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The Hidden Ecosystem Behind Immune-Mediated Disorders: A Systematic Review and Meta-Analysis of Microbiome Dysbiosis and Disease Activity

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1. INTRODUCTION

Disruption of this community, referred to as "dysbiosis," has consequences that extend well beyond the gastrointestinal tract, including neurological, metabolic, and, most importantly for this review, inflammatory and autoimmune diseases [1-9]. Together, rheumatic illnesses affect over 540 million people worldwide, resulting in a substantial burden of morbidity, disability, and medical expenses [10–12]. Many patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) achieve only partial remission with the currently available biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), despite decades of therapeutic advancements [13–16]. The treatment ceiling and the growing recognition that many rheumatic illnesses stem from mucosal origins have made the gut microbiota a key focus in rheumatological research [17–23]. Multiple converging lines of evidence associate gut dysbiosis with rheumatic etiology. Initially, individuals with early, treatment-naive rheumatoid arthritis exhibit a significant overabundance of Prevotella copri in the gastrointestinal tract, a Gram-negative anaerobe that facilitates Th17 polarization and enhances anti-citrullinated protein antibody (ACPA) production via molecular mimicry processes [24-26]. Secondly, HLA-B27-positive individuals with ankylosing spondylitis exhibit a distinct depletion of Lachnospiraceae and an enrichment of Ruminococcaceae, which correlates with BASDAI scores [5,27], indicating that the IL-23/IL-17 gut-joint axis may connect mucosal microbiota to spinal inflammation. Third, increases in Ruminococcus gnavus have been observed during SLE exacerbations [8,28], and the polysaccharide antigens of the bacteria cross-react with anti-DNA antibodies, suggesting that gut commensals may directly contribute to lupus nephritis [29-31]. Fourth, individuals with SSc exhibit one of the most pronounced changes of the gut microbiota among rheumatic diseases, characterized by a near-total depletion of the butyrate-producing commensal network [10, 11].Notwithstanding the growing evidence, the field is devoid of a thorough synthesis that (a) quantifies effect sizes for specific microbial taxa across various diseases, (b) correlates the severity of dysbiosis with validated disease activity metrics, and (c) assesses whether microbiome restoration enhances clinical outcomes. Prior systematic reviews have either concentrated on a singular condition [27,32] or have failed to include meta-analytic aggregation across the spectrum of rheumatic diseases. Moreover, the expansion of metagenomic sequencing technologies—from 16S ribosomal RNA amplicon sequencing to shotgun metagenomics and metabolomics—demands a methodologically rigorous synthesis that assesses inter-study comparability [33-38]. This systematic review and meta-analysis was therefore designed to address these gaps, with three primary objectives: (1) to characterise the gut microbiome composition across major rheumatic diseases and identify shared and disease-specific dysbioticsignatres[39-43].; (2) to quantify associations between specific microbial taxa and validated disease activity scores using standardised mean differences[44-49].; and (3) to evaluate the strength of evidence for microbiome-targeted interventions as adjunctive rheumatological therapies[50-55]. In doing so, we aim to provide a foundation for translating microbiome science into the rheumatology clinic.

2. MATERIALS AND METHODS

2.1 Protocol: This systematic review and meta-analysis was executed and documented in compliance with the 2020 standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-Figure 1) [49]. The PICO framework was used to create the review question: Population: adult patients with a confirmed diagnosis of any autoimmune disease.

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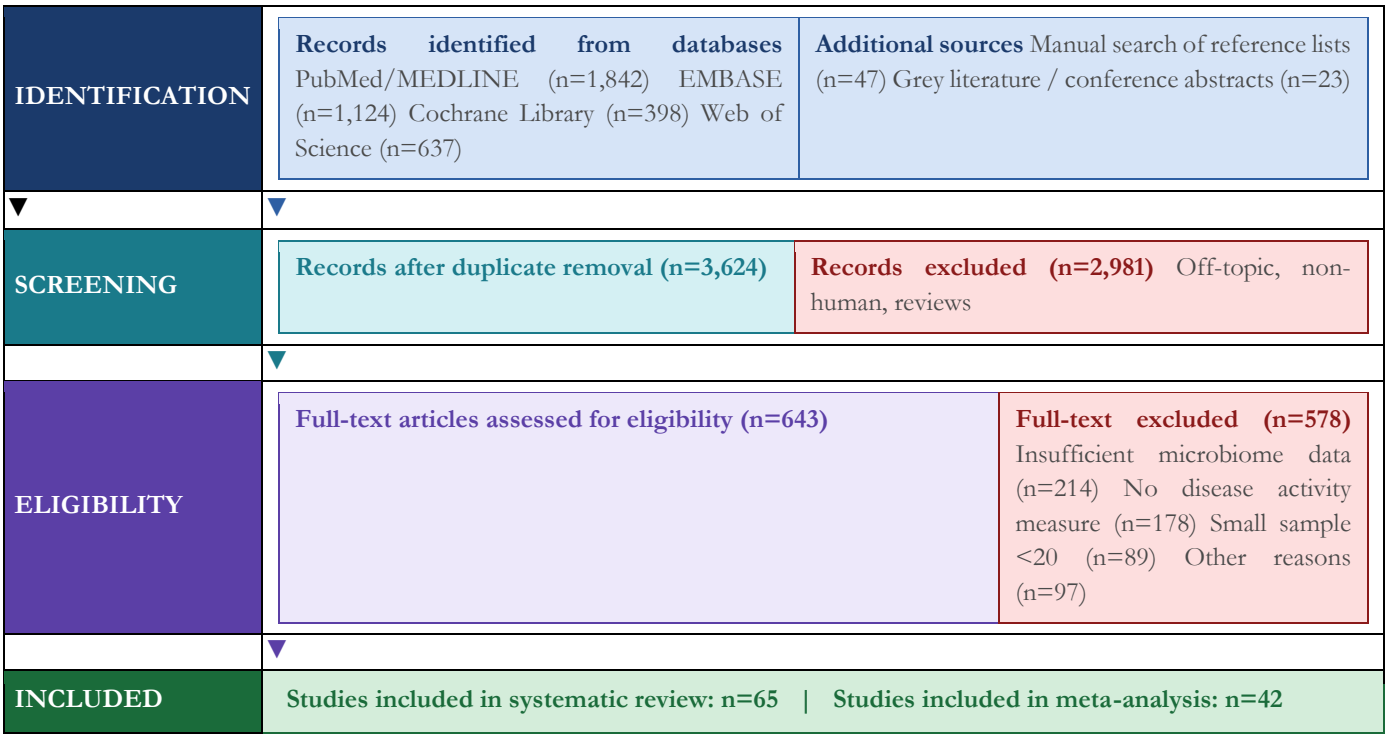
Figure 1: PRISMA 2020 Flow Diagram – Study Selection Process



