounds, indicating broad metabolic dysregulation in OA[26,41–44].

Building on these insights, several studies have applied targeted metabolomics approaches, which enable the precise identification and quantification of predefined metabolites, to investigate metabolite–OA associations with greater specificity. Two independent cohorts showed that altered microbial bile acid metabolism, characterized by reduced levels of ursodeoxycholic acid (UDCA) species, specifically glycoursodeoxycholic acid (GUDCA), was associated with higher prevalence and severity of symptomatic knee OA[9]. A hospital-based study reported distinct amino acid signatures in knee OA, identifying alanine, GABA (γ-aminobutyric acid) and 4-hydroxy-L-proline as key biomarkers that differentiate individuals with knee OA from healthy individuals[45]. For hand OA, data from the Xiangya OA study revealed that higher levels of 5-hydroxyindoleacetic acid and 5-hydroxytryptophol, but lower levels of indole-3-lactic acid, skatole and 3-hydroxyanthranilic acid, were associated with symptomatic hand OA[18]. A validation cohort confirmed the association between lower levels of indole-3-lactic acid and symptomatic hand OA[18]. Further analyses revealed higher levels of L-5-hydroxytryptophan, 3-indoleglyoxylic acid, 5-hydroxyindoleacetic acid, indoleacrylic acid and serotonin, and lower levels of L-tryptophan and indole-3-acetyl-aspartate in erosive hand OA[19]. Consistently, in the DIGICOD study, inverse associations between erosive hand OA and tryptophan, indole-3-aldehyde and 3-hydroxyanthranilic acid were observed, and a positive association with levels of 5-hydroxytryptophan[46]. Early studies of synovial fluid from individuals with OA showed higher concentrations of kynurenic acid and quinaldic acid (metabolites of the tryptophan-derived kynurenine pathway) than in individuals with rheumatoid arthrtitis[47,48].

Collectively, these findings suggest that dysbiosis and disrupted microbial metabolite profiles are associated with OA, supporting the emerging concept of a gut–joint axis in OA. However, microbiome-associated features observed in human studies vary widely owing to differences in demographics, geographic locations, dietary patterns and affected joint sites. Heterogeneity in sequencing technologies and analytical pipelines further contribute to inconsistent results[49]. Given the substantial variability, results from a single study should be considered with caution and validated in diverse cohorts to ensure reproducibility and generalizability. Moving forward,

Table 1 | Key human studies evaluating the association between gut microbiota, microbial metabolites and osteoarthritis

Year	Study population	OA type	*n*	Measurement	Findings	Ref.
Gut microbiota						
2021	Hospital-based study	Knee OA	182	16S rRNA gene sequencing	In people with OA and overweight, 9 phyla and 87 genera were altered when compared with people with overweight without OA	16
2021	Hospital-based study	Knee OA	10	16S rRNA gene sequencing	The relative abundances of *Peptococcus*, *Shimwellia*, *Propionibacterium*, *Intestinimonas* and *Pavimonas* were more enriched in individuals with knee OA than in healthy individuals	21
2021	Hospital-based study	Knee OA	80	16S rRNA gene sequencing	Bacteroidota, Bacteroidia and Bacteroidales were enriched in people with OA, whereas *Prevotella copri* was enriched in healthy individuals	22
2023	Hospital-based study	Knee OA	89	16S rRNA gene sequencing and shotgun metagenomic sequencing	81 genera were different in abundance when comparing individuals with OA and healthy individuals, including *Agathobacter*, *Ruminococcus*, *Roseburia*, *Subdoligranulum*, *Lactobacillus*, *Prevotella_7*, *Clostridium*, *Flavonifractor* and *Klebsiella*	17
2025	The Xiangya OA study	Symptomatic knee OA	981	Shotgun metagenomic sequencing	Individuals with OA had a lower relative abundance of *Clostridium bolteae* and higher relative abundances of *Clostridium sp001517625*, *Blautia obeum*, *CAG-279 sp00043795*, *Agathobaculum butyriciproducens*, *Lachnospira rogosae*, *Sutterella wadsworthensis* and *Gemmiger formicilis* compared with those without OA	9
2021	The Xiangya OA study	Symptomatic hand OA	1,388	16S rRNA gene sequencing	Higher relative abundances of the genera *Bilophila* and *Desulfovibrio* and lower relative abundance of the genus *Roseburia* were associated with symptomatic hand OA	23
2023	The Xiangya OA study	Symptomatic hand OA	1,359	Shotgun metagenomic sequencing	People with symptomatic hand OA showed higher relative abundances of *Bilophila wadsworthia*, *Lactobacillus mucosae*, *Citrobacter koseri* and *Hungatella hathewayi* but lower relative abundances of *Roseburia intestinalis*, *Bacteroides* spp. and *Haemophilus* spp. compared with individuals without hand OA	18
2025	The Xiangya OA study	Erosive hand OA	1,324	Shotgun metagenomic sequencing	People with erosive hand OA had higher relative abundance of *Alistipes senegalensis* and *Fournierella massiliensis* compared with individuals without either erosive or non-erosive hand OA	19
2022	The Johnston County OA Project	Hand OA and knee OA	92	16S rRNA gene sequencing	No statistically significant differences in α-diversity or β-diversity or genus-level composition between people with obesity-associated OA and people with obesity without OA	24
2025	The Johnston County OA Project	Hand OA and knee OA	64	16S rRNA gene sequencing	Five enterotypes were identified: enterotypes 3 and 4 were dominated by *Akkermansia* and *Bacteroides*, respectively, and enterotype 5 was dominated by *Ruminococcus* and *Phascolarctobacterium;* enterotypes 3, 4 and 5 were inversely associated with the presence of OA	11
2025	The Johnston County Health study	Radiographic polyarticular OA	100	16S rRNA gene sequencing	Greater abundances of *Eubacterium siraeum* and *Akkermansia* but lower levels of *Faecalibacterium* and *Coprococcus* were associated with radiographic polyarticular OA; a lower abundance of the Christensenellaceae R-7 group but a higher abundance of *Lachnoclostridium* was associated with pain severity	25
2021	UK Twins Project	Unspecified OA	114	Shotgun metagenomic sequencing	*Bifidobacterium longum* and *Faecalibacterium prausnitzii* were decreased, whereas *Clostridium* spp. were increased in the OA group compared with healthy individuals	20
2022[a]	Hospital-based study	Unspecified OA	46	Shotgun metagenomic sequencing	Several species were altered in people with OA, including *Coprococcus catus*, *Blautia torques* and *Dialister invisus* compared with healthy individuals	33
2024[a]	Hospital-based study	Unspecified OA	46	Shotgun metagenomic sequencing	Compared with healthy people, the OA group showed a reduction in the Bacteroidetes phylum, and 38 differentially expressed species were identified between the two groups (including *Bacteroides uniformis*, *Bacteroides cellulosilyticus* and *Blautia obeum*)	27
2025	Hospital-based study	Unspecified OA	38	16S rRNA gene sequencing	The abundance of *Bacteroides plebeius* and *Faecalibacterium prausnitzii* was reduced in the OA group compared with healthy individuals	26
2019	Rotterdam study; Lifelines-DEEP study	Knee OA-related pain	1,427; 867	16S rRNA gene sequencing	The gut microbiome, particularly a greater relative abundance of *Streptococcus* spp., was associated with higher knee WOMAC pain, and this association was driven by local inflammation in the joint	34

Table 1 (continued) | Key human studies evaluating the association between gut microbiota, microbial metabolites and osteoarthritis

Year	Study population	OA type	*n*	Measurement	Findings	Ref.
Microbial metabolites						
2016	Newfoundland OA study; CODING study	Knee OA	109; 148	Untargeted plasma metabolomics analysis	Six metabolites were associated with knee OA, of which arginine was the most statistically significant metabolite in individuals with knee OA	41
2021	Community-based study	Symptomatic knee OA	142	Untargeted urine metabolomics analysis	The urinary profiles of people with inflammatory OA were different from those without OA; 26 metabolites were identified as potential OA urine biomarkers (such as 2-hydroxyhippuric acid, 4-hydroxybutyric acid and pipecolic acid)	42
2022	Hospital-based study	Hip OA	76	Untargeted serum metabolomics analysis	Differences between individuals with OA and individuals without bone pathologies included: amino acids; energy metabolism metabolites; some bacterial co-metabolism metabolites (such as methylamines, acetate and butyrate derivatives) and phospholipid precursors	43
2022	The Johnston County OA Project	Hand OA and knee OA	92	Untargeted faecal metabolomics analysis	People with OA had higher levels of dipeptides and tripeptides and perturbations in microbial metabolites (including propionic acid, indoles and other tryptophan metabolites) than those without OA	44
2025	Hospital-based study	Unspecified OA	38	Untargeted serum metabolomics analysis	Serum metabolites, including pyrogallol and 3-hydroxybutyrate, were lower in the OA group than in healthy individuals	26
2018	Hospital-based study (discovery cohort; validation cohort)	Knee OA	67; 60	Serum amino acids	Alanine, GABA and 4-hydroxy-L-proline distinguished people with OA from healthy people	45
2025	The Xiangya OA study; validation cohort	Symptomatic knee OA	1,714; 154	Plasma bile acids	The findings from these two independent cohorts suggest that decreased levels of UDCA species, specifically GUDCA, were associated with a higher prevalence of OA and more severe OA	9
2023	The Xiangya OA study; validation cohort	Symptomatic hand OA	1,359; 142	Plasma tryptophan metabolites	People with symptomatic hand OA had higher levels of 5-hydroxyindoleacetic acid and 5-hydroxytryptophol, but lower levels of indole-3-lactic acid, skatole and 3-hydroxyanthranilic acid than individuals without hand OA; findings from the validation cohort verified that lower levels of ILA were related to symptomatic hand OA	18
2025	The Xiangya OA study	Erosive hand OA	1,324	Plasma tryptophan metabolites	Higher levels of L-5-hydroxytryptophan, 3-indoleglyoxylic acid, 5-hydroxyindoleacetic acid, indoleacrylic acid and serotonin and lower levels of L-tryptophan and indole-3-acetyl-L-aspartic acid were found in erosive hand OA than in individuals with neither erosive nor non-erosive hand OA	19
2023	DIGICOD study	Erosive hand OA	416	Serum tryptophan metabolites	Erosive hand OA was negatively associated with tryptophan, indole-3-aldehyde and 3-hydroxyanthranilic acid and positively associated with 5-hydroxytryptophan levels	46

GABA, γ-aminobutyric acid; GUDCA, glycoursodeoxycholic acid; OA, osteoarthritis; UDCA, ursodeoxycholic acid; WOMAC, the Western Ontario and McMaster Universities Arthritis Index. [a]Both studies were based on the same sequencing dataset, which was originally generated and released by the study published in 2022.

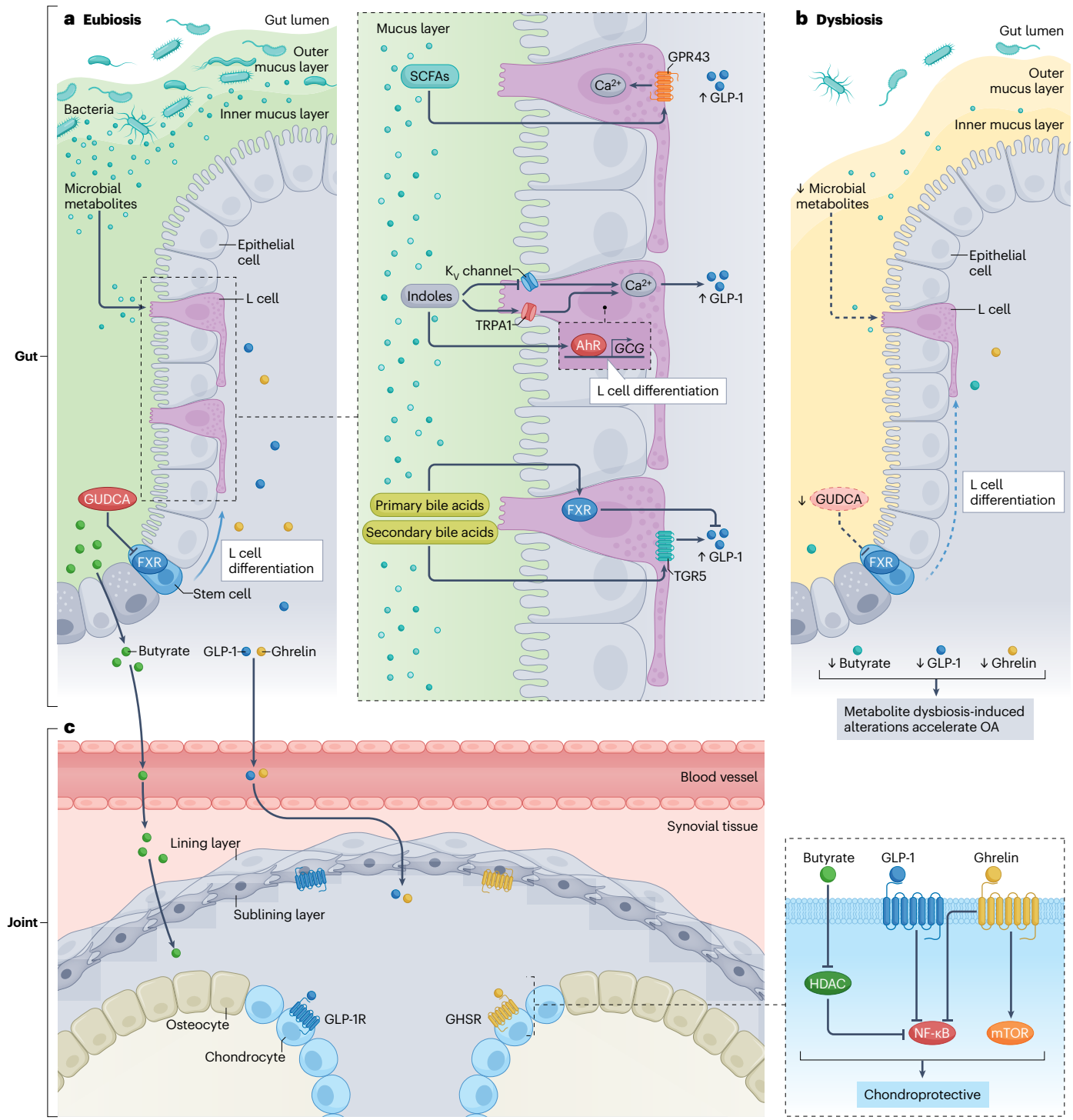
efforts should focus on identifying consistent downstream pathogenic mechanisms and unified molecular pathways that mediate the microbiome–OA relationship.

A causal gut–joint axis

Compelling mechanistic evidence substantiating a causal gut–joint axis in OA comes primarily from preclinical models using germ-free mice and faecal microbiota transplantation (FMT). Germ-free mice exhibit attenuated OA severity following destabilization of the medial meniscus compared with specific pathogen-free animals[50]. Moreover, alterations in microbiota composition correlate with OA progression independent of metabolic confounders[51]. In humans, a distinct microbial DNA signature within OA cartilage has been identified, marked by enrichment of Gram-negative taxa during disease progression[52]. Definitive causality has been further established through FMT studies: transferring microbiota obtained from people with OA exacerbates OA pathology in recipient mice[53], whereas transferring microbiota from OA-resistant MRL/MpJ (referred to as 'super-healer') mice confers protection against joint degeneration[10]. Sex hormones, particularly oestrogen, are known to interact with the gut microbiota and can influence microbial composition and inflammatory responses relevant to OA[54,55]. Male C57BL/6J mice have worse OA histology, synovitis and osteophyte formation than female mice[56]. Moreover, transferring microbiota from male mice into female mice and vice-versa worsened and improved OA outcomes, respectively[56]. Collectively, these experimental paradigms solidify the direct causal role of the gut microbiota in OA pathogenesis.

Gut–joint axis mechanisms

Mechanistically, gut dysbiosis promotes OA by disrupting several major gut functions: its endocrine role as the body's largest hormone-producing organ (leading to impaired enteroendocrine signalling)[57,58], its barrier role (causing increased intestinal permeability)[59] and its immunological role as a primary immune outpost (driving systemic immune hyperactivation)[60]. Furthermore, dysbiosis alters plasma levels of microbial metabolites that can directly influence



joint tissues. Together, these disturbances contribute to distant joint degeneration[61].

Endocrine disruption and microbial metabolite alterations

The gut functions as a major endocrine organ through enteroendocrine cells (EECs), which secrete more than 20 different hormones, including glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) from L cells, serotonin from enterochromaffin cells and ghrelin from X/A-like cells[57]. These cells regulate systemic physiology via paracrine, endocrine and neuroendocrine pathways. GLP-1, beyond its roles in glycaemic regulation and satiety, exhibits anti-inflammatory, chondroprotective and bone-modulating effects, making it a critical mediator of the gut–joint axis in OA[9]. Under physiological conditions, GLP-1 secretion from L cells is tightly regulated by microbial

Fig. 1 | Altered microbial metabolite-induced endocrine disruption and joint inflammation in osteoarthritis. a, Under eubiosis, microbial metabolites stimulate glucagon-like peptide-1 (GLP-1) secretion from L cells via numerous mechanisms: short-chain fatty acids (SCFAs) activate G-protein-coupled receptor 43 (GPCR43) and Ca^{2+}–cAMP signalling; indoles activate aryl hydrocarbon receptor (AhR) to promote L cell differentiation and *GCG* expression, with acute release mediated by transient receptor potential ankyrin 1 (TRPA1), voltage-gated potassium (K_V) channel inhibition and Ca^{2+} influx; bile acids exert dual effects, primary bile acids suppress GLP-1 through FXR, whereas secondary bile acids stimulate it via Takeda G-protein-coupled receptor 5 (TGR5). **b**, Under dysbiosis, altered microbiota disrupts this crosstalk, reducing GLP-1 and ghrelin output. Notably, decreased glycoursodeoxycholic acid (GUDCA, a key FXR antagonist) enhances farnesoid X receptor (FXR) signalling, impairs L cell differentiation and GLP-1 synthesis. Additionally, protective microbial metabolites (such as butyrate) are also reduced under dysbiosis. Collectively, metabolite dysbiosis-induced alterations accelerate osteoarthritis (OA). **c**, GLP-1, ghrelin and butyrate protect cartilage mainly by inhibiting nuclear factor-κB (NF-κB) signalling, with ghrelin additionally activating the mechanistic target of rapamycin complex (mTOR) pathway. Solid arrows indicate stimulatory effects; arrows with a perpendicular bar indicate inhibitory effects; dashed arrows indicate diminished effects under dysbiosis. GHSR, growth hormone secretagogue receptor; GLP-1R, GLP-1 receptor; HDAC, histone deacetylase.

metabolites[58]. First, SCFAs, produced from microbial fermentation of dietary fibre, primarily activate G-protein-coupled receptors (GPCRs; specifically GPCR41 and GPCR43), triggering Ca^{2+} to stimulate GLP-1 release[62]. Second, microbiota-derived indoles, generated from tryptophan metabolism, enhance GLP-1 through multiple pathways: they promote L cell differentiation and proglucagon (*GCG*, the gene encoding GLP-1) transcription via aryl hydrocarbon receptor (AhR) activation[63,64] and acutely stimulate secretion by inhibiting voltage-gated potassium channels and activating transient receptor potential ankyrin 1 to trigger Ca^{2+} influx and membrane depolarization[65,66]; however, chronic exposure can suppress GLP-1 release by reducing ATP production[67]. Third, bile acids regulate EECs in a receptor-specific manner. Primary bile acids, particularly chenodeoxycholic acid, activate farnesoid X receptor (FXR) to inhibit *GCG* transcription and glycolytic ATP production, suppressing both GLP-1 synthesis and exocytosis[68]. By contrast, secondary bile acids, such as lithocholic acid and deoxycholic acid (DCA), activate Takeda G-protein-coupled receptor 5 (TGR5), increasing cAMP–PKA (protein kinase A) and cAMP–EPAC (exchange factor directly activated by cAMP) signalling, Ca^{2+} mobilization and subsequent GLP-1 release[69,70] (Fig. 1a).

Gut dysbiosis disrupts the finely tuned metabolite–EEC crosstalk, leading to a complex imbalance in gut-derived peptide hormones that regulate joint homeostasis. Notably, loss of *Clostridium bolteae* reduces GUDCA, an FXR antagonist, which enhances FXR signalling, impairs L cell differentiation, reduces GLP-1 secretion and promotes OA progression by weakening GLP-1 receptor (GLP-1R)-mediated inhibition of chondrocyte extracellular matrix degradation[9]. Ghrelin is an orexigenic gut hormone that stimulates appetite and promotes growth hormone release[71]. Parallel to this GLP-1 deficit, emerging evidence identifies ghrelin as another key protective factor that is locally depleted in the OA joint[72].

Mechanistically, both GLP-1 and ghrelin preserve cartilage integrity primarily by binding to their respective receptors (GLP-1R and growth hormone secretagogue receptor), thereby suppressing nuclear factor-κB (NF-κB) signalling[73–75]; ghrelin also activates the mechanistic target of rapamycin (mTOR) pathway[76]. Moreover, reduced levels of other protective microbiota-derived metabolites, including SCFAs (such as butyrate)[43], indole-3-lactic acid[18], L-tryptophan and indole-3-L-aspartic acid[19], might also diminish GLP-1 secretion and downstream joint-protective signalling, exacerbating OA progression (Fig. 1b,c).

Beyond endocrine disruption, depletion of SCFAs and indoles directly aggravates OA pathology. Butyrate protects cartilage by inhibiting histone deacetylase to suppress NF-κB signalling (Fig. 1c), which in turn suppresses matrix metalloproteinases (MMPs) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs), preserves type II collagen, restores autophagy and reduces inflammation, apoptosis and oxidative stress[77,78]. Additionally, butyrate attenuates synovial inflammation by inducing fibroblast senescence and inhibiting necroptosis[79]. Similarly, indole derivatives, particularly indole-3-propionic acid and indole-3-aldehyde, exert chondroprotective and anti-inflammatory effects via AhR-dependent NF-κB inhibition[80,81]. Collectively, gut dysbiosis-driven depletion of protective microbial metabolites accelerates OA through both endocrine disruption and direct pro-inflammatory effects on joint tissues.

Impaired barrier integrity and immune function

The intestinal barrier consists of a mucus layer, commensal microbiota, an epithelial monolayer and underlying immune cells. This multilayered system, supported by tight junction proteins, antimicrobial peptides, secretory IgA and gut-associated lymphoid tissues, balances nutrients, enabling selective absorption while excluding luminal threats. Under homeostasis, microbiota-derived signals and metabolites preserve barrier integrity and immune tolerance[82]. Segmented filamentous bacteria induce epithelial serum amyloid A production to promote T helper 17 (T_H17) cell differentiation and IL-17-driven antimicrobial peptide production[83,84]. Polysaccharide A from *Bacteroides fragilis* engages Toll-like receptor 2 (TLR2) on dendritic cells, inducing IL-10-producing regulatory T (T_{reg}) cells and innate lymphoid cell 3-derived IL-22 to reinforce epithelial integrity[85] (Fig. 2a). SCFAs signal through GPCR41, GPCR43 and GPCR109A and inhibit histone deacetylase, enhancing tight junction integrity and mucin production while suppressing pro-inflammatory cytokines[86]. Indole derivatives activate AhR and pregnane X receptor signalling to strengthen mucus and tight junctions, induce IL-22 and IL-10 receptor expression and inhibit T_H17 cell responses[65]. Specific bile acids activate FXR and TGR5 to promote T_{reg} cell differentiation, inhibit T_H17 cells, NF-κB signalling and NLRP3 inflammasome activation and maintain immune homeostasis[69] (Fig. 2b). Collectively, these cues sustain a selectively permeable, anti-inflammatory barrier for gut and systemic health.

Gut dysbiosis disrupts this equilibrium, compromising both barrier integrity and immune function[52,87–94]. Consequently, impaired barrier function can lead to 'leaky gut', characterized by increased intestinal permeability. Clinically, such hyperpermeability, evidenced by increased levels of serum lipopolysaccharide (LPS), has been observed in individuals with OA[24,87]. Corroborating these findings, individuals with erosive hand OA show increased serum levels of the permeability markers LPS-binding protein and zonulin-related proteins[95]. In addition to LPS, the 'leaky gut' facilitates the translocation of viable bacteria (such as Proteobacteria[96,97], *Cutibacterium acnes*[98] or Firmicutes[99]), microbial components (for example, peptidoglycan or flagellin[100]) and metabolites (such as DCA[101] and trimethylamine *N*-oxide[102]) into the systemic circulation. These gut-derived factors promote systemic

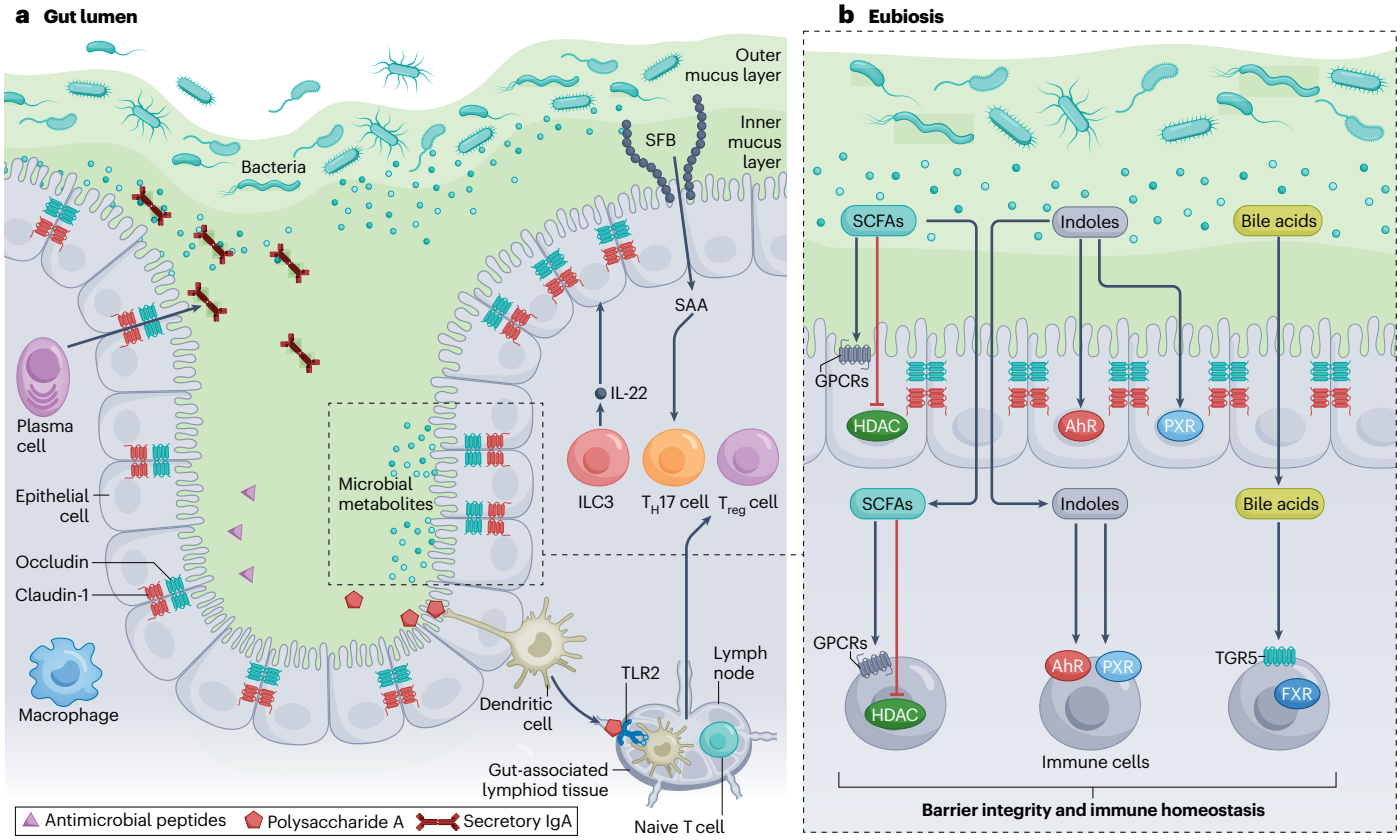


Fig. 2 | Maintenance of gut mucosal barrier integrity and immune homeostasis under eubiosis. a, Under eubiosis, the intestinal barrier, comprising the mucus layer, commensal microbiota, epithelial tight junctions and mucosal immune components (secretory IgA, dendritic cells, macrophages, T helper 17 (T_H17) cells, T_{reg} cells and gut-associated lymphoid tissues) maintains homeostasis through two key mechanisms: microbial signals (such as segmented filamentous bacteria (SFB) driving T_H17 cell differentiation via serum amyloid A (SAA) and polysaccharide A promoting T_{reg} cell induction via Toll-like receptor 2 (TLR2) on dendritic cells. **b**, Under eubiosis, metabolite signals include: short-chain fatty acids (SCFAs) activating G-protein-coupled receptors (GPCRs; specifically GPCR41, GPCR43 and GPCR109A) and inhibiting histone deacetylases (HDACs); indole derivatives activate aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR); specific bile acids activate farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). Solid arrows indicate stimulatory effects or transport; arrows with a perpendicular bar indicate inhibitory effects.

inflammation: LPS activates TLR4 signalling whereas DCA and trimethylamine *N*-oxide promote pro-inflammatory macrophage polarization via the M2 muscarinic acetylcholine receptor–Src–TLR2 axis and NLRP3 inflammasome activation, respectively[101,102]. Dysbiosis also skews mucosal immunity towards a pro-inflammatory profile, marked by an increased T_H17 cell/T_{reg} cell ratio and insufficient anti-inflammatory regulation[103]. Systematically, circulating mediators and activated immune cells reach the joint, triggering synovial inflammation and chondrocyte catabolism[104]. Increased IL-17 and related cytokines (such as IL-1β, IL-6 and TNF)[105] induce matrix-degrading enzymes (such as MMPs and ADAMTS), promote chondrocyte death and enhance osteoclast activity, which promotes cartilage loss and subchondral bone remodelling[104,106–108]. Collectively, these OA-associated alterations of joint microenvironmental factors fuel chronic low-grade inflammation and accelerate joint degeneration, underscoring the crucial role of the gut–joint axis in OA progression (Fig. 3). Beyond joint degeneration, emerging evidence links gut dysbiosis and increased intestinal permeability to OA pain severity through the translocation of bacterial products (such as LPS[100]) and the upregulation of pro-inflammatory tryptophan–kynurenine metabolites[46,109]. These findings support a gut–brain–joint axis, wherein microbiota-derived signals contribute not only to local joint pathology but also to neuroinflammation[110]. Understanding these multi-level interactions could provide novel avenues for targeting OA-associated pain beyond peripheral joint structures.

