Gut dysbiosis in rheumatic diseases: A systematic review and meta-analysis of 92 observational studies

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Summary

Background Emerging evidence suggests that dysbiosis in gut microbiota may contribute to the occurrence or development of several rheumatic diseases. Since gut microbiota dysbiosis is potentially modifiable, it has been postulated to be a promising preventive or therapeutic target for rheumatic diseases. However, the current understanding on the potential associations between gut microbiota and rheumatic diseases is still inadequate. Therefore, we aimed to synthesise the accumulating evidence for the relation of gut microbiota to rheumatic diseases.

Methods The PubMed, Embase and Cochrane Library were searched from inception to March 11, 2022 to include observational studies evaluating the associations between gut microbiota and rheumatic diseases. Standardised mean difference (SMD) of α-diversity indices between rheumatic diseases and controls were estimated using random-effects model. β-diversity indices and relative abundance of gut microbes were summarised qualitatively.

Findings Of the included 92 studies (11,998 participants), 68 provided data for α-diversity. Taken together as a whole, decreases in α-diversity indices were consistently found in rheumatic diseases (observed species: SMD = −0.36, [95%CI = −0.63, −0.09]; Chao1: SMD = −0.57, [95%CI = −0.88, −0.26]; Shannon index: SMD = −0.33, [95%CI = −0.48, −0.17]; Simpson index: SMD = −0.32, [95%CI = −0.49, −0.14]). However, when specific rheumatic diseases were examined, decreases were only observed in rheumatoid arthritis (observed species: SMD = −0.51, [95%CI = −0.78, −0.24]; Shannon index: SMD = −0.31, [95%CI = −0.49, −0.13]; Simpson index: SMD = −0.31, [95%CI = −0.54, −0.08]), systemic lupus erythematosus (Chao1: SMD = −1.60, [95%CI = −2.54, −0.66]; Shannon index: SMD = −0.63, [95%CI = −1.08, −0.18]), gout (Simpson index: SMD = −0.64, [95%CI = −1.07, −0.22]) and fibromyalgia (Simpson index: SMD = −0.28, [95%CI = −0.44, −0.11]), whereas an increase was observed in systemic sclerosis (Shannon index: SMD = 1.25, [95%CI = 0.09, 2.41]). Differences with statistical significance in β-diversity were consistently reported in ankylosing spondylitis and IgG4-related diseases. Although little evidence of disease specificity of gut microbes was found, shared alterations of the depletion of anti-inflammatory butyrate-producing microbe (i.e., *Faecalibacterium*) and the enrichment of pro-inflammatory microbe (i.e., *Streptococcus*) were observed in rheumatoid arthritis, Sjögren's syndrome and systemic lupus erythematosus.

Interpretation Gut microbiota dysbiosis was associated with rheumatic diseases, principally with potentially non-specific, shared alterations of microbes.

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Research in context

Evidence before this study

We searched PubMed, Embase and Cochrane Library databases for observational studies evaluating the association between gut microbiota and rheumatic diseases, from inception to March 11, 2022, with no language restrictions. We identified 92 observational studies with inconsistent results on the precise relationship between the human gut microbiota and specific rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, osteoarthritis and Sjögren's syndrome). Several systematic reviews on gut dysbiosis in specific rheumatic diseases have been published. However, these systematic reviews have focused on only one specific rheumatic disease, and thus are not always suitable to answer some research questions. For example, the identification of disease-specific gut microbes, which are consistently enriched or depleted in a rheumatic disease, would shed light on disease diagnostics and phenotyping, a pathway to intervention or therapy, or to address causality. In addition, the identification of non-specific and shared gut microbes across different rheumatic diseases is also important because this knowledge could help us understand potentially shared pathogenesis of multiple rheumatic conditions.

Added value of this study

Through a systematic review and meta-analysis based on 92 observational studies with 11,998 participants spanning 14 rheumatic diseases, we provided comprehensive evidence that gut microbiota dysbiosis were associated with a shared alteration with a depletion of anti-inflammatory butyrate-producing microbe (i.e., *Faecalibacterium*) and an enrichment of pro-inflammatory microbe (i.e., *Streptococcus*) in rheumatic diseases in general. Meanwhile, evidence of distinct disease-specific alterations in gut microbes was sparse.

Implications of all the available evidence

Studies should be interpreted with caution, as many identified microbial associations may be indicative of a shared alteration to multiple rheumatic diseases rather than a disease-specific biological difference. These microbes and their metabolites could also be used as general targets for innovative preventive or therapeutic tools for different rheumatic diseases. In addition, little evidence of distinct disease-specific alterations in gut microbes was evident. This suggests that gut microbes serving as diagnostics for specific rheumatic diseases warrants further studies.