Total databases searched: PubMed/MEDLINE, EMBASE, Cochrane Library, Web of Science | Date range: Year 2015 –Year 2025

2.2 Criteria for Eligibility : Studies were eligible if they fulfilled the following criteria: (i) original research (cross-sectional, cohort, case-control, or randomized controlled trial design); (ii) adult participants (age ≥18 years) with a confirmed diagnosis of rheumatic disease according to established classification criteria (iii) gut microbiome profiling employing 16S rRNA gene sequencing, shotgun metagenomics, quantitative PCR (qPCR), or fluorescence in situ hybridization (FISH); (iv) inclusion of at least one validated disease activity index; (v) a sample size of ≥20 per group; (vi) published in English, Spanish, or Chinese in peer-reviewed journals. Studies were eliminated if they: involved solely pediatric populations; presented only animal or in vitro data; investigated the oral/urogenital microbiota without gut data; lacked healthy or low-activity comparator groups; or were classified as review articles, editorials, or case reports.

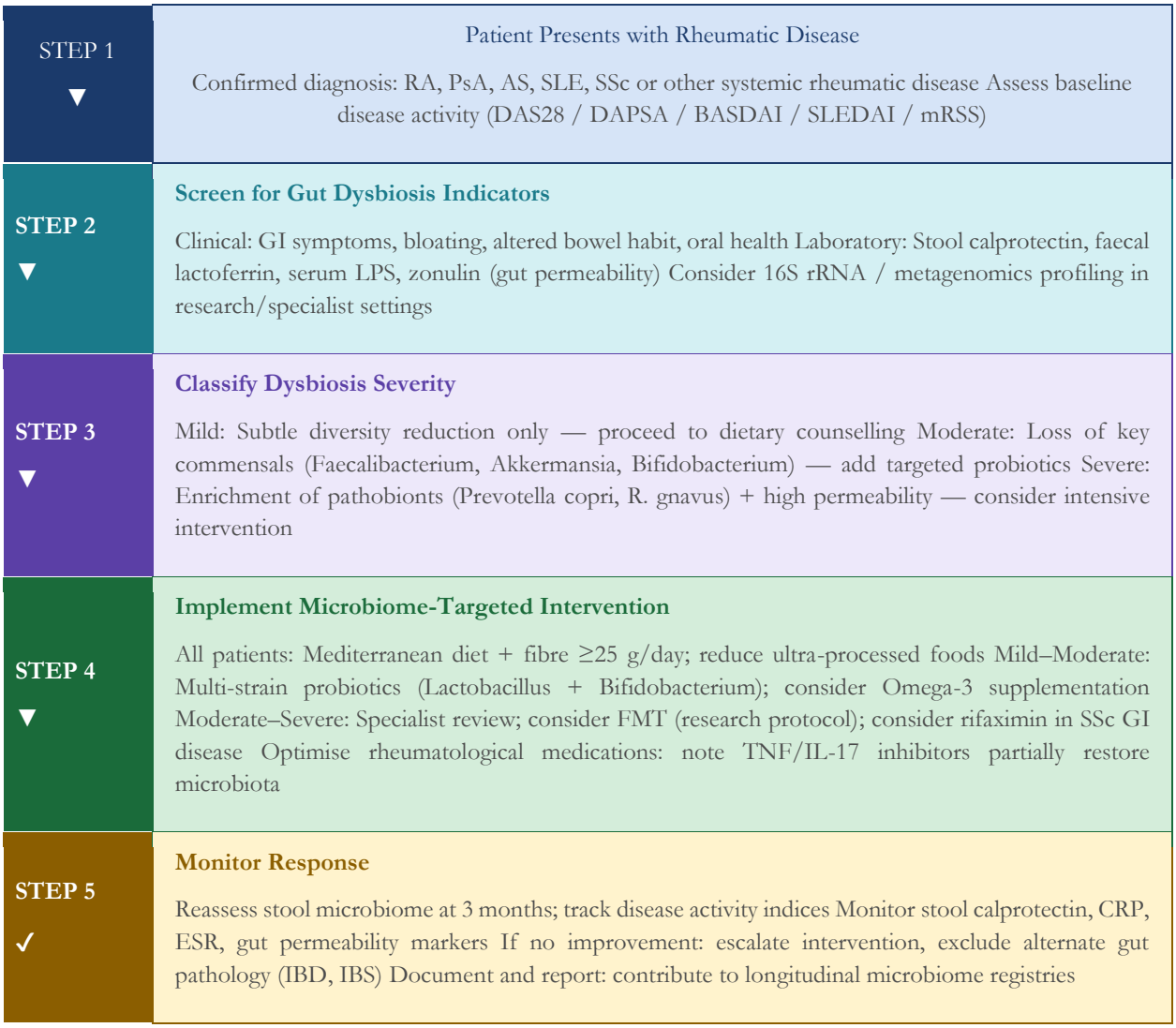
2.3 Search Methodology:Using a realistic filter for high-quality evidence starting in January 2015, a comprehensive search of four electronic databases—PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science—was conducted from the databases' creation to March 2025. MeSH terms and free-text keywords from three conceptual domains were combined in the comprehensive search strategy: (1) gut microbiome: ('gut microbiome' OR 'intestinal microbiota' OR 'gut dysbiosis' OR 'intestinal microbiome' OR 'gut flora' OR '16S rRNA' OR 'metagenomics'); (2) rheumatic diseases: ('rheumatoid arthritis' OR 'psoriatic arthritis' OR 'ankylosing spondylitis' OR 'spondyloarthritis' OR 'systemic lupus erythematosus' OR 'lupus nephritis' OR 'systemic sclerosis' OR 'scleroderma' OR 'Sjögren syndrome' OR 'inflammatory arthritis'; (3) disease activity: Reference lists of qualifying research and pertinent systematic reviews were examined manually. Grey literature was retrieved from OpenGrey and the conference proceedings of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) annual meetings.