Targeting the gut–joint axis

Altered gut microbiota and microbial metabolites in OA have stimulated interest in therapies that target the gut–joint axis, including probiotics, prebiotics, supplementation of gut hormones or metabolites and dietary interventions (Table 2).

Oral probiotic and prebiotic agents

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host[111]. Growing evidence supports their potential role in OA management. In a randomized double-blind, placebo-controlled trial of 461 individuals with knee OA, the oral probiotic *Lactobacillus casei* Shirota improved Western

Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and visual analogue scale (VAS) scores compared with placebo[112]. A randomized controlled trial (RCT) of 70 patients with knee OA showed that the probiotic *Saccharomyces boulardii* was superior to placebo in reducing pain, acetaminophen use, levels of high-sensitivity C-reactive protein (CRP) and oxidative stress, while improving quality of life[113]. Two additional RCTs evaluated the effect of a high-potency probiotic (Vivomixx 112 billion) which contains 112 billion live bacteria from eight specific strains, in patients with knee OA[114,115]. Both studies reported reductions in pain intensity and disease severity, and improved functional outcomes such as hand-grip strength and walking speed[114,115]. Another RCT involving 80 people with knee OA reported reductions in serum collagen type II C-telopeptide and CRP levels in patients treated with the probiotic *Streptococcus thermophilus*; however, no clear superiority over placebo was observed. Furthermore, no statistically significant changes in WOMAC pain, stiffness or function scores were observed in the *Streptococcus thermophilus* group over the study period, whereas the placebo group showed improvements in pain and function[116].

Prebiotics are substrates that are selectively used by host microorganisms to confer health benefits[117]. Beyond probiotics, prebiotics have shown promise for OA therapy, although human evidence remains limited. In an RCT, patients with obesity and knee OA who received oligofructose-enriched inulin demonstrated considerable improvements in physical function, including the timed-up-and-go test, 40-m fast-paced walk test and hand-grip strength test, and reductions in

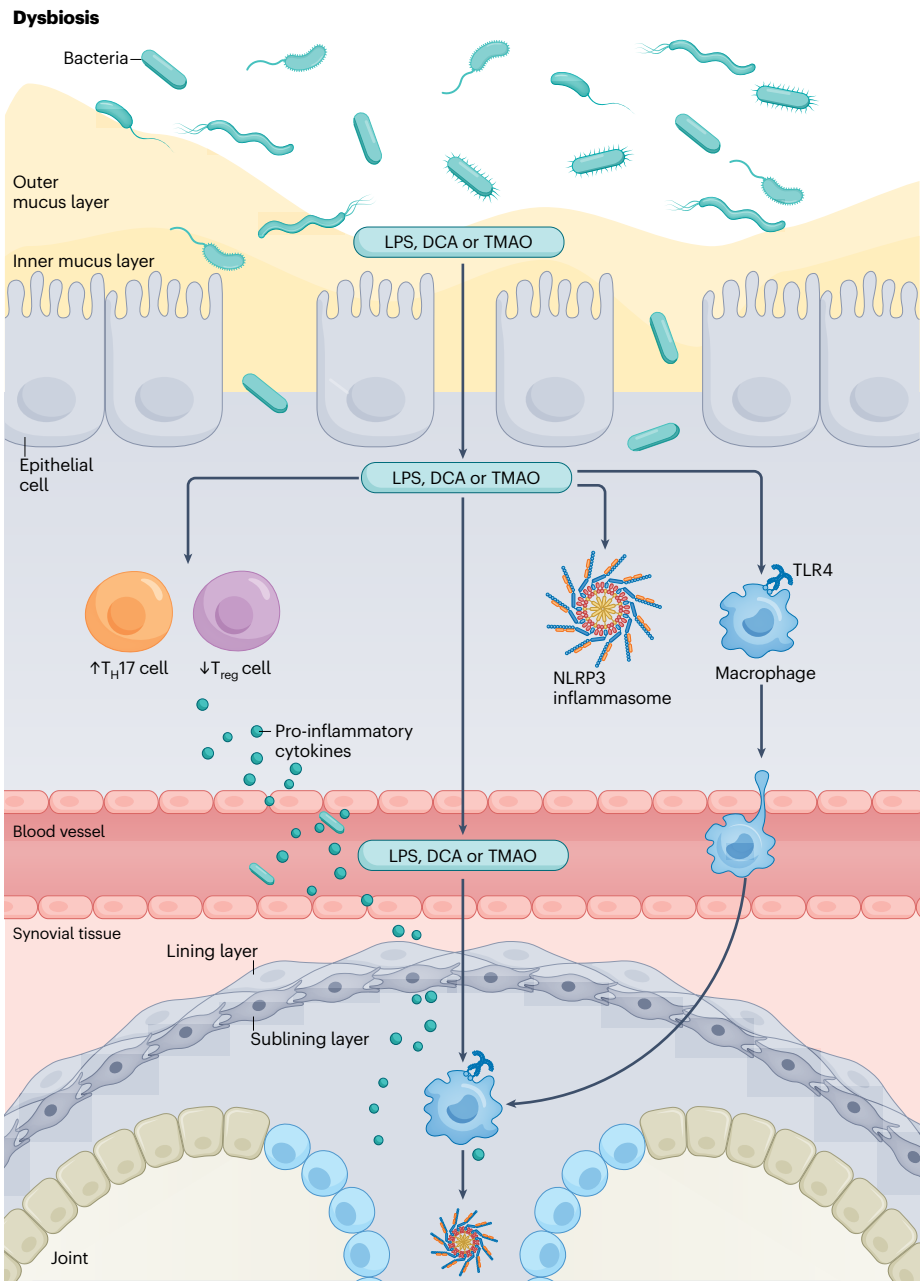


Fig. 3 | Disrupted gut mucosal barrier integrity and immune homeostasis in osteoarthritis. Dysbiosis causes a 'leaky gut', which facilitates the translocation of bacteria, lipopolysaccharide (LPS) and metabolites (such as deoxycholic acid (DCA) and trimethylamine *N*-oxide (TMAO)), which activate the Toll-like receptor 4 (TLR4)–NLRP3 pathway and induce systemic inflammation accompanied by altering the ratio of T helper 17 (T_H17) cells to regulatory T (T_{reg}) cells. This inflammatory cascade drives immune-cell migration to joints and accelerates the progression of osteoarthritis (OA). Solid arrows indicate stimulatory effects or transport.

Table 2 | Randomized controlled trials targeting the gut–joint axis in osteoarthritis

Year	*n*	Female sex (%)	Intervention	Results	Refs.
2017	461	55.7%	Probiotics (skimmed milk containing *Lactobacillus casei* Shirota)	In individuals who received *Lactobacillus casei* Shirota, WOMAC and VAS scores improved and serum levels of high sensitivity CRP were reduced compared with placebo (plain skimmed milk) after 6 months	112
2024	70	65.7%	Probiotics (*Saccharomyces boulardii)*	Compared with placebo, treatment with *Saccharomyces boulardii* decreased pain intensity, the use of pain relief medication (that is, acetaminophen), serum levels of high sensitivity CRP and oxidative stress index and increased quality of life over 12 weeks	113
2024	147	68.0%	Vivomixx 112 billion (a highly potent probiotic capsule containing 112 billion live bacteria from eight specific strains)	Those receiving probiotics had reduced pain intensity, disease severity and WOMAC scores, and improvement in balance scores, hand-grip strength and walking speed at 12 weeks compared with baseline, with no such chang\es observed in the placebo group	114
2025	115	n/a	Vivomixx 112 billion (a highly potent probiotic capsule containing 112 billion live bacteria from eight specific strains)	Treatment reduced plasma zonulin and pain intensity during walking, alongside notable improvements in the OKS, knee-flexion range of movement, gait speed, hand-grip strength and short physical performance battery scores from baseline to week 16	115
2020	80	79.1%	Probiotics (*Streptococcus thermophilus* (TCI633 strain))	After 12 weeks of treatment, *Streptococcus thermophilus* lowered serum collagen type II C-telopeptide and levels of serum CRP; however, no clear superiority over placebo was observed; no statistically significant changes in WOMAC pain, stiffness or function scores were observed in the treatment group, whereas the placebo group showed improvements in pain and function	116
2024	54	90.7%	Prebiotics (oligofructose-enriched inulin)	Consumption of prebiotic fibre increased the abundance of *Bifidobacterium* and *Faecalibacterium* at 3 months and upregulated the serum metabolites phenylalanine and tyrosine at 6 months; these changes were accompanied by small but statistically significant improvements in numerous tests of physical function (for example, timed-up-and-go test at 3 and 6 months, 40-m fast paced test at 3 months and hand-grip strength test at 6 months), reductions in trunk adipose tissue (kg) at 6 months and trunk adipose tissue (%) at 3 months when comparing the prebiotic treatment versus placebo (maltodextrin)	118
2024	33	81.8%	Microbial metabolites (butyrate sustained-release tablets)	After 4 weeks, sustained-release butyrate treatment restored immune balance in people with hand OA, as indicated by a reduced percentage of activated T helper (T_H) cells and IL-9$^+$ T_H9 cells, and an improved T_H17 cell/T_{reg} cell balance within ex vivo anti-CD3 and anti-CD28-activated peripheral blood mononuclear cells	121
2025	132	n/a	Microbial metabolites (butyrate capsules	Compared with baseline, treatment improved hand-grip strength, walking speed, OKS, balance and walking ability, preserved chair sit-to-stand test performance and reduced plasma levels of zonulin, lipopolysaccharide-binding protein and CRP at week 12, with no statistically significant changes observed in the placebo group	122
2021	156	64.7%	Gut hormones (liraglutide)	After 52 weeks, no difference in pain was observed between the placebo and treatment groups. Moreover, liraglutide did not induce changes in physical activity except for better outcomes for body weight and self-reported physical function	126,127
2024	407	81.6%	Gut hormones (semaglutide)	Semaglutide was better than placebo in reducing body weight and pain related to knee OA and was associated with improved physical function at week 68	128
2008	32	78.1%	Gut hormones (ghrelin)	At week 6, ghrelin did not alter muscle strength, walking ability, mid-thigh muscle cross-sectional area and hip joint function, but did increase lean body mass and decrease adipose tissue mass compared with placebo	133
2013	38	73.7%	Diet and nutraceuticals (green-lipped mussel extract)	Both green-lipped mussel extract and glucosamine (comparator intervention) reduced OA symptoms, alongside a decrease in Clostridia abundance over 12 weeks	136

CRP, C-reactive protein; n/a, not applicable; OA, osteoarthritis; OKS, Oxford knee score; T_{reg} cells, regulatory T cells; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

trunk adipose tissue[118]. These benefits were accompanied by increased abundance of *Bifidobacterium* and *Faecalibacterium*, and elevated levels of the serum metabolites phenylalanine and tyrosine[118]. Animal studies also support these findings. In a mouse model of post-traumatic OA, supplementation of oligofructose prebiotic fibre reduced cartilage degeneration, osteophyte formation and inflammation, while improving gut barrier integrity and normalizing faecal metabolites[119]. Similarly, in a mouse model of obesity trauma-induced, oligofructose restored obesity-related gut microbiota dysbiosis, reduced systemic and joint inflammation, preserved articular cartilage and attenuated obesity-induced structural damage in the joint[120].

Thus, current trials suggest that probiotics and prebiotics might have potential as adjunctive interventions for OA; however, the available evidence remains limited and should be interpreted with caution. Many studies are characterized by small sample sizes, short follow-up durations and methodological limitations such as inadequate blinding or design constraints. Larger, long-term and well-designed clinical trials are therefore needed to validate efficacy, determine

appropriate dosing and identify the most effective probiotic strains for the management of OA.

Supplementation of microbial metabolites

Mechanistic data indicate that microbial metabolites (including SCFAs, bile acids and tryptophan metabolites) function as key signalling mediators and have been proposed to be important contributors to OA management.

Butyrate, an SCFA produced through microbial fibre fermentation, has demonstrated therapeutic potential in OA. In an RCT of 33 patients with hand OA, sustained-release butyrate improved immune balance, evidenced by reduced activated T_H cells and IL-9$^+$ T_H9 cells, and a more favourable T_H17 cell/T_{reg} cell ratio in ex vivo anti-CD3 and anti-CD28-activated peripheral blood mononuclear cells[121]. Another RCT involving 132 people with knee OA showed that butyrate supplementation alleviated pain and stiffness, improved physical function and reduced OA severity[122]. These benefits were accompanied by lower levels of the intestinal permeability marker zonulin, LPS-binding proteins and the inflammatory marker CRP compared with baseline[122].

UDCA, a secondary bile acid approved by the FDA for treatment of primary biliary cholangitis, is also known to antagonize intestinal FXR. Clinical evidence from a cohort study of 5,972 people showed that treatment with UDCA was associated with a lower risk of OA-related joint replacement than in those who did not receive UDCA[9]. In animal models, UDCA supplementation mitigated OA progression and substantially reduced the Osteoarthritis Research Society International scores[9]. Additionally, in a rat model of OA, cholic acid had anti-inflammatory effects on chondrocytes by modulating NF-κB, PERK and SIRT1 signalling, thereby ameliorating cartilage degradation[123].

Clinical evidence of the therapeutic role of tryptophan metabolites in OA remains limited, although several animal studies have explored their effects. In an antibiotic-pretreated rat model of OA, tryptophan supplementation activated microbiome-related tryptophan metabolism, antagonized antibiotic effects and exacerbated OA synovitis[124]. Conversely, skatole, a microbial tryptophan derivative, alleviated cartilage damage by rebalancing catabolic and anabolic processes[125]. In a surgical rat model of OA, indole-3-propionic acid exerted protective effects by reducing cartilage degradation and synovial inflammation and also substantially decreasing Osteoarthritis Research Society International synovitis scores[81].

Together, microbial metabolites offer promising avenues for OA treatment. Future studies should validate animal findings in humans, evaluate efficacy and safety in RCTs and determine the long-term effectiveness, optimal delivery strategies and appropriate dosing in large-scale real-world studies.

Supplementation of gut hormones

The gastrointestinal tract functions as an endocrine organ, releasing bioactive peptides and amines, including GLP-1, glucose-dependent insulinotropic peptide, PYY and ghrelin. These hormones regulate physiological processes, such as nutrient absorption, intestinal growth, gut motility, fluid secretion, insulin release and appetite[57].

Emerging evidence suggests that GLP-1 receptor agonists (GLP-1RAs) might have therapeutic potential for OA, mediated through both weight reduction and gut–joint axis-related mechanisms. In an RCT of 156 adults with overweight and symptomatic knee OA, liraglutide reduced body weight and improved self-reported function, but did not improve pain or physical activity over 1 year[126,127]. By contrast, a multicentre RCT involving 407 people with obesity and moderate-to-severe knee OA demonstrated that semaglutide reduced body weight, alleviated OA-related pain and improved physical function[128]. Notably, two additional studies that were not restricted to individuals with overweight or obesity also reported beneficial effects of GLP-1RAs on OA outcomes. Data from the Shanghai Osteoarthritis Cohort study further indicated that GLP-1RA use reduced WOMAC scores, slowed cartilage loss and lowered knee surgery incidence[129]. Another study linked GLP-1RAs to a lower risk of knee replacement in individuals with knee OA and diabetes, and demonstrated anti-cartilage degrading effects in mice[9]. Moreover, evidence suggests that GLP-1RAs might exert weight-independent effects, including modulation of systemic metabolism, inflammation and cartilage homeostasis[130]. Collectively, these findings indicate that the therapeutic benefits of GLP-1RAs in OA are probably multifactorial, involving both biomechanical (weight loss-related) and gut-mediated mechanisms.

Evidence regarding other gut hormones in OA is limited. Ghrelin can reduce muscle wasting and improve functional capacity in individuals with cachexia[131]. It also inhibits the expression of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF[132]. In an RCT of 32 patients with OA undergoing total hip replacement, ghrelin injection increased lean body mass and decreased adipose tissue mass but did not affect muscle strength, walking or hip-joint function[133]. In OA mouse models, systemic and local ghrelin administration markedly alleviated OA severity by suppressing NF-κB signalling[73]. Together, these findings suggest that ghrelin could have a role in mitigating OA-related pathology.

Overall, understanding of gut hormones in OA is growing, but further research into the underlying mechanisms is needed. Targeting the gut hormone receptor, such as the GLP-1R and growth hormone secretagogue receptor, holds promise for developing novel OA therapies.

Diet and nutraceuticals

Diet profoundly influences gut microbiota by shaping its composition, diversity and functional capacity, with different nutritional regimens producing substantial shifts in microbial community structure and metabolic potential and overall ecological dynamics[134]. In a 4-week open-label pilot trial of 20 patients with knee OA, an anti-inflammatory dietary intervention induced notable changes in gut microbiome and metabolome, particularly in Lachnospiraceae taxa, accompanied by considerable improvements in pain and overall health[135]. Nutritional supplements such as green-lipped mussel extract and glucosamine might relieve OA symptoms, alongside a decrease in Clostridia abundance, which modulates colonic T_H17 cells and CD4$^+$ T_{reg} cells[136]. Fibre is a key dietary component that can modulate the gut microbiota by serving as a substrate for microbial fermentation and promoting the production of anti-inflammatory metabolites such as SCFAs[137]. Observational studies consistently show that higher dietary fibre intake is associated with a lower prevalence and risk of OA[138,139], supporting its potential as a dietary intervention. In animal studies, dietary fibre interventions can induce specific changes in the gut microbiome that alleviate OA symptoms. High dietary fibre intake in a rat model of OA increased Bacillota abundance, upregulated Sestrin2 expression in the knee joint and mitigated cartilage damage[140]. Oral gavage of quercetin, a plant flavanol, altered gut microbiota and metabolic profiles in rat models of OA, increasing *Lactobacillus* abundance and SCFAs levels, ultimately reducing joint pain and inflammation[141].

Together, clinical and animal studies suggest that diet and nutraceuticals might protect against OA via gut microbiota regulation. However, substantial interindividual variability exists, probably

reflecting differences in baseline microbiome composition and host factors. Furthermore, whether sustained dietary changes can produce long-lasting microbiota alterations remains uncertain, as long-term dietary intervention studies and extended follow-up data are scarce.

Future prospects

To better understand the gut–joint axis and develop novel therapies for OA, future studies are needed to standardize sample collection and sequencing, integrate multi-omics approaches and multicentre cohorts, investigate host–environment–microbiota interactions and develop next-generation biotics.

Method standardization

To enhance the credibility, comparability and reproducibility of gut microbiome studies, standardized protocols for sample collection, processing and sequencing are essential. Key considerations include controlling contamination, preserving microbial diversity and preventing DNA degradation. Faecal samples should be collected from the inner, middle section, avoiding the surface layer, which contains host intestinal cells and is prone to environmental contamination[142]. Disposable DNase- and RNase-free tubes should be used, and samples processed within 3 h, when possible, then stored at −80 °C[143]. Aliquoting samples according to the volume required for a single extraction prevents repeated freeze–thaw cycles that can damage microbial cells and reduce DNA yield. As gut microbiota exhibits natural temporal fluctuations, consistent sampling times are recommended, and verification that the lifestyle or health status of the individual has not changed (such as episodes of diarrhoea)[144]. DNA extraction should combine physical (for example, bead vortexing, liquid-nitrogen grinding or ultrasonication) and chemical lysis methods (such as sodium dodecyl sulfate or lysozyme) to efficiently lyse hard-to-break cells, particularly Firmicutes, as insufficient lysis can underestimate their abundance[145]. Post-extraction, DNA purity and integrity should be confirmed (no degradation observed via agarose gel electrophoresis) to ensure sequencing quality. Finally, library preparation and sequencing must be standardized. Samples from the same batch should be processed together on the same sequencer using an identical sequencing mode, as differences in platforms or protocols can compromise comparability. Adhering to these procedures is essential for generating reliable, reproducible and interpretable gut microbiome data.

Integration of multicentre cohorts and multi-omics approaches

The gut microbiota is highly heterogeneous owing to its dynamic nature, which can lead to inconsistent findings across studies. This variability complicates the identification of universal mechanisms and therapeutic targets in OA, underscoring the need for large-scale, prospective, multicentre cohorts to define OA-associated gut microbiota profiles and characterize alterations linked to disease progression[23]. Beyond compositional differences, investigating the functional activity and spatial ecological niche of gut microbiota is crucial. Technologies such as metabolomics and other multi-omics approaches have greatly expanded understanding of the function of gut microbiota[146] (Box 1). Integrating these methods with standardized analytical workflows can provide systematic insights into microbiota function, adaptation and evolution within complex ecosystems. A comprehensive understanding of the gut–joint axis also requires integrating host-derived multi-omics data, as these modulate endocrine, metabolic and immune functions. For example, combining metagenomic analysis with plasma bile acid profiling revealed that intestinal *Clostridium bolteae* regulates GUDCA levels, mediating OA-related cartilage degeneration[9]. Coupling microbiota and host multi-omics data with high-resolution analytical methods will be essential to elucidate the precise molecular and cellular mechanisms that drive the gut–joint axis in OA. Such integrative approaches promise to uncover actionable targets for therapy and advance the mechanistic understanding of OA pathogenesis.

Genetic–environmental–microbiota interactions

Host genetics and lifestyle factors profoundly influence the composition and diversity of gut microbiota. For instance, global or intestinal-specific deletion of GPR35 induces gut dysbiosis, characterized by an increased abundance of *Ruminococcus gnavus*[147]. Conversely, the gut microbiota can modulate host epigenetics. FMT not only alters microbial composition but also affects liver DNA methylation in individuals with metabolic dysfunction-associated steatotic liver disease[148]. Similarly, gut microbiota-derived SCFAs regulate histone acetyltransferases and histone deacetylases, which control histone acetylation and deacetylation[149,150]. Both DNA methylation and histone modifications are core epigenetic regulators[151], enabling differential gene expression from the same genomic blueprint. This regulatory system not only directs phenotypic determination during development but is also recognized as governing gene expression across a wide range of biological processes, including in disease[152]. In particular, epigenetic alterations have been increasingly implicated in the pathogenesis of OA[153,154]. These observations underscore the complex interplay between host genetics, epigenetic modifications, lifestyle and gut microbiota in OA, highlighting the need to study their interconnected roles to fully understand microbial contributions to OA.

The role of gut fungi and viruses in osteoarthritis

Beyond bacteria, gut viruses and fungi are key components of microbiota. Gut viruses are predominantly bacteriophages, which integrate their genetic material into bacterial genomes, modulating bacterial populations in a host-specific manner[155]. Bacteriophages can influence host metabolism and health. For example, transferring faecal viral communities from lean mice to mice with obesity reduced weight gain and normalized glucose levels[156]. Gut fungi also influence host health by promoting translocation of microbial antigens across mucosae or altering bacterial tryptophan metabolism[157]. Individuals with OA exhibit distinct viral and fungal dysbiosis. Viruses that are depleted in faecal samples from individuals with OA mainly belonged to the *Siphoviridae* (95 viral operational taxonomic units (vOTUs)), *Myoviridae* (70 vOTUs), and *Microviridae* (5 vOTUs) families, whereas *Siphoviridae* (30 vOTUs) were enriched in individuals with OA, compared with healthy individuals[158]. Fungal shifts include enrichment of *Debaryomyces fabryi*, *Candida parapsilosis* and *Apophysomyces trapeziformis*, alongside depletion of *Malassezia restricta*, *Aspergillus fumigatus* and *Mucor circinelloides*[158]. Despite these observations, the precise mechanisms through which gut fungi and viruses contribute to OA pathogenesis remain largely unexplored. Further research that integrates multi-omics approaches and functional studies is required to clarify their roles and interactions with bacterial communities, host genetics and immune pathways, which might uncover novel targets for OA prevention and therapy.

Next-generation biotics

The lack of effective pharmacotherapies underscores the need for novel OA treatments. Targeting the gut microbiome with biotics

Box 1 | Using omics technologies to analyse the gut microbiota

A series of omics technologies have progressed remarkably with successful application in gut microbiota research. Through the detection of metabolomics[166], metaproteomics[167], metatranscriptomics[168], single-microorganism genomics[169] and single-microorganism transcriptomics[170], understanding of the functional roles of the gut microbiota has been greatly expanded[146]. Here, we briefly highlight the current application status of these omics technologies to the gut microbiota and future directions.

Metabolomics

Compared with metagenomics, metabolomics focuses on the metabolites produced by microbial communities, directly linking microorganism-derived molecules and their role in microbiomes to host health and behaviour. Gut microbiota-focused metabolomics can detect several types of metabolites, including organic acid, biogenic amines, vitamins and polyamines[171]. This approach enables the screening of disease-associated metabolic biomarkers derived from the gut microbiota and elucidates the regulatory mechanisms through which microbial metabolites influence the host[172]. Metabolomic analysis of faecal samples from individuals with osteoarthritis (OA) revealed considerable dysregulation of gut microbial metabolites, such as propionic acid, indoles and other tryptophan metabolites. Pathway analysis identified markedly disrupted metabolic pathways associated with OA, including leukotriene metabolism, amino acid metabolism and fatty-acid use[44].

Metaproteomics

Metaproteomics use mass spectrometry-based technologies to characterize the proteome generated by the gut microbiota, directly reflecting the functional activity state of the microbial community and functioning as a crucial tool for exploring protein-level interactions between the gut microbiota and the host[173]. Metaproteomics can also be used to identify potential biomarkers for diseases. A cross-sectional analysis of faecal samples from individuals with new-onset type 1 diabetes mellitus, islet autoantibody-positive individuals, low-risk autoantibody-negative individuals and healthy people, revealed that microbiome-derived proteins could distinguish recent-onset (<6 months) and islet autoantibody-positive individuals from those at a low risk[174].

Metatranscriptomics

Metatranscriptomics analyses the total RNA expression profiles of gut microbiota, directly reflecting the gene transcription activity of the microbial community under specific physiological conditions, thereby providing a refined perception of the gut metagenome[175]. It can identify increased transcriptional activity of specific gut bacteria in disease states, thereby revealing actively functioning pathways within the microbiota, such as energy metabolism and metabolite synthesis, and elucidating the abnormal activation or suppression of microbial functions under pathological conditions[176].

Single-microorganism genomics

Single-microorganism genomics obtains complete genomic information of individual gut microbiota through single-cell droplet encapsulation coupled with whole-genome amplification. Compared with metagenomics, this technology better resolves the genomes of low-abundance and unique bacterial species. Furthermore, droplet-based encapsulation enables the investigation of physical associations between individual microorganisms and their co-localized bacteriophages[177].

Single-microorganism transcriptomics

Single-microorganism transcriptomics uses microfluidic droplets to capture individual microorganisms and uses random primers for in situ cDNA generation. Droplets facilitate single-microorganism barcoding, whereas CRISPR-based rRNA depletion is applied for mRNA enrichment. The smRandom-seq technique, developed by Xu et al.[177], successfully captured transcriptomic variations across thousands of individual *E. coli* and identified several antibiotic-resistant subpopulations, providing a high-throughput analytical tool for single-microorganism transcriptomics.

Application in osteoarthritis

Apart from metabolomics, the rest of these omics techniques have not yet been applied to the analysis of the gut microbiota in people with OA. Future studies should integrate these technologies and establish standardized analytical workflows, thereby gaining an in-depth understanding at the systematic level of the functions, adaptation and evolution of the gut microbiota within complex ecosystems.

offers a promising approach to restoring microbial homeostasis and mitigating OA progression. Biotics encompass material derived from living or formerly living organisms. Beyond traditional probiotics, next-generation biotics now include engineered microorganisms and postbiotics. These next-generation biotics hold great therapeutic potential for OA, and their development must be anchored in the well-characterized regulatory mechanisms of the gut–joint axis[159]. In one study, reduced abundance of intestinal *Clostridium bolteae* lowered UDCA and GUDCA levels, decreasing GLP-1 secretion by intestinal L cells and exacerbating cartilage degeneration[9]. However, as *Clostridium bolteae* can function as an opportunistic pathogen[160], direct transplantation is unsafe. A feasible strategy involves engineering probiotics to express 7β-HSDH (an enzyme that catalyses UDCA biosynthesis) within safe strains, such as lactic acid bacteria, to restore beneficial bile acid signalling[161]. Alternatively, postbiotics such as UDCA or GUDCA could directly supplement these metabolites[9]. Both approaches show promise but require further preclinical, translational and clinical studies to evaluate efficacy and safety comprehensively. By harnessing targeted microbial interventions, these biotics-based strategies could provide innovative, mechanism-driven therapies for OA.

Translational challenges

Several key pitfalls must be considered in gut–joint axis research. First, substantial differences in gut microbiota composition exist between animal models and humans, which constitute the frequent failure of translating preclinical findings to the clinic[162]. Second, most OA animal models typically rely on surgically induced traumatic OA, diet-induced obesity-related OA and other approaches, representing a singular aetiology, whereas for most people with primary OA the origin is unclear[163,164]. Third, articular cartilage thickness differs markedly –

Glossary

α-diversity
Within-sample diversity in terms of richness and evenness.

β-diversity
Between-sample diversity that reflects differences in community composition.

16S rRNA gene sequencing
A culture-independent method that amplifies and sequences conserved and variable regions of the 16S rRNA gene to characterize the taxonomic composition and diversity of microbial communities.

Enterochromaffin cells
Enteroendocrine cells that produce most of the serotonin in the body. These cells regulate gastrointestinal motility, secretion and gut–brain signalling.

Enteroendocrine cells
Gut epithelial cells that sense luminal contents and secrete hormones that regulate digestion, appetite and metabolism.

Enterotypes
A classification of the gut microbiome based on the bacteriological composition of the gut microbiota.

Gut microbiota dysbiosis
An imbalance in gut microbial communities, characterized by a loss of beneficial bacteria, an overgrowth of harmful bacteria or reduced microbial diversity.

Kyoto Encyclopedia of Genes and Genomes
(KEGG). A database resource for understanding high-level functions and use of biological systems, such as cells, organisms, ecosystems and the biosphere from molecular-level information.

L cells
Enteroendocrine cells in the distal ileum and colon that secrete glucagon-like peptide-1 and peptide YY. These cells are key for glucose and appetite regulation.

Leaky gut
Increased intestinal permeability that enables bacteria-derived products and antigens to enter tissues, which promotes inflammation.

Operational taxonomic unit
(OTU). A pragmatic definition used to group closely related or uncharacterized microorganisms based on sequence similarity.