Introduction

The human gut is colonised by a complex microbial ecosystem, collectively called the gut microbiota, which plays a pivotal role in key biological processes such as metabolic interactions and host immune responses.[1–4] The gut microbiota has an association not only with the well-being of human but also with a range of disease conditions, such as obesity, growth disorders, metabolic diseases, and mental illness.[5–9] The emerging evidence in the past decades suggests that dysbiosis in gut microbiota and its impact on the balance between pro- and anti-inflammatory immune responses[10] may contribute to the occurrence or development of several rheumatic diseases, such as rheumatoid arthritis,[11–13] ankylosing spondylitis,[14,15] systemic lupus erythematosus,[16,17] systemic sclerosis,[18,19] Sjogren's syndrome,[20,21] and osteoarthritis.[22,23] Since gut microbiota dysbiosis is potentially modifiable, it has been postulated to be a promising preventive or therapeutic target for rheumatic diseases.[24,25]

However, the current understanding on the potential associations between gut microbiota and rheumatic diseases are far from adequacy.[26,27] For example, there has been a common assumption that high α-diversity (e.g., taxonomic richness and evenness) is desirable for the gut microbial ecosystem[28]; however, results from individual studies with various sample sizes are inconsistent.[29–32] In addition, the identification of disease-specific gut microbes, which are consistently depleted or enriched in disease conditions across different populations with various characteristics, would shed light on disease diagnostics and phenotyping, a pathway to intervention or therapy, or to address causality.[33] Furthermore, the identification of non-specific and shared gut microbes across different rheumatic diseases is also important because this knowledge could help us understand potentially shared pathogenesis of multiple rheumatic conditions.[34] However, these research questions remain unsolved, and individual studies are not always suitable to answer them.

Systematic review and meta-analysis is a powerful approach to synthesise the existing knowledge for the purpose of identifying consistencies across multiple studies, but to our best knowledge, no such research work has been performed yet on gut microbiota alterations across a spectrum of rheumatic diseases. Therefore, our study aimed to synthesise the accumulating evidence on the associations between gut microbiota and multiple rheumatic diseases.

Methods

Protocol

The protocol of study was preregistered with PROSPERO (CRD42021282397). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline[35] was followed.

Search details

Two independent investigators (Wei Li and Haibin Xie) from the research team were responsible for systematic literature search across PubMed, Embase and Cochrane Library databases from inception to March 11, 2022 (see **Appendix 1** for the full electronic search strategy). No restriction was applied, and non-English written articles were translated. For all the finally included articles, their references and related reviews were manually reviewed.

Selection criteria

The same two investigators (Wei Li and Haibin Xie) implemented study selection on an independent basis by firstly screening the titles and abstracts, followed by reviewing the full texts of eligible articles. Disagreements, if any, were resolved by consulting a third investigator (Yilun Wang). Specifically, the inclusion criteria were: (1) applied an observational design (e.g., case-control study, cross-sectional study, and cohort study); (2) performed gut microbiota analysis with available data on diversity or abundance measures; and (3) included participants with a rheumatic disease.

Data extraction

A pre-designed template was used to extract desired information, which was then cross-checked by four investigators (Yilun Wang, Wei Li, Haibin Xie and Ning Wang). The primary outcomes of interest were community-level measures of gut microbiota composition (i.e., α-diversity and β-diversity) and phylum-, family- and genus-level taxonomic findings (i.e., relative abundance). The α-diversity, as a summary of microbial community in individual samples, can be compared among multiple groups to assess the richness (i.e., number of taxa) and evenness (i.e., how well each taxon is represented) in the sample.[36] The β-diversity can be used to measure the inter-sample diversity that assesses the phylogenetic structure of communities in comparison with other samples analysed. In addition, other information including publication details, participant demographics and methodology was also extracted.

Quality assessment

The methodological quality of included studies was examined by two reviewers (Wei Li and Haibin Xie) independently based on the Newcastle–Ottawa Scale (NOS). Any disagreement in quality scoring would be resolved by mutual discussion as far as possible; if failed, the first author (Yilun Wang) would make the final verdict. The NOS is a quality assessment approach for observational studies based on three criteria: selection, comparability, and outcome. Under recommendation by the Cochrane Collaboration, it has been widely adopted to assess the quality and bias of systematic reviews and meta-analyses.[37] A total NOS score of ≤ 5 was considered low quality, 6 or 7 was considered moderate quality, and 8 or 9 was considered high quality.[38]

Statistics

Quantitative synthesis. We performed a meta-analysis on the differences in α-diversity (e.g., observed species, Chao1, abundance coverage estimator, incidence coverage estimator, Pielou, Shannon index, Simpson index, inverse Simpson index, and faith phylogenetic diversity) between patients with rheumatic diseases and individuals without rheumatic diseases (i.e., controls) in terms of the indices with data available in at least 10 studies.[36] The pooled standardised mean difference (SMD) and its 95% confidence interval (CI) were computed for each index through inverse-variance random-effects meta-analysis. The effect size was categorised as trivial ($SMD \leq 0.2$), small ($0.2 < SMD < 0.5$), moderate ($0.5 \leq SMD < 0.8$), or large ($SMD \geq 0.8$).[36] Medians and inter-quartile ranges were converted to means and standard deviations (SD).[39] Where necessary, numerical data was extracted from graphs using WebPlotDigitizer V.4.42. The inter-study heterogeneity was quantified by the DerSimonian-Laird estimator, and was interpreted based on the I^2 statistic ($I^2 > 50\%$ was considered heterogeneous).[40] Publication bias was examined by funnel plots and Egger's test.

As part of our meta-analysis, three subgroup analyses were performed, which were stratified by the specific type of rheumatic disease, the regional distribution of study populations (i.e., Eastern countries versus Western countries), and the administration of antirheumatic medication (i.e., on treatment versus treatment naÿve), respectively. While grouping the participants from Eastern and Western countries, typical lifestyle and diet habit were considered to control for geographical differences in genetics and diet. More specifically, Eastern countries were defined as countries or regions in East and South Asia, whereas western countries referred to those in Europe, North America, Oceania and Middle East. A study with ≥80% of the patients receiving antirheumatic medications (e.g., nonsteroidal anti-inflammatory drugs and disease-modifying anti-inflammatory drugs) was considered a study with patients on treatment.[36] Further, two sensitivity analyses were conducted to evaluate the robustness of findings by removing low-quality studies ($NOS \leq 5$) and those with

no matching of any variable, since such studies were susceptible to confounding bias (e.g., age, sex and body mass index).