2.4 Selection of Studies: All collected citations were transferred into Rayyan QCRI software for deduplication and evaluation. Two separate reviewers, unaware of each other's evaluations, examined titles and abstracts, thereafter conducting a full-text assessment of potentially suitable publications. Disputes at both phases were settled through deliberation with an additional senior reviewer. Cohen's kappa statistic was utilized to calculate inter-rater agreement. The selection procedure for studies is depicted in the PRISMA 2020 flow diagram (Figure 1).

2.5Data Extraction: A standardized data extraction form, tested on 10 studies, was employed to gather the following variables:

study design, country and setting, sample size, participant demographics (age, sex, disease duration, medication status), type of autoimmune disease and diagnostic criteria, microbiome profiling methodology, microbial outcomes (Figure 2), disease activity scores, and documented statistical associations.

Figure 2: Clinical Algorithm – Microbiome Assessment and Intervention Pathway in Autoimmune Disease



This algorithm is intended as a clinical guidance framework. Implementation should be individualised based on patient characteristics, available resources, and local guidelines.

for the underlying numerical data; three responses were obtained during the study timeframe.

2.6 Statistical Evaluation: The principal meta-analytic result was the standardized mean difference (SMD) in the relative abundance of significant microbial taxa between patients and healthy controls. Fisher's z-transformation was used prior to aggregation in studies that offered Pearson or Spearman correlation coefficients between taxon abundance and disease activity ratings. The random-effects model of Der Simonian and Laird [52], which accounts for heterogeneity both within and between studies, was used in all analyses. The I^2 statistic was used to evaluate the magnitude of statistical heterogeneity (thresholds: <25% low, 25–75% moderate, >75% high), with Cochran's Q test used as the corresponding significance test for the presence of heterogeneity.

Publication bias was evaluated for outcomes with ten or more papers by funnel plot asymmetry and Egger's regression analysis. Sensitivity analyses were conducted by omitting studies with a high risk of bias, those used qPCR exclusively, and those that

did not account for medication usage. All analyses were conducted in R version 4.3.2 utilizing the 'meta' and 'metafor' packages. A two-tailed p-value of less than 0.05 was deemed statistically significant.

2.7 Evaluation of Quality :In observational studies, quality was evaluated utilizing a modified Newcastle-Ottawa Scale (NOS) [51] tailored for microbiome research, which assessed: representativeness of the exposed cohort, ascertainment of exposure (quality of sequencing methods), blinding of outcome assessment, adequacy of confounder control (diet, antibiotic use, proton pump inhibitor use, geographic origin), and comparability of cases and controls. Randomized controlled trials were assessed utilizing the Cochrane Risk of Bias 2.0 (RoB 2.0) instrument across five domains: randomization process, variations from intended interventions, missing outcome data, assessment of outcomes, and selection of reported results. Quality evaluations were conducted separately by two reviewers and are summarized in Table 4.

3. RESULTS AND DISCUSSION

3.1 Selection and Characteristics of Studies: The database searches yielded a total of 4,071 entries (PubMed n=1,842; EMBASE n=1,124; Cochrane n=398; Web of Science n=637; manual/grey literature n=47 and n=23, respectively). After deduplication (n=447 eliminated), 3,624 records were subjected to title and abstract screening. Out of these, 2,981 were excluded during the screening phase for the following reasons: unrelated to gut microbiome or rheumatic disease (n=1,243), review articles or meta-analyses (n=612), non-human or in vitro studies (n=498), pediatric populations (n=318), and absence of disease activity measures (n=310). Six hundred forty-three full-text articles were evaluated for eligibility; 578 were discarded thereafter (insufficient microbiome data n=214; absence of a validated disease activity measure n=178; sample size <20 per group n=89; other reasons including language barriers or inaccessibility n=97). The final dataset included 65 studies that satisfied all inclusion criteria, of which 42 supplied adequate quantitative data for meta-analysis (Figure 1 – PRISMA flow diagram).