Primary bile acids
Bile acids that are synthesized from cholesterol in the liver and secreted into bile.

Secondary bile acids
Bile acids that are produced by intestinal microbiota through enzymatic modification of primary bile acids.

Shotgun metagenomic sequencing
A culture-independent method that randomly fragments and sequences total DNA from a sample, enabling simultaneous identification of microorganisms and analysis of their gene content and metabolic functions.

T_H17 cell/T_{reg} cell ratio
The balance between pro-inflammatory T helper 17 cells and anti-inflammatory regulatory T cells; this imbalance contributes to chronic inflammation.

X/A-like cells
Gastric endocrine cells that secrete ghrelin, the main hunger-stimulating hormone.

~0.3 mm in mice and rats versus ~2.35 mm in humans — resulting in divergent cartilage degeneration dynamics[165]. Most importantly, OA is highly heterogeneous, encompassing distinct patient subgroups; animal models with homogeneous genetic backgrounds and controlled environments cannot capture this variability, posing challenges for clinical translation. These limitations underscore the need for a comprehensive, multi-tiered approach such as intestinal organoids, large animal models, clinical trials and real-world studies. Such an approach would bridge the translational gap, enhance mechanistic understanding and ensure that interventions that target the gut–joint axis are both safe and effective across diverse patient populations.

Conclusions

Evidence increasingly supports the concept of the gut–joint axis in OA, whereby gut dysbiosis disrupts endocrine and immune functions, contributing to disease progression. Therapeutic strategies targeting this axis include probiotics and prebiotics, microbial metabolite or gut hormone supplementation and dietary interventions. Future research should standardize sample collection and sequencing, integrate multi-omics approaches and multicentre cohorts, investigate interactions among host genetics, environment and the gut microbiota (including fungi and viruses) and develop next-generation biotics. Rigorous preclinical and clinical validation of safety and efficacy will be essential for translating these interventions into effective OA therapies.

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Review article

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Sex and gender differences in rheumatology: clinical impact and future directions

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Abstract

Sex and gender shape disease presentation, diagnostic accuracy, treatment response and clinical outcomes in rheumatology, yet these dimensions remain insufficiently embedded in clinical practice. Owing to the markedly unbalanced sex prevalence ratios across many rheumatic diseases, the 'minority' sex is consistently under-represented in clinical studies, limiting the interpretation of long-term outcomes and treatment effectiveness. Sex-related differences in pain perception, inflammatory biomarkers and imaging patterns further complicate disease assessment, and treatment allocation and drug persistence also differ between women and men. Gender-related factors — including disparities in care-seeking behaviours, social roles and lifestyle factors — additionally modulate symptom burden and disease trajectories. Evidence remains particularly scarce for transgender, gender-diverse and intersex individuals, who are rarely captured in clinical cohorts, restricting the development of inclusive and generalizable evidence. Embedding sex-aware and gender-aware approaches into diagnostic reasoning, risk assessment and therapeutic decision-making is therefore essential for advancing precision, equity and truly personalized rheumatological care. Such integration enables clinicians to interpret disease signals more accurately, anticipate divergent multimorbidity trajectories and tailor treatment strategies to the biological and sociocultural contexts of each patient.

Sections

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Key points

- Sex and gender contribute to systematic variation in rheumatic disease trajectories, influencing how these conditions emerge, evolve and impact daily functioning.
- Under-representation of the minority sex in clinical studies restricts interpretation of disease outcomes and undermines the robustness of comparative evidence.
- Diagnostic accuracy is reduced when sex-related differences in symptom patterns, imaging features and inflammatory markers are overlooked.
- Treatment patterns and therapeutic responses diverge by sex, contributing to differential drug persistence and achievement of treatment goals.
- Comorbidity profiles differ between sexes, affecting risk stratification and shaping long-term prognosis.
- Current rheumatology guidelines rarely incorporate sex-sensitive or gender-sensitive recommendations, highlighting an urgent need for structured integration into clinical pathways.

Introduction

In rheumatology, biological sex and gender remain among the most powerful yet underutilized determinants of clinical diversity[1,2]. Each dimension shapes disease onset, progression and therapeutic response, but the explanatory potential of sex-related and gender-related factors is still constrained by conceptual ambiguity and fragmented implementation. Instead of being integrated into diagnostic reasoning or therapeutic algorithms, sex and gender are too often treated as background descriptors — acknowledged in principle yet peripheral in clinical practice. A major conceptual barrier is the persistent conflation of sex, defined by biological attributes such as genetic, epigenetic and hormonal factors, and gender, which encompasses sociocultural norms, identities and lived experiences (Table 1). Although interrelated, these dimensions are not interchangeable. Nevertheless, much of the rheumatology literature continues to misuse gender to describe biological differences, obscuring the distinct biological and sociocultural mechanisms that shape disease expression and outcomes. This conceptual ambiguity ultimately undermines the precision and equity of disease characterization and management.

Importantly, gender extends beyond gender identity and comprises several interrelated domains. These dimensions include gender roles, which reflect social expectations that influence behaviours such as symptom reporting and health-seeking; gender relations, which include caregiving responsibilities, power dynamics and social positioning; and institutionalized gender, which refers to structural factors such as access to care, economic resources and clinical decision-making. Each domain operates across the entire population and could influence disease onset, severity and therapeutic response, meaning that categorizing individuals solely by gender identity does not capture the broader gender-related determinants of health.

This article uses 'men' or 'male' and 'women' or 'female' to reflect the language used in specific cited studies, but recognizes that it is rarely clear how such information was collected or defined (for example, on the basis of endocrine or chromosomal analysis or assignment of sex at birth in medical records or health registry data). Moreover, even if data collection methods are specified, sex and gender information could still be inaccurate or incomplete; for example, when only binary categories such as 'male' and 'female' are available. *Nature Reviews Rheumatology* also acknowledges that sex and gender both exist on a spectrum, are not necessarily aligned and that people with rheumatic diseases might not identify as either women or men. Whereas sex-related differences are widely reported across rheumatology, gender-related determinants are far less consistently captured in clinical datasets, meaning that discussions within individual disease sections reflect the uneven availability of evidence.

Notably, several rheumatic diseases exhibit pronounced imbalances in prevalence between the sexes, and this unequal distribution contributes to persistent knowledge gaps because the minority sex (that is, the sex in which the disease is comparatively less common) remains consistently under-represented in clinical and therapeutic research[1,2]. Consequently, sex-related differences are often regarded as secondary observations rather than fundamental determinants of disease heterogeneity and management.

The complexity of sex-related and gender-related determinants becomes particularly evident in populations whose biological characteristics or gender experiences fall outside traditional binary frameworks. Transgender and gender-diverse individuals are estimated to represent approximately 0.5–4.5% of the adult population[3]. Although this population is numerically small, transgender and gender-diverse individuals are clinically relevant in rheumatology because chronic psychosocial stress, barriers to care and gender-affirming hormone therapy can influence immune and metabolic pathways, with potential implications for disease susceptibility, disease activity and treatment response[4,5] (Box 1). In parallel, individuals born with variations in sex characteristics (often referred to as intersex conditions or differences of sex development) represent another population rarely considered in rheumatology. These variations, estimated to occur in approximately 0.02–1.7% of the population[6], involve differences in chromosomal, gonadal or hormonal profiles that are biologically relevant to immune function. Despite this relevance, implications for rheumatic disease remain largely unexplored[7].

In this Review, we provide a clinically oriented synthesis of sex-related and gender-related differences across selected rheumatic diseases. Rather than offering an exhaustive overview of all conditions, we focus on a set of representative disease models that capture distinct inflammatory paradigms encountered in rheumatology practice. Specifically, we discuss rheumatoid arthritis (RA), a prototypical chronic inflammatory arthritis; systemic lupus erythematosus (SLE) and Sjögren disease, representing systemic autoimmune diseases with marked female predominance; axial spondyloarthritis (axSpA) as a representative model of the spondyloarthritis spectrum; and gout, a prototypical crystal-induced inflammatory arthritis. Together, these conditions illustrate complementary patterns of sex-related and gender-related differences across epidemiology, clinical phenotype, comorbidities and therapeutic response. Where relevant, selected clinical evidence from psoriatic arthritis (PsA) is incorporated to contextualize sex-related and gender-related differences across the spondyloarthritis spectrum.

Despite a growing body of evidence, current rheumatology guidelines seldom translate sex-related and gender-related findings into clinical recommendations, perpetuating inconsistencies in care and reinforcing diagnostic and therapeutic bias (Table 2). By highlighting

Table 1 | Sex and gender terms relevant to rheumatology

Term	Definition	Clinical relevance in rheumatology
Sex	Biological and physiological characteristics of women, men and intersex individuals, including genetic, epigenetic and hormonal factors	Influences immune dimorphism and differential pharmacokinetics, disease prevalence, progression and treatment outcomes
Gender	Socially constructed norms, roles, behaviours and power structures that shape expectations, opportunities and lived experiences across the lifespan; gender is a multidimensional and dynamic construct that cannot be fully captured by binary classifications	Shapes exposure to risk factors, health-seeking behaviour and access to care; influences treatment adherence and disease perception
Gender identity	An individual's deeply felt internal sense of gender, regardless of genetic factors and sex assigned at birth	Relevant to patient experience, exposure to stigma and barriers to gender-responsive health care
Transgender and gender-diverse people	Individuals whose gender identity or expression differs from the sex assigned at birth; irrespective of whether they receive gender-affirming hormone therapy or surgery	Chronic stress and gender-affirming hormone therapy might influence immune and metabolic profiles; binary research frameworks have contributed to the under-representation of non-binary individuals, highlighting the need for their inclusion to improve clinical evidence and equity of care
Intersex people and differences of sex development	Individuals born with natural variations in sex characteristics (chromosomal, gonadal or hormonal characteristics) that do not fit typical binary notions of male or female bodies	Variations in genetic and hormone profiles might affect immune pathways; this population remains under-represented in rheumatology research
Minority stress	Chronic psychosocial stress related to stigma, discrimination and social marginalization experienced by sexual and gender minority populations	Potential contributor to inflammation, comorbidity burden and barriers to health care access

Definitions of key terms describing biological and sociocultural dimensions relevant to sex, gender and diversity in rheumatology research and care are adapted from the World Health Organization[175], the Istituto Superiore di Sanità (the Infotrans and InfoIntersex portals) and from Coleman and colleagues[176].

shared clinical patterns and persistent knowledge gaps, this Review provides actionable insights to support the integration of sex and gender perspectives into everyday rheumatology practice, a critical step towards equity, precision and patient-centred care.

Rheumatoid arthritis

RA is a chronic inflammatory form of arthritis characterized by persistent synovial inflammation that can lead to progressive joint damage and disability. RA also exemplifies how sex-related and gender-related differences can influence disease activity assessment, treatment response and functional outcomes in routine clinical practice.

Epidemiology and clinical presentation

RA affects approximately 0.5–1% of the population and shows a clear female predominance, with a female-to-male ratio of roughly 2–3:1 (refs. 8,9). Several epidemiological datasets indicate that the incidence of RA has increased over the past 30 years[10]. The underlying causes remain unclear and could involve environmental factors[10].

Sex-related and gender-related factors influence diagnostic pathways and disease presentation. Women have historically experienced longer diagnostic delays, although this gap has narrowed over time[11–15]. Patterns of health care utilization also differ: women more frequently consult primary care physicians and rheumatologists before diagnosis, whereas men more often present to emergency services[16]. Across multiple cohorts, women consistently report higher disease activity and greater disability than men[17]. In a UK early RA cohort, female sex was identified as an independent predictor of persistent fatigue, a core symptom of RA, together with higher pain levels, poorer mental health and greater baseline disability[18]. Such differences reinforce the need to integrate sex-related and gender-related considerations into early diagnostic assessment of RA.

Life-course hormonal factors

Across the life course, hormonal transitions seem to influence RA risk and disease activity. Approximately half of people with RA who become pregnant experience clinical improvement during pregnancy, whereas postpartum flares occur in up to 30–50% of cases, underscoring the need for close monitoring after delivery[19].

The menopausal transition represents another biologically relevant phase. Early menopause is associated with an increased incidence of RA and higher levels of disease activity and structural progression[20]. A meta-analysis comprising over 22 million person-years reported a modest increase in incident RA risk among hormone replacement therapy users, particularly among current and long-term users[21]. Researchers have also examined hormonal contraceptive use, with meta-analytical evidence suggesting a modest association between ever-use and reduced RA risk; however, substantial heterogeneity across studies and uncertainty regarding timing, formulation and residual confounding limit definitive conclusions[22].

Overall, the available evidence points to modest and heterogeneous associations between hormonal exposures and RA risk. Rather than indicating a uniformly protective or harmful effect of exogenous oestrogens, these findings highlight the complexity of hormonal modulation in RA and reinforce the need for an individualized risk–benefit approach when considering hormonal therapies in those with autoimmune susceptibility.

Therapeutic considerations

Sex influences treatment allocation in RA, although the magnitude of sex-related differences varies across drug classes. In a large German nationwide cohort[23], women had slightly lower odds of receiving conventional synthetic DMARDs (csDMARDs) and glucocorticoids within the first year after diagnosis, although the observed differences were small and of uncertain clinical relevance. More pronounced differences emerged for biological DMARDs (bDMARDs), with women showing lower odds of bDMARD initiation during the first year than men (OR 0.62; 95% CI 0.57–0.69)[23]. Data from the Spanish BIOBADASER registry[24] did not identify major overall sex differences in time to initiation of bDMARDs or targeted synthetic DMARDs, although women diagnosed in the later years of the registry (2017–2023) initiated therapy slightly later than men.

Beyond differences in treatment allocation, sex also seems to influence therapeutic outcomes. Female sex, higher baseline disease activity

and delay in treatment initiation have been identified as predictors of refractory disease, defined as failure to achieve low disease activity after ≥3 DMARDs, including at least one biologic. In multivariable analysis, female sex was associated with approximately threefold higher odds of refractory disease[25]. Consistent with this pattern, analyses of clinical trial datasets indicate that male sex, lower baseline disease activity and shorter disease duration are associated with a greater likelihood of achieving treatment targets[26]. However, evidence remains mixed. A meta-analysis of phase II–III randomized controlled trials evaluating multiple biologic agents did not detect clear sex-related differences in American College of Rheumatology (ACR)20 response rates[27]. Similarly, post hoc analyses of the NORD-STAR trial in early RA did not identify meaningful sex-related differences in remission rates across treatment groups[28]. By contrast, data from the DANBIO registry show that women receiving TNF inhibitors exhibit smaller reductions in Disease Activity Score in 28 joints (DAS28) scores, lower rates of good treatment response according to European Alliance of Associations for Rheumatology (EULAR) criteria and shorter treatment persistence than men[29].

Sex differences in the components of composite disease activity indices might partly explain these observations. In the BARFOT early RA cohort, women had higher DAS28 scores than men, primarily driven by patient-reported components such as pain and global assessment, whereas swollen joint counts and inflammatory markers were similar[30]. Well-documented sex differences in pain perception and pain thresholds — influenced by hormonal, neurobiological and immunoregulatory mechanisms — provide additional context. Although these differences are not specific to RA, they can affect patient-reported components of composite disease activity indices without necessarily reflecting greater inflammatory burden. Supporting this interpretation, meta-analytic evidence indicates that women with RA report higher pain scores across the disease course, even when receiving similar DMARD therapies[31]. Such differences can influence clinical assessment of disease severity and the likelihood of reaching composite treatment targets, including those based on DAS28 or EULAR criteria. Sex-related differences in inflammatory markers could further influence evaluation of treatment response. For example, lower erythrocyte sedimentation rate (ESR) values in men can increase the probability of meeting remission thresholds according to DAS28-ESR[32]. After correction for sex-related differences in ESR, approximately 12% of men were reclassified, indicating that DAS28-ESR might overestimate remission rates in male patients.

Despite these differences in disease activity measures and treatment targets, long-term structural outcomes seem broadly similar in women and men. In a Dutch treat-to-target cohort, women presented with higher disease activity over time and required more frequent treatment adjustments, yet radiographic outcomes of the sexes remained comparable[33]. This pattern suggests a partial dissociation between composite disease activity indices and structural progression.

Sex could also influence treatment persistence. Meta-analytical evidence indicates that female sex is associated with slightly higher rates of biologic discontinuation[34], although the magnitude of this effect is modest. Discontinuation is most often related to lack or loss of efficacy or safety concerns, but sex-specific patterns of comorbidities and extra-articular manifestations might also contribute. Similar findings emerged from the PROPER study, which reported higher discontinuation risk among women following treatment transition to a biosimilar (HR 3.53; 95% CI 1.07–11.67)[35], although given the wide confidence intervals, these findings should be interpreted with caution. Such findings suggest that sex-related and gender-related differences can influence multiple aspects of RA treatment, from treatment allocation and response assessment to treatment persistence, whereas long-term structural outcomes seem broadly comparable.

Box 1 | Transgender and gender-diverse people in rheumatology

Transgender and gender-diverse individuals remain virtually absent from rheumatology research, despite increasing awareness that gender-affirming hormone therapy and psychosocial factors might influence immune, inflammatory and metabolic pathways relevant to rheumatic diseases[4,5,191]. Existing data are limited to small case series and cross-sectional studies, often derived from non-rheumatological populations, yet these data highlight potentially important implications for disease expression, treatment response and comorbidity risk[4,5].

Oestrogen and testosterone — central components of gender-affirming hormone therapy — exert pleiotropic effects on immune regulation[192,193]. Longitudinal studies in transgender men demonstrate that masculinizing hormonal treatment regimens can attenuate type I interferon responses and enhance TNF-driven and NF-κB-driven, T_H1-skewed inflammatory pathways[194,195]. By contrast, the immunological effects of feminizing hormonal treatment regimens remain largely unstudied. Available prospective data, including longitudinal autoantibody profiling, do not show a clear increase in autoimmunity during gender-affirming hormone therapy[196], highlighting the need for robust, long-term studies to determine whether hormonal modulation influences disease onset or clinical presentation in susceptible individuals. Evidence from other clinical contexts that involve hormone suppression, such as endocrine therapies for breast and prostate cancer, further supports the concept that modulation of sex steroids can exert systemic effects on multiple physiological systems, including immune regulation and bone metabolism, although direct extrapolation to transgender populations requires caution[197–199]. Data on gender-diverse people, who might receive individualized, partial or no hormonal interventions according to their gender-affirmation goals, remain extremely limited[176].

Beyond hormonal mechanisms, gender-related factors, such as minority-specific stressors, barriers to care and reduced uptake of preventive services, further shape disease experience and outcomes in transgender and gender-diverse populations[176,200]. Moreover, gender-affirming hormone therapy can interact with conventional antirheumatic drugs, affecting pharmacokinetics, cardiovascular and thrombotic risk, and bone metabolism, underscoring the need for individualized therapeutic monitoring[176].

Closing these knowledge gaps will require systematic inclusion of gender identity and sex assigned at birth in clinical registries, equitable participation of transgender and gender-diverse individuals in clinical trials and the development of multidisciplinary, gender-affirming care pathways.

Comorbidities and clinical outcomes

Comorbidity patterns also differ by sex, influencing overall disease burden and prognosis. In a cohort of >150,000 individuals with RA, women had a higher prevalence of multimorbidity — defined as the coexistence of two or more chronic conditions — and more frequent mood, neurological and diffuse musculoskeletal disorders, whereas men were more prone to cardiovascular disease[36]. Although cardiovascular disease represents the leading comorbidity in RA for both sexes, cardiovascular risk could be underestimated in women. In a Dutch cohort of 863 individuals with RA, 36% of women who experienced a cardiovascular event had been classified as low risk by the Systematic Coronary Risk Evaluation algorithm, compared with 10% of men[37]. Reduced performance of conventional cardiovascular risk-prediction tools in women has also been documented in the general population and might reflect sex-related differences in atherosclerotic biology, clinical presentation and calibration of existing algorithms.

Cardiometabolic outcomes provide another area where sex shapes disease trajectories. RA-associated cardiometabolic risk is further influenced by the well-described 'lipid paradox', in which active systemic inflammation is associated with lower total cholesterol and LDL concentrations yet confers higher cardiovascular risk[38]. Sex-related and menopause-related differences in lipid profiles add further complexity: postmenopausal women often exhibit a more atherogenic pattern, suggesting that hormonal status modulates cardiovascular risk trajectories[39].

Body composition represents another important sex-specific modifier of cardiometabolic risk and RA outcomes[40], with higher BMI associated with greater RA disease activity in women, but not in men[41]. Beyond biological factors, gender-related determinants also influence functional outcomes. Women with RA are at a higher risk of work disability than men, influenced by socioeconomic and psychosocial determinants such as educational attainment, employment conditions and mental health status[42].

Despite these sex-related and gender-related differences in morbidity, effects on mortality are less consistent. Although all-cause mortality is increased in patients with RA compared with the general population, available evidence does not indicate consistent sex differences in cause-specific mortality[43].

Overall, sex seems to shape multiple clinical dimensions of RA. Women show higher prevalence and generally greater disease activity,

Table 2 | Integration of sex and gender considerations across prevention, diagnosis and management in major rheumatology guidelines

Disease	Guidelines and recommendations	Prevention and risk stratification	Diagnosis and classification	Clinical trials: conducting and reporting	Treatment and management
Rheumatoid arthritis	EULAR (2021 (refs. 177,178) and 2018 (ref. 179)) guidelines	None; no sex-specific or gender-specific prevention strategies or risk stratification approaches	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender-specific symptom profiles	Minimal; sex and gender are included in the core dataset for clinical trials and observational studies	None. No sex-specific or gender-specific treatment or management recommendations
Systemic lupus erythematosus	EULAR (2025 (refs. 180,181), 2024 (refs. 182,183), 2022 (ref. 184) and 2017 (ref. 185)) and ACR (2025 (refs. 186,187), 2020 (ref. 63)) guidelines	Minimal; predominance in reproductive-aged women is acknowledged; male sex is mentioned as a risk factor for lupus nephritis and chronic kidney disease, end-stage kidney disease and kidney flares; incorporating gender in cardiovascular risk stratification is highlighted as a future challenge	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender specific symptom profiles	Minimal; sex (but not gender) is included in the core dataset recommended for clinical trials and observational studies	Limited. Recommendations explicitly address drug safety in relation to reproductive health (including contraception, pregnancy, fertility preservation and menopause). Transgender reproductive health noted as a research need
Axial spondylo-arthritis	ASAS-EULAR (2023 (ref. 188)) and ACR (2016 (ref. 189)) guidelines	None; men are recognized as having a higher propensity for progressive spinal fusion	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender-specific symptom profiles	None; no sex-specific or gender-specific recommendations for conducting or reporting clinical trials	Minimal. The guidelines highlight the need to investigate drug efficacy stratified by gender as a research priorities
Sjögren disease	n.a.	None; no sex-specific or gender-specific prevention strategies or risk stratification strategies	None; no sex-specific or gender-specific diagnostic recommendations or classification criteria; no reference to sex-specific or gender-specific symptom profiles	None; no sex-specific or gender-specific recommendations for conducting or reporting clinical trials	None. No sex-specific or gender-specific treatment or management recommendations
Gout	EULAR (2020 (ref. 190)) guidelines	None; no sex-specific or gender-specific prevention strategies or risk stratification strategies	Minimal; male sex is recognized as a clinical feature supporting diagnosis, although both sex-informed and gender-informed diagnostic guidance remain limited	None; no sex-specific or gender-specific recommendations for conducting or reporting clinical trials	None. No sex-specific or gender-specific treatment or management recommendations

We limited our review to European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) guidelines (published from 2015 to 2025), which consistently apply standardized evidence-grading frameworks (for example, GRADE) and provide internationally adopted clinical recommendations in rheumatology. This table is not aimed at providing an exhaustive list of all available guidelines for each rheumatic disease. Only guidelines that explicitly mention or incorporate sex and/or gender differences in their recommendations or discussion were included. General disease management guidelines without specific reference to sex and/or gender considerations were excluded. 'None' indicates no mention of sex or gender; 'Minimal' indicates acknowledgement without specific recommendations; 'Limited' indicates recommendations restricted to specific subpopulations (such as pregnancy). Use of the terms 'sex' and 'gender' in the table reflects the terminology adopted in the original guideline documents. Use of the terms 'men' and 'women' in this table reflects the terminology adopted in the original published research; however, *Nature Reviews Rheumatology* recognizes that not everyone affected by rheumatic disease is a woman or man. ASAS, Assessment of Spondyloarthritis International Society; n.a., not available.

with a higher burden of pain and fatigue and, on average, less favourable treatment responses, as well as higher rates of treatment discontinuation and work disability, despite similar or less structural damage. Men, by contrast, more often exhibit an erosive phenotype and faster radiographic progression and show a higher burden of cardiovascular comorbidities. Gender-related factors, such as health care engagement and lifestyle, together with sex-related and gender-related influences on pain perception, could further modulate functional outcomes.

Systemic lupus erythematosus

SLE is a systemic autoimmune disease characterized by heterogeneous clinical manifestations and multisystem involvement. SLE provides one of the clearest examples of how sex-related and gender-related factors shape autoimmune disease. This disease is characterized by marked sex imbalances, distinctive age-related patterns of disease onset and notable differences in clinical expression, serological profiles and outcomes.

Epidemiology and clinical presentation

SLE is one of the most female-predominant autoimmune diseases, particularly during the reproductive years, with a female-to-male ratio of approximately 8–15:1 that decreases to 2–8:1 in prepubertal and late-onset disease[44,45]. These age-related and sex-related patterns have long suggested a role for hormonal factors in disease susceptibility[46,47], although current evidence also implicates X-linked genetic mechanisms and abnormalities in X chromosome inactivation as contributing factors[48,49].

Sex-related differences in age at disease onset have been reported. In a large Italian multicentre cohort, women developed SLE at a younger age than men (28 versus 35 years) and received a diagnosis earlier (30 versus 38 years), although diagnostic delay of the sexes remained similar (2.8 ± 5.2 versus 2.2 ± 4.2 years)[50]. Despite these differences, the 2019 EULAR–ACR classification criteria perform comparably across sexes, with sensitivity of 97% and 93% and specificity of 94% and 96%, respectively[51].

Distinct sex-specific clinical phenotypes are evident at disease onset. Men more often present with major organ involvement, including serositis, discoid lupus, thrombocytopenia and lupus nephritis, whereas women more commonly develop malar rash, alopecia, arthritis and leukopenia[44,50,52–57]. In the Attikon Lupus Cohort, male sex, younger age and higher serological activity were independent predictors of renal involvement[58], although the relatively small number of male participants warrants cautious interpretation. Despite the higher prevalence of nephritis among men, renal biopsy class distributions of the sexes seem comparable[58].

Sex-related differences are also evident in serological profiles. Men with SLE more frequently have lupus anticoagulant and anticardiolipin antibodies, whereas women show higher prevalence of anti-Ro/SSA and other extractable nuclear antigen antibodies, including anti-SSB, anti-RNP and anti-Sm antibodies[59]. Such findings highlight how sex-related and gender-related differences shape the epidemiology and clinical expression of SLE.

Life-course hormonal factors

Hormonal exposures across the life course, including pregnancy, hormonal contraception and postmenopausal hormone therapy, have been extensively investigated in SLE because of the potential implications for disease activity and clinical management. During pregnancy, most studies report predominantly mild flares, typically cutaneous, musculoskeletal or haematological, occurring in approximately 25–65% of pregnancies depending on baseline disease activity and study population[60]. Debate around hormonal contraception has persisted for decades. Although early observational studies suggested an increased risk of flares or thrombosis, two randomized controlled trials showed no increase in disease activity among individuals using hormonal contraceptives, regardless of formulation[61,62]. Because these trials included only women with inactive or stable disease, the 2020 ACR guideline recommends avoiding oestrogen-containing contraceptives in those with active SLE or antiphospholipid antibodies, while supporting their use in women with stable disease[63]. Notably, although some women report subjective symptom fluctuations, such as fatigue or pain, across the menstrual cycle, hormonal contraceptive use does not seem to trigger clinically meaningful flares[64].

Debate around the use of hormone replacement therapy in postmenopausal women with SLE has also persisted for decades. Some observational studies reported no increase in disease activity, whereas the SELENA trial identified a modest rise in mild-to-moderate flares without changes in severe flares[65]. Thrombotic risk remains the primary concern, particularly among women who test positive for antiphospholipid antibodies, although hormone replacement therapy seems safe in well-selected patients with stable disease[47].

Collectively, these findings indicate that hormonal exposures across the life course can have important implications for SLE management, particularly in relation to flare risk and thrombotic complications.

Therapeutic considerations

Therapeutic management in SLE shows several sex-related differences[59]. Across observational cohorts and registry studies, men receive cyclophosphamide more often than women, a pattern that probably reflects the higher prevalence of severe organ involvement, particularly lupus nephritis, among male patients[55,66]. Conversely, antimalarial drugs, particularly hydroxychloroquine, seem to be prescribed less frequently in men[67,68]. For most other therapies, including glucocorticoids and commonly used immunosuppressive drugs such as azathioprine, mycophenolate mofetil and biologic drugs, prescription patterns of the sexes remain broadly similar, although findings vary across studies[55,67]. Evidence of sex-related differences in treatment adherence remains limited and inconsistent: most studies report comparable adherence to antimalarial drugs, whereas some administrative datasets suggest slightly lower adherence to immunosuppressive therapies among women[67,69,70].

Whether biological sex modifies treatment efficacy remains insufficiently explored. Because SLE predominantly affects women, most pivotal randomized controlled trials enrol overwhelmingly female populations, limiting the feasibility of robust sex-stratified analyses and reducing the generalizability of treatment-effect estimates to male patients. In a pooled post hoc analysis of five phase III belimumab trials, male patients showed a higher risk of neuropsychiatric flares (HR 3.26, 95% CI 1.51–7.04), although the small number of men warrants cautious interpretation[71]. In the phase III trial of obinutuzumab for lupus nephritis, women seemed more likely to achieve a complete renal response, although this difference largely reflected a higher placebo response among men and again probably reflects the small number of male participants[72]. Such available evidence suggests that observed sex-related differences in SLE treatment largely reflect differences in disease severity, whereas limited representation of men in clinical trials constrains conclusions on sex-specific treatment response.

Comorbidities and clinical outcomes

Sex-related and gender-related differences extend to comorbidities and long-term clinical outcomes in SLE. Several studies report that men with SLE accumulate greater overall organ damage than women[50,57–59,73–78]. A scoping review found higher rates of chronic kidney disease and progression to end-stage renal disease among men across multiple cohorts, consistent with evidence that damage accrues more rapidly in men than in women[59]. Notably, in a large Chinese cohort, serologically active but clinically quiescent phenotypes were also associated with cumulative organ damage, with the highest burden occurring among antiphospholipid-positive men[78].