All analyses were conducted in Review Manager V.5.2 (RevMan V.5.2, The Cochrane Collaboration, Oxford, UK) and STATA V.11.0 (StataCorp LP). *P* values less than 0.05 were considered statistically significant.

Qualitative synthesis. Differences in β-diversity between patients with rheumatic diseases and controls were summarised in a qualitative manner. A consistently different β-diversity was defined as that all included studies for a specific disease reported significant differences in β-diversity between patients and controls. To confirm disease-specific and shared alterations, we firstly summarised within disease findings for each microbe reported by at least two studies.[36] Then, we categorised those microbes using the following rules[36]: (1) the microbes were labelled as increased, decreased, or "not consistent" in patients with rheumatic disease versus the control group; (2) a "not consistent" finding was defined as any finding with < 75% agreement among studies reporting this microbe; (3) a consistent finding among three or more studies (from at least two research groups) was considered potentially associated with the disease, whereas a consistent finding between only two studies was deemed worth future verification; (4) a microbe was regarded as a candidate for disease-specific alteration if it was altered (in a consistent direction) in one disease only; (5) a shift replicated across at least three rheumatic diseases was considered a shared alteration.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Ethics

Since no private or confidential patient data will be contained in the reporting, approval from an ethics committee is not required.

Results

Search results

A total of 2,741 articles were preliminarily retrieved from the database search, and 92 studies across 14 rheumatic diseases were included (**Appendix 2**). The most researched disease was rheumatoid arthritis, followed by systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, osteoarthritis and Sjögren's syndrome. Regarding individual diagnoses, the total number of included participants varied from 77 (psoriatic arthritis) to 2,184 (rheumatoid arthritis), the mean age ranged from 2.6 (Kawasaki disease) to 63.7 (osteoarthritis) years, and the percentage of females ranged from 4.1% (gout) to 95% (fibromyalgia) (Table 1).

Characteristics of included studies

Characteristics of included studies are presented in **Appendix 3**. Slightly over half of the studies (53 [57.6%]) were carried out in Eastern countries, 38 (41.3%) in Western countries, and only 1 (1.1%) in Africa. Medication usage varied substantially, with 25 studies (27.2%) performed in medication-free or drug-naive groups, 9 studies (9.8%) in groups on treatment, and the remainder not controlling for this, resulting in anywhere between 13.0% and 89.7% of patients receiving medication. The methodology of stool processing (**Appendix 4**) and composition analysis (**Appendix 5**) also varied remarkably, with 16S ribosomal RNA (rRNA) sequencing being most commonly adopted (75 studies [81.5%]), followed by shotgun metagenomics (13 studies [14.1%]), quantitative polymerase chain reaction or real-time quantitative polymerase chain reaction (3 studies [3.3%]), and GA-map Dysbiosis test (1 study [1.1%]). Matching-variables between patients and controls in each included study are listed in **Appendix 3**. A total of 21 studies did not match any variable. The NOS of the included studies ranged from 2–8 (**Appendix 6**). According to the total NOS score, 31 of the included studies were rated as low quality, 54 were rated as moderate quality, and 7 were rated as high quality.

α-diversity

Sixty-eight studies provided data for α-diversity, which was then assessed by 7 indices, namely estimates of richness (observed species, Chao1, abundance coverage estimator), evenness (Pielou), richness/evenness (Shannon, Simpson), and biodiversity (Faith phylogenetic diversity). Among them, 4 indices with sufficient studies ($n \geq 10$) (i.e., observed species, Chao1, Shannon index and Simpson index) were included in the meta-analysis. No evidence of publication bias was found in any analysis (**Appendix 7**).

As for the richness, 26 studies reported data on observed species in patients with rheumatic diseases ($n = 1{,}311$) versus controls ($n = 994$). Taken together as a whole, the pooled estimate indicated a significant decrease of gut microbiome richness in the patients with rheumatic diseases versus controls, though showing a small effect size (SMD = −0.36, [95%CI = −0.63, −0.09], $P = 0.01$; inverse-variance, random-effects) and high heterogeneity ($I^2 = 88\%$). When specific diseases were examined, a significant decrease of gut microbiome richness was observed only in rheumatoid arthritis (SMD = −0.51, [95%CI = −0.78, −0.24], $P < 0.001$, $I^2 = 65\%$; inverse-variance, random-effects) (Figure 1a). Thirty studies reported data on Chao1 in patients with

Disorder	Included studies	Number of participants	Mean age	Female ratio
Rheumatoid arthritis	21	2,184	45.3	58.6
Systemic lupus erythematosus	15	2,040	40.4	70.8
Ankylosing spondylitis	13	1,214	41.4	34.3
Systemic sclerosis	9	765	54.8	77.5
Osteoarthritis	7	1,887	63.7	62.3
Sjögren's syndrome	6	1,176	51.9	58.4
Gout	5	402	43.8	4.1
Juvenile idiopathic arthritis	5	490	9.0	55.0
Behcet's disease	4	217	42.4	69.8
Fibromyalgia	4	2,141	60.2	95.0
IgG4-related diseases	2	321	55.5	56.5
Kawasaki disease	2	154	2.6	47.9
Psoriatic arthritis	2	77	44.1	64.9
Microscopic polyangiitis	1	105	60.0	NA

***Table 1*: Summary characteristics of the included studies by rheumatic diseases.**
NA, not available.

rheumatic diseases (n = 1,495) versus controls (n = 3,244). The pooled estimate for combined rheumatic diseases indicated a significant decrease versus controls with a moderate effect size (SMD = −0.57, [95%CI = −0.88, −0.26], P < 0.001, I^2 = 93%; inverse-variance, random-effects), but individually, a significant decrease was found only in systemic lupus erythematosus (SMD = −1.60, [95%CI = −2.54, −0.66], P < 0.001, I^2 = 94%; inverse-variance, random-effects) (Figure 1b).