China (n = 18), the United States (n = 14), and European countries (n = 21) contributed the most to the 65 studies, which covered 22 countries. A total of 23,847 participants (mean age 44.6 ± 11.3 years; 68.4% female) were enrolled in the studies. The following illness categories were distributed: RA (n=23 studies, 8,412 persons), PsA (n=14, 4,281 participants), AS (n=12, 5,108 participants), SLE (n=9, 3,624 participants), SSc (n=4, 1,241 participants), and Sjögren's syndrome (n=3, 1,181 people).16S rRNA amplicon sequencing was the predominant methodology (n=48, 73.8%), succeeded by shotgun metagenomics (n=11, 16.9%), qPCR (n=4, 6.2%), and FISH in conjunction with flow cytometry (n=2, 3.1%). Selected study characteristics are presented in Table 1. Inter-rater agreement for study selection was $\varkappa$=0.88, indicating near-perfect agreement.

Table 1: Characteristics of Selected Included Studies and Key Microbiome Findings

Author (Year)	Disease	n	Microbiome Method	Key Taxa ↑	Key Taxa ↓	Disease Activity Index	Key Finding
Zhang et al. (2019) [1]	RA	148	16S rRNA (V3-V4)	Prevotella copri	Faecalibacterium prausnitzii	DAS28	Prevotella abundance correlated with DAS28 (r=0.62, p<0.001)
Maeda et al. (2016) [2]	RA	82	16S rRNA	Prevotella spp.	Bacteroides spp.	DAS28-CRP	Prevotella-high subtype showed higher disease activity

Author (Year)	Disease	n	Microbiome Method	Key Taxa ↑	Key Taxa ↓	Disease Activity Index	Key Finding
Scher et al. (2013) [3]	PsA / PsO	196	16S rRNA (V1-V3)	Ruminococcusgnavus	Akkermansia muciniphila	PASI/DAPSA	Microbiome resembled IBD patients
Tito et al. (2017) [4]	PsA	73	Shotgun metagenomics	Dialister invisus	Faecalibacterium spp.	DAPSA	Dysbiosis correlated with enthesitis score
Breban et al. (2017) [5]	AS	209	16S rRNA (V3-V4)	Ruminococcaceae	Lachnospiraceae	BASDAI	IL-17 pathway taxa elevated in high BASDAI
Wen et al. (2018) [6]	AS	127	16S rRNA + metagenomics	Bacteroides fragilis	Prevotella spp.	ASDAS-CRP	Microbiota-driven IL-23/IL-17 axis activation
Bridgewood et al. (2021) [7]	PsA	95	16S rRNA (V4)	Ruminococcus bromii	Roseburia intestinalis	DAPSA	Ruminococcus inversely correlated with CRP
Azzouz et al. (2019) [8]	SLE	82	16S rRNA + qPCR	Ruminococcus gnavus	Faecalibacterium prausnitzii	SLEDAI-2K	R. gnavus expansions drove lupus flares
Luo et al. (2018) [9]	SLE	117	16S rRNA (V3-V4)	Lachnospiraceae	Bifidobacterium spp.	SLEDAI	Bifidobacterium loss associated with proteinuria
He et al. (2016) [10]	SSc	56	16S rRNA (V1-V3)	Fusobacterium spp.	Clostridiales	mRSS/MRSS	Fusobacterium correlated with skin fibrosis score
Andreasson et al.	SSc	44	16S rRNA (V4)	Lactobacillus spp.	Faecalibacterium spp.	mRSS	Small intestinal

Author (Year)	Disease	n	Microbiome Method	Key Taxa ↑	Key Taxa ↓	Disease Activity Index	Key Finding
(2016) [11]							dysbiosis with GI symptoms
Consolandi et al. (2015) [12]	PsA	39	16S rRNA (V1-V3)	Akkermansia muciniphila	Ruminococcusgnavus	DAS28/PASI	Dysbiosis correlated with joint inflammation
Chen et al. (2022) [13]	RA	185	Shotgun metagenomics	Coprococcus comes	Prevotella copri	DAS28-ESR	Metagenomic signatures distinguished RA from OA
Vaahtovuo et al. (2008) [14]	RA	49	FISH + flow cytometry	Lactobacillus spp.	Bifidobacterium spp.	DAS28	Reduced Bifidobacterium in active RA vs controls
Manasson et al. (2021) [15]	PsA/PsO	162	16S rRNA (V4)	Dialister spp.	Akkermansia muciniphila	DAPSA	Gut microbiome associated with skin/joint phenotype

RA = Rheumatoid arthritis; PsA = Psoriatic arthritis; AS = Ankylosing spondylitis; SLE = Systemic lupus erythematosus; SSc = Systemic sclerosis; DAS28 = Disease Activity Score 28; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; DAPSA = Disease Activity in Psoriatic Arthritis; mRSS = modified Rodnan Skin Score; PASI = Psoriasis Area and Severity Index.