Despite accumulating less objective organ damage, women with SLE frequently report poorer health-related quality of life than men. In a multiethnic cohort of 1083 individuals with SLE, men scored lower in social support domains, whereas women reported worse SLE-specific symptoms, cognitive function, physical health and pain–vitality domains, particularly during reproductive years[79]. Functional consequences are also substantial: work disability affects approximately 20–40% of patients with SLE and frequently leads to reduced productivity or early withdrawal from the workforce, particularly among women[80].

Cardiovascular disease remains a major sex-related determinant of prognosis in SLE[81]. In the general population, men have a higher baseline risk of cardiovascular disease, which partly explains the higher absolute cardiovascular disease rates observed among men with SLE. However, the sex gap seems larger within the SLE population than in the general population, suggesting amplification by disease-related mechanisms. SLE also markedly attenuates the usual female cardiovascular advantage: women aged 35–44 years with SLE have up to a 50-fold higher risk of myocardial infarction than age-matched women in the general population[82]. Accordingly, women with SLE often have an altered lipid profile, including dysfunctional, pro-inflammatory HDL particles associated with increased carotid intima–media thickness[83,84].

Despite therapeutic progress, sex-specific mortality patterns persist in SLE. Mortality remains markedly higher in women than in men. In a US population-based analysis covering 1999–2020, age-adjusted mortality rates reached 6.21 per million in women and 1.20 per million in men — an approximately fivefold difference — although both sexes showed declining trends over time[85]. A separate cross-sectional analysis based on the US national death certificate data found that women with SLE died on average approximately 22 years earlier than women without SLE, whereas men died approximately 12 years earlier than their counterparts in the general population[86]. Causes of death also differ by sex: sepsis and hypertension are more frequent among women, whereas cardiovascular disease and diabetes-related complications predominate in men[86]. Notably, among patients with lupus nephritis, mortality is nearly twice as high in men as in women (24.2% versus 13.4%), with infection-related causes contributing substantially to this excess risk[87].

Overall, sex shapes the clinical spectrum and outcomes of SLE. Men more frequently develop severe organ involvement and accumulate greater organ damage, whereas women experience a substantial disease burden characterized by poorer health-related quality of life and greater functional impact. SLE also substantially reduces the typical cardiovascular protection associated with female sex, thereby increasing cardiometabolic risk.

Axial spondyloarthritis

Axial spondyloarthritis (axSpA), a prototypical condition within the spondyloarthritis spectrum, is a chronic inflammatory disease of the axial skeleton characterized by inflammatory back pain and variable peripheral and extra-musculoskeletal manifestations[88,89]. Patients are classified as having radiographic axSpA or non-radiographic axSpA on the basis of structural changes detected on imaging[90]. AxSpA provides a useful clinical model for examining sex-related and gender-related differences across the spondyloarthritis spectrum, particularly regarding diagnostic pathways, disease burden and treatment outcomes. Similar patterns have also been described in PsA, supporting the role of sex and gender as important clinical modifiers across these conditions. A comparative overview of shared and distinct sex-related and gender-related clinical features between axSpA and PsA is provided in Box 2.

Epidemiology and clinical presentation

Historically, clinicians regarded axSpA as more prevalent and more severe in men; however, contemporary epidemiological evidence shows an almost equal overall sex distribution. This apparent balance reflects differing subtype patterns: men develop radiographic axSpA more often, with an approximate female-to-male ratio of 1:3, whereas non-radiographic axSpA has a more even sex distribution. Men are also at a higher risk of structural progression and severe disease, with a male-to-female ratio of approximately 2:1 among individuals with radiographic axSpA[91].

Prevalence strongly aligns with *HLA-B*27* positivity, which occurs more frequently in men, particularly in radiographic axSpA, whereas women, especially women with non-radiographic axSpA, less often carry *HLA-B*27* (refs. 92–94). Genetic differences between sexes extend beyond *HLA-B*27* (ref. 94). In a large longitudinal cohort, other *HLA-B* alleles, including *HLA-B*15* and *HLA-B*37*, were associated with peripheral musculoskeletal manifestations, and women showed a higher burden of enthesitis and peripheral arthritis, highlighting sex-related variation in genetic–phenotypic associations[95]. Transcriptomic analyses further reveal sex-specific gene expression signatures[96], with differentially expressed genes enriched in immune and inflammatory pathways. These findings support sex-specific immune activation profiles[97] and could contribute to sex-related heterogeneity in clinical presentation, treatment response and outcomes[91,98].

These biological differences align with distinct clinical presentation patterns in women and men. Men more often present with inflammatory back pain and limited peripheral or entheseal involvement, whereas women more often report diffuse or widespread pain patterns that might overlap with fibromyalgia, potentially complicating clinical assessment[99,100]. Women with axSpA are also more likely to develop cervical spine disease, although estimates vary substantially across cohorts[101].

Diagnostic delay in axSpA remains substantial and tends to be longer in women than in men[89,101]. Several factors could contribute to this disparity. Women more frequently present with less specific imaging findings, which can complicate diagnostic interpretation[101,102]. Assessment of bone marrow oedema on MRI can be particularly challenging in women, as physiological and mechanical factors, including postpartum changes, can produce sacroiliac signal alterations that mimic inflammatory lesions[103]. Such findings highlight how sex-related and gender-related differences contribute to distinct clinical phenotypes and diagnostic challenges in axSpA.

Life-course hormonal factors

Reproductive life stages also intersect with disease expression in axSpA, although available evidence remains limited. Contemporary prospective data indicate that overall obstetric outcomes in women with axSpA are largely comparable with those in the general population. In a French national prospective matched study of women with SpA,

Box 2 | Comparative sex-related and gender-related features in axial and psoriatic spondyloarthritis

Sex-related and gender-related differences described in axial spondyloarthritis (axSpA) show important similarities to those observed in psoriatic arthritis (PsA), particularly in clinical presentation, disease burden and treatment outcomes, supporting the relevance of sex and gender as clinical modifiers across the spondyloarthritis spectrum[201–204].

Shared clinical patterns

Across both axSpA and PsA, women consistently report higher disease activity, greater functional limitation and worse patient-reported outcomes, including pain, fatigue and reduced health-related quality of life, despite similar levels of objective inflammatory activity[99,201–204]. In PsA, clinical trial data show a comparable pattern, with higher pain scores, functional impairment and patient global assessment in women, compared with higher inflammatory markers and more severe skin involvement in men[202]. This discordance between higher patient-reported disease burden in women and higher objective inflammatory measures in men seems to be a consistent feature across the spondyloarthritis spectrum.

Sex differences in treatment outcomes also show similar trends. In both axSpA and PsA, men generally achieve higher response rates and maintain longer persistence with biologic therapies, whereas women more frequently discontinue treatment or report suboptimal clinical responses[202,204]. Real-world studies in PsA further suggest lower rates of minimal disease activity and less favourable treatment outcomes in women[205,206].

Distinct clinical features

Important differences between the two diseases should also be considered. AxSpA remains more strongly associated with male sex, particularly with respect to structural damage and radiographic progression, whereas PsA shows a more balanced sex distribution, with emerging data suggesting a higher proportion of women than historically reported[201,202]. PsA is also characterized by multidomain disease involvement, including peripheral and polyarticular disease patterns and differences in skin involvement, with sex differences largely reflecting the distribution of clinical domains. By contrast, sex differences in axSpA are more strongly reflected in structural damage, radiographic progression and diagnostic delay[201,202].

Implications for clinical practice

Taken together, these observations highlight the importance of incorporating sex and gender into the interpretation of symptoms, the evaluation of treatment response and the assessment of disease impact across the spondyloarthritis spectrum. Differences in disease expression between axSpA and PsA underscore the need for disease-specific interpretation of sex-related and gender-related differences when planning management strategies.

rates of preterm birth, hypertensive disorders, congenital anomalies and caesarean delivery were similar to those observed among matched women in the general population[104].

Data regarding hormonal contraception remain limited but are generally reassuring[105]. Available data indicate that combined oral contraceptives do not worsen disease activity in axSpA, and no consistent association with disease onset or severity has emerged[106]. Evidence regarding menopause remains indirect. Both axSpA and the menopausal transition are independently associated with increased cardiovascular risk. However, current data do not conclusively show that menopause itself specifically increases cardiovascular risk or accelerates structural disease progression in women with axSpA[107].

Such findings suggest that reproductive and hormonal factors influence disease expression in axSpA, although their clinical relevance remains uncertain owing to limited data.

Therapeutic considerations

Treatment patterns and response to therapy show consistent sex-related differences in axSpA. In a large US claims-based study, women were more likely to continue NSAIDs after diagnosis and initiated bDMARDs later than men (adjusted HR 0.61; 95% CI 0.52–0.72)[108]. Observational data further indicate that women are less likely to receive biologic therapies despite reporting a greater disease burden[109].

Men generally achieve higher remission rates and greater improvements in disease activity with TNF inhibitors, whereas women tend to show less favourable responses and shorter treatment persistence[110–115]. Evidence from large observational cohorts reinforce these differences. In an analysis drawing on multiple European registries within the European Spondyloarthritis Research Collaboration Network[116], women had higher disease activity and functional impairment at baseline — reflected in higher Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index scores — and these differences persisted after TNF inhibitor therapy. Similarly, in the Swiss Clinical Quality Management cohort, men with non-radiographic axSpA were more likely to achieve an Assessment of Spondyloarthritis international Society 40 response after 1 year of treatment with a first TNF inhibitor (38% versus 17% in women)[93]. Data from the Swedish registry also show lower discontinuation rates of TNF inhibitors in men than in women (HR for discontinuation 0.36, 95% CI 0.19–0.68)[117], a pattern replicated in the Rheumatology Informatics System for Effectiveness registry, where women discontinue TNF and IL-17 inhibitors more frequently, whereas JAK inhibitor discontinuation shows no sex difference[118].

In randomized controlled trials of IL-17 inhibition, clinical responses seem to occur earlier in men, whereas women more often show a slower but progressive improvement, with broadly comparable outcomes at longer follow-up[119,120]. Importantly, the higher discontinuation rates observed in women across different cohorts and therapeutic classes do not seem to arise from differences in patient behaviour alone, suggesting that a combination of biological factors, differences in disease phenotype and variations in treatment allocation or clinical decision-making could contribute to these disparities.

Comorbidities and clinical outcomes

Sex influences several dimensions of long-term disease burden in axSpA, including structural progression, comorbidity patterns and overall clinical outcomes. Men more frequently develop structural damage, including bilateral sacroiliitis and spinal syndesmophytes[121], than women. In a Swiss longitudinal cohort, syndesmophytes occurred

in 40% of men compared with 15% of women[122]. Radiographic progression is also more pronounced in men, whereas women generally show slower or minimal structural progression over time; over 2 years, mean progression reached 1.0 ± 2.8 units in men compared with 0.3 ± 1.1 in women ($P < 0.001$)[122].

Sex-related differences extend beyond structural damage and include systemic manifestations and cardiovascular risk. In a Spanish cohort, women showed a lower prevalence of carotid atherosclerosis overall, but among those at a high cardiovascular risk, greater disease activity correlated more strongly with subclinical atherosclerosis in women than in men, suggesting sex-related differences in the interaction between inflammation and cardiovascular risk[123].

Metabolic factors could further contribute to sex differences in clinical outcomes. Although BMI does not consistently differ between sexes, women tend to have higher fat mass and a greater prevalence of central obesity, both of which have been associated with worse functional outcomes and poorer quality of life[124,125]. Consistently across multiple cohorts, women report higher disease activity scores and worse patient-reported outcomes than men, including greater fatigue, reduced physical function, poorer health-related quality of life, a higher level of psychological distress and greater impairment in work productivity and daily activities[91,97,99,126–130].

Sex differences are also evident in the distribution and impact of comorbidities. Data from the international COMOSPA cohort indicate that cardiovascular comorbidities occur more frequently in men, whereas fibromyalgia is more prevalent in women, and these comorbid conditions influence disease activity and functional outcomes in sex-specific ways[131].

Mortality also differs by sex. Available data suggest that excess mortality occurs primarily in men with axSpA, whereas no consistent increase has been reported in women[132]. In retrospective cohort analyses, male sex, older age and elevated C-reactive protein levels were associated with increased mortality[133], highlighting the contribution of persistent systemic inflammation to long-term risk.

In summary, sex shapes the clinical spectrum and disease trajectory of axSpA. Men more frequently develop radiographic disease with faster structural progression, whereas women more often present with non-radiographic disease, greater symptom burden and longer diagnostic delay. Differences in body composition, comorbidity patterns and treatment response could further contribute to sex-related variation in clinical outcomes.

Sjögren disease

Sjögren disease is a systemic autoimmune disease characterized by exocrine gland dysfunction and a wide spectrum of systemic manifestations[134,135]. Being one of the most female-predominant autoimmune diseases, this disease provides a compelling clinical model for examining how sex-related and gender-related factors influence disease susceptibility, clinical phenotype and long-term outcomes.

Epidemiology and clinical presentation

Sjögren disease predominantly affects middle-aged women, with a female-to-male ratio of approximately 9:1 (ref. 136). Men with Sjögren disease often display a more systemic disease phenotype than women[137–140]. In a large Swedish population-based cohort, men were diagnosed at a younger age than women and exhibited a higher frequency of extra-glandular manifestations, particularly interstitial lung disease, cutaneous vasculitis and lymphadenopathy[138]. Similar patterns have been reported in Korean cohorts[139,140], where male sex was associated with more frequent systemic involvement and fewer sicca symptoms; interstitial lung disease is particularly common among men and most frequently shows a non-specific interstitial pneumonia pattern on imaging. Cardiopulmonary involvement also seems more pronounced in men; in an Italian cohort, men had poorer pulmonary function (reduced forced vital capacity and first second of forced expiration) together with earlier echocardiographic signs of right-sided and diastolic dysfunction[141].

Life-course hormonal factors

Hormonal transitions across the life course influence disease expression and clinical management in Sjögren disease. Meta-analytic evidence indicates that pregnancy increases the risk of adverse obstetric outcomes, including preterm birth, hypertensive disorders and fetal growth restriction[142]. The most severe complication is autoimmune congenital heart block in approximately 2% of foetuses exposed in utero to maternal anti-Ro/SSA or anti-La/SSB-positive antibodies, with substantially higher recurrence risk in women with a previously affected child[143]. Use of hydroxychloroquine during pregnancy has been associated with reduced recurrence of congenital heart block.

Data on the impact of hormonal contraception on disease activity in Sjögren disease remain limited[144]. The menopausal transition represents another biologically relevant phase. Sjögren disease frequently manifests around midlife, and the decline in oestrogen has been implicated in exocrine gland dysfunction and immune dysregulation[145]. Observational data suggest possible associations between hormone replacement therapy and autoimmune conditions, including Sjögren disease, but reported effect sizes are modest and findings remain inconsistent[146].

Overall, life-course hormonal changes could modulate disease expression and complication risk, although the precise impact on the long-term disease trajectory remains incompletely understood.

Therapeutic considerations

Although several novel agents targeting pathways such as type I interferon signalling, B cell activation and signalling, co-stimulation pathways and FcRn-mediated IgG recycling have undergone evaluation over the past decade[135], the management of important symptoms such as fatigue, dryness and pain — symptoms that disproportionately affect women[136] — remains challenging with currently available therapies. A systematic review of biologic and targeted synthetic agents reported modest or inconsistent clinical benefits overall[147], with limited evidence of differential efficacy between sexes. Interpretation of the existing evidence is further constrained by the under-representation of men in clinical trials. Men account for only ~6% of participants in randomized controlled trials, and sex-disaggregated analyses are rarely predefined. These observations highlight the need for more sex-balanced clinical trials to better inform personalized therapeutic strategies in Sjögren disease.

Comorbidities and clinical outcomes

Sex-related and gender-related differences in comorbidities and long-term outcomes are prominent in Sjögren disease. Evidence indicates a higher risk of lymphoproliferative disorders among men. In a multicentre study, the prevalence of lymphoma was higher in men than in women (18% versus 5.2%; $P = 0.0014$), despite similar distributions of conventional lymphoproliferative risk factors between sexes[148].

Cardiopulmonary complications might also contribute to adverse outcomes. In a large Chinese cohort of patients with Sjögren disease-associated interstitial lung disease, rates of pulmonary

hypertension were higher in men than in women[149]. In a large retrospective cohort study, the prevalence of cardiovascular conditions was also higher in men, including myocardial infarction, atherosclerosis, cardiomyopathy, stroke and congestive heart failure[150]. Environmental exposures might contribute to these differences; notably, smoking, which is still more prevalent among men than among women worldwide[151], represents an independent risk factor for interstitial lung disease[152].

These patterns are also reflected in survival. A systematic review and meta-analysis reported a 1.46-fold increase in mortality risk among individuals with Sjögren disease compared with the general population, with male sex, older age, vasculitis, hypocomplementaemia, anti-La/SSB positivity and cryoglobulinaemia emerging as independent predictors of mortality[153].

By contrast, women with Sjögren disease more commonly experience a substantial chronic disease burden driven by comorbid conditions and patient-reported symptoms. In a large retrospective analysis, the prevalence of fibromyalgia, depression, chronic pain, migraine, fatigue-related symptom burden, hypermobility syndromes (including Ehlers–Danlos syndrome) and other rheumatic autoimmune diseases were reported more frequently among women than among men with Sjögren disease[150]. Mucosal and sexual health complications are also common yet remain under-recognized in routine clinical care. Vulvovaginal dryness and genital atrophy — manifestations of exocrine dysfunction — are often associated with sexual dysfunction and psychological distress[154]. Consistent with this broader symptom burden, women with Sjögren disease show substantial impairment in work productivity and daily activities, with reduced work performance and high overall disability independently associated with xerostomia, arthritis and depression[155].

In summary, Sjögren disease displays marked sex-related differences in clinical expression and outcomes. Most affected individuals are women, who typically present with classical glandular dysfunction and a substantial symptom burden, including fatigue and pain. By contrast, men, although less frequently affected, more often present at a younger age and display a more systemic disease phenotype, particularly pulmonary and lymphoproliferative involvement, which could contribute to poorer outcomes. Hormonal transitions across the life course and gender-related factors, such as smoking patterns and psychosocial burden, could further influence clinical presentation and disease management.

Gout

Gout is a prototypical crystal-induced inflammatory form of arthritis and results from chronic hyperuricaemia with deposition of monosodium urate crystals in and around joints. Unlike many autoimmune rheumatic diseases, gout shows a marked male predominance and distinct sex differences in age at onset, clinical presentation and comorbidity profiles. These features make gout a useful clinical model for examining how sex-related and gender-related factors influence disease presentation and management in inflammatory arthritis.

Epidemiology and clinical presentation

The reported prevalence of gout varies globally from < 1% to nearly 7%, with a marked male predominance[156]. This difference is most evident in middle age, when gout occurs up to ten times more frequently in men, but narrows in later life owing to rising prevalence among postmenopausal women[157]. Women are diagnosed with gout approximately 8 years later than men on average[158].

Clinical presentation also differs between sexes. Men typically develop acute monoarthritis of the first metatarsophalangeal joint, whereas women more often present with polyarticular involvement or with disease affecting other joints, including the ankles, knees or upper limb joints such as the wrists, elbows and small joints of the hands[158–160]. Tophi occur more frequently in men and tend to present later in women, often at atypical sites such as the hands or elbows[158–160]. These sex-specific clinical patterns might contribute to diagnostic uncertainty or misclassification of gout as RA or osteoarthritis.

Life-course hormonal factors

Unlike other inflammatory rheumatic diseases, gout is uncommon in women of reproductive age and typically develops after menopause. Pregnancy-related modulation of gout has therefore not been systematically investigated, and available evidence remains limited. After menopause, loss of oestrogen-mediated uricosuric effects leads to rising serum urate concentrations and increased risk of gout[158,161]. Accordingly, in the Nurses' Health Study, postmenopausal women had a modestly higher risk of gout than premenopausal women[162], whereas hormone replacement therapy was associated with a moderate reduction in risk[162]. However, findings are inconsistent across cohorts. In a nationwide Korean study of more than one million postmenopausal women, exogenous hormone exposure, including hormone replacement therapy, was associated with a small but statistically significant increase in incident gout[163].

These observations suggest that hormonal factors contribute to gout risk in women, although further studies are needed to clarify their clinical impact.

Therapeutic considerations

Treatment strategies for gout are broadly similar in men and women, although sex-related differences in comorbidity burden, renal function and drug safety profiles can influence therapeutic decisions. For acute flares, standard options (NSAIDs, colchicine and glucocorticoids) are effective in both sexes; however, treatment choices in women are often constrained by a higher prevalence of chronic kidney disease and polypharmacy. In these settings, clinicians generally favour glucocorticoids because these drugs provide comparable efficacy with a lower risk of renal and gastrointestinal toxicity[164].

Long-term urate-lowering therapy with xanthine oxidase inhibitors such as allopurinol or febuxostat remains the cornerstone of chronic management. Severe hypersensitivity reactions to allopurinol occur more frequently in women, a pattern that probably reflects the higher prevalence of chronic kidney disease and multiple drug exposures[165]. The *HLA-B*5801* allele is a recognized genetic predictor of allopurinol hypersensitivity, and international guidelines recommend testing individuals of East Asian or African American ancestry before starting allopurinol[166]. Despite this rare but serious adverse event, post hoc analyses suggest broadly comparable efficacy and overall safety of urate-lowering therapies in women and men[167].

Together, these data support broadly similar treatment approaches in women and men, with attention to sex-specific comorbidities and safety considerations.

Comorbidities and clinical outcomes

Patients with gout frequently present with a substantial comorbidity burden, with distinct patterns in the sexes. Women more commonly show cardiometabolic and renal comorbidities — including obesity, diabetes, dyslipidaemia, heart failure and chronic kidney disease — together with other conditions such as urinary tract infections, malignancies and concurrent rheumatic diseases. By contrast, men more frequently present with chronic respiratory disease, coronary artery disease and peripheral vascular disease[159,168,169]. Additionally, women experience

greater disease impact and higher disability scores than men, even after adjustment for age, disease duration and comorbidity burden[170,171].

Beyond the comorbidity burden, hyperuricaemia itself could contribute to adverse outcomes. In a large Chinese case–control study, hyperuricaemia was independently associated with idiopathic deep venous thrombosis, with a markedly stronger effect in women than in men (OR 7.48 versus 2.64)[172].

Gout and hyperuricaemia are associated with increased mortality risk, although this relationship seems largely influenced by age and comorbidity burden. Observational studies have reported sex-specific patterns, with higher serum uric acid concentrations predicting increased mortality in women but not consistently in men. Accordingly, in a large prospective cohort of older adults, elevated serum uric acid concentrations were associated with increased all-cause mortality among women, whereas no such association was observed in men[173]. Consistent with these observations, studies conducted specifically in patients with gout also suggest sex differences in mortality patterns. In a nationwide Korean cohort of patients with gout receiving

Table 3 | Important sex-related and gender-related gaps in clinical features and management of rheumatic diseases

Clinical domain	Rheumatoid arthritis	Systemic lupus erythematosus	Axial spondyloarthritis	Sjögren disease	Gout
Epidemiology	Many large datasets lack harmonized, life-course-sensitive measures (including menopausal status, reproductive history and hormone exposures), limiting causal inference on risk modifiers	Severe under-representation of men restricts the reliability of sex-stratified incidence and prevalence data	Misclassification of non-radiographic axSpA as chronic back pain or fibromyalgia in women contributes to underestimation of prevalence in women	Epidemiological data in men remain scarce owing to very low case numbers	Epidemiological data in women, particularly women of reproductive age, remain limited and heterogeneous
Disease presentation and activity	Drivers of higher pain and fatigue in women remain unclear; mechanisms underlying similar radiographic damage in women and men — despite higher disease activity in women — are insufficiently characterized	Evidence of sex differences in disease activity remains inconsistent. Sex-related differences in organ involvement (for example, more renal and serosal disease in men, and more cutaneous and articular disease in women) remains inadequately characterized in longitudinal datasets	Characteristic female phenotypes (such as more diffuse pain, lower inflammatory markers and lower frequencies of imaging positivity) are under-recognized; contributors to higher BASDAI and BASFI scores in women remain poorly understood	Male-associated features (including earlier onset of disease, interstitial lung disease, lymphoma and cardiopulmonary involvement) are incompletely characterized; in women, mucosal and vaginal dryness is under-recognized	Sex-specific contributors to female-predominant polyarticular and atypical joint involvement patterns remain insufficiently studied
Access to care and diagnostic delay	Unclear whether diagnostic delay in women primarily reflects health care-provider factors or differences in symptom reporting and care-seeking behaviour	Sex-stratified data on diagnostic delay remain scarce, particularly for men owing to low representation	Misclassification of axSpA as fibromyalgia or chronic back pain, and difficulty in interpreting sacroiliac MRI findings (including postpartum changes) contribute to diagnostic delay in women	Sparse data preclude robust assessment of sex differences in diagnostic delay	Limited sex-stratified data on diagnostic delay; atypical presentations in women are often misattributed to osteoarthritis or RA, contributing to delayed diagnosis
Comorbidities	Cardiovascular risk in women is frequently underestimated; and life-stage influences and sex-specific comorbidity trajectories remain poorly defined	Sex-specific renal, cardiovascular and thrombotic contributors to damage and mortality remain poorly characterized; and the impact of reproductive life stages on flare risk and long-term outcomes remains insufficiently defined	Sex differences in inflammation-driven cardiovascular risk remain insufficiently characterized, including across reproductive life stages	Drivers of male-predominant interstitial lung disease and lymphoma remain unclear; and female symptom burden and reproductive life-stage effects are insufficiently characterized	Sex differences in multimorbidity (including higher rates of chronic kidney disease and cardiometabolic disease in women; and more respiratory and peripheral vascular disease in men) are insufficiently integrated in gout management and outcomes
Treatment and management	Women receive fewer DMARDs and glucocorticoids; and contributors to poorer response and shorter drug survival in women remain unclear. The under-representation of men limits sex-stratified outcome analyses	Very limited sex-stratified evidence exists regarding treatment efficacy and safety beyond reproductive-health considerations	Mechanisms underlying poorer response and higher TNF inhibitor discontinuation in women remain undefined; and data on sex differences beyond TNF inhibitors are scarce	Sex-stratified therapeutic evidence remains very limited	Higher multimorbidity and chronic kidney disease in women complicate pharmacological management, and under-representation of women in gout clinical trials limits evidence of sex-specific treatment responses and safety
Cross-disease gaps	Systematic under-representation of the minority sex (that is, the sex in which the disease is comparatively less common); limited sex-stratified and gender-stratified longitudinal data; inadequate integration of gender-related variables; and scarce sex-stratified evidence of diagnostic delay, multimorbidity trajectories, life-stage risk modifiers and treatment outcomes				

Use of the terms 'men' or 'male' and 'women' or 'female' in this table reflects the terminology adopted in the original published research; however, *Nature Reviews Rheumatology* recognizes that not everyone affected by rheumatic disease is a woman or man. axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; RA, rheumatoid arthritis.

Box 3 | Clinical priorities for sex-sensitive and gender-sensitive rheumatology

Strengthen sex-stratified evidence
Ensure balanced recruitment and systematic sex-stratified analyses in cohorts and clinical trials to generate interpretable data on disease activity, progression and therapeutic outcomes. Adopt a life-course framework by incorporating reproductive transitions, including puberty, pregnancy and menopausal transition, into study design and data interpretation.

Refine diagnostic pathways
Incorporate sex-specific and gender-specific clinical patterns into early assessment. Consider the influence of reproductive ageing and hormonal therapies on symptom expression, inflammatory biomarkers and musculoskeletal manifestations. Artificial intelligence (AI)-assisted diagnostic tools should be trained and validated on sex-balanced datasets to minimize algorithmic bias.

Optimize therapeutic decision-making
Advance sex-stratified pharmacokinetic, pharmacodynamic and immunological research to support personalized treat-to-target strategies. Evaluate how endogenous and exogenous hormonal milieu across the lifespan modify therapeutic response and adverse-event profiles. Integrate sex and gender variables into prediction models, including AI-based tools for treatment response.

Address sex-specific comorbidity risk
Incorporate sex-related differences in multimorbidity trajectories into routine screening and prevention strategies to ensure accurate risk assessment and timely intervention. Integrate reproductive ageing into long-term risk stratification models.

Integrate gender-related determinants
Routinely evaluate behavioural and social factors (such as gender-related care-seeking patterns, pain appraisal, physical activity and treatment adherence) that shape disease burden independently of biological sex.

Improve outcome measurement
Refine composite indices to account for sex-related variation in subjective components, such as patient global assessment, that can distort disease activity estimates and target achievement. Develop digital and AI-supported outcome systems using sex-balanced training datasets.

Ensure inclusion of transgender, gender-diverse and intersex populations
Collect sex assigned at birth, gender identity and hormonal status in clinical datasets; evaluate how gender-affirming hormone therapy and variations in sex characteristics influence immune function, disease expression and treatment response.

Enhance guideline integration
Promote the systematic incorporation of sex and gender considerations into international rheumatology guidelines. Future European Alliance of Associations for Rheumatology–American College of Rheumatology recommendations should include sex-aware diagnostic criteria, sex-stratified interpretation of disease activity and biomarkers, and guidance on screening and management pathways reflecting sex-specific and gender-specific risks.

urate-lowering therapy[168], mortality was higher among women than among men, largely reflecting older age and greater multimorbidity at diagnosis. Causes of death also differed by sex, with chronic kidney disease representing the leading cause of death among women and lung cancer the leading cause among men. In multivariable analyses, older age, chronic kidney disease, malignancy, low haemoglobin and low BMI were independent predictors of mortality in both sexes, whereas smoking was associated with mortality only in men.

In summary, gout exhibits clear sex-related differences in epidemiology, clinical presentation and comorbidity burden. Men develop the disease earlier and more frequently, typically presenting with acute monoarticular flares and earlier tophus formation. By contrast, women are diagnosed later in life, often after menopause, and more frequently present with polyarticular disease, greater disease impact and a higher burden of cardiometabolic and renal comorbidities. Despite these variations in disease expression and multimorbidity profiles, therapeutic strategies remain largely similar in the sexes and women remain under-represented in clinical trials.