As for the richness/evenness, 58 studies reported the Shannon index in patients with rheumatic diseases (n = 2,893) versus controls (n = 7,444). A significant decrease in the combined rheumatic diseases with a small effect size (SMD = −0.33, [95%CI = −0.48, −0.17], P < 0.001; inverse-variance, random-effects) but high heterogeneity (I^2 = 87%) was found by pooling the data during meta-analysis. However, when specific diseases were examined, there was a significant decrease in rheumatoid arthritis (SMD = −0.31, [95%CI = −0.49, −0.13], P < 0.001, I^2 = 63%; inverse-variance, random-effects) and systemic lupus erythematosus (SMD = −0.63, [95%CI = −1.08, −0.18], P = 0.007, I^2 = 82%; inverse-variance, random-effects); and there was a significant increase in systemic sclerosis (SMD = 1.25, [95%CI = 0.09, 2.41], P = 0.03, I^2 = 96%; inverse-variance, random-effects) (Figure 2a). Twenty-seven studies reported the Simpson index (n = 1,460 patients; n = 2,903 controls), and the pooled effect size indicated a significant decrease in the combined rheumatic diseases with a small effect size (SMD = −0.32, [95%CI = −0.49, −0.14], P < 0.001, I^2 = 79%; inverse-variance, random-effects). When the associations between gut microbiome richness/evenness and specific rheumatic diseases were assessed, a significant decrease in gut microbiome richness/evenness was observed only in rheumatoid arthritis (SMD = −0.31, [95%CI = −0.54, −0.08], P = 0.007, I^2 = 48%; inverse-variance, random-effects), gout (SMD = −0.64, [95%CI = −1.07, −0.22], P = 0.003, I^2 = 69%; inverse-variance, random-effects), and fibromyalgia (SMD = −0.28, [95%CI = −0.44, −0.11], P = 0.001, I^2 = 0%; inverse-variance, random-effects) (Figure 2b).

We further conducted subgroup analyses according to the regional distribution of the included participants for the purpose of understanding the sources of inter-study heterogeneity. Most of the α-diversity indices showed a decrease in patients from Eastern countries only rather than those from Western countries. Substantial heterogeneity, however, was still observed (I^2 ranged from 62 to 95%) (**Appendix 8**). Then, we also compared results from medication-free or drug-naïve studies with those from studies with patients on treatment (≥ 80% of the patients receiving medications) (**Appendix 9**). Decreases in α-diversity indices were mainly seen in studies where patients did not receive any treatment. Heterogeneity of the Simpson index was substantially reduced, and the SMD did not vary significantly in studies with patients on treatment (SMD = −0.61, [95%CI = −0.84, −0.37], P < 0.001, I^2 = 0%; inverse-variance, random-effects). In addition, sensitivity analyses were performed by removing low-quality studies (**Appendix 10**) and those with no matching of any variable (**Appendix 11**), and all α-diversity indices were still significantly decreased in patients with rheumatic diseases versus controls. However, substantial heterogeneity still existed (I^2 ranged from 76 to 94%).

β-diversity

The comparison of β-diversity between patients with rheumatic diseases and controls was conducted in 64 studies (Figure 3). More than half of the studies in 7 rheumatic diseases (i.e., rheumatoid arthritis, systemic