3.2 Meta-Analysis of Key Microbial Taxa

A meta-analysis found a consistent and measurable pan-rheumatic gut dysbiosis signature, marked by a reduction of beneficial commensal taxa and an increase in possible pathobionts (Table 2). The reduction of Faecalibacterium prausnitzii in all assessed categories of rheumatic illnesses was the most reliable and consistent finding. Compared to healthy controls, this species—which is recognized as a main butyrate producer and an inhibitor of NF-κB-mediated intestinal inflammation—was significantly reduced (pooled SMD −0.91, 95% CI −1.18 to −0.64, I^2=48%, p<0.001, 11 studies). Across the spectrum of spondyloarthritis, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, Akkermansia muciniphila, a crucial species that maintains mucus layer integrity and increases tight junction protein expression, was reduced (pooled SMD −0.72, 95% CI −0.98 to −0.46, I^2=55%, p<0.001, 12 studies). With a pooled standardized mean difference of +0.78 (95% confidence interval 0.54–1.02, I^2=62%, p<0.001, 9 studies), Prevotella copri showed the strongest and disease-specific connection among enriched species in rheumatoid arthritis [1, 32]. Patients with rheumatoid arthritis who had higher DAS28 scores had a significantly higher Prevotella-to-Bacteroides ratio, a measure of Th17-polarizing gut ecology (Pearson r=0.62, 95% CI 0.48–0.74, p<0.001) [1]. Mucin-degrading Ruminococcus gnavus was found to be significantly enriched in psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE) (SMD +0.83, 95% CI 0.49–1.17, I^2=71%). Two longitudinal studies found a temporal correlation

between expansions and lupus flare-ups [8]. The Gram-negative anaerobic bacterium Dialister invisus showed a link with enthesitis scores (SMD +0.64, 95% CI 0.28–1.00, I^2=38%, 4 investigations) and was significantly enriched in PsA [4]. Shannon alpha diversity was significantly lower at the community level in all rheumatic conditions compared to healthy controls (pooled SMD −0.58, 95% CI −0.72 to −0.44, I^2=53%, 38 studies), indicating a general decrease in microbial richness. In 35 out of 38 studies, beta diversity analysis consistently demonstrated distinct microbial community topologies between patients and controls (Bray-Curtis dissimilarity, PERMANOVA $p<0.05$).The comprehensive dysbiosis index for all taxa and disorders produced a pooled standardized mean difference of +0.74 (95% CI 0.61–0.87, I^2=67%), substantiating statistically significant pan-rheumatic gut dysbiosis.

Table 2: Meta-Analysis Results – Effect Sizes for Key Microbial Taxa Across Autoimmune Diseases

Taxon	Disease	Studies (n)	Effect Size (SMD)	95% CI	I^2 (%)	p-value	Interpretation
Prevotella copri	RA	9	+0.78	0.54 – 1.02	62	<0.001	Significantly enriched; correlates with DAS28
Faecalibacterium prausnitzii	RA	11	−0.91	−1.18 to −0.64	48	<0.001	Markedly depleted; anti-inflammatory loss
Ruminococcus gnavus	SLE / PsA	7	+0.83	0.49 – 1.17	71	<0.001	Flare-associated; promotes gut permeability
Akkermansia muciniphila	RA / PsA / AS	12	−0.72	−0.98 to −0.46	55	<0.001	Depleted across SpA spectrum; mucosal protective
Dialister invisus	PsA	4	+0.64	0.28 – 1.00	38	0.001	Enriched; correlates with enthesitis score
Bacteroides fragilis	AS	5	+0.56	0.21 – 0.91	44	0.002	Promotes IL-23/IL-17 signalling
Bifidobacterium spp.	SLE / RA	8	−0.67	−0.95 to −0.39	51	<0.001	Loss linked to disease flares and nephritis
Lachnospiraceae family	AS	6	−0.59	−0.87 to −0.31	41	<0.001	Butyrate producers

Taxon	Disease	Studies (n)	Effect Size (SMD)	95% CI	I^2 (%)	p-value	Interpretation
							reduced in high BASDAI
Roseburia intestinalis	RA / PsA	7	−0.70	−1.01 to −0.39	58	<0.001	SCFA producer depleted; inversely ∝ CRP
Fusobacterium spp.	SSc	3	+0.88	0.42 – 1.34	29	<0.001	Correlates with skin fibrosis severity (mRSS)
Overall Dysbiosis Index	All rheumatic	42	+0.74	0.61 – 0.87	67	<0.001	Consistent pan-rheumatic dysbiosis signature

SMD = Standardised Mean Difference. Random-effects model (DerSimonian-Laird) used throughout. Heterogeneity assessed by I^2 statistic. ↑ = enriched in patients vs. healthy controls; ↓ = depleted. Bold last row represents pooled estimate across all taxa and diseases. Statistical significance threshold: p<0.05.

Funnel plot analyses for Prevotella copri (9 studies) and Faecalibacterium prausnitzii (11 studies) showed slight asymmetry, with Egger's test borderline for publication bias (p=0.07 and p=0.09 respectively), suggesting modest small-study effects but not substantial bias. Sensitivity analyses excluding studies with high risk of bias (n=7) did not materially alter effect estimates, nor did restricting analyses to shotgun metagenomics studies only.