Future directions

Sex and gender shape the clinical trajectory of rheumatic diseases in ways that directly affect diagnostic accuracy, therapeutic effectiveness and clinical outcomes. The evidence synthesized in this Review supports the view that these dimensions are core contributors to disease biology, symptom interpretation, comorbidity development and treatment response. Failure to account for these factors leads to delayed diagnosis, suboptimal drug selection, inappropriate risk stratification and missed treatment targets.

Persistent gaps in the characterization of sex-related and gender-related differences across clinical features and therapeutic responses (Table 3) reflect the consequences of not systematically integrating these variables into research and clinical decision-making. Closing this gap requires moving beyond descriptive epidemiology and treating sex and gender as operational variables embedded within routine clinical decision-making. This paradigm shift requires integrating sex-specific clinical patterns into early diagnostic reasoning, applying sex-informed treat-to-target strategies, refining outcome indices to prevent sex-related misclassification and recognizing multimorbidity trajectories that differ in women and men (Box 3). A life-course perspective is essential within this framework. Reproductive ageing, particularly the menopausal transition, introduces substantial hormonal changes that can influence disease activity, symptom burden and cardiometabolic risk. Integrating this dimension into routine assessment should therefore be considered a priority in sex-informed rheumatology practice.

The systematic integration of sex-informed and life-course-informed clinical reasoning into routine care requires clinical datasets that adequately capture biological and sociocultural diversity across the population. Decision-support systems, including digital and artificial intelligence-assisted tools, must be trained and

validated on representative data to minimize bias and support sex-aware diagnostic and therapeutic decisions. At the same time, operationalizing gender remains methodologically complex. Gender is a multidimensional sociocultural construct, and variables capturing gender-related behaviours, such as caregiving responsibilities, work strain or risk-taking[174], should be assessed using standardized and validated tools.

Ultimately, achieving precision and equity in rheumatology demands that clinicians interpret biomarkers, imaging findings, treatment responses and patient-reported outcomes through a sex-sensitive and gender-sensitive lens. Embedding these dimensions into guidelines, risk assessment algorithms and therapeutic pathways is an important step towards delivering high-quality, personalized care for all people living with rheumatic diseases.

Conclusions

Sex and gender are fundamental determinants of clinical heterogeneity across rheumatic diseases, influencing disease susceptibility, clinical expression, diagnostic pathways, treatment response and long-term outcomes. As illustrated across the disease models discussed in this Review, these dimensions function as cross-cutting modifiers of disease trajectories and should be considered core components of clinical reasoning rather than descriptive variables.

A consistent theme emerging from the available evidence is the persistent under-representation of the minority sex in clinical studies, which limits the interpretation of therapeutic effectiveness and long-term outcomes. At the same time, sex-related differences in pain perception, inflammatory biomarkers and imaging findings can influence the interpretation of disease activity indices, with potential consequences for diagnostic accuracy and treatment optimization. Differences in treatment allocation, drug persistence and safety profiles further highlight how sex can shape therapeutic pathways, whereas distinct comorbidity patterns — particularly cardiovascular, metabolic and psychosocial conditions — contribute to sex-specific risk trajectories.

Beyond biological factors, gender-related determinants, including health care-seeking behaviours, occupational exposures, caregiving roles and structural barriers to care, further modulate disease burden and functional outcomes. Despite growing awareness of these influences, sex-related and gender-related variables remain insufficiently integrated into clinical trials, registries and practice guidelines, limiting the translation of this knowledge into routine care.

Addressing these gaps requires a shift from descriptive recognition to systematic implementation. Integrating sex-disaggregated analyses into research, ensuring more representative clinical cohorts and embedding sex-aware and gender-aware considerations into guidelines and decision-support tools will be essential steps towards this goal. Ultimately, recognizing sex and gender as integral dimensions of disease heterogeneity represents not only a scientific priority but also a necessary step towards improving diagnostic precision, therapeutic effectiveness and equity in rheumatology care.

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Author contributions

M.P., M.B. and E.O. researched data for the article. M.P. and E.O. contributed substantially to discussion of content. All authors wrote the article. M.P., F.R.S., F.C., H.W., K.W.M., U.K. and E.O. reviewed and/or edited the manuscript before submission.

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Review article

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The complexity of pain in osteoarthritis

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Abstract

Chronic pain is the hall-mark symptom of osteoarthritis (OA) and although several therapies are available, a sizeable number of patients do not gain adequate pain relief from these therapies. Predicting those patients who will not respond to current therapies remains a challenge. Although psychosocial, sensitivity, inflammation and genetic factors have been identified as pain mechanisms that predict response to pain therapy, none of these is a sufficiently strong predictor alone. An emerging approach to this challenge is the use of machine-learning algorithms that integrate several pain mechanisms, which are superior to previous prediction models. Importantly, these machine-learning algorithms identify networks of pain mechanisms that could be targeted therapeutically. From these models, a new mechanistic framework is proposed, in which pain in OA can be viewed either as a simpler joint disease with inflammation or as a complex pain problem that involves multiple factors. The latter is associated with a higher risk of poor response to standard OA pain therapy. Understanding the complexity of pain in OA and predicting those who are at risk of not responding to standard OA pain therapy are essential for improving the management of pain in OA.

Sections

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Key points

- Osteoarthritis (OA) pain is major clinical challenge, driven by factors that extend beyond the joint.
- OA pain can be stratified into two main phenotypes: low-complexity (localized, responsive to standard care) and high-complexity (localized pain amplified by extra-articular, systemic factors).
- The complexity of pain, based on data from the nervous system, immune system, psychological factors and genetics, determines the predictability of response to standard therapies.
- Modifiable lifestyle factors (such as obesity, physical activity and sleep quality) and psychosocial variables are crucial modulators of OA pain mechanisms and can affect management regimes.
- Identifying the mechanistic pain networks that connect peripheral and central drivers in a biopsychosocial context is key to achieving a breakthrough in understanding and effectively treating high-complexity OA pain in a stratified way.

Introduction

The hallmark symptom of osteoarthritis (OA), the most common form of arthritis (which affects approximately 7.7% of the general population[1]), is chronic pain. OA presents a major global health care burden and is primarily a consequence of ageing[2]. In the past, OA was regarded as solely a 'wear-and-tear' joint-related problem. Therefore, most therapeutic development efforts have been directed towards the joint[3,4]. Joint replacement surgery is effective, but 10–20% of patients experience chronic postoperative pain[5,6]. Pharmacological therapies, non-pharmacological and non-surgical therapies (such as exercise therapy and patient education) seem to provide similar levels of pain relief[7,8]. Drugs such as acetaminophen and NSAIDs have considerable adverse effects on the gastrointestinal, renal or cardiovascular systems and cannot be used for extended periods of time[9,10].

Imaging techniques (such as radiography, micro-CT and MRI) are often used to characterize the extent of joint degradation, but imaging findings do not effectively correlate with the clinical pain experienced by the patient[11,12]. Additionally, individuals with OA are more likely to develop comorbidities than the general population[13,14], and an increased number of comorbidities are associated with increased clinical pain[14,15]. OA pain is therefore more than just a localized joint pain problem[16–19]. Understanding the multifaceted aspects of pain in OA is crucial to improve management, including the assessment of the psychosocial, sensitivity, inflammation and genetic factors[20].

Access to an increasing number of parameters and mechanisms has led to the use of novel statistical analyses that integrate clinical and mechanistic data into longitudinal prediction studies[21–23], opening up new avenues for fundamental discoveries. These statistical analyses are broadly categorized as artificial intelligence (AI) models, and are being increasingly used in the field of pain science[24]. Using the right AI model for the right data is important as different models will provide different results[25], similar to more traditional statistical tests[26]. These new models could, in time, provide targeted, stratified pain-management regimes for patients with OA, addressing a substantial unmet need.

In this Review, we describe how different pain mechanisms, including those not directly related to the joints, are associated with OA pain. We explain how these mechanisms can be used to predict the analgesic efficacy of pain therapies and how AI models can pave the way for new discoveries. In addition, we suggest how this knowledge can be incorporated into existing treatment guidelines to promote a more stratified and multimodal approach to pain management (Fig. 1). Moreover, we highlight factors that influence various pain mechanistic domains and provide insights into how future studies can integrate multiple mechanistic domains. This approach could reveal new opportunities for the interaction of large-scale data using AI technologies, thereby improving understanding of OA pain and paving the way for more stratified management strategies.

Inflammation and pain

Inflammation can influence pain in OA locally (the joint), systemically and at a central nervous system (CNS) level[27]. Pro-inflammatory cytokines can sensitize neurons, which amplifies the intensity of pain[28,29].

Proteomics have been widely used to study OA and to identify groups of individuals who are at risk of developing OA[30,31]. Targeting proteomics towards inflammatory markers is a promising approach to addressing pain, as inflammation is a key component of OA[27]. Inflammation can occur locally in the joint, systemically and in the CNS[32,33]. The International Association for the Study of Pain have identified three pain descriptors: nociceptive, neuropathic and nociplastic pain[34]. The nociceptive descriptor is characterized by a local well-defined injury and/or trauma, and this type of pain is considered inflammatory in nature[34]. Neuropathic pain occurs owing to a lesion or disease affecting the somatosensory nervous system, such as diabetic neuropathies or central post-stroke pain[35]. Nociplastic pain is pain that arises despite no clear evidence of tissue damage, disease or lesion in the somatosensory nervous system[34]. Traditionally, pain in OA has been considered as nociceptive owing to local inflammation, such as synovitis, but it has now become clear that OA is more than just a joint problem. This section discusses pain in OA from an inflammatory perspective.

Localized inflammation

Local inflammation is evident in OA (synovitis, effusion and bone-marrow lesions[36]). Although the severity of synovitis and effusion has been associated with increased OA pain, this association is only weak-to-moderate[37]. Findings suggest that people with severe synovitis who have undergone total knee arthroplasty (TKA) experience considerable pain relief if the inflamed synovial membrane is removed during surgery[38]. In addition, when comparing people with and without chronic postoperative pain after TKA surgery, those with pain are more likely to display postoperative synovitis[39], placing synovitis as a potential local driver of both pain in OA and chronic postoperative pain.

Although the underlying reason for joint inflammation is not completely clear, immunometabolic alterations have been proposed as key drivers[40,41]. Chondrocytes, synoviocytes, subchondral bone cells and synovial macrophages undergo metabolic shifts that promote matrix degradation via matrix metalloproteinases and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs), leading to the release of reactive oxygen species and nitric oxide, which further amplify catabolic pathways and apoptosis[40]. Obesity leads to the production of adipokines, which sustain systemic low-grade inflammation and might also target the joint microenvironment[40,42]. Single-cell multi-omics analyses have identified pro-inflammatory

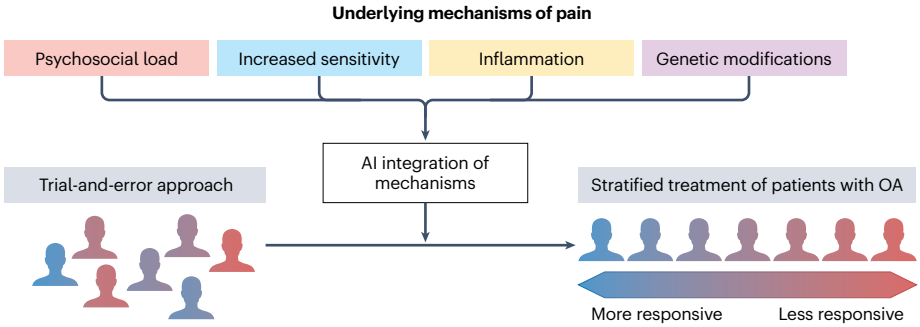


Fig. 1 | A novel approach to developing stratified pain care for patients with osteoarthritis. The current trial-and-error approach that is often used in the management of osteoarthritis (OA) is not optimal for patient care as a sizeable proportion of patients do not gain sufficient pain relief. The integration of the different underlying mechanisms for pain in OA using advanced algorithms (such as artificial intelligence (AI) models) could lead to the stratification of patients who are likely to be more or less responsive to standard pain therapies. This approach is based on two decades of research that has identified pain mechanisms as factors associated with treatment outcomes and uses this information to select patients who are more or less likely to respond to standard pain therapy. Implementing this novel approach would be a major step forward for the management of OA.

and pre-inflammatory chondrocyte subtypes, stress-metabolizing populations and senescent SPP1$^+$ cells with angiogenic signalling[43]. Modulating glycolysis, oxidative stress and adipokine-driven pathways and/or targeting inflammatory chondrocyte networks represent rational strategies to reduce inflammation and, ultimately, pain in OA.

The interplay between the nervous and vascular systems is an important feature of OA pathogenesis[44]. The progressive degradation of articular cartilage and subchondral bone in OA is strongly driven by aberrant growth signals that originate from nerves and blood vessels[45]. Nerve growth factor (NGF) has a role in the innervation and pathological growth of sensory nerve fibres into joint tissues, which contribute to OA pain[46]. Concurrently, vascular-derived growth factors (particularly vascular endothelial growth factor) stimulate neovascularization in the subchondral bone and synovium in OA. These new vessels function as conduits, delivering pro-inflammatory mediators to the joint, thus forging a neurovascular link that fuels the vicious cycle of inflammation, structural damage and pain signalling in synovitis and OA progression[47].

Systemic inflammation

Systemic inflammation also affects OA pain[48] and is moderately associated with local inflammation[37]. Systematic inflammation can be influenced by localized joint inflammation but also by several factors outside the joint (such as poor quality of sleep[49] or comorbidities, such as obesity[50] and diabetes[51]). IL-1β, IL-6 and TNF have been associated with OA pain[52]; elevated preoperative levels of these cytokines are associated with chronic postoperative pain[33,53]. However, targeting systemic IL-1β and TNF pharmacologically has yielded limited results[54–56]. Notably, clinical trials of interarticular anti-IL-1β and anti-TNF antibodies have demonstrated analgesic effects[57], but more evidence is needed.

Findings from proteomic studies have revealed a range of other important pro-inflammatory cytokines and chemokines in OA. A 2024 study reported inflammatory networks that could be used to identify people at risk of developing chronic postoperative pain after TKA[48].

Central neuroinflammation

Data on central neuroinflammation in people with OA is limited. Preclinical data suggest that prostaglandin E2 levels in the cerebrospinal fluid (CSF) are elevated after peripheral injury[58] and that this elevation is associated with sensitization of central pain mechanisms[59,60]. This finding has not been confirmed in humans, but a proportion of people with severe OA display increased temporal summation and impaired conditioned pain modulation[61,62]; these assessments are considered surrogate measures of sensitization of central pain mechanisms[63]. Additionally, findings from animal models indicate that the analgesic effect of NSAIDs (mainly COX-2 inhibitors) is partly caused by penetration of these drugs into the CSF, which subsequently attenuates the central neuroinflammation[58]. Interestingly, in one study, high levels of preoperative inflammation were associated with greater pain after TKA surgery than lower levels of inflammation[64]. In a small study of 50 patients scheduled for total hip arthroplasty, the potential predictive value of preoperative inflammatory markers in the CSF was assessed, but no link between these markers and chronic postoperative pain was observed[33]. More studies are needed to investigate if inflammation in the CSF is linked to pain in OA and/or postoperative pain.

Gut microbiome and pain

The gut microbiome has emerged as a potential important area of investigation, as microbial metabolites affect innate and adaptive immune responses[65,66]. Microbial dysbiosis has been linked to pain in OA[67–69]. Data from both humans and mouse models suggest that targeting the farnesoid X receptor using glucagon-like peptide-1 receptor agonists (GLP-1RAs) could be a potential new therapy for pain in OA[70]. The use of GLP-1RAs for the treatment of pain in OA has been assessed in two randomized controlled trials[71,72]. In one study[71], 168 patients with knee OA and a body-mass index (BMI) of at least 27 kg/m^2 were randomized to liraglutide (3 mg daily, subcutaneous administration) or placebo for 52 weeks. No statistical difference in the Knee Injury and Osteoarthritis Outcome Score pain subscale was observed despite considerable weight loss in the liraglutide group compared with the placebo group. Importantly, this study included an 8-week diet intervention prior to randomization and only included patients who achieved a weight loss of at least 5%. In another study[72], 407 patients with OA and a BMI of at least 30 kg/m^2 were randomized to semaglutide (2.4 mg weekly, subcutaneous administration) or placebo. Those receiving semaglutide demonstrated weight loss and considerable improvement in pain compared with the placebo group[72]. GLP-1 receptors are widely distributed in the gastrointestinal tract, but also in the peripheral and central nervous

systems and the pancreas[73,74]. The involvement of each of these systems with the observed pain relief from GLP-1RAs in OA has not yet been shown, but studies suggest that the analgesic effect is independent of weight loss and potentially occurs via anti-inflammatory properties[75].

In summary, inflammation can occur locally within the joint, systemically and in the CSF, and increased inflammation is associated with increased clinical pain. Removing the local inflammatory drivers, such as the neurovascular signalling hubs that drive synovitis might provide better long-term pain relief. Preliminary evidence suggests that inflammatory markers might predict response to standard pain therapy in OA, but the predictive value of these inflammatory markers alone is not sufficient. Combining inflammatory markers with other known predictors of analgesic responses might increase predictability.

The central nervous system

Preclinical animal models of OA pain show that the peripheral and central nervous systems can be sensitized[29,52]. These assessments are not feasible in humans but quantitative sensory testing (QST) can indicate peripheral and central pain mechanisms[63,76–78]. In people with OA, the assessment of pressure-pain thresholds is used to assess localized hyperalgesia, such as soreness around the knee in OA[18]. In people, temporal summation of pain functions as a proxy assessment of the 'wind-up' process that occurs at dorsal horn neurons and is a measure for spinal excitability[18]. Conditioned pain modulation is used to assess descending inhibitory and facilitatory pain pathways, which, if functioning correctly, can impair incoming nociception[18]. On the basis of these assessments, pain sensory phenotypes have been identified[61]; generally, people with OA experience more pain sensitivity than pain-free, age-matched individuals[16,18,79,80]. These sensory phenotypes do not seem to be associated with cartilage degeneration or synovitis[62,81,82]; however, these studies have shown that the mismatch between cartilage degeneration and clinical pain intensities can be explained by the extent of pain sensitivity as assessed by QST[62,81]. This finding indicates a more generalized phenomenon whereby increased sensitivity is not explained by joint mechanisms. Additionally, those patients with OA who are more sensitive to pain have poorer outcomes following standard pain therapy (such as exercise-based therapy, NSAIDs and joint replacement surgery[80,83,84]) than those patients who are less sensitive to pain. These findings indicate that mechanisms outside the joint are important for driving pain; however, the overall predictive value of QST remains low to moderate[80,83,84] (Fig. 2).

The experience of pain includes affective-motivational and cognitive-evaluative dimensions, which reflects the interplay between the periphery and higher-order brain centres[85]. The presence, intensity and impact of pain depend on the physiological homeostasis of several body systems, and not only on the nociceptive drive from degenerated or inflamed joints, which is important to consider when assessing people with OA and pain; pain intensity is often underestimated by clinicians[86]. Patients with OA pain exhibit reduced intracortical inhibition and altered cortical excitability, particularly in the motor cortex[87–89]. The motor cortex has wide connections with extra-motor brain areas implicated in cognitive control, management of energy regulation (allostasis) and pain modulation[90]. Evidence suggests that chronic pain could be associated with impaired adaptability to an allostatic load that exceeds the adjustment capacity of an individual[91,92], which might lead to impairments in pain inhibitory systems and have negative effects on mood and behaviour. The use of transcranial magnetic stimulation to study cortical facilitation and inhibition has shown associations with pain in OA[93]. Loss of inhibitory tone (a measure of the balance between cortical facilitation and inhibition), which results in higher excitability, is associated with enhanced pain sensitivity and widespread activation of sensory and non-nociceptive brain areas, especially in women with OA[93]. The underlying reasons are not clear, but studies suggests that chronic pain is associated with accelerated brain ageing[94–97], which is an area that requires further research.

Overall, evidence shows that assessing the nervous system in people with OA could provide important information about pain and indicate if a patient will respond to standard pain therapies. However, these assessments alone are not sufficient to predict response to standard pain therapy and combining them with other assessments could provide stronger prediction models in the future.

Behavioural and psychosocial factors

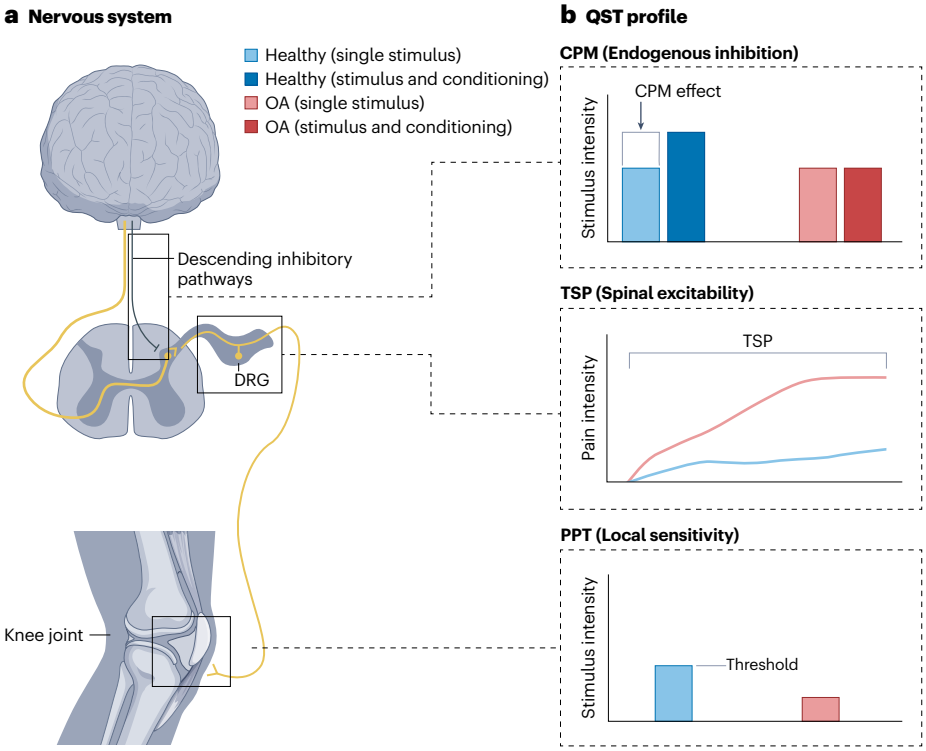
The biopsychosocial model of pain highlights the dynamic, multimodal interactions among physiological, psychological and social factors that reciprocally influence one another and pain-related outcomes[98]. Specialized biopsychosocial models proposed for older adults with chronic pain[99] and patients with OA pain[100] emphasize the importance of psychosocial factors; a 2024 scoping review noted that over 80% of OA studies report psychological factors as having considerable influence on pain outcomes[100]. Diagnosis in patients with OA pain mainly focuses on the joint, and psychosocial factors are often underestimated[101]. Some of the most robust predictive psychosocial factors that influence the experience of OA pain are discussed below.

Affect and mood

Symptoms of depression, anxiety and emotional distress form a cluster of negative emotions, thoughts and behaviours termed 'negative affect'. Negative affect, defined as unpleasant emotions such as sadness, anxiety, anger or fear, is among the most commonly assessed categories of psychological factors in patients with musculoskeletal pain conditions such as OA[102]. In addition to being a consequence of chronic pain, premorbid negative affect is a risk factor for the future development of chronic musculoskeletal pain in general, particularly in OA[100,103]. Negative affect can also increase the likelihood of transitioning from acute to chronic pain, for example, following joint replacement surgery[104]. By contrast, individual differences in 'positive affect' (that is, the tendency to experience moods such as happiness, joy, contentment and enthusiasm) is associated with less pain in micro-longitudinal studies of daily OA symptoms[105]. Moreover, high positive affect seems to function as a factor of psychological resilience in chronic pain, as positive affect seems to outbalance negative effect if both positive and negative affect occur simultaneously[106–108].

Catastrophizing

Catastrophizing is a cognitive and emotional response to pain that involves magnification of the threat value of pain, helplessness and rumination about pain[109]. Catastrophizing can be assessed using a wide range of questionnaires, the most frequently used being The Pain Catastrophizing Scale[110], but other questionnaires such as the Coping Strategies Questionnaire[111] and the Pain Anxiety Symptoms Scale[112] also capture catastrophizing thoughts. Catastrophizing is associated with increased pain intensity and disability[102], and is one of the most important pre-treatment risk factors that impairs the effectiveness of pain-relief interventions for musculoskeletal pain[113–115] and management of chronic pain in general[102]. High levels of pain catastrophizing predicts more severe pain intensity and persistence, more opioid use and reduced physical function following surgical procedures, including



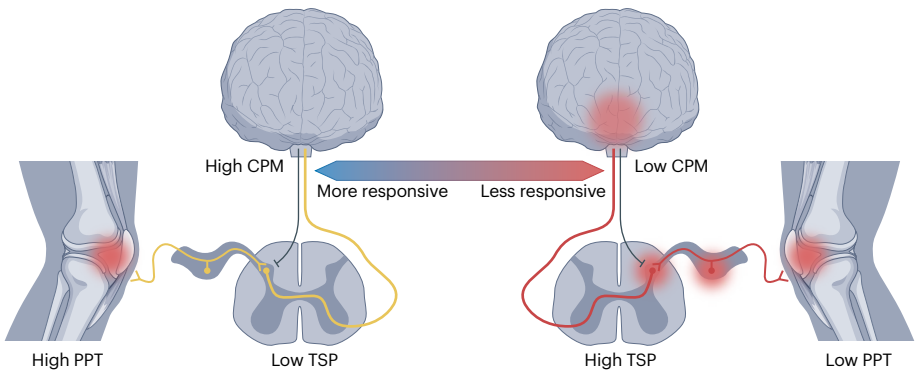


Fig. 2 | Sensory profiling of the nervous system using quantitative sensory testing. Sensory profiling is used to assess functions in the nervous system. **a**, Conditioned pain modulation (CPM) is a surrogate assessment of the descending pain inhibitory and facilitatory system in humans and is believed to assess endogenous inhibition. Temporal summation of pain (TSP) is used to assess the 'wind-up' process of dorsal horn neurons in humans and is therefore thought to reflect spinal excitability. Pressure-pain thresholds (PPTs) assess localized sensitivity to pain. **b**, In general, patients with osteoarthritis (OA, red) display lower PPTs, higher TSP and an impaired CPM effect compared with pain-free individuals (blue). CPM is assessed using a test stimulus that is assessed before (light red and light blue) and after (dark red and dark blue) applying a conditioning stimulus. The CPM effect (indicated by the grey outline) is calculated as the difference in intensity of the test stimulus with and without the conditioning stimulus. **c**, Patients with OA do, however, have different sensory profiles and, in general, having a lower PPT and CPM and higher TSP is associated with non-response to standard pain therapies. Although depicted schematically as a single nerve (yellow) for simplicity, the joint is innervated with multiple nerves at different sites. DRG, dorsal root ganglion; QST, quantitative sensory testing.

OA-related joint replacement[116]. Furthermore, higher levels of catastrophizing can magnify pain associated with physical activity and is associated with chronic inflammation in OA[117,118]. In multivariate predictive models, catastrophizing is the single strongest predictor of pain variability in knee OA, analgesic responses to an anti-inflammatory treatment regimen[119] and pain relief following TKA surgery[120–122]. Non-pharmacological interventions (such as cognitive behavioural therapy) that reduce catastrophizing can improve pain-related outcomes in patients with OA undergoing joint replacement[123]; however, this area of research is still developing and conflicting results have been reported[115].

Adverse experiences and trauma

An early life traumatic experience, including childhood physical, sexual and psychological abuse, is a robust risk factor for the development of persistent pain in adulthood, especially widespread joint and musculoskeletal pain[124,125]. These findings were confirmed in a systematic review that showed a dose–response relationship between the amount of early-life adversity and the subsequent likelihood of developing OA pain[126]. Moreover, an increased number of adverse childhood experiences is associated with more intense pain and greater functional disability in patients with OA[127]. Several mechanisms seem to link trauma with the subsequent development and worsening of OA pain, including hypervigilance and negative cognitions (such as catastrophizing, affective distress, CNS sensitization and behavioural avoidance)[124,128].

Social support

Social isolation is associated with greater pain, disability and all-cause mortality in patients with OA[129] and limited social support is a robust risk factor for enduring pain following joint replacement[104]. According to

the stress-buffering hypothesis, the pain-magnifying effects of stressors and other risk factors can be reduced by social support and positive social interactions[130]. Additional indicators of social vulnerability, such as insecurity in housing and residing in an unsafe neighbourhood, can also have detrimental effects[131]. Incremental increases in the number of social risk factors (such as food insecurity, housing insecurity, financial insecurity, unsafe neighbourhoods and health care access hardship) are associated with increased painful arthritis and arthritis-related disability[131].

Coping

Individual differences in pain coping (including the use of behavioural, emotional and cognitive techniques to manage pain-related symptoms) strongly influence pain outcomes, including pain intensity, quality of life and function[132]. Active coping efforts, comprising strategies to reduce the experience and effects of pain, are linked to improved psychological adjustment, whereas passive coping strategies, such as relinquishing control of pain to others, are linked to poorer outcomes across musculoskeletal pain conditions[132]. Results from a meta-analysis show that the addition of active pain-related coping skills training (such as relaxation skills, pacing activities and cognitive reframing) to standard OA pain care can have moderate long-term benefits (that is, reduced pain and improved physical function)[133].

Thus, behavioural and psychological factors are important considerations when managing pain in OA and an increased psychological burden is associated with increased pain. Additionally, psychological factors are well-described predictors of treatment outcomes in patients with OA but are not robust enough predictors alone to be implemented in clinical practice. It could be argued that combining psychological factors with other known predictors could increase the strength of prediction models, but further research is required.

Genetic and epigenetic modifications

Genetic and epigenetic mechanisms have a role in the development of pain in OA. Genome-wide association studies (GWAS) have identified SNPs or genetic variations linked to OA pathogenesis and pain[134–137]. A large-scale GWAS investigating hip pain within the UK Biobank identified seven independent genetic loci associated with hip pain and two statistically significant loci associated with hip pain, distinguishing patients with hip pain from healthy individuals[138,139]. Genes such as *EXD3*, *GDF5* and *COL27A1* have been implicated in essential biological processes (including nuclear export, the maintenance or repair of synovial joint tissues and the calcification of cartilage), meaning that genetic variations in these regions might disrupt joint homeostasis by altering the cellular transport required for signalling, impairing the protective repair of skeletal tissues or compromising the structural stability of cartilage and tendons[138,139]. Moreover, these associations have been validated and vastly expanded by a multi-ancestry GWAS meta-analysis of nearly 2 million individuals, which identified 962 independent genetic associations for different OA phenotypes (513 of which were novel), and 700 causal effector genes and 8 core biological pathways linked to pain phenotypes[140]. These associations include glial-cell-related processes that influence immune responses; neuroinflammation and peripheral and central sensitization; circadian clock regulation of joint repair and pain perception; and embryonic skeletal development pathways, suggesting that the origins of OA and joint pain might be established during early fetal growth[140].