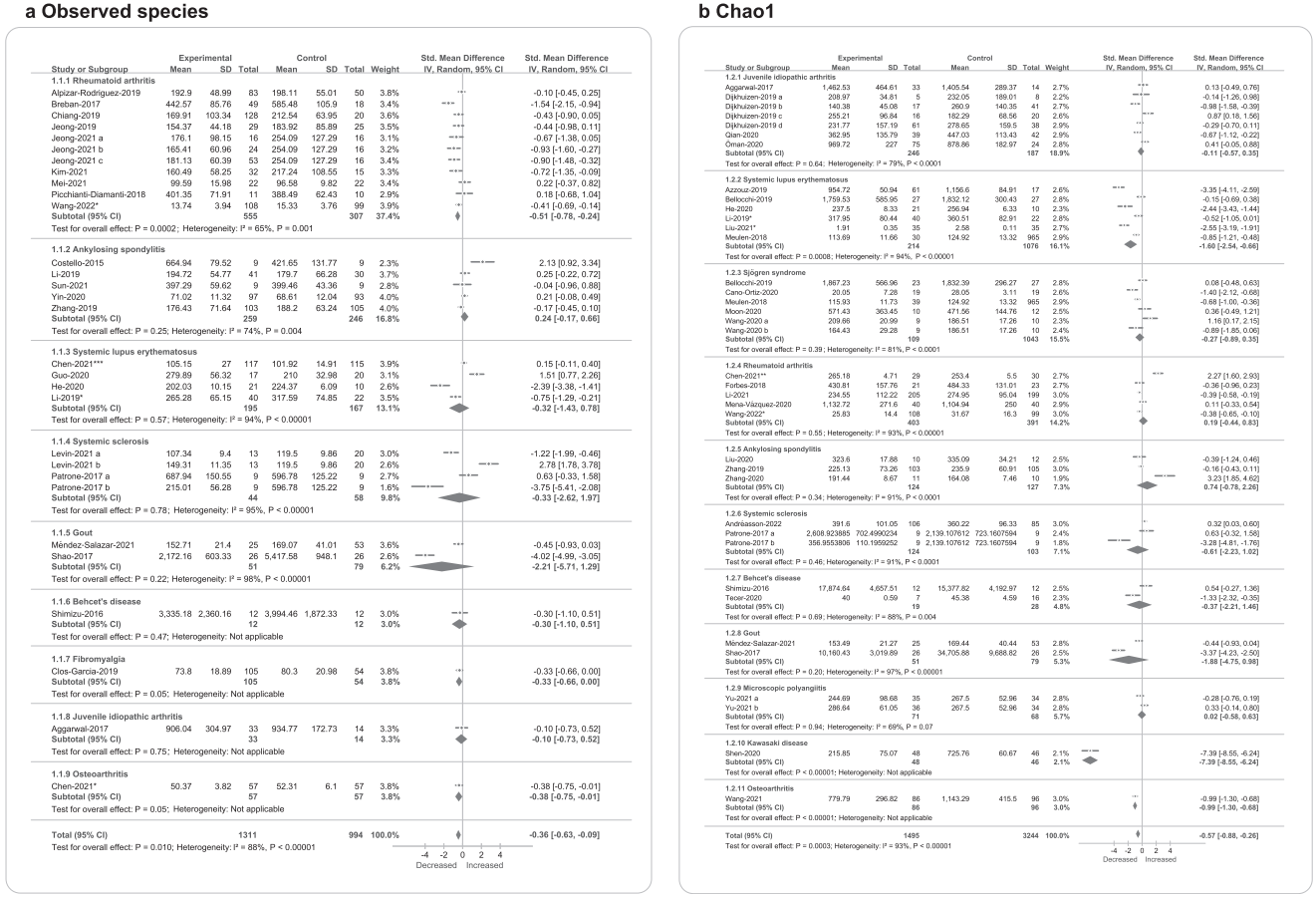

Figure 1. Forest plots of α-diversity richness estimators in the gut microbiota of patients with rheumatic diseases compared with healthy controls. Panel a. Observed species in patients with rheumatic diseases versus controls (n = 1,311 versus n = 994, P=0.01; inverse-variance, random-effects). Panel b. Chao 1 in patients with rheumatic diseases versus controls (n = 1,495 versus n = 3,244, $P < 0.001$; inverse-variance, random-effects). SD, standard deviation; CI, confidence interval.