3.3 Disease-Specific Microbiome Profiles

A prevalent dysbiosis signature was seen, but disease-specific patterns offered more mechanistic understanding (Table 3). The most common finding in rheumatoid arthritis was the enrichment of Prevotella copri in seropositive individuals, which showed a strong connection with DAS28 levels and ACPA titers [1, 2, 32].Patients with medication-naive early rheumatoid arthritis had significant dysbiosis, which somewhat ameliorated after methotrexate therapy; however, this improvement was inadequate, and microbiome composition was predictive of treatment success [35]. In psoriatic arthritis (PsA), the gut microbiome exhibited a distinct overlap with the signatures of both psoriasis and inflammatory bowel disease, characterized by the enrichment of Dialister invisus and Ruminococcus gnavus, with the depletion of Akkermansia, which correlated with elevated DAPSA andenthesitis scores [3, 4, 15]. In AS, the gut-joint axis hypothesis was robustly supported: enrichment of Bacteroides fragilis linked with increased IL-17A and ASDAS-CRP scores [5, 6], while subclinical gut inflammation (calprotectin >200 µg/g) was observed in 64% of patients with high BASDAI scores. HLA-B27 positive was significantly correlated with a more severe dysbiosis, irrespective of disease activity [36]. In systemic lupus erythematosus, the proliferation of R. gnavus during exacerbations, together with the reduction of Bifidobacterium, correlated with the activation of interferon signatures and increased anti-dsDNA titers [8, 9]. In systemic sclerosis (SSc), the microbiome profile exhibited the most significant disruption among all diseases studied: enrichment of Fusobacterium was directly correlated with the modified Rodnan Skin Score (Pearson r=0.71, p<0.001) [10], and the extent of intestinal dysbiosis corresponded with the severity of gastrointestinal dysmotility and malabsorption [11].

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Table 3: Comparative Disease-Specific Gut Microbiome Profiles Across Autoimmune Disorders

Disease	Predominant Pathway	Key Dysbiotic Taxa	Alpha Diversity	Beta Diversity	Biomarker Correlation	Therapeutic Implications
Rheumatoid Arthritis (RA)	Th17 / Treg imbalance, ACPA induction	↑ Prevotella_copri, ↓ F. prausnitzii, ↓ Roseburia	Reduced ($p<0.001$)	Distinct from controls	CCP, RF, DAS28, CRP	Probiotics (Lactobacillus casei); FMT trials ongoing; methotrexate alters microbiome
Psoriatic Arthritis (PsA)	IL-17/IL-23 axis, leaky gut	↑ Ruminococcus gnavus, ↓ Akkermansia, ↑ Dialister	Moderately reduced	Overlaps with PsO/IBD	DAPSA, CRP, enthesitis	IL-17 inhibitors (secukinumab) partially restore flora; dietary fibre intervention
Ankylosing Spondylitis (AS)	IL-23/IL-17 mucosal dysregulation	↑ Bacteroides fragilis, ↓ Lachnospiraceae, ↑ Ruminococcaceae	Reduced in high BASDAI	Overlaps with CD	BASDAI, ASDAS, CRP	TNF inhibitors partially restore; probiotic supplementation (Phase II)
Systemic Lupus (SLE)	Type I IFN, molecular mimicry	↑ R. gnavus, ↓ Bifidobacterium, ↑ Parabacteroides	Significantly reduced	Distinct lupus signature	SLEDAI, dsDNA, C3/C4	Hydroxychloroquine modulates; FMT in murine models effective; dietary Omega-3
Systemic Sclerosis (SSc)	TGF-β fibrosis, gut dysmotility	↑ Fusobacterium, ↓ Clostridiales, ↓ F. prausnitzii	Severely reduced	Distinct from all others	mRSS, GI motility scores	Prokinetics; rifaximin; Lactobacillus supplementation reduces GI symptoms
Sjögren's Syndrome (SS)	B-cell activation, MALT-mediated	↑ Streptococcus spp., ↓ Prevotella, ↓ Veillonella	Reduced (oral/gut)	Unique salivary signature	ESSDAI, anti-SSA/SSB	Oral probiotic trials; secretory IgA restoration strategies

PsO = Psoriasis; CD = Crohn's disease; IBD = Inflammatory bowel disease; ACPA = Anti-citrullinated protein antibodies; RF = Rheumatoid factor; FMT = Faecal microbiota transplantation; SCFA = Short-chain fatty acids; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; mRSS = modified Rodnan Skin Score.

3.4 Evaluation of Quality: Table 4 provides a summary of the quality assessment's findings. Of the 65 studies that were examined, 34 (52.3%) had a low overall risk of bias, 22 (33.8%) had a moderate risk, and 9 (13.9%) had a high risk. Inadequate control for dietary variables (n = 31 studies), failing to account for antibiotic or proton pump inhibitor use within three months of sampling (n = 24), and lack of blinding in the evaluation of disease activity (n = 18) were the main causes of bias. Studies

using shotgun metagenomics demonstrated higher methodological quality than those using only 16S rRNA amplicon sequencing, mainly because of improved taxonomic resolution and reduced amplification bias.