Beyond these variants, genetic factors can also the modulate neuroimmune pathways involved in pain regulation. The cholinergic anti-inflammatory pathway is a neuroimmune mechanism through which activation of the alpha-7 nicotinic acetylcholine receptor (α7nAChR) on immune cells suppresses pro-inflammatory cytokine production, representing a promising target for attenuating inflammation and pain in OA[141]. A back-translational study using transgenic mice that express the human gene *CHRFAM7A* displayed increased cartilage damage, heightened allodynia and reduced response to α7nAChR agonists[142]. Thus, *CHRFAM7A* could be a dominant-negative modulator of cholinergic anti-inflammatory pathways and a potential genetic risk factor for the sensitization of peripheral and central pain mechanisms[142]. Further associations have been reported for SNPs such as rs3745368 and rs4721 in the *RETN* and *RARRES2* genes, respectively, which correlate with both structural severity (Kellgren–Lawrence grade) and pain scores in hand OA[143]. Beyond genomic DNA variants, dynamic biomarkers such as circulating cell-free DNA (cfDNA) are gaining interest in preclinical and clinical studies[144,145]. Mitochondrial-derived circulating DNA has emerged as a potential biomarker of joint stress and inflammation[145]. In patients with knee OA, increased levels of plasma mitochondrial-derived circulating DNA correlated with Western Ontario and McMaster Universities Osteoarthritis pain scores and radiographic severity, suggesting a role in both joint degeneration and nociceptive signalling[145].

Epigenetic mechanisms (that is, changes in gene expression that do not involve alterations to the underlying DNA sequence) have also been implicated in modulating pain in OA. In an epigenome-wide association study, nearly 20,000 hypermethylated and over 5,000 hypomethylated CpG sites associated with pain in knee OA were identified, which highlights an enrichment in immune-related and antigen presentation pathways[146]. Although histone modifications have been less frequently studied in the context of OA in humans, preclinical models indicate that they might contribute to nociceptive sensitization[147]. Histone methylation has been implicated in nociception via the inhibition of the histone methyltransferase enhancer of zeste homologue 2 (EZH2), which reduces cartilage degradation but also alleviates pain-like behaviours (such as improving motor function in a mouse model of OA)[148]. These findings support the role of chromatin remodelling in pain modulation in OA, although clinical evidence in human populations remains limited.

Among epigenetic modifications, non-coding RNAs have emerged as important post-transcriptional regulators of pain in OA. Preclinical and clinical studies have identified several micro RNAs (miRNAs) that are involved in OA-related pain. In tissue samples obtained from patients with OA and mouse models of OA, miR-183 is downregulated[149]. In mouse models, overexpression of miR-183 inhibits the expression of pro-inflammatory cytokines and pain-related ion channels in the dorsal root ganglia[149]. In human studies, miRNAs that regulate inflammatory responses (such as miR-146a-5p, miR-130b and miR-145) have been linked to the persistence of pain after surgery and are upregulated preoperatively in patients who experience chronic postoperative pain after TKA[150].

Long non-coding RNAs (lncRNAs) might also have a role in modulating pain pathways in OA. In preclinical studies, the lncRNA MEG3 alleviates inflammatory pain by downregulating TRPV1, a key nociceptive receptor, suggesting that lncRNA MEG33 could be a therapeutic target[151]. Clinical evidence further supports the role of lncRNAs by showing that preoperative expression of specific lncRNAs differed between patients who experienced chronic postoperative pain after TKA and those who did not[152].

Together, these findings highlight the complex and multi-layered influence of genetic and epigenetic mechanisms on OA pain. Notably, some of these discoveries have been observed in clinical populations, but most of the evidence stems from preclinical studies and requires further validation in human studies. Additionally, pain management in OA is an understudied area owing to the complexity of pain pathways and pain perception[153], and most genetic association studies rely on clinical pain scores or radiographic endpoints that do not enable mechanistic discrimination between peripheral joint processes and central neuronal pain processing[153,154]. Future strategies that use tissue-specific transcriptomics, single-cell RNA sequencing of joint and dorsal root ganglia tissues or imaging genetics paradigms might help to disentangle the contributions of specific genetic variants to OA pain. Elucidating these pathways could pave the way for personalized, mechanism-based interventions aimed at reducing chronic pain in OA and improving patient outcomes.

Lifestyle and demographic factors

The current Review highlights that OA pain is influenced by several mechanisms and therefore understanding the origin of these mechanisms is important. Preclinical data indicate that factors such as sex (that is, sex assigned at birth; throughout the article, 'sex' is used as a shorthand for biological sex), age and modifiable lifestyle factors (such as obesity, physical inactivity and poor quality of sleep) might modulate pain mechanisms and therefore, influence pain in OA (Fig. 3).

Strong evidence indicates that female sex is associated with a higher risk of developing OA and chronic pain than male sex[155,156]. Female and male individuals experience pain differently but the underlying reasons are not yet completely understood[157]. Sex hormones such as oestrogen, testosterone or androstenedione influence inflammation, but these effects are complex and remain incompletely understood[57,158].

The prevalence of OA increases with age but older age also impacts several pain mechanisms[2]. Evidence suggests that older age is associated with increased pain sensitivity[159], but further research is needed to confirm these findings[160,161]. Inflammaging, the concept that lifelong stressors lead to increased inflammation[162], is also associated with OA[163]. Importantly, older age can lead to a decrease in activity levels, which could be associated with obesity and can also influence pain in OA.

Obesity increases the risk of developing OA[164] and is associated with low-grade chronic inflammation[50]; increased obesity and visceral adiposity are positively associated with elevated cytokine levels such as IL-6 (ref. 165). Low-grade inflammation owing to obesity might lead to some of the pain sensitivity changes discussed previously and thereby increase OA pain. Additionally, obesity is linked to poor quality of sleep[166].

Poor quality of sleep is a prevalent issue in chronic pain conditions, reported by up to 75% of patients[167]. Disruptions related to either sleep or pain can cause mutual exacerbation of the other[168,169], mainly owing to the many shared biological and psychological mechanisms[105]. Preliminary data suggest that poor quality of sleep is associated with increased inflammation[170], potentially furthering the effects of inflammation on pain sensitivity. Supporting this claim, poor quality of sleep aggravates pain-related symptoms, including increased pain intensity[171], functional limitations[172] and spreading of pain[173], and experimental reductions in quality of sleep are associated with increased pain sensitization in healthy, pain-free individuals[174,175]. Poor quality of sleep also affects the psychological domain and is associated with increased levels of anxiety, depression and pain catastrophizing in patients with OA[171].

Physical inactivity is often consequential to chronic musculoskeletal pain and is associated with increased pain sensitivity and inflammation[176–179]. Animal studies suggest an anti-inflammatory effect of intense exercise[179,180], which could be linked to pain sensitivity, but these studies have not been replicated in humans. Furthermore, increased physical activity is associated with better sleep quality in the general population[181], and as sleep quality is linked to psychological factors[171,182] and inflammation[49], physical activity could improve several pain-relevant domains[170].

In summary, sex, age and modifiable lifestyle factors are not necessarily directly linked to pain in OA or treatment outcomes but they can influence pain mechanisms and thereby put a patient at risk of increased severe pain or poor treatment outcomes.

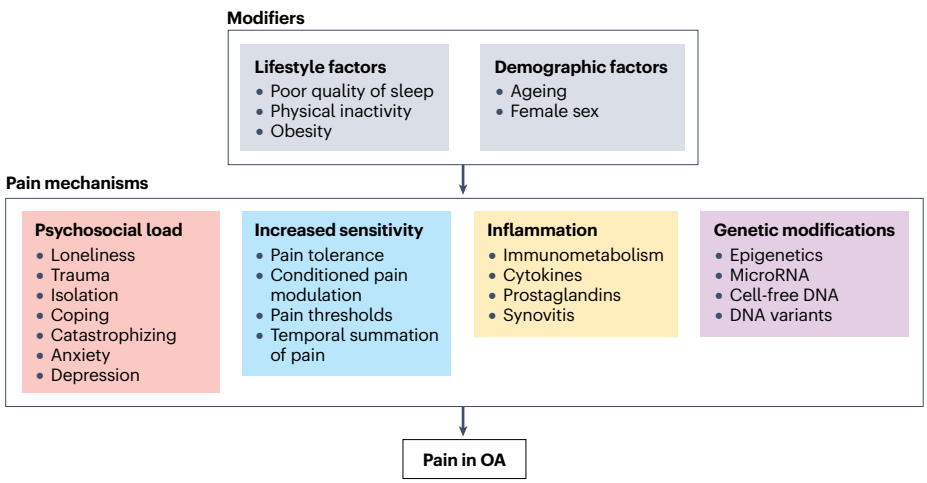


Fig. 3 | Linking sex and lifestyle factors to pain in OA through pain mechanisms. Female sex and lifestyle factors such as poor quality of sleep, physical inactivity and obesity are associated with increased pain in osteoarthritis (OA). Mechanistically, these factors act as negative modifiers of pain mechanisms. A person will become more vulnerable to pain when the pain mechanisms are negatively impacted by several modifiers and therefore, that person is more likely to experience more pain.

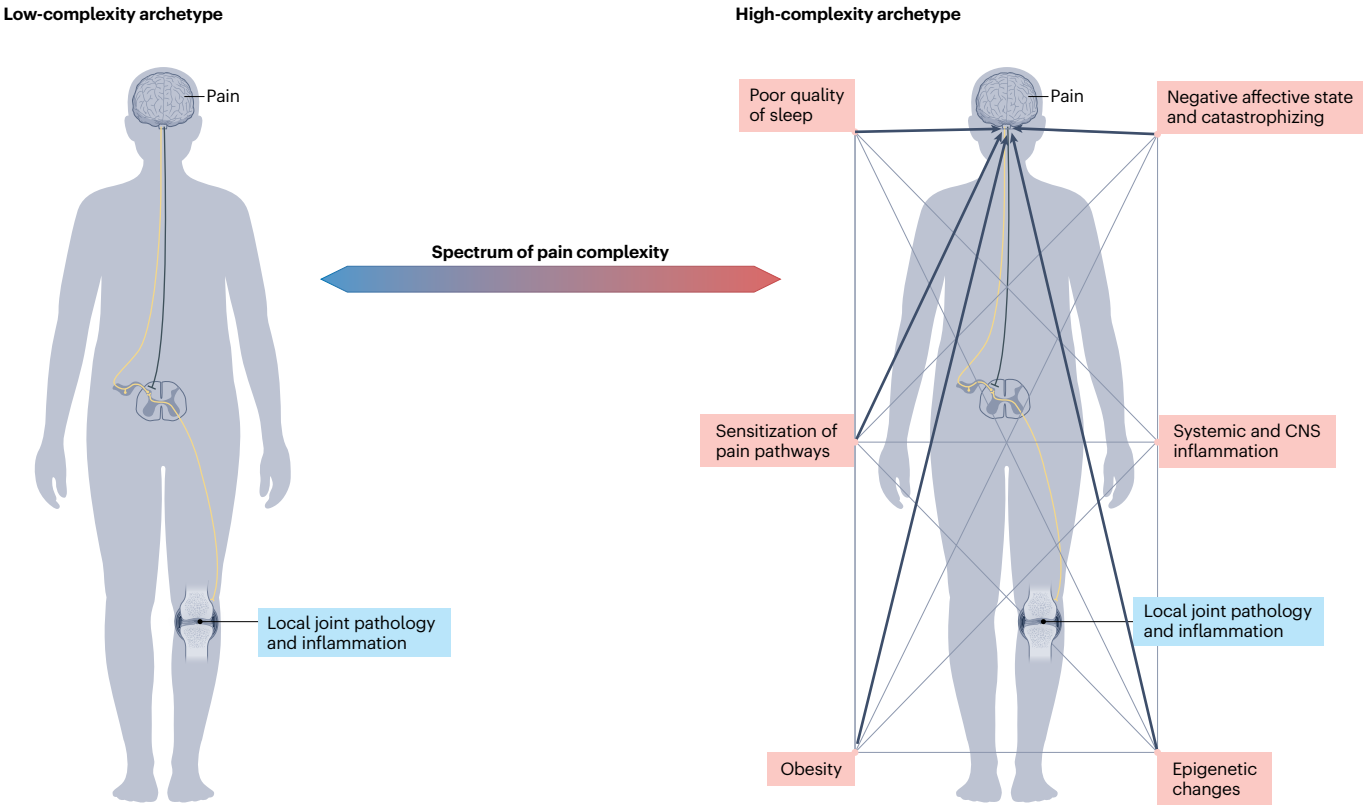


Fig. 4 | Pain complexity for stratified pain management. Stratification of osteoarthritis (OA) pain along a complexity spectrum can indicate the likelihood of therapeutic response. Two overall archetypes can be generated when addressing pain in osteoarthritis. A person has localized joint pain with inflammation in which the complexity of the pain is low. By contrast, a person can have localized joint pain with the addition of several other factors that can amplify pain, and the addition of these factors increases the complexity of the pain. Importantly, neither of the two archetypes shown are likely to exist, but here they depict two ends of a spectrum and most patients can be placed along this spectrum. Understanding the complexity of pain in people with OA might help to inform the optimal treatment approach. CNS, central nervous system.

Assessing multifactorial pain domains

As discussed previously, numerous biopsychosocial pathways influence pain in OA and these can be divided into specific pain mechanistic domains (that is, psychosocial, sensitivity, inflammation and genetic factors). Combining pain mechanistic domains might elucidate different pain profiles in OA[19,183].

Preliminary evidence suggests that combining pain mechanistic domains is favourable when attempting to predict treatment outcomes[16]. Combining pain sensitivity and psychosocial domains has proven more effective for predicting the risk of chronic postoperative pain and for identifying those patients with OA who do not respond to NSAIDs when compared with only assessing one domain[119,121,184].

Using inflammatory and genetic markers to explain pain or predict treatment outcomes has been problematic owing to the high number of potentially relevant biomarkers and the inability of traditional statistics to handle large-scale complex data sets unless the sample is large (many thousands of patients). The introduction of AI (particularly advanced machine-learning models) enables new statistical analyses that accommodate large, complex data sets and can incorporate thousands of parameters[185]. Some of these models can be supervised to select the most important parameters to explain OA pain or response to therapy[23,186]. By identifying core parameters, the model can assist in the development of future studies that do not require thousands of patients.

Studies using these AI models show that combining psychosocial, sensitivity, inflammation and genetic factors help to explain why some patients experience chronic postoperative pain after TKA while others do not[23]. Furthermore, these improved models can predict which patients will respond to NSAID therapy, the predictive value of which is higher than with previous models[186]. Importantly, these AI models can develop pain mechanistic networks, which are complex systems based on the assessment of different domains (such as psychosocial, sensitivity, inflammation and genetic domains). These networks are revealing associations between different pain mechanistic domains and have identified markers that bridge multiple mechanistic domains[23]. Targeting such markers has the potential to address several aspects of OA pain simultaneously, offering new avenues for multimodal treatment. In one study, these combined mechanistic pain networks explained 81% of the variability in chronic postoperative pain[23] and in another study, these networks could be used to predict response and non-response to 3 weeks of NSAID therapy (accuracy of 84%, sensitivity of 83% and specificity of 87%)[186]. These explanatory and predictive values are higher than those reported when only a single mechanistic domain is assessed, but thus far there have been no head-to-head comparison studies[33,53,84,104].

Many elements of pain mechanistic networks remain unknown, and higher-order regulators might exist that shape interactions across domains. Discovering these key factors could represent a major breakthrough in the development of precision therapies for OA pain. As mentioned previously, the use of different AI models on the same data set can generate different results[25] and so selecting the right AI models for the data being analysed is key[26].

Overall, evidence suggests that pain in OA is a multifactorial complex problem, and it could be argued that each of the pain mechanistic domains adds to the complexity of chronic pain in OA. We propose a spectrum of pain complexity in patients with OA (Fig. 4), whereby a low-complexity archetype exists at one end of the spectrum, that is, a person with localized joint pain including inflammation, in which other mechanistic factors can be excluded; those with this archetype will probably respond to standard pain therapies[16,23,171,186–188]. At the other end of the spectrum is the high complexity archetype, in which several pain mechanistic domains are involved in driving pain (such as increased systematic inflammation, central pain mechanisms, pain catastrophizing, less favourable epigenetic profiles and several comorbid lifestyle factors); people with this archetype are less likely to respond to standard pain therapy. Importantly, these two archetypes are not likely to exist and are used to illustrate the extremes of the pain-complexity spectrum; instead, OA pain should be viewed as a spectrum in which pain is considered more or less complex (Fig. 4).

In theory, the development of novel pharmacological therapies that target one mechanistic domain will be most suitable for patients with low-complexity pain with no comorbidities. For example, patients with low-complexity pain respond to NSAIDs, whereas those patients with high-complexity pain do not[186]. Developing a combined pharmacological and non-pharmacological approach that targets several pain mechanistic domains simultaneously is more likely to be successful in treating those patients with high-complexity pain and comorbidities. Although few examples of this approach exist, results from a 2019 randomized control trial[189] that enrolled patients at a high risk of chronic postoperative pain showed that preoperative treatment and 6-week postoperative treatment with duloxetine (an anti-depressant also used to target neuropathic pain) lowered 6-month postoperative pain scores when compared with placebo, suggesting that targeting the nervous system and depression in those patients with high pain complexity might be advantageous. Thus, advanced machine learning can integrate complex data from multiple domains to identify pain mechanistic networks[23,186] and can offer higher predictive value for treatment outcomes than single-domain assessments. Identifying and/or developing therapies that can target these pain mechanistic networks has the potential to offer pain relief for patients with OA who have high-complexity pain.

Future directions

There have been no major breakthroughs in analgesics for OA pain in decades. Opioids are not recommended for long-term treatment of OA[7] and instead attempts have been made to target the different mechanistic domains such as inflammation (using NSAIDs or anti-NGF antibodies[190,191]) targeting the nerve system (using gabapentinoids[4,192]) or targeting the psychological and nervous system (using anti-depressants[193,194]), but these have had limited success and adverse effects.

As discussed in this Review, subsets of patients with OA have complex chronic pain and therapies that target only a single pain mechanistic domain will probably not be effective for these patients. The development of pharmacological and non-pharmacological therapies that target several pain mechanistic domains are more likely to be successful. Pain mechanistic domains are probably reciprocally influential[23,186] and understanding these interactions in more detail could reveal novel therapeutic targets. Personalized pain prevention and pain management based on the factors that are relevant to the individual patient could guide treatment in the future[195]; however, relevant factors and their interactions need to be identified first. Another key area is the identification of the underlying factors that explain heightened vulnerability to pain, as targeting these factors could address numerous pain mechanistic domains. These interactive networks and factors that cause pain vulnerability must be considered as the missing link in OA pain research, and the identification of these could lead to a major breakthrough within the field.

Conclusions

Chronic pain in OA can be influenced by several factors, such as psychosocial load, increased sensitivity, inflammation and genetic modifications. Evidence shows that individual patients have a unique profile when these features are assessed. The features can be viewed as indicators of the complexity of pain in a patient with OA; a more complex pain profile is linked to poor response to standard pain therapy. Emerging technologies (such as AI) enable the assessment of a combination of many different pain-related domains and will probably increase understanding of OA pain and lead to tailored interventions. These technologies will also facilitate further insights into how different pain mechanistic domains impact one another. Future research should also be aimed at identifying the currently unknown factors or mechanisms that cause pain vulnerability. Combined, these discoveries are likely to pave the way for stratified pain medicine and provide new analgesic therapies for people with OA.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

L.A.N. declares that they have served as an adviser for Grünenthal, Merz, Vertex, Almirall, Tenvie, Contura, NCBD and CombiGene in the past 5 years. All other authors declare no competing interests.

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Review article

Check for updates

Innate lymphoid cells in rheumatoid arthritis as mediators of pathology and resolution

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Abstract

Innate lymphoid cells (ILCs) are emerging as critical modulators of inflammation in rheumatoid arthritis, contributing to both disease pathology and resolution. Group 3 ILCs (ILC3s) mirror T_H17 cells in their production of IL-17A and IL-22, promoting fibroblast activation, neutrophil recruitment and synovial inflammatory cascades. By contrast, group 2 ILCs (ILC2s) engage reparative and immunoregulatory pathways via secretion of IL-9, IL-13 and IL-10. Lymphoid tissue inducer (LTi) ILCs contribute to ectopic lymphoid tissue neogenesis and stromal remodelling in early disease. Clinically, alterations in ILC subset composition correlate with disease activity, therapeutic responsiveness and inflammatory burden. Advances in high-dimensional immunophenotyping, spatial transcriptomics and single-cell multi-omics now enable precise mapping of ILC subsets and their effector programmes across peripheral blood and synovial tissue, supporting their use in biomarker discovery and treatment pipelines. Furthermore, modulation of ILCs by targeting upstream cytokines, signalling pathways or the use of microbiota-derived metabolites is a potential therapeutic strategy. Finally, cell-based avenues include IL-10-producing ILC2s ($ILC2_{10}$) and engineered chimeric antigen receptor (CAR)-ILC2s for targeted, tissue-resident immune modulation. Although still in the preclinical stages, these approaches highlight the translational potential of ILCs as biomarkers and therapeutic targets in rheumatoid arthritis.

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Key points

- Innate lymphoid cells (ILCs) have dual roles in rheumatoid arthritis (RA); ILC3s and ILC1s promote inflammation, whereas ILC2s mediate protection through the production of IL-4, IL-9, IL-10 and IL-13.
- $CCR6^+$ ILC3s accumulate in the joints in RA and correlate with disease activity; the interaction of these cells with synovial fibroblasts promotes IL-17A-driven inflammation, myeloid skewing and tissue remodelling.
- ILC2s show context-dependent effects in RA, exerting regulatory functions during early inflammation but contributing to pathogenesis via GM–CSF production under specific inflammatory conditions, such as in SKG mice.
- Alterations in ILC subset composition in blood, lymph nodes and synovial tissue could serve as dynamic biomarkers reflecting disease stage, immune activation and treatment response in RA.
- Targeting ILCs via cytokine signals (for example, IL-33), microbial metabolites (such as isoLCA), or pharmacological inhibitors (including JAK inhibition) offers promising therapeutic strategies in combination with conventional DMARDs.
- Preclinical studies support the feasibility of ILC-based cell therapies, including IL-10-producing ILC2s expanded from peripheral blood mononuclear cells or pluripotent stem cells, with the potential to restore immune homeostasis in RA.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the small joints, permanent joint damage, disability and increased mortality[1]. Nevertheless, no curative treatments currently exist[2]. Achieving sustained remission remains a notable challenge; evidence from randomized controlled trials demonstrates that tapering anti-TNF therapy among patients in durable remission results in disease flares in 65% of individuals within 1 year[3]. These observations imply that underlying immunological imbalances persist, even in patients who are clinically in remission, reflecting a critical gap in understanding of disease triggers and limitations of current therapies in restoring complete immunological homeostasis.

Twin studies show that individuals with an identical twin diagnosed with RA have a ~15% risk of developing the disease themselves, indicating a modest but meaningful genetic contribution[4]. However, the rapid rise in the incidence of RA across industrialized regions suggests that environmental factors also have a pivotal role[5]. Epidemiological research has identified key environmental risk factors for RA, including smoking, periodontal disease and exposure to inhaled particulates such as silica and coal dust[6–8]. These risk factors share a common feature: each functions as an inflammatory or toxic insult at mucosal surfaces, particularly within the oral mucosa and respiratory tracts. This pattern supports the concept that mucosal sites could serve as initiation points for autoimmune priming[9]. These surfaces are densely colonized by commensal microbes that are increasingly associated with immune dysfunction and a greater risk of RA in later life[10]. Studies using germ-free mouse models have highlighted the critical role of specific microbial taxa in driving inflammation; for example, segmented filamentous bacteria promote T_H17 cell differentiation and can precipitate autoimmune pathology[11]. In K/BxN mice, which develop spontaneous arthritis, germ-free conditions completely abrogate disease, whereas colonization with segmented filamentous bacteria is sufficient to trigger rapid-onset arthritis within days[11,12]. Together, these findings support the concept that microbial exposures represent a second class of immune-priming signals, alongside environmental inflammatory irritants, that shape susceptibility to RA and other autoimmune diseases.

Innate lymphoid cells (ILCs) seed mucosal tissues during early microbial colonization and persist thereafter as long-lived tissue-resident sentinels. By functioning as rapid first responders during inflammatory perturbations, these cells are uniquely poised to influence the long-term sculpting of immune responses[13]. These features collectively position ILCs as prime candidates for involvement in RA pathogenesis. Moreover, these cells are implicated in establishing susceptibility to chronic inflammation in several other inflammatory diseases, including allergic asthma, dermatitis, psoriasis and intestinal inflammation[14]. For example, depletion of short-chain fatty acid-producing commensal bacteria leads to aberrant activation of ILC2s, which in turn drives the production of natural innate IgE antibodies by B1 cells and increases susceptibility to allergic inflammation[15,16]. Similarly, loss of specific bile acid-modifying microbes and enrichment of branched-chain amino acids (such as leucine) results in the expansion of ILC3s and pathogenic T_H17 responses that enhance susceptibility to hypersensitivity pneumonitis, a T_H1-driven and T_H17-driven neutrophilic inflammation[17].

These findings converge on a broad principle: immune dysregulation arising from disrupted immune sculpting, whether through early microbial perturbation or persistent environmental insult, might represent a shared feature of chronic inflammatory diseases. Building on this framework, we propose that both juvenile and adult-onset RA could be primed much earlier in life than previously appreciated, shaped by exposure-driven changes in the long-term behaviour of ILCs. In this Review, we critically examine the role of ILCs in RA, emphasizing the importance and urgency of elucidating their contributions to rheumatic diseases.

Innate lymphoid cell biology and subsets

ILCs are a family of lymphocytes that lack antigen-specific receptors but in all other ways resemble polarized T cells. Unlike T cells, however, each ILC subset rapidly integrates epithelial, stromal, neural and microbial cues to coordinate early immune responses and maintain tissue homeostasis. In this section, we describe the major ILC subsets and the functional parallels between these populations and T cells, and then summarize key concepts in ILC development and tissue residency that inform the potential roles of these cells in autoimmune diseases such as RA.

Innate lymphoid cells as innate homologues of adaptive T cells

ILCs are an emerging family of potent, tissue-resident immunomodulatory cells responsible for homeostasis and the early stages of host defence[13,18]. The ILC family comprises five major groups defined by developmental trajectories and functional characteristics: natural killer (NK) cells, ILC1s, ILC2s, ILC3s and lymphoid tissue inducer (LTi) cells. Although listed as a separate group in this five-subset schema, LTi cells are developmentally related to the broader ILC3 lineage. LTi cells express RORγt and promote lymphoid

tissue organogenesis; in the absence of these cells, the formation of lymph nodes, Peyer's patches and the lymphoid architecture in the thymus and spleen is severely disrupted[19]. NK cells primarily function as cytotoxic cells and can be viewed as the innate counterpart to cytotoxic $CD8^+$ T cells. In addition, each T helper cell subset (T_H1, T_H2 and T_H17 cells) corresponds to a functionally analogous ILC population (ILC1, ILC2 and ILC3, respectively) (Table 1).

Unlike T helper cells, which exhibit antigen specificity through the expression of diverse T cell receptor (TCR) repertoires, ILCs lack TCRs and respond rapidly to a variety of environmental factors in an antigen-independent manner[20,21]. Following local insult or infection, tissue epithelial cells and stroma release key 'alarmins', including thymic stromal lymphopoietin (TSLP), IL-33 and IL-25, which activate ILC2s to prime the initial immune response[22–25]. This provides a mechanistic explanation for how the immune system instantly initiates rapid helper responses tailored to the appropriate pathogens long before the development and polarization of antigen-specific T cells in the lymph nodes. In this model, these ILCs serve as tissue-resident first responders that orchestrate the appropriate downstream polarized inflammatory cascade. To fulfil this function, ILCs colonize most mucosal barrier surfaces of the body (such as the lungs, gut and skin) very early in ontogeny[26].

Given this strategic positioning and involvement in early and sustained responses, ILC dysregulation has been linked to a number of chronic inflammatory diseases, including asthma and atopy, psoriasis, inflammatory bowel disease, fibrosis and cancer[27]. These observations highlight the need to define the mechanisms governing ILC development, fate and function (Box 1), as such knowledge will be essential for future efforts to modulate ILC behaviour therapeutically in systemic autoimmune diseases including RA.

Developmental lineage and tissue residency

ILC development begins in the fetal liver and continues postnatally in the adult bone marrow[28,29]. Intriguingly, lineage tracing studies have shown that certain ILC subsets, particularly LTi cells, can also arise from the embryonic haemogenic endothelium, rather than exclusively from fetal liver-derived progenitors, suggesting a distinct developmental route for this lineage[30]. This embryonic pathway seems largely restricted to LTi cells, whereas the development of most ILC subsets during later ontogeny follows the conventional pathway via progenitors in the fetal liver and adult bone marrow. In adult mice, ILCs arise from α4β7-expressing common progenitors known as α-lymphoid precursors (αLPs)[28,31,32]. These progenitors progress through a continuum of downstream differentiation stages that ultimately give rise to distinct ILC subsets[33] (Fig. 1). Early innate lymphoid progenitors (EILPs) are defined by expression of TCF1 and the absence of PLZF and these cells retain broad multilineage potential; in clonal differentiation assays, EILPs can generate NK cells as well as ILC1s, ILC2s and ILC3s[32]. Notably, EILPs are transcriptionally heterogeneous and retain the capacity to generate dendritic cells, highlighting a degree of flexibility and imprecision during ILC specification before further lineage commitment[32].