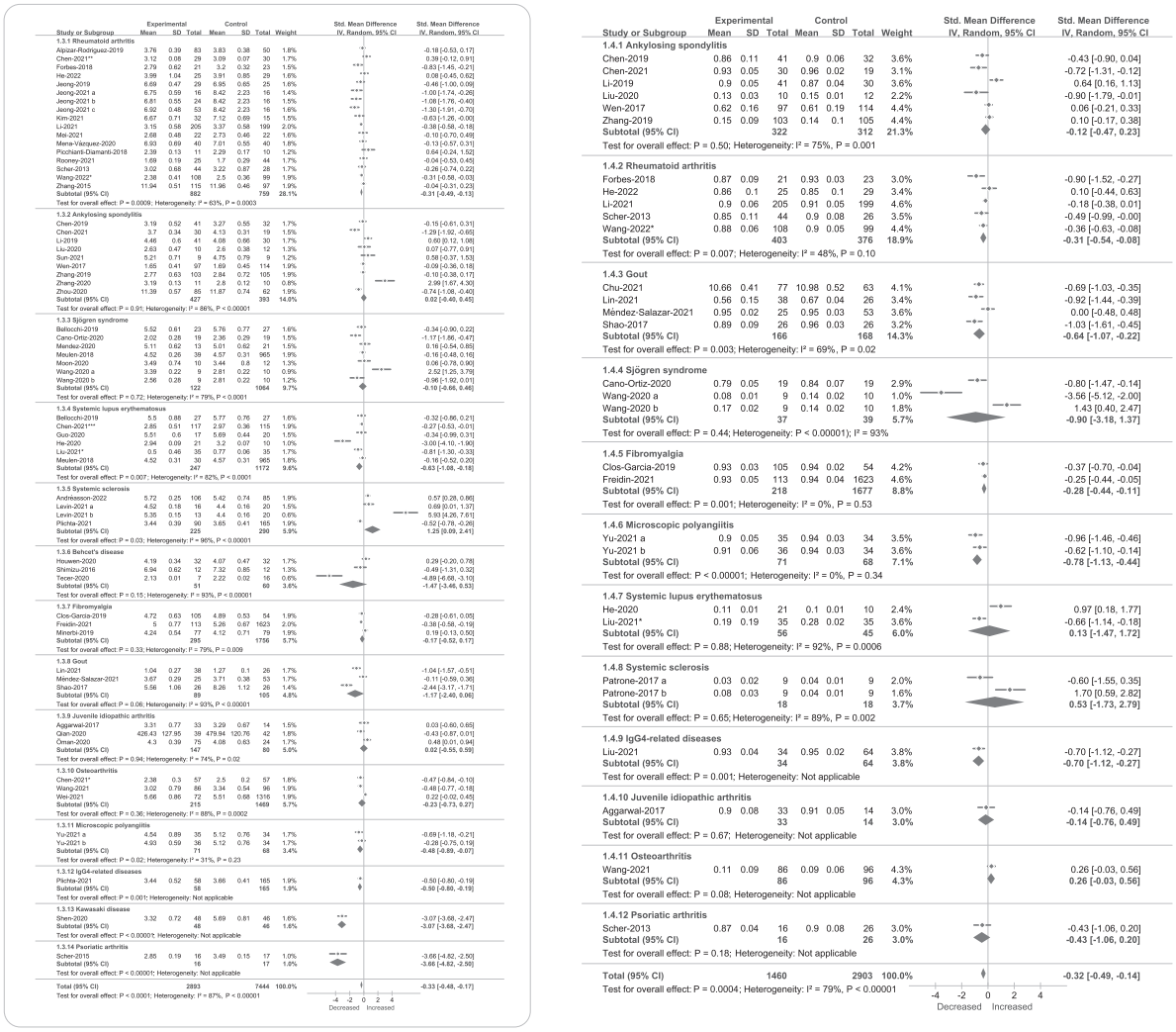

Figure 2. Forest plots of α-diversity richness/evenness in the gut microbiota of patients with rheumatic diseases compared with healthy controls. Panel a. Shannon index in patients with rheumatic diseases versus controls (n = 2,893 versus n = 7,444, $P < 0.001$; inverse-variance, random-effects). Panel b. Simpson index in patients with rheumatic diseases versus controls (n = 1,460 versus n = 2,903, $P < 0.001$; inverse-variance, random-effects). SD, standard deviation; CI, confidence interval.

Figure 3. β-diversity comparison between patients with rheumatic diseases and healthy controls. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; AS, ankylosing spondylitis; SS, systemic sclerosis; JIA, juvenile idiopathic arthritis; OA, osteoarthritis; FM, fibromyalgia; KD, Kawasaki disease; MPA, microscopic polyangiitis; PsA, psoriatic arthritis; IgG4-D, IgG4-related diseases; BD, Behcet's disease; SjS, Sjögren's syndrome.

lupus erythematosus, systemic sclerosis, ankylosing spondylitis, gout, Sjögren's syndrome and IgG4-related diseases) reported significant difference of β-diversity. Among these diseases, consistently different β-diversity was only reported in ankylosing spondylitis and IgG4-related diseases.

Differentially abundant microbes

Seventy-four studies examined the relative abundance of gut microbes in patients with rheumatic diseases versus controls at phylum, family, or genus levels. Differences spanning 11 phyla, 23 families, and 112 genera were observed. The study-level findings can be found in **Appendix 12** and **Supplementary Tables 1–3**.

Figure 4 summarises the within and across rheumatic disease comparison for the microbes reported by two or more studies. A high within disease inconsistency was observed, and most of the consistent within disease changes were replicated by only 2 studies, suggesting that there is little evidence for disease-specific alteration regarding relative abundance of gut microbes. Instead, our findings indicate a shared alteration across multiple rheumatic diseases for certain microbes. The most consistent changes were the enrichment of *Streptococcus* in ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus and systemic sclerosis (20 of 21 studies reported this genus) and *Lactobacillus* in ankylosing spondylitis, systemic lupus erythematosus and systemic sclerosis (11 of 11 studies). We also observed the depletion of *Faecalibacterium* in rheumatoid arthritis, Sjögren's syndrome and systemic lupus erythematosus (8 of 9 studies).

Discussion

This study assessed gut microbiota alterations across a spectrum of rheumatic diseases through a systematic review and meta-analysis. The main findings were: (1) small to moderate decreases in α-diversity indices were found consistently in rheumatic diseases taken as a whole. When specific rheumatic diseases were examined, decreases in α-diversity were only observed in rheumatoid arthritis, systemic lupus erythematosus, gout, and fibromyalgia; whereas an increase was observed in systemic sclerosis; (2) significant differences of β-diversity were frequently reported in a qualitative manner but only consistently in ankylosing spondylitis and IgG4-related diseases; (3) patients with rheumatoid arthritis, Sjögren's syndrome and systemic lupus erythematosus shared the alterations of the depletion of anti-inflammatory butyrate-producing microbe (i.e., *Faecalibacterium*) and the enrichment of pro-inflammatory microbe (i.e., *Streptococcus*); (4) whenever gut microbes merited specificity, these alterations were weakly reproduced, suggesting that disease-specific alterations remain uncertain and thus need further verification.

A meta-analysis which included 28 case-control gut microbiome studies involving 10 diseases (i.e., diarrhea, colorectal cancer, inflammatory bowel disease, obesity, human immunodeficiency virus, autism spectrum disorder, type I diabetes, liver diseases, arthritis, Parkinson's disease) indicated that many associations were likely to be non-disease-specific but rather part of a non-specific, shared alteration to health and disease.[34] Several systematic reviews on gut dysbiosis in specific rheumatic diseases have been published.[41–44] Of these, Chu et al. analysed 26 case-control studies and found that either decreased or unchanged α-diversity was commonly seen in patients with rheumatoid arthritis, and the depletion of genus *Faecalibacterium* was also reported frequently in such patients.[43] The review by Wang et al., including 14 case-control studies, reported a remarkably increased α-diversity in patients with ankylosing spondylitis, accompanied by increased amounts of genus *Dialister* and *Streptococcus* as well as decreased amounts of genus *Parasutterella*.[44] The remaining two reviews concluded that the gut microbiota in patients with psoriatic arthritis[42] and fibromyalgia[41] was different from that in controls, but the findings were heterogeneous. In our study, we included 92 observational studies spanning 14 rheumatic diseases and revealed that gut microbiota dysbiosis was associated with rheumatic diseases in general with predominantly non-specific, shared alterations of microbes.