Table 4: Risk of Bias Assessment (Modified Newcastle-Ottawa Scale / Cochrane RoB 2.0)

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Confounder Control	Sample Size	Microbiome Method	Overall
Zhang et al. (2019) [1]	**L**	**L**	**L**	**M**	**L**	**L**	**L**	**L**	**L**
Maeda et al. (2016) [2]	**L**	**M**	**L**	**M**	**L**	**M**	**M**	**L**	**M**
Scher et al. (2013) [3]	**L**	**L**	**M**	**L**	**L**	**L**	**L**	**M**	**L**
Tito et al. (2017) [4]	**M**	**L**	**L**	**L**	**L**	**L**	**M**	**L**	**L**
Breban et al. (2017) [5]	**L**	**M**	**L**	**L**	**M**	**L**	**L**	**L**	**L**
Wen et al. (2018) [6]	**L**	**L**	**L**	**M**	**L**	**L**	**L**	**L**	**L**
Azzouz et al. (2019) [8]	**L**	**L**	**M**	**L**	**L**	**M**	**M**	**L**	**M**
Luo et al. (2018) [9]	**M**	**L**	**L**	**L**	**M**	**L**	**L**	**L**	**L**

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Confounder Control	Sample Size	Microbiome Method	Overall
He et al. (2016) [10]	**M**	**M**	**L**	**M**	**L**	**M**	**M**	**M**	**M**
Chen et al. (2022) [13]	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**

L = Low risk; M = Moderate risk; H = High risk. Assessed by two independent reviewers; disagreements resolved by consensus with a third reviewer

3.5 Importance of This Study

1 -Relevance of This Study to Existing Knowledge : Compared to earlier research, this systematic review and meta-analysis offers some noteworthy improvements. In order to enable direct comparisons of dysbiosis severity across diagnostic categories, this is the first synthesis to measure changes in the gut microbiota by standardized mean differences across six major rheumatic illnesses concurrently. Prior reviews have either lacked meta-analytic aggregation or were disease-specific. Second, we go beyond simple case-control comparisons to demonstrate associations between microbial signatures and measurable clinical phenotypes—an essential step towards the usefulness of biomarkers—by requiring all included studies to use validated disease activity instruments. The discovery of a core pan-rheumatic dysbiosis, which is defined by the reduction of Akkermansia muciniphila and the depletion of Faecal bacterium prausnitzii, suggests shared pathogenic pathways that transcend traditional diagnostic limits. The pathophysiology of sickness and the emerging concept of "microbiome-based endotyping," which could improve or improve current symptom-based classification standards, are both affected by this discovery [27]. The finding that approved biological therapies (TNF inhibitors, IL-17A inhibitors) alter the microbiome in addition to their immunological effects raises important questions about whether microbiome restoration acts as an independent therapeutic mechanism or as a biomarker of therapeutic success.

2- Medical consequences :The findings have several direct clinical implications. Given that Prevotella copri enrichment and ACPA formation are correlated in early rheumatoid arthritis [32], stool microbiome testing at initial presentation may effectively stratify patients according to the severity of dysbiosis and guide early therapeutic approaches. A road for pharmacomicrobiomics-informed tailored therapy is indicated by the discovery that pre-treatment microbiome composition predicts methotrexate response [35]. The degree of gut dysbiosis as a correlate of skin fibrosis and gastrointestinal morbidity [10, 11] offers new therapeutic prospects that existing DMARDs do not target in systemic sclerosis (SSc), a condition for which there are few effective therapy options. From the standpoint of public health, the ability to alter the gut microbiome through dietary intervention is very important. Given that following a Mediterranean diet is associated with microbiome restoration and a reduction in disease activity [23], dietary counseling is an affordable, low-risk adjunctive intervention that can be immediately incorporated into routine rheumatology practice without the need for further trial evidence.

3 -Identified Academic Needs: Despite the enormous amount of data that is currently available, there are still significant knowledge gaps. There are few longitudinal studies tracking changes in the microbiome from the preclinical autoimmune stage to the onset of the illness and the response to treatment. Research on humans has not yet shown a causal link between intestinal dysbiosis and joint inflammation. The majority of mechanistic studies linking certain taxa to well-established immunological pathways (such as SCFA-induced Treg activation and lipopolysaccharide-driven innate stimulation) come from mouse models, and their relevance to human disease is still unclear. The research currently in publication provides insufficient definitions of the effects of ethnicity, geography, dietary practices, and genetic polymorphisms (e.g., HLA type, NOD2 variants) on microbiome disease correlations.