Progressing beyond this stage, a committed ILC progenitor (ILCP) population emerges, defined by co-expression of TCF1 and PLZF[34]. Adoptive transfer studies have shown that these ILCPs can generate mature, tissue-resident ILCs, including NK cells[31]. However, more recent studies have also revealed the presence of locally maintained ILC progenitors in peripheral tissues, indicating that in situ differentiation also contributes to ILC development and phenotypic heterogeneity[35–37]. Notably, single-cell RNA sequencing (scRNA-seq) of gut ILCs in mice has revealed that, contrary to current dogma, some tissue-resident ILCs display evidence of abortive, neonatal-type TCR rearrangements, suggesting that at least a fraction might arise from neonatal thymic precursors rather than solely from bone marrow progenitors[38–40]. Furthermore, reports of mature ILC 'plasticity' in response to inflammatory cytokines are increasing, suggesting that ILC subset identity might be more flexible than previously thought, with potential for trans-differentiation and alternative cell-fate adoption[41,42]. However, such findings should be interpreted with caution. Apparent 'plasticity' could instead reflect rapid in situ expansion of rare, pre-existing tissue-resident ILC subsets[43–45], recruitment of ILCs from other sites[46,47] or the differentiation of locally maintained precursor-like cells[36,37,48–50]. Evidence corroborating each of these mechanisms has been reported in various tissues and disease contexts, but the relevance of each process warrants further investigation in autoimmune diseases such as RA.

Table 1 | Comparative overview of innate lymphoid cell subsets: functions, transcriptional programmes, stimuli and T cell analogues

ILC subsets	Primary function or context	Key transcription factors	Key activating stimuli	Cytokines and effector molecules produced	Analogous T cell subset
NK cells	Viral immunity, tumour surveillance and chronic inflammation	T-bet and EOMES	IL-12, IL-15, IL-18 and type I interferons	TNF, IFNγ, perforin, granzymes and IL-10	$CD8^+$ T cells
ILC1	Immunity to viruses and intracellular pathogens, and chronic inflammation	T-bet and low EOMES expression	IL-12, IL-15 and IL-18	TNF, IFNγ and granzyme B	$CD4^+$ T_H1 cells
ILC2	Helminths defence, allergic inflammation, tissue repair and metabolic regulation	GATA3, RORα, BCL11b and GFI1	IL-25, IL-33, TSLP, PGD_2, NMU and TL1A	IL-4, IL-5, IL-9, IL-13, amphiregulin and IL-10	$CD4^+$ T_H2 cells
$ILC2_{10}$	Immunoregulation, tolerance and control of inflammation	GATA3, ID3 and AhR (context-dependent)	TGFβ, IL-10, IL-27 and retinoic acid	IL-10, TGF and IL-35 (in some cases)	$CD4^+$ T_{reg} cells
ILC3	Defence against extracellular bacteria and fungi, barrier maintenance and chronic inflammation	RORγt, and T-bet (in some NCR^+ ILC3)	IL-1β, IL-23, IL-7, TGFβ and AhR ligands	IL-17A, IL-17F, IL-22, GM–CSF and IFNγ	$CD4^+$ T_H17 and T_H22 cells
LTi cells	Embryonic and adult lymphoid tissue development	RORγt and ID2	IL-7, LTα, LTβ and CXCL13	IL-17A, IL-17F, IL-22, LTα and LTβ	Not applicable

AhR, aryl hydrocarbon receptor; BCL11b, B cell lymphoma/leukaemia 11B; EOMES, eomesodermin; GATA3, GATA binding protein 3; GFI1, growth factor independent 1; GM–CSF, granulocyte–macrophage colony-stimulating factor; ILC, innate lymphoid cell; $ILC2_{10}$, IL-10-producing ILC2; LT, lymphotoxin; LTi, lymphoid tissue inducer; NK cell, natural killer cell; NMU, neuromedin U; NCR, natural cytotoxicity receptor; PGD_2, prostaglandin D_2; RORα, retinoic acid receptor-related orphan receptor alpha; RORγt, retinoic acid receptor-related orphan receptor gamma t; TGFβ, transforming growth factor beta; T_H, T helper; TL1A, TNF-like ligand 1A; TSLP, thymic stromal lymphopoietin.

Box 1 | Genetic tools for dissecting ILC subset-specific functions

Interpretation of the divergent roles of innate lymphoid cells (ILCs) has been hampered by the lack of mouse models that enable selective manipulation of individual ILC subsets. Commonly used transgenic lines, such as *Il7r*-Cre, *Id2*-CreERT2 and *Gata3*-Cre, target the entire ILC compartment, for the purpose of lineage-tracing, fate-mapping and deletion of genes of interest[140], and therefore preclude discrimination of subset-specific contributions. Compounding this issue, models involving pan-haematopoietic deletion of *Rora* influence ILC3 functions by restraining their secretion of IL-17, further complicating the use or targeting of *Rora* in ILC2s[39].

These challenges have prompted growing recognition of the need for improved animal models with subset-specific reporter systems that enable precise fate mapping and lineage tracing of individual ILC subsets, approaches that will be essential for resolving current controversies and elucidating the physiological role of each subset in health and disease. For example, *Il17rb* (encoding the IL-25 receptor) has been identified as a highly specific marker of ILC2s, irrespective of tissue-specific co-receptor expression programmes[68]. Moreover, several studies have also taken advantage of *Nmur1*-Cre, which shows largely selective activity in ILC2s[141,142].

Progress has similarly been made in developing strategies to target ILC3s specifically. One elegant study outlined multiple approaches for specifically targeting ILC3s to disentangle ILC3 function from that of other ILCs and T_H17 cells[93]. Deletion of a Rorc(γt) cis regulatory element located 7 kb downstream of the Rorc(γt) transcription start site resulted in mice lacking ILC3s and RORγt$^+$ dendritic cells while leaving other ILCs and T_H17 cells unaffected[93]. In parallel, *Serinc2* was identified as a gene with high, selective expression in ILC3s (but not RORγt$^+$ dendritic cells or other T_H17 cells), enabling the generation of *Serinc2*-iCre transgenic mice for ILC3-specific fate-mapping and conditional allele deletion[93].

Existing tools also have limitations. For instance, the current RORγt-GFP knock-in reporter disrupts one *Rorc* allele, resulting in *Rorc* haploinsufficiency and a partial reduction in RORγt$^+$ cell numbers[143]. Therefore, the generation of the new reporter mouse line targeting *Gm38411* (which faithfully marks RORγt$^+$ cells without altering *Rorc*) will be a valuable tool for investigating the role of ILC3 in RA[93].

Human ILC development remains less well defined than that of mice, largely because studies of human embryonic tissues face substantial ethical and practical constraints. In human umbilical cord blood and adult peripheral blood, researchers have described a specific subset of ILCs expressing IL-7R, CD45RA and c-Kit but lacking a mature ILC phenotype[43,51] (Fig. 2). Transcriptomic and chromatin-accessibility analyses indicate that these cells notably overlap with haematopoietic stem cells, while maintaining an ILC profile in a poised state[51]. Both in vitro cloning assays and in vivo transfer experiments have demonstrated that these circulating precursors are multipotent and capable of giving rise to all ILC subsets. Although these cells are also found in the fetal liver, paediatric tonsils and adult lungs, their differentiation potential varies by tissue[51]: clonal analyses reveal that tonsillar precursors retain broad multipotency, whereas fetal liver-derived precursors are predisposed towards the ILC3 lineage and lung-derived precursors are biased towards ILC2s. These findings suggest that local environmental signals shape in situ ILC differentiation and function (Fig. 2). Collectively, these data show that, in both mice and humans, ILC development is not restricted to the bone marrow and can proceed within peripheral tissues[35,52].

Innate lymphoid cell precursor metabolism and functional regulation

Metabolic reprogramming is a central regulator of ILC activation, differentiation and effector function. Distinct ILC subsets engage specialized metabolic programmes that integrate nutrient availability, cytokine signals and local tissue cues to shape immune responses[53]. ILC1s rely primarily on glycolysis to support rapid IFNγ production, whereas ILC2s use a flexible combination of fatty acid oxidation and glycolysis to sustain type 2 cytokine output. By contrast, ILC3s depend on oxidative phosphorylation and lipid metabolism to maintain IL-22 secretion and tissue repair[54,55]. Disruption of these metabolic pathways can skew the cytokine balance and prolong inflammatory responses. The availability of specific amino acids, particularly arginine and methionine, functions as a key rheostat of ILC activation, and mitochondrial STAT3 signalling couples methionine metabolism with type 2 cytokine production[56,57]. Furthermore, microbially induced dysbiosis has been shown to enrich pathways involved in branched-chain amino acid (BCAA) biosynthesis, thereby enhancing type 3 responses in ILC3s[17]. Collectively, these findings highlight metabolism as an important determinant of ILC effector potential.

Evidence also links such metabolic adaptations to autoimmune pathogenesis. In chronic inflammatory settings, nutrient competition, hypoxia and altered redox balance reshape ILC metabolic states, promoting persistent and sustained cytokine production[58]. Although direct evidence of metabolic adaptation in synovial ILCs in RA is currently lacking, studies in other inflamed tissues demonstrate that ILC2s and ILC3s depend on mitochondrial and lipid metabolic programmes to sustain cytokine production (IL-5, IL-13, IL-22) under hypoxic and nutrient-limited conditions[54,55,59].

The rheumatoid joint is characterized by profound hypoxia and dynamic metabolic reprogramming[60]. In this context, adiponectin, an adipokine substantially upregulated in the inflamed synovium, could further contribute to the metabolically permissive environment that sustains inflammation, and could promote ILC function in RA via AMPK-dependent and lipid-driven signalling pathways[61]. Determining whether similar pathways govern ILC persistence and functional crosstalk with macrophages and fibroblasts in driving chronic inflammation represents an important area for investigation. These tissue-specific metabolic states highlight how ILCs integrate environmental and intrinsic metabolic signals to maintain effector activity in autoimmune disease. Targeting shared metabolic checkpoints, particularly the AMPK–mTOR–STAT3 axis, amino acid transport systems and mitochondrial bioenergetics, is a potential strategy for attenuating ILC-driven pathology while preserving homeostatic immunity. In support of this concept, selective inhibition of mTORC1 was shown to restore immunological balance in streptomycin-induced dysbiosis and attenuate pathological ILC3 responses in mice[17]. Moreover, diagnostic monitoring of ILC metabolic signatures in conjunction with metabolic signalling

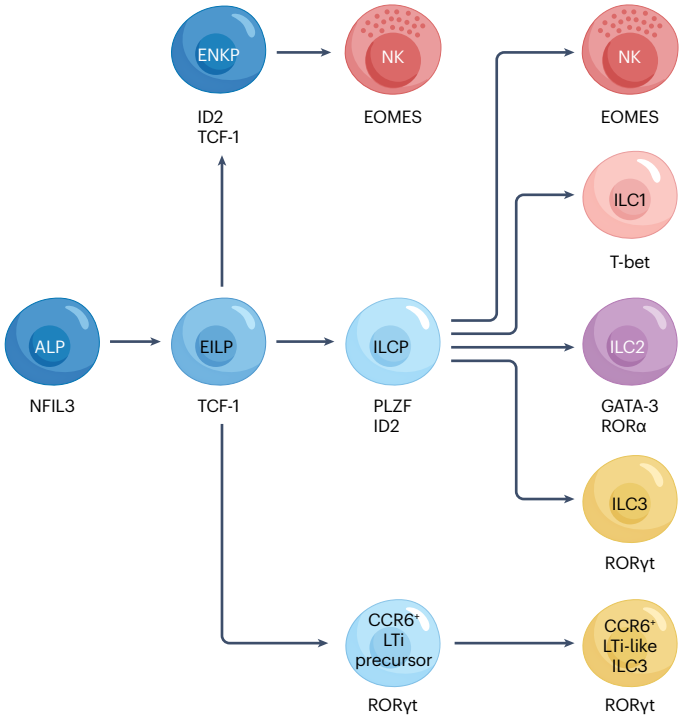

Fig. 1 | Developmental pathways of bone-marrow-derived innate lymphoid cells in adult mice. In the adult bone marrow of mice, all lymphoid progenitors (ALPs), which depend on the transcription factor NFIL3, give rise to early innate lymphoid progenitors (EILPs) characterized by expression of TCF1. EILPs retain dendritic cell potential but sequentially differentiate into innate lymphoid cell precursors (ILCPs), which lack this potential. ILCPs, defined by expression of PLZF and ID2, generate the three major ILC lineages, ILC1, ILC2 and ILC3, as well as natural killer (NK) cells. CCR6$^+$ lymphoid tissue inducer (LTi)-like ILC3s develop from distinct LTi-lineage precursors in the bone marrow. Notably, the majority of NK cells arise from a distinct, recently identified population of early NK progenitors (ENKPs).

molecules such as adiponectin might refine disease stratification and improve prediction of therapeutic outcomes in RA.

Preclinical and clinical evidence of innate lymphoid cells in rheumatoid arthritis

RA can begin many years before overt joint symptoms become apparent, and innate lymphoid cells are emerging as key regulators of tolerance and pathogenesis across this extended preclinical window. Among these populations, ILC2s have been positioned as immune regulatory cells during RA, although their functions seem context dependent and can include both protective cytokine programmes and pathogenic effector outputs. By contrast, ILC3 subsets and type 3 cytokine production, particularly IL-17A-driven inflammation, have been consistently associated with disease severity. ILC3-driven inflammation intersects with fibroblast activation and inflammatory loops implicated in flares. Relatively little, however, is known about specific roles of ILC1s in RA.

Regulatory and inflammatory functions of group 2 innate lymphoid cells

Type 2 immunity, characterized by cytokines such as IL-4, IL-5, IL-9 and IL-13, evolved primarily to promote hypersensitivity reactions and to counter large extracellular parasites, such as helminths, that evade elimination by conventional cytotoxic mechanisms[62,63]. Rather than relying on direct killing, type 2 responses enhance barrier integrity and promote tissue remodelling, most notably through mucus secretion and collagen deposition, to expel or contain these threats. These responses rely heavily on eosinophils, basophils, mast cells and B cells, and are closely linked to IgE-mediated humoral immunity. Interestingly, type 2 immune pathways are also integral to tissue-repair processes, suggesting an evolutionarily conserved role in wound healing[64].

ILC2s, central mediators of type 2 immunity, are present in the blood and synovial tissue of patients with RA and are frequently associated with protective immunoregulation, although abundance and function vary with disease context[65,66]. Notably, several studies report elevated frequencies of circulating ILC2s in patients with RA compared with healthy individuals, with higher levels correlating inversely with disease severity[65,67]. This inverse relationship suggests a potential regulatory function for ILC2s in dampening RA pathology. Supporting this protective role, data from mouse models of arthritis show that expansion of GATA3$^+$ ILC2s, both in K/BxN serum transfer-induced arthritis and in collagen-induced arthritis, reduces disease severity by increasing production of IL-4 and IL-13 (ref. 67). Furthermore, depletion of ILC2s in GATA-3-Cre x *Rora*$^{fl/fl}$ mice results in increased numbers of macrophages and exacerbated arthritis, whereas enhancing ILC2 function through adoptive transfer or pre-emptive administration of IL-25 or IL-33 mitigates inflammation and bone erosion[67]. Interestingly, adoptive transfer of ILC2s during the peak of disease activity fails to confer protection in the K/BxN model, highlighting a critical window in early arthritis to mitigate disease risk.

In line with these observations, a complementary study identified IL-9-producing ILC2s as key regulators of inflammation resolution in antigen-induced arthritis[65]. ILC2s were the predominant cellular source of IL-9 within the arthritic joints, and analysis of *Il9*$^{-/-}$ mice demonstrated that loss of IL-9-dependent ILC2 activity disrupted immunological homeostasis, resulting in sustained type 3 inflammatory responses mediated by IL-17A-producing T_H17 cells[65]. Notably, adoptive transfer of wild type ILC2s into *Il9*$^{-/-}$ mice was sufficient to reduce joint swelling in antigen-induced arthritis. However, the study did not selectively deplete ILC2s or specifically target IL-9 within the ILC2 compartment, leaving the requirement for IL-9 production by ILC2s in chronic arthritis resolution unresolved. Interestingly, adoptive transfer of ILC2s into *Il9*$^{-/-}$ mice also reduced circulating IL-17A protein levels[65]. In addition, ILC2s are capable of producing IL-10, and thus the contribution of IL-10-producing ILC2s to immune regulation during RA remained undefined[68,69].

These observations align closely with previously proposed cross-regulatory interactions between ILC2s and type 3 lymphocytes (T_H17 and ILC3s), first characterized in studies of Crohn's disease-like fibrosis[68]. In earlier work, selective depletion of ILC2s using the *Il17rb*$^{CreERT2\text{-}eGFP}$ × *Rora*$^{fl/fl}$ transgenic mouse model led to enhanced accumulation of IL-17A-producing ILC3s and T_H17 cells, exacerbating chronic fibrotic inflammation. Conversely, depletion of ILC3s and T_H17 cells reduced fibrotic pathology[68]. Collectively, these findings demonstrate that ILC2s function as regulators that constrain pathogenic type 3 immune activity in the gut[68].

The relationship between type 2 and type 3 immune responses in RA seems complex (Fig. 3a,c). Elevated IL-25 levels in patients with RA have been shown to promote ILC2 activation and concurrently suppress

RORγt expression and IL-17A production in CD4$^+$ T cells derived from peripheral blood mononuclear cells[70,71]. Consistent with these observations, IL-25 administration in collagen-induced arthritis enhances type 2 responses and reduces *IL17A* and *RORC* expression in synovial tissues, resulting in diminished inflammation[70]. However, not all studies align with a protective role for ILC2s. One investigation revealed that GATA-3$^+$ST2$^+$ ILC2s produce GM–CSF within the inflamed joints of arthritic SKG mice, positioning the ILC2 subset GATA-3$^+$ST2$^+$ as an important initiator of autoimmune arthritis in this mouse model[66]. The SKG strain carries a point mutation in *Zap70* that impairs T cell receptor signalling and disrupts thymic selection, predisposing the mice to autoimmune arthritis upon innate immune stimulation[72,73]. This pathogenic function contradicts with previous studies describing immune-regulatory and disease-attenuating functions for ILC2s during the initiation phase of arthritis[65,67]. In line with the functional importance of GM–CSF in this setting, GM–CSF-deficient *Csf2*$^{-/-}$ SKG mice exhibit strong resistance to autoimmune arthritis[66,74]. Moreover, adoptive transfer experiments demonstrated that arthritis induction depends specifically on GM–CSF-producing ILC2s rather than GM–CSF-producing CD4 T cells, highlighting a distinct pathogenic facet of ILC2 biology[66].

This GM–CSF-dependent ILC2 pathway also holds translational relevance, as neutralizing GM–CSF monoclonal antibodies ameliorate established disease across multiple inflammatory arthritis models, including collagen-induced arthritis, zymosan-induced arthritis and K/BxN serum-transfer arthritis[75,76]. Given the early induction of GM–CSF by ILC2s during the course of RA, this pathway could present a unique therapeutic target; indeed, clinical trials investigating GM–CSF-directed therapies have shown promising results so far[77,78]. However, a critical outstanding question concerns the conditions under which ILC2s adopt regulatory functions (through cytokines such as IL-4, IL-13, IL-9 and IL-10) versus pathogenic functions (mediated by GM–CSF or other unknown cytokines). Future investigations employing selective and temporally controlled deletion of ILC2 subsets will be essential to clarify the therapeutic potential of modulating pathogenic ILC2 responses.

The pathogenic roles of group 3 innate lymphoid cell subsets

Whereas ILC2s can adopt regulatory or pathogenic functions depending on context, ILC3s are more consistently linked to IL-17-driven inflammatory pathways in RA. Neutralizing IL-17A in the K/BxN serum-transfer arthritis model blocks disease progression, underscoring the pathogenic role of this cytokine[12]. Similarly, IL-17-deficient mice exhibit markedly reduced arthritis severity in collagen-induced arthritis and *Il17a*$^{-/-}$ SKG mice are highly resistant to autoimmune arthritis[66,79]. IL-17A production by ILC3s typically depends on STAT3-activating cytokines, such as IL-6 and IL-23 (refs. 80,81). Genetic deletion studies have demonstrated that loss of the IL-23p19 subunit, critical for STAT3 signalling and IL-17A induction, effectively mitigates autoimmune pathology across multiple models, including collagen-induced arthritis, antigen-induced arthritis and experimental autoimmune encephalomyelitis[82–84]. These observations align with the expansion of ILC3 populations reported in the inflamed joints of patients with RA and mice with collagen-induced arthritis[85,86].

ILC3 subsets, including CCR6$^+$ LTi-like ILC3s, NCR$^+$RORγt$^+$T-bet$^+$ ILC3s and NCR$^-$ ILC3s, exhibit distinct and sometimes opposing roles

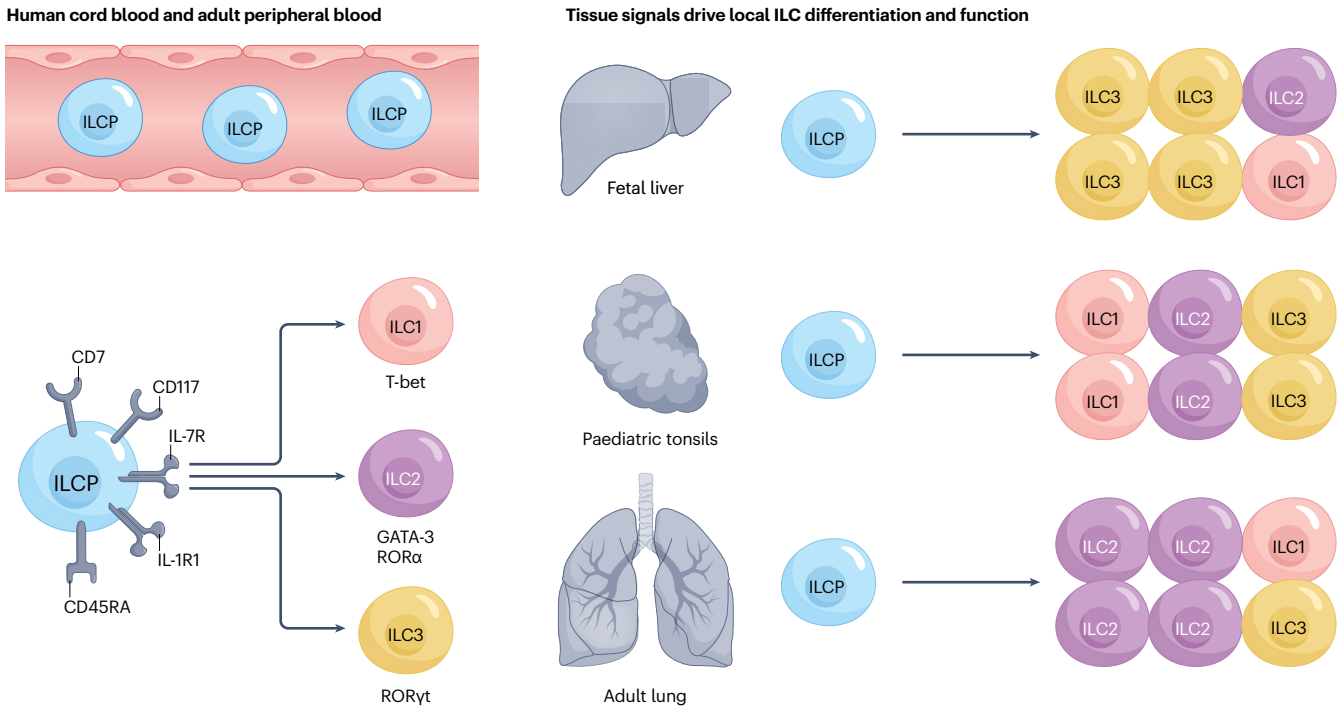

Fig. 2 | Tissue-specific environmental signals shape local differentiation and function of human innate lymphoid cells. Human circulating innate lymphoid cell precursors (ILCPs), characterized by the expression of IL-7R, CD45RA and c-Kit, are present in cord blood and adult peripheral blood. These precursors also reside in the fetal liver, paediatric tonsils and adult lungs, but have a tissue-specific differentiation potential. For example, fetal liver precursors show a preferential commitment towards the ILC3 lineage, whereas lung-derived precursors are biased towards ILC2 differentiation. Together, these patterns suggest that local environmental signals regulate in situ ILC differentiation and functional specialization.

in arthritis pathogenesis[87]. Among these populations, CCR6$^+$RORγt$^+$ LTi-like ILC3s show preferential and robust accumulation in the joints of mice with collagen-induced arthritis[85]. This subset expresses high levels of IL-17A, and increased frequencies of CCR6$^+$ LTi-like ILC3s in the synovial fluid of patients with RA correlate strongly with disease severity[85]. LTi cells (c-Kit$^+$NKp44$^-$) support the development and organization of secondary lymphoid tissues through the $LT\alpha_1\beta_2$–LTβR signalling axis, which induces stromal production of adhesion molecules such as VCAM-1 and ICAM-1 and homeostatic chemokines including CXCL13, CCL19 and CCL21 (ref. 87). In early RA, reduced frequencies of LTi cells in lymph nodes correlate with decreased stromal expression of VCAM-1 and ICAM-1, suggesting that impaired ILC–stromal interactions contribute to the loss of immune tolerance and early inflammatory remodelling[88]. However, as CCR6$^+$ LTi-like ILC3s have not yet been selectively depleted, neither pharmacologically nor genetically, the extent to which this subset contributes to disease pathogenesis remains unresolved.

By contrast, NOX2-deficient *Ncf1* mice, which are highly sensitive to K/BxN-induced arthritis, exhibit a selective expansion of NCR$^+$ ILC3 subsets but not CCR6$^+$ ILC3s or other ILC subsets[89]. NCR$^+$ ILC3s produce elevated levels of IL-17A within affected joints, and treatment with an IL-1 receptor antagonist selectively reduces the number of NCR$^+$ ILC3s, without affecting other ILC subsets, thereby decreasing joint swelling[89]. Human data add further complexity to these observations; some studies report reduced total ILC3 frequencies in the synovial fluid of patients with RA alongside increased ILC1s[90], whereas others describe increased ILC3 frequencies in the lymph nodes and blood of patients with active RA, suggesting the potential migratory behaviour of these cells[86,88]. Notably, increased frequencies of NCR$^+$ ILC3s in the lymph nodes of mice with collagen-induced arthritis correlate positively with disease severity[91]. In the same study, NCR$^+$ ILC3s isolated from mice with collagen-induced arthritis, but not from naive mice, promoted the differentiation of IL-17A-producing CD4$^+$ T cells when co-cultured under T_H17 polarizing conditions that included IL-6 and TGF-β[91]. However, the mechanisms by which ILC3s influence T_H17 cell differentiation in vivo during arthritis and whether this phenomenon extends to other preclinical models of RA remain unknown.

Additional insight comes from a study showing that ILC3s migrate from the circulation to the central nervous system during experimental autoimmune encephalomyelitis[92]. These ILC3s display an inflammatory phenotype characterized by the expression of CCR6, T-bet, IFNγ and MHC class II and, unlike gut-resident ILC3s, express multiple co-stimulatory molecules, including CD80 and CD86, promoting T cell responses in the central nervous system[92]. Genetic deletion of

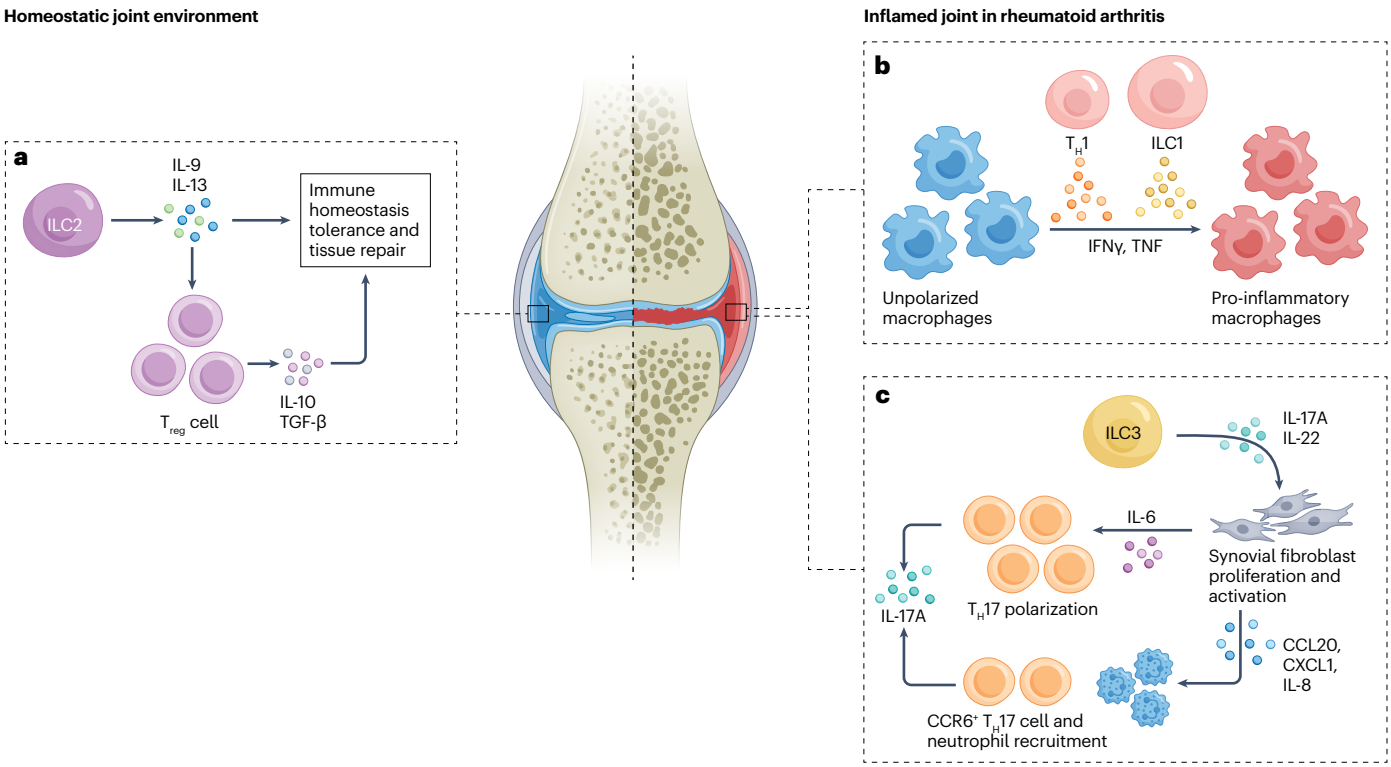

Fig. 3 | Dual roles of innate lymphoid cells in the pathogenesis and resolution of rheumatoid arthritis. a, In the healthy or resolving joint, group 2 innate lymphoid cells (ILC2s) help to maintain immune homeostasis by secreting IL-9 and IL-13, promoting regulatory T (T_{reg}) cell induction and IL-10 production, limiting inflammation and supporting tissue repair. **b**, In the inflamed joint in rheumatoid arthritis (RA), group 1 innate lymphoid cells (ILC1s) and T helper 1 (T_H1) cells produce IFNγ and TNF, amplifying type 1 inflammation and promoting myeloid cell activation and macrophage polarization. **c**, Group 3 innate lymphoid cells (ILC3s) exacerbate RA pathogenesis by producing IL-17A and IL-22, which stimulate synovial fibroblast proliferation and activation. In turn, activated fibroblasts secrete IL-6 to promote T helper 17 (T_H17) polarization and produce CCL20, CXCL1 and IL-8, recruiting CCR6$^+$ T_H17 cells and neutrophils to the joint. Recruited neutrophils adopt a pro-inflammatory phenotype, amplifying joint damage. Reductions in lymphoid tissue inducer (LTi) cells during early RA might reflect disrupted lymphoid tissue organization and stromal remodelling. Overall, the contribution of ILCs to RA reflects a dynamic between pro-inflammatory and homeostatic signals, modulated by cytokine milieu, disease stage and therapeutic intervention.