While it is challenging to establish the causal relationship between gut dysbiosis and the risk of rheumatic diseases based on case-control studies or cross-sectional studies,[10] experimental evidence indicated that gut dysbiosis could lead to changes in systemic immune responses, loss of tolerance and development of autoimmunity.[45–47] Data derived from animal models,[48] results obtained from patients with early-stage diseases,[49] and findings generated from causal analytical approaches (e.g., Mendelian randomization and polygenic risk score)[50,51] also suggested that gut dysbiosis might precede the onset of disease and somehow act as a concealed trigger for systemic inflammation.

The biological mechanisms linking gut dysbiosis to systemic inflammation have been postulated. The gut epithelial cells can form a dynamic physical barrier to strictly control antigen trafficking through paracellular pathways. However, the barrier integrity of the gut may be breached by zonulin production following the development of gut dysbiosis, causing disassembly of tight junction proteins.[52–54] This phenomenon had been reported in patients with rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus and other rheumatic diseases.[48,55–59] Abnormal gut barrier function may result in increased epithelial permeability, allowing microbial fragments and products to enter the sub-epithelial space and lamina propria.[60] Upon

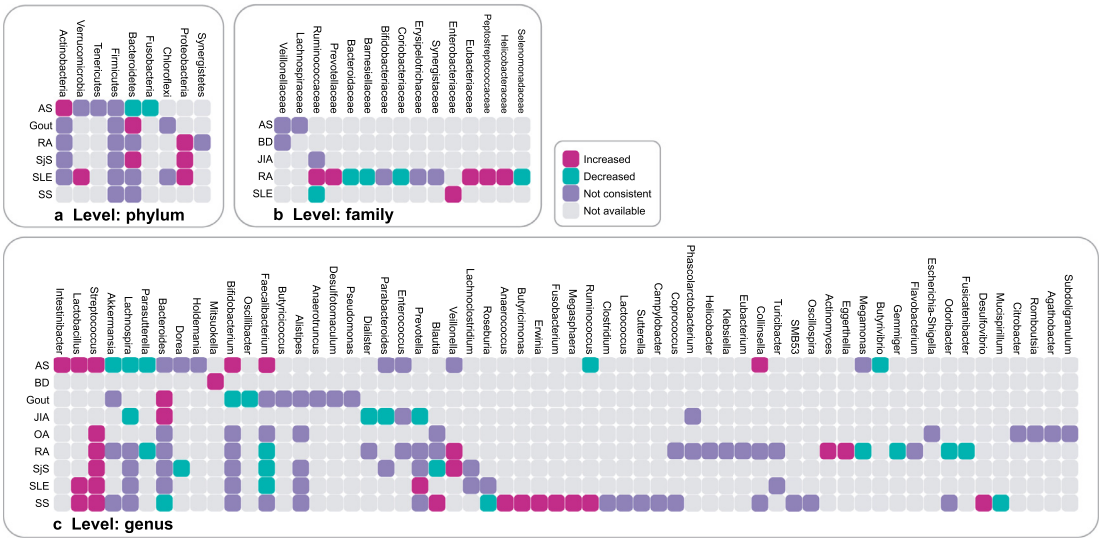

Figure 4. Changes in relative abundance of microbes reported by at least two studies from a diagnostic category. AS, ankylosing spondylitis; BD, Behcet's disease; JIA, juvenile idiopathic arthritis; OA, osteoarthritis; RA, rheumatoid arthritis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SS, systemic sclerosis.

binding to specific receptors of antigen-presenting cells, these molecules will activate pro-inflammatory T cells (including T helper 1 and T helper 17 cells), thus inducing B cells to differentiate into autoantibody-producing plasma cells. At the same time, under the condition of protective molecules, the anti-inflammatory pathway will be activated, and the regulatory T cells will be polarized afterwards.[61] These immune cells primed in the gut can traffic to other organs and tissues.[48,62,63] For example, the synovium of patients with rheumatoid arthritis contains T cells in expression of the gut homing receptor $\alpha E\beta 7$ integrin.[64] Once trafficking to target organs or tissues, the immune cells and their products will activate macrophages, release pro-inflammatory cytokines, or inactivate the inflammatory pathway by producing anti-inflammatory cytokines.[10] Taken together, in case that pathobiont microbes occupy a predominant position, a persistent chronic inflammatory condition will be likely to induce the occurrence or development of rheumatic diseases.[27]