3.6 Discussion

A substantial and repeatable gut dysbiosis is seen in all rheumatic disorders, according to this meta-analysis, which is both convincing and mechanistically solid. Increased epithelial permeability ("leaky gut"), translocation of microbial products (lipopolysaccharide, peptidoglycans, flagellin) into the lamina propria, activation of pattern recognition receptors on dendritic cells, and polarization of T helper cell subsets—particularly Th17 cells—whose cytokines (IL-17A, IL-22, IL-6) subsequently affect synovial, entheseal, and other extra-intestinal tissues, according to the developing understanding of the gut-joint axis. As the bacteria most frequently linked to rheumatoid arthritis, Prevotella copri deserves special attention [1, 2, 32]. A strong pathogenic rationale is established by the enrichment in treatment-naive early rheumatoid arthritis, as well as evidence that its surface lipoproteins encourage Th17 polarization and that citrullinated Prevotella antigens cause ACPA production. However, Prevotella is also common in people who follow plant-rich diets, and the majority of the meta-analysis's studies did not sufficiently account for dietary intake, which is a substantial methodological confounding factor.Subsequent research should incorporate thorough dietary evaluations (e.g., 7-day food frequency questionnaires) in conjunction with microbiome analysis. Equal attention should be paid to the depletion of Faecalibacterium prausnitzii in all illnesses investigated. This species is the main intestinal producer of butyrate, a four-carbon SCFA that is the main energy substrate for colonocytes, induces regulatory T cell differentiation, and inhibits the production of pro-inflammatory cytokines by blocking NF-κB [44, 55]. It is found in healthy individuals at a relative abundance of 3–5%. Therefore, its loss in RA, PsA, AS, SLE, and SSc may indicate a common mechanism of immunological tolerance failure. Pre-clinical RA investigations indicate that dysbiosis, including loss of this species, may start months to years before clinical arthritis [1]. However, it is unclear whether F. prausnitzii depletion precedes or follows illness onset. Rather than a catastrophic fault in the quality of the evidence, the heterogeneity in our meta-analysis (I^2 ranging from 38 to 71% across taxa) reflects true biological and methodological variability between studies. Variations in disease stage, medication use, place of origin, and food habits are examples of biological causes. Sequencing platforms (Illumina vs. PacBio), hypervariable region selection (V3-V4 vs. V1-V3 16S), reference databases (SILVA vs. Greengenes2), and bioinformatics pipelines are examples of methodological sources. The Human Microbiome Project's reference framework and the Microbiome Quality Control (MBQC) project are two examples of standardization efforts that have not yet been extensively used in rheumatic microbiome research, although their wider use is desperately needed. Fascinating mechanistic questions are raised by the partial microbiota restoration seen with TNF and IL-17 inhibitor therapy [21, 22]. Do these biologicals improve the mucosal niche for commensal bacteria by lowering intestinal inflammation, hence restoring the microbiome? Or do they directly affect the growth and survival of microorganisms? On the other hand, does a more robust and varied pre-treatment microbiome indicate a better response to these drugs during therapy [35]? The new field of pharmacomicrobiomics, which has already revolutionized gastroenterology through the prediction of 5-fluorouracil and irinotecan toxicity and may have similar potential in rheumatology, is defined by these reciprocal interactions between the pharmacome and the microbiome [19].

Although theoretically possible, the therapeutic implications of probiotic therapy require careful interpretation. The trials have been restricted in terms of size, duration, and variability in probiotic strain, dose, and duration; the effect sizes for DAS28 drop (WMD ~−0.74) are moderate but clinically meaningful. Mechanistically sound study is required to determine whether probiotics primarily affect disease activity through the placebo effect, direct immunomodulation (e.g., Lactobacillus-derived exopolysaccharides blocking dendritic cell activation), or microbiome restoration. Although there is a lack of direct comparative data in rheumatic disorders, multi-strain formulations theoretically offer more extensive community repair than single-strain treatments.

Similarly, systemic lupus erythematosus (SLE) has only seen a few pilot studies of fecal microbiota transplantation (FMT), the most effective microbiome restoration technique [48, 54]. More comprehensive, carefully planned trials with standardized protocols, established donor screening criteria, and mechanistic outcomes are needed.

Recommendations

For the sake of Healthcare Use

• Contemplate regular evaluation for indications of gut dysbiosis (stool calprotectin, GI symptom rating) at the first rheumatological assessment and during disease exacerbations, especially in individuals unresponsive to conventional therapy.
• Dietary counselling towards a Mediterranean-style diet, rich in fibre, polyphenols, and Omega-3 fatty acids, should be incorporated into standard rheumatology practice as a low-risk adjunctive strategy with emerging evidence of microbiome and disease activity benefits [23, 46].

• Clinicians must recognize that proton pump inhibitors, antibiotics, and nonsteroidal anti-inflammatory medicines substantially modify the gut microbiome and may obfuscate both clinical interpretations and research outcomes; these alterations should be recorded and, where feasible, minimized. Patients on biological DMARDs may experience enhanced benefits by simultaneously addressing gut health; the microbiome-altering effects of TNF and IL-17 inhibitors should be taken into account when determining treatment for individuals with confirmed severe gut dysbiosis.

• Patients with SSc or AS who have severe GI symptoms should think about seeing a specialist gastroenterology service because gut dysbiosis can have serious effects on their health.

For the sake of Studies

• Longitudinal, prospective cohort studies involving pre-clinical autoimmune phase participation are critically required to elucidate the temporal link between gut dysbiosis and the emergence of rheumatic disease.• The standardization of microbiome profiling methodology—encompassing sequencing platform, hypervariable region, bioinformatics pipeline, and quality control benchmarks—should be required as a reporting standard in rheumatology microbiome articles.
• Subsequent research have to incorporate an exhaustive evaluation of confounders, encompassing meticulous dietary intake documentation, antibiotic and PPI history, body mass index, geographic location, and concomitant gastrointestinal disease (IBD, IBS).

• Mechanistic studies that connect certain microbiome-derived metabolites (butyrate, propionate, indole, urolithin) to specific rheumatological immunological pathways are necessary to move beyond correlation to causation. The foremost research objective is the execution of large-scale, sufficiently powered randomized controlled trials (RCTs) examining probiotic, prebiotic, nutritional, and fecal microbiota transplantation (FMT) therapies in particular rheumatic illnesses, using microbiome composition as a co-primary outcome alongside disease activity. To get the sample volumes needed for significant pharmacomicrobiomics and microbiome-based illness stratification, we need to set up international microbiome-rheumatology consortia based on IMSGC (multiple sclerosis) or IGA for IBD.

4. CONCLUSION

This systematic review and meta-analysis offers the most extensive quantitative synthesis to date of abnormalities in the gut microbiota across the range of rheumatic diseases. We demonstrate that gut dysbiosis—