MHC class II using *Rorc*-Cre mice resulted in reduced frequencies of IFNγ$^+$IL-17A$^+$ myelin-specific CD4 T cells in the central nervous system, suggesting a requirement for antigen-presenting ILC3s in sustaining pro-inflammatory T cell responses. However, these findings warrant cautious interpretation, as *Rorc*-Cre-mediated deletion of MHC class II also targets a RORγt-expressing dendritic-cell population known as Thetis cells[93–95]. These cells have a critical role in the induction of peripheral regulatory T cells in response to dietary antigens and contribute to the establishment of immune tolerance to the gut microbiota[93,96,97].

Together, these findings highlight functional heterogeneity within the ILC3 compartment in RA and autoimmune disease, suggesting that spatial localization, cytokine profiles and stromal interactions critically influence the contribution of ILC3s to disease progression.

Innate lymphoid cell–fibroblast interactions

Much like ILCs, synovial fibroblasts have historically been overlooked in the development of targeted therapeutics. Perhaps the most definitive evidence of the role of these cells in disease comes from studies using the SCID mouse model[98]. In these experiments, synovial fibroblasts isolated from patients with established RA were transplanted within a cartilage matrix into immunodeficient SCID mice. Notably, the transplanted fibroblasts continued to invade and degrade the articular cartilage even in the absence of the original human inflammatory milieu[98]. These findings support the concept of epigenetic imprinting, whereby chronic exposure to an inflammatory microenvironment fundamentally establishes a stable, pathogenic fibroblast phenotype that persists independently of continuous external stimuli[98].

Interestingly, activated fibroblast gene signatures have been detected in peripheral blood shortly before RA flares, highlighting the importance of fibroblast–immune interactions[99]. Both ILC2 and ILC3 subsets interact closely with fibroblasts during chronic inflammation. ILC2s are situated near fibroblasts in adventitial niches[100], and IL-17A-producing ILC3s directly activate fibroblasts, inducing expression of pro-inflammatory mediators (such as IL-6 and serum amyloid A3 (SAA3)) that sustain pathogenic type 3 responses during chronic fibrosis[68]. Similarly, fibroblast-like synoviocytes isolated from the joints of SKG arthritic mice upregulate *Ccl20* and *Il6* upon exposure to IL-17A, supporting a role for ILC3–fibroblast crosstalk in driving RA pathogenesis[66]. Targeted deletion of pathogenic fibroblast subsets expressing fibroblast activation protein alpha (FAPα), using the FAP-DTR model, substantially reduces arthritis duration in mice[101].

Additional mechanistic insight comes from work in *Il23*mc-treated mice (mice treated with IL-23 minicircle DNA for sustained IL-23 overexpression) that also overexpress human TNF, where scRNA-seq analysis of synovial mesenchymal cells has demonstrated that IL-17A inhibition prompts the emergence of a specialized CD200$^+$ sublining fibroblast population[102]. Unlike the pathogenic CD200$^-$IL-6-producing fibroblasts that drive joint destruction, these CD200$^+$ fibroblasts express *Dkk3* and *Cdh11*, are transcriptionally enriched for pathways that dampen inflammation and are notably increased during the resolution phase of serum-transfer arthritis. Both human and murine ILC2s express high levels of CD200R1, the cognate receptor for fibroblast-derived CD200 (ref. 102). This interaction serves as a critical survival signal whereby CD200$^+$ fibroblasts maintain the ILC2 phenotype by sustaining high expression levels of CD127 and ST2 while limiting ILC2 apoptosis, thereby establishing a pro-resolving network necessary for restoring tissue homeostasis[102].

This fibroblast–ILC2 axis provides a compelling mechanistic explanation for the reported discrepancies in ILC2-mediated protection. For example, the inability of adoptively transferred ILC2s to confer protection during the peak of K/BxN serum-induced arthritis probably reflects the absence of pro-resolving CD200$^+$ fibroblasts at this inflammatory stage and highlights the importance of the activation state within the resident fibroblast compartment[67]. In the hyper-inflammatory environment during peak disease activity, the sublining *Il6*$^+$ pathogenic fibroblast population might fail to support, or perhaps might even actively suppress, the survival and tissue residency of pro-resolving ILC2s. Consequently, the therapeutic efficacy of ILC2s seems to be temporally constrained by the activation state of resident fibroblasts; thus, an imbalance between ILC subsets and fibroblast-driven inflammatory loops could constitute a fundamental pathogenic mechanism in RA.

RA disease flares are characterized by enhanced neutrophil and inflammatory monocyte responses[99]. IL-17A produced by ILC3s and T_H17 cells has been shown to directly influence haematopoietic stem and progenitor cells, skewing haematopoiesis towards increased myeloid-cell generation, leading to more neutrophils and inflammatory monocytes during pathological peripheral type 3 responses[17]. Therefore, elevated neutrophils and monocytes during RA flares could reflect amplified IL-17A-driven myelopoiesis in the bone marrow, implicating ILC3-driven responses as critical factors in RA pathogenesis.

Perinatal origins and pathogenic role of group 1 innate lymphoid cells

Initially identified in the liver as an atypical subset of NK cells, ILC1s provide type 1 immunity against tumours, intracellular microbes and viruses[103,104]. In mice, ILC1s characteristically express NK1.1 and NKp46 but lack the majority of Ly49 inhibitory receptors that recognize MHC class I; instead, these cells sense non-classical MHC class I molecules via NKG2 receptors[105]. ILC1s are activated by cytokines such as IL-7, IL-15 and IL-12, which regulate not only their survival but also their effector functions. Upon activation, ILC1s secrete high levels of IFNγ and TNF, thereby amplifying the inflammatory response[105]. A study analysing nephritic mice demonstrated that tissue-resident NKp46$^+$ ILC1s, rather than NK cells, were the dominant cellular producers of GM–CSF, a functional capacity abolished in *Ncr1*-deficient mice[106]. Notably, GM–CSF blockade in this model reduced epithelial cell injury, and NKp46$^+$ ILC1s were required for autoimmune organ damage[106].

In the collagen-induced arthritis model, ILC1 frequencies in the spleen are notably increased 5 weeks after immunization compared with non-arthritic controls, whereas NK cell and total ILC3 frequencies remain unchanged[107]. The mechanistic relevance of this finding remains unclear, especially as accumulating evidence highlights the distinct functional diversity among ILC1s across tissues. Fate-mapping using *Id2*-CreERT2 X R26-YFP mice has shown that uterine ILC1s undergo rapid turnover, whereas liver and splenic ILC1s have markedly slower turnover rates[108]. Furthermore, scRNA-seq in the same study showed that ILC1s emerge during embryogenesis and expand perinatally, whereas NK cells originate and mature much later, from the postnatal period into adulthood[108]. This developmental timeline aligns with our hypothesis that both juvenile and adult-onset RA might be primed much earlier in life than previously recognized, raising the possibility that perinatally derived ILC1s constitute an underappreciated contributor to pathogenesis. Within the inflamed RA joint, IFNγ and TNF produced by ILC1s could amplify type 1 inflammatory pathways and favour classical (M1-like) macrophage polarization, a mechanism closely associated with RA synovitis[107,109] (Fig. 3b). Such a role could

involve the transcription factor Hobit, a regulator of tissue-residency programmes in lymphocytes, including the perinatal emergence of cytotoxic ILC1s[110,111].

Future research utilizing temporally controlled deletion strategies will be necessary to define the specific window during which ILC1s influence RA pathogenesis. For example, in a liver metastasis model using *Ncr1*-Cre X R26-DTR mice, early depletion of ILC1s increased the metastatic load, whereas deletion in later stages was less effective[112]. Therefore, the temporal regulation of ILC1s in RA warrants rigorous investigation, as the contribution of these cells might be stage-specific and crucial for the early phase of disease initiation.

Therapeutic and diagnostic implications of innate lymphoid cells

As important early responders within the inflamed synovium, ILCs are increasingly recognized for their potential translational relevance in RA. Dynamic regulation by cytokines and stromal cues, together with the capacity to both mirror and influence inflammatory trajectories, positions distinct ILC subsets as promising biomarkers of disease activity, targets for immunomodulatory intervention and candidates for emerging cellular therapies.

Innate lymphoid cells as biomarkers for disease activity and immune dynamics

Accumulating evidence indicates that ILCs can serve as tissue-resident and circulating biomarkers, with shifts in ILC abundance and activation state mirroring RA disease activity, cytokine gradients and stromal remodelling. Disease-specific expansion of CCR6$^+$ ILC3s has been reported in both the peripheral blood and synovial fluid[85]. In a translational study integrating analysis of patient samples with experimental validation, circulating ILC3 frequencies correlated positively with the abundance of T_H1 and T_H17 cell subsets in the peripheral blood, as well as with clinical disease activity scores[91], supporting the role of ILC3s as amplifiers or reflectors of local inflammation. Complementary findings from lymph node biopsies in early RA have revealed a redistribution of ILC subsets, characterized by marked reductions in LTi cells and increases in ILC1 and ILC3 populations relative to both at-risk individuals and healthy individuals[88]. Again, these shifts were often paralleled by elevated expression of VCAM-1 and ICAM-1 in the lymph-node endothelium, suggesting a potential bidirectional interaction between ILCs and stromal scaffolding during disease initiation.

Within the synovial microenvironment, CCR6$^+$ ILC3s are selectively enriched in RA compared with osteoarthritis[85]. The abundance of this population correlates closely with CCL20 concentrations, a chemokine critical for T_H17 cell recruitment, indicating a shared chemotactic axis[85]. This axis supports the concept that CCR6$^+$ ILC3s not only reflect T_H17 pathway activation, but might also reinforce this axis through the production of IL-17 and IL-22 (ref. 85). These findings support the hypothesis that CCR6$^+$ ILC3s not only reflect activation of the T_H17 axis but could also actively contribute to this axis via IL-17 and IL-22 secretion.

Conversely, ILC2s seem to exhibit an anti-inflammatory profile. In comparative analyses of patients with active RA versus patients with stable disease, those with stable disease displayed higher peripheral ILC2 frequencies; by contrast, ILC1 levels correlated positively with disease activity[107]. Notably, ILC2 proportions also correlated inversely with Disease Activity Score in 28 joints (DAS28), consistent with an association between ILC2 abundance and disease quiescence. ILC2-derived IL-13, which is present in synovial fluid and tissue from patients with arthritis, further supports this regulatory phenotype, as ex vivo and in vitro studies show that IL-13 suppresses pro-inflammatory cytokine production and modulates synovial immune activation[113,114].

Comparative studies in psoriatic arthritis and ankylosing spondylitis further underscore the utility of ILC profiling for disease stratification. IL-17A-producing NKp44$^+$CCR6$^+$ ILCs, largely absent in RA, are abundant in psoriatic arthritis synovial fluid and show an inverse correlation with clinical disease activity[90]. In ankylosing spondylitis, IL-17A-producing and IL-22-producing ILC3s are expanded in the gut, synovial tissue and bone marrow. This expansion seems to be driven in part by synovial myeloid cells expressing CX3CR1 and IL-23 (refs. 115,116).

Together, these studies provide a compelling rationale for incorporating ILC subset profiling into biomarker discovery frameworks, offering a dynamic readout of immunological perturbations that could enable longitudinal monitoring of disease progression and prediction of therapeutic outcomes. Unlike conventional serological markers such as rheumatoid factor or anti-citrullinated protein antibodies, ILCs provide temporal and spatial resolution of immune activity, reside in both tissue and circulatory niches and could reflect dynamic shifts in inflammatory networks. The integration of ILC profiling into the RA biomarker landscape is becoming increasingly feasible owing to advances in high-resolution immunophenotyping and proteomic technologies. Techniques such as spectral flow cytometry and antibody-dependent proximity-ligation proteomics enable multiplexed, deep immunophenotyping of ILC subsets and their effector cytokines and chemokines (for example, IL-13, IL-22 and GM–CSF). These approaches could be leveraged in future studies to comprehensively profile ILCs in both peripheral blood and synovial fluid, facilitating integration into RA biomarker frameworks[117,118].

Single-cell multi-omics provide additional opportunities to interrogate ILC heterogeneity and functional plasticity. Spatial transcriptomics platforms (for example, Visium and Stereo-seq) have already been applied to map ILCs in various healthy and diseased tissues[119–123] and could be used to localize cytokine-producing ILCs within inflamed synovial niches and define context-dependent interactions with stromal and immune cells. In parallel, AI-based tools such as CellPhenoX support the identification of disease-relevant immune phenotypes across multimodal datasets, enabling predictive modelling of ILC-driven inflammation[124]. Collectively, these advances provide a multidimensional framework for tracking ILC dynamics that might enhance biomarker development in RA[125] (Box 2).

Nonetheless, translating ILC profiling into clinically actionable biomarkers will require further standardization of phenotyping protocols across platforms, as well as integration with longitudinal clinical and multi-omics datasets to validate utility across disease stages, clinical variables and treatment contexts. Alterations in circulating ILC subsets might not fully capture the frequency, phenotype or functional state of ILCs within synovial tissue. Given the compartmentalized nature of ILC responses, peripheral blood analyses should therefore be interpreted cautiously and ideally complemented by synovial profiling to delineate tissue-resident dynamics from systemic immune changes.

Immunomodulatory targeting of innate lymphoid cells in rheumatoid arthritis

ILCs have emerged not only as biomarkers but also as promising therapeutic targets in RA. Rapid responsiveness to local cues, marked functional plasticity and tissue-specific distribution position these populations

Box 2 | Therapeutic and diagnostic implications of innate lymphoid cells in rheumatoid arthritis

Innate lymphoid cells as biomarkers of disease activity and immune state

- Quantification of innate lymphoid cell (ILC) subsets in peripheral blood and synovial fluid
- Identification of disease-associated profiles (for example, ILC3 enrichment or ILC2 depletion)
- Correlation with clinical indices (such as Disease Activity Score in 28 joints (DAS28), C-reactive protein concentration and erythrocyte sedimentation rate)
- Integration with multi-omics approaches (for example, single-cell RNA sequencing and proteomics) to delineate ILC-driven inflammatory pathways

Immune stratification and patient segmentation

- Definition of ILC-based endotypes (for example, ILC3 and T_H17-dominant versus ILC2-associated profiles)
- Identification of predictive biomarkers of therapeutic response (for example, changes in $PD1^+$ ILC3 cells during JAK inhibitor therapy)
- Integration with cytokine profiles (for example, IL-18 and IL-23) to distinguish JAK-dependent from JAK-independent inflammation

Therapeutic modulation of innate lymphoid cells

- Conventional synthetic DMARDs and biologic DMARDs:
  - Methotrexate
  - TNF inhibitors*
  - GM–CSF inhibitors
- Targeted synthetic DMARDs
  - JAK inhibitors (such as tofacitinib and baricitinib)
  - PI3Kδ inhibitors (for example, seletalisib)
- Cytokine and metabolic modulation
  - Recombinant cytokines or cytokine blockade
  - Microbial metabolites (such as isoLCA that modulate $ROR\gamma t^+$ ILC3s)

Emerging innate lymphoid cell-directed therapeutic strategies

- Selective targeting of pathogenic ILC subsets (for example, the ILC3-T_H17 axis)
- Enhancement of regulatory ILC2 functions (for example, IL-13-mediated anti-inflammatory activity)
- Combination approaches that integrate ILC modulation with existing DMARDs

Experimental innate lymphoid cell-based cellular therapies

- Generation of ILC2-like cells from induced pluripotent stem cells
- Expansion of peripheral blood mononuclear cell-derived ILC2 populations

*As part of a combination therapy with conventional DMARDs.

as ideal candidates for immunomodulatory interventions aimed at restoring balance within chronically disrupted immune networks.

Efforts to therapeutically modulate the ILC landscape have focused on promoting regulatory subsets while dampening inflammatory populations. Administration of IL-33 expands IL-10-producing ILC2 populations and has demonstrated protective effects in multiple inflammatory disease models[126,127]. Complementary approaches leverage microbiota-derived metabolites such as short-chain fatty acids, which restrain ILC2 effector functions and pathological type 2 immune skewing, or secondary bile acid metabolites such as isoLCA, an inverse agonist of RORγ that inhibits $ROR\gamma t^+$ ILC3s and thereby limits IL-17A-driven inflammation during pathological peripheral type 3 responses[15–17,68]. Collectively, these examples illustrate the therapeutic potential of targeting upstream signals to reprogramme ILC activity.

Another promising strategy involves disrupting pro-inflammatory effector functions, such as GM–CSF secretion by ILC2s. This cytokine promotes the differentiation of inflammatory monocytes into dendritic cells, exacerbating synovial inflammation. The IL-33–ILC2–GM–CSF axis is a critical driver of this process[45,66]. Therapeutic agents that target IL-33 or GM–CSF signalling, including otilimab and mavrilimumab, are currently under clinical investigation and could offer a route to dampen ILC-driven inflammation in RA. Overall, these approaches highlight a growing therapeutic toolbox capable of rebalancing ILC subsets, promoting regulatory ILC2 responses while attenuating pathogenic ILC1 and ILC3 populations (Box 2).

Existing DMARDs can also modulate ILC activity. For example, clinical data indicate that the JAK inhibitor baricitinib reduces circulating $PD1^+$ ILC3 frequencies, and these reductions are accompanied by improvements in inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate, swollen joint count and DAS28 (ref. 128). Notably, shifts in ILC3 subsets, characterized by decreased $PD1^+$ ILC3s and increased $CTLA\text{-}4^+$ ILC3s, correlate with clinical response, suggesting that these populations reflect JAK-dependent inflammatory activity rather than simply serving as baseline predictors of therapeutic responsiveness.

Similarly, patients with RA receiving the JAK inhibitor tofacitinib exhibited marked reductions in circulating ILC1 frequencies and IFNγ production after 3 months, whereas anti-TNF therapy did not yield similar changes[129]. Mechanistically, JAK–STAT signalling is known to regulate ILC development and function, providing a rationale for why JAK inhibition might impact ILC networks[130]. Other small molecule inhibitors such as the selective PI3Kδ inhibitor seletalisib suppress IL-17A and IL-17F production by innate-like lymphocytes, including ILC3s, suggesting that drugs designed to modulate adaptive immunity can also influence innate lymphoid circuits[128].

Together, these data suggest that DMARDs not only suppress adaptive inflammation but could also modulate ILC-driven circuits, thereby offering an opportunity to combine ILC-directed therapies with standard treatments to enhance efficacy and restore balance in RA immune networks.

ILC profiles also hold the potential to guide treatment decisions in RA, particularly in the context of therapeutic resistance. For instance, baseline ILC1, ILC2 and ILC3 numbers have been shown to correlate with ultrasound-detected synovitis and predict methotrexate

responsiveness in a cohort of patients with RA or spondyloarthritis[131]. In patients undergoing JAK inhibitor therapy, a subset of patients with persistently elevated systemic IL-18 exhibited reduced responsiveness to JAK inhibition, consistent with IL-18-driven inflammation operating through JAK-independent pathways[119]. Together, these findings highlight the potential for immune stratification based on ILC and cytokine profiles to refine therapeutic decision-making. Although the contribution of ILC2 modulation to RA pathogenies remains uncertain, aligning therapeutic strategies with underlying immune phenotypes, including ILC signatures, offers a route towards more effective, individualized treatment regimens[132] (Box 2).

Together, these findings underscore the therapeutic relevance of ILCs in RA and support a multidimensional strategy that includes immune profiling, cytokine modulation, metabolite intervention and targeted pharmacological inhibition. Strategically targeting ILC subsets might not only mitigate inflammation but also help to restore immune homeostasis, paving the way for more precise and durable treatment outcomes.

Emerging innate lymphoid cell-based cellular therapies for rheumatoid arthritis

At the forefront of immunotherapy innovation are cellular strategies that harness the regulatory potential of ILCs, particularly ILC2s. Among the most promising are autologous ILC2-based approaches, in which IL-10-producing ILC2s are expanded ex vivo from peripheral blood mononuclear cells and reinfused to restore immune homeostasis. Although these strategies have not yet been tested in RA, related preclinical studies provide compelling proof of concept. In a mouse model of islet transplantation, IL-10-producing human ILC2s improved graft function and prevented allograft rejection[133]. In a separate mouse model of xenogeneic graft-versus-host disease, the same cell type limited disease by suppressing pathogenic human T cell responses in vivo[134]. Despite differences between islet transplantation and graft-versus-host disease, the shared mechanism of action highlights the broad immunoregulatory potential of IL-10-competent ILC2s. Given the parallels in effector T cell dysregulation and tissue-specific inflammation in RA, these findings support the feasibility of adapting ILC2-based cellular therapy to suppress synovial immune activation and promote tissue repair in autoimmune arthritis (Box 2).

These ILC-based strategies conceptually parallel advances in chimeric antigen receptor (CAR)-T_{reg} cell therapies, in which regulatory T cells are engineered to recognize synovial autoantigens and suppress local inflammation. For example, preclinical studies of CAR-T_{reg} cells directed against antigens such as citrullinated vimentin and type II collagen have shown that these cells can dampen T_H17 responses and joint damage in mouse models of arthritis[135,136]. However, regulatory T cells in RA can exhibit context-dependent plasticity, acquiring T_H17-like features and losing suppressive function within the synovial milieu under the influence of IL-6 and IL-23, which might limit their therapeutic stability in chronic inflammation[137]. By contrast, the innate characteristics of ILCs, such as their rapid effector function, TCR-independent activity and lower risk of inflammatory reprogramming, might provide a more stable platform than CAR-T_{reg} cell approaches for achieving tissue-localized immune regulation in autoimmune arthritis.

Advancing this concept, induced pluripotent stem cell (iPSC)-derived ILC-like cells engineered with CARs could, in principle, be adapted to target citrullinated vimentin, a post-translational neoantigen enriched in the synovial extracellular matrix of patients with RA[138]. Foundational studies have shown that iPSCs can be differentiated into ILC-like cells and further modified to express CARs, establishing a platform capable of generating scalable, antigen-specific regulatory ILC populations[139]. In an RA setting, such CAR-ILC_{reg} cells could be directed to sites of joint inflammation, where these cells would be expected to release suppressive cytokines (such as IL-10 and IL-13) and promote local immune regulation in an antigen-restricted, tissue-resident manner.

Although CAR-ILC therapies remain untested in RA or other autoimmune conditions, the concept represents a promising translational avenue. Future work should prioritize rigorous preclinical assessment in relevant inflammatory models to evaluate safety, phenotypic stability and therapeutic potential.

Conclusions

ILCs have emerged as context-dependent regulators in RA pathogenesis, capable of both sustaining and resolving inflammation. Pathogenic roles are primarily attributed to ILC1s and ILC3s, which produce pro-inflammatory cytokines such as IFNγ and IL-17, thereby exacerbating synovial inflammation. By contrast, ILC2s, particularly those producing IL-10 or IL-13, are increasingly implicated in tissue protection and restoration of immune homeostasis.

Emerging evidence suggests that modulating the balance of ILC subsets could offer therapeutic benefit in RA by tipping immune responses towards tolerance and resolution of inflammation. ILCs could also serve as valuable biomarkers in peripheral blood or synovial fluid, contributing to disease stratification and the monitoring of therapeutic responses. Advances in multi-omics technologies, such as single-cell RNA sequencing and proteomics, are beginning to elucidate subset-specific roles and uncover novel therapeutic targets. Innovative strategies, including the expansion of autologous IL-10-producing ILC2s, the development of iPSC-derived ILCs and the engineering of CAR-expressing ILCs directed against synovial autoantigens, hold considerable promise for next-generation cell therapies. Combining ILC-directed interventions with established DMARDs, such as methotrexate or JAK inhibitors, might further enhance therapeutic efficacy while mitigating systemic toxicity. The incorporation of ILC-targeted strategies into personalized medicine paradigms has the potential to reshape RA treatment; however, successful clinical translation will require a deeper mechanistic insight and rigorous validation in human trials.

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Author contributions

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Is cam morphology a cause of osteoarthritis?

Heerey et al. present a comprehensive review of cam morphology and its proposed role in femoroacetabular impingement syndrome and the development of hip osteoarthritis (Heerey, J. et al. Cam morphology and the development of femoroacetabular impingement syndrome and hip osteoarthritis. *Nat. Rev. Rheumatol.* **22**, 199–212 (2026))[1]. The authors clearly outline the long-standing and consistent observational association between cam morphology and osteoarthritis[2,3], and they highlight important longitudinal evidence demonstrating that incorporating hip shape measures alongside symptoms can improve prediction of individuals most likely to develop osteoarthritis[4].

The temporal nature of the association between cam morphology, which typically arises during adolescence, and hip osteoarthritis, which develops decades later, has led many, including the authors, to infer a causal pathway[1]. This inference underpins the rationale that cam morphology could be an attractive target for surgical interventions aiming to prevent or delay hip osteoarthritis. Yet, to date, the longest randomized controlled trial of surgery (3-year follow-up) has not demonstrated clinically meaningful superiority over physiotherapy, nor evidence of reduced radiographic osteoarthritis progression[5]. This limited benefit, together with the high prevalence of asymptomatic cam morphology[2,6], raises the question: does cam morphology really cause hip osteoarthritis?

Mendelian randomization, which is a genetic form of instrumental variable analysis, provides a way to look at this question[7]. We applied this method in two large UK Biobank studies, using genetic instruments for alpha angle (n = 44,214) and statistical shape modelling (n = 43,485)[8,9]. Neither investigation found strong support for a causal effect of cam morphology on hip osteoarthritis. In fact, we found stronger evidence that a genetic predisposition to osteoarthritis increases the risk of developing cam morphology[8,9]. These findings challenge the central causal hypothesis of Heerey et al.[1], and suggest instead that the relationship between cam morphology and increased risk of hip osteoarthritis might reflect shared mechanistic pathways. Possible candidates include an increased tendency towards bone formation, supported by the genetic associations between cam morphology, risk of hip osteoarthritis and bone-related gene variants[9]. If this explanation is correct, targeting cam morphology with surgery to prevent future hip osteoarthritis is unlikely to be successful.

Our Mendelian randomization analyses were conducted in older populations (mean age 63 years old)[8,9], raising the possibility that some cam morphology in this population reflects secondary shape changes of the femoral head and neck owing to existing osteoarthritis, rather than primary cam morphology[10]. However, the prevalence of cam morphology in these participants, and its cross-sectional associations with symptoms and future total hip replacement, mirrored patterns reported in younger populations, suggesting that cam morphology seen in older adults largely developed at younger ages[2].

To robustly test the causal hypothesis that primary cam morphology leads to hip osteoarthritis, long-term follow-up (≥5–10 years) from existing and future trials of cam-corrective surgery will be essential. Furthermore, even if such evidence were to emerge, further research would be needed to distinguish primary from secondary cam morphology in clinical practice, to avoid directing femoroacetabular impingement-targeted treatments towards patients whose morphology reflects established osteoarthritis rather than its cause.

There is a reply to this letter by Heerey, J. et al. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-026-01374-6 (2026).

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Competing interests

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Reply to 'Is cam morphology a cause of osteoarthritis?'

We thank Faber et al. for their interest in our Review (Heerey, J. et al. Cam morphology and the development of femoroacetabular impingement syndrome and hip osteoarthritis. *Nat. Rev. Rheumatol.* **22**, 199–212 (2026))[1] and for highlighting their recent work[2,3] that raises important questions about the temporal relationship between cam morphology and hip osteoarthritis (OA) (Faber, B. G. et al. Is cam morphology a cause of osteoarthritis? *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-026-01373-7 (2026))[4]. We appreciate their thoughtful engagement with our manuscript, which provides a valuable perspective to the ongoing discussion on this topic.

In our Review[1], we summarized available observational studies conducted across the lifespan and within diverse populations, including patients undergoing surgery for femoroacetabular impingement (FAI) syndrome[5], athletes[6–8] and older adults from the general population[9]. Across this broad body of work, consistent associations have been observed between cam morphology and various stages of the hip OA continuum, including cartilage loss[5,6,8], labral tears[6,7] and radiographic disease[9]. We acknowledge, however, that these studies have not investigated the role of genetic factors in the way that Faber et al.[2,3] have done. Incorporating genetic data could further clarify or modulate the observed relationships. However, any such finding will need to be confirmed across these varying cohorts. An important consideration is that the population studied by Faber et al.[2,3] is generally older (mean age 63.6 years) than other cohorts and could represent individuals who have 'survived' with cam morphology, meaning that shared mechanistic pathways could only apply to this specific older subgroup. Most participants in these studies did not report symptoms (8% reported hip pain lasting more than 3 months) and did not exhibit clinical signs consistent with FAI syndrome, which limits the generalizability of these findings to younger adults — the group most affected by the condition[10].

Faber et al.[4] suggest that the proposed causal link between cam morphology and hip OA underpins the rationale for considering cam morphology an attractive target for surgical interventions to prevent or delay the onset of hip OA. However, we would like to clarify that, in our Review[1], we never referred to hip arthroscopy as a preventive measure for hip OA. Instead, we discussed hip arthroscopy primarily in the context of individuals with FAI syndrome, characterized by both cam morphology and symptoms of impingement. In this context, hip arthroscopy is aimed at improving symptoms and quality of life, and clinical trials have demonstrated its efficacy for FAI syndrome[1]. We do not advocate hip arthroscopy as a preventive option for hip OA, as currently there is insufficient evidence available to support its use for this purpose.

We agree that disentangling the contributions of cam morphology, genetics and hip OA risk in different populations, beyond those undergoing cam-corrective surgery, is a crucial focus for future research. Encouragingly, several international initiatives are already underway to address this issue.

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Competing interests

The authors declare no competing interests.