Short-chain fatty acids (SCFAs), which are generated by the bacterial metabolism of dietary elements, exert a direct function of immunomodulation.[65] Studies have found that SCFAs have an effect on both anti-inflammation and promoting bone formation, through which they could reduce the risk or improve the prognosis of rheumatic diseases including rheumatoid arthritis, gout and ankylosing spondylitis.[66–71] It has been established that *Faecalibacterium* possesses anti-inflammatory properties[72] and will be depleted in some immune-mediated inflammatory diseases (e.g., Crohn's disease and inflammatory bowel disease).[73,74] Such associations may be mediated by the SCFA butyrate, as *Faecalibacterium* plays a role in its production.[75] Butyrate is critically involved in maintaining the mucosal integrity, alleviating inflammation (through the macrophage function and a decrease in proinflammatory cytokines), and increasing anti-inflammatory mediators.[75–77] Also the well-known pro-inflammatory microbe *Streptococcus* has been linked to inflammatory pain disorders, such as osteomyelitis,[78,79] rheumatic fever[80,81] and post-streptococcal reactive arthritis.[82,83] Metabolites and membrane vesicles produced by *Streptococcus* can penetrate the gut-blood barrier and enter the general circulation so as to activate macrophages to pro-inflammatory macrophages; this may trigger a systemic inflammatory status at a low grade, causing or exacerbating the inflammation and damage to human body.[84] Interestingly, we observed that *Lactobacillus*, classically considered as a beneficial commensal genus and inversely related to inflammatory states,[85] was also enriched across multiple rheumatic diseases. This phenomenon might be explained by the activation of different components of the immune response in rheumatic diseases by species from this genus.[86]

We provided comprehensive evidence by assessing gut microbiota alterations across a wide range of rheumatic diseases through a systematic review and meta-analysis including 92 observational studies with 11,998 participants. Our results showed a comprehensive overview of current evidence regarding the microbial diversity, disease-specific and shared alterations of gut microbes. In addition, all included studies were human observational studies, so the results may have implications of clinical relevance. However, limitations of this study should also be sincerely pointed out. Firstly, most of the included studies were of a modest sample size;

thus, our analyses might still be underpowered and preliminary, and require further verification with studies of larger sample sizes. Secondly, substantial heterogeneity was observed in the meta-analysis. When more evidence becomes available, additional analyses are required to identify the sources of heterogeneity. For example, there is evidence that microbial composition varied in different disease statuses (active versus inactive)[87] and durations (i.e., newly diagnosed versus previously diagnosed).[88] Thirdly, this study aimed to examined the gut microbial composition rather than its function, whereas previous evidence implied that functional potentials related to rheumatic diseases, such as SCFAs synthesis,[89] tryptophan and lipoprotein metabolism, may be important in pathogenesis.[90,91] In view of the noted functional redundancy,[92] the role of gut microbiota in rheumatic diseases should be further elucidated by functional analysis. Fourthly, our qualitative summary of gut microbes may suffer from different computational pipelines that were used to analyse the microbiome community. When more published raw data become available, future meta-analyses using standard processing and analysis methods are warranted to compare gut microbes across different studies. Finally, the gut microbiota among most of the included studies was profiled by 16s rRNA gene sequencing. This technique is not capable of pinpointing any specific microbial species and strains, so it is still not clear whether the species or strains of *Faecalibacterium, Streptococcus* or *Lactobacillus* are shared across rheumatic diseases. Thus, further metagenomic studies are expected to identify the specific species or strains of these genera.

Sufficient microbial diversity lays the foundation in creating good adaptability and enhanced resistibility for the gut microbiota in case of environmental challenges. Reduced diversity may provide a favourable condition for the emergence of pathogenic microbes, which can disrupt the gut barrier and promote the production of inflammatory mediators through mucosal epithelial cells in the intestinal lamina propria and mesenteric lymph nodes.[93] Our meta-analysis revealed that α-diversity was significantly reduced in patients with rheumatic diseases, which provides a helpful framework to form hypotheses for further studies on the associations between rheumatic diseases and gut microbiota. Since the results were mainly driven by studies from Eastern countries, it might be necessary to distinguish the Eastern microbiota from other Western nations as new evidence becomes available. Also, decrease of the α-diversity indices was mainly seen in studies where patients did not receive any treatments, suggesting that decreased microbial diversity in rheumatic diseases may be relieved by antirheumatic treatment.[13,54] However, when specific rheumatic diseases were examined, decrease in microbial diversity was only observed in rheumatoid arthritis, systemic lupus erythematosus, gout and fibromyalgia. It is worth noting that a significant increase, meanwhile, was observed in systemic sclerosis. This surprising finding suggests a more heterogenic gut microbial compositional profile in patients with this disease.

We also found that alterations in some microbes (i.e., *Faecalibacterium, Lactobacillus, Streptococcus*) may be associated consistently with multiple rheumatic diseases. This suggests that many identified microbial associations might indicate a shared alteration to multiple rheumatic diseases rather than a disease-specific biological difference, so the included studies should be interpreted cautiously. These microbes and their metabolites could also be used as general targets for innovative preventive or therapeutic tools for different rheumatic diseases. Finally, little evidence of distinct disease-specific alterations in gut microbes was evident. This suggests that gut microbes serving as diagnostics for specific rheumatic diseases warrants further investigations.

In conclusion, gut microbiota dysbiosis was associated with rheumatic diseases, principally with potentially non-specific, shared alterations of microbes.

Contributors

Chao Zeng and Guanghua Lei had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Chao Zeng, Guanghua Lei, Yilun Wang and Jie Wei. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Yilun Wang, Jie Wei, Chao Zeng and Guanghua Lei. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Yilun Wang and Jie Wei. Obtained funding: Chao Zeng, Guanghua Lei and Jie Wei. Administrative, technical, or material support: Chao Zeng and Guanghua Lei. Supervision: Chao Zeng and Guanghua Lei. All authors have read, provided critical feedback on intellectual content and approved the final manuscript. The interpretation of these data is the sole responsibility of the authors.

Declaration of interests

No conflict of interest for any of the authors.

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Data sharing statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104055.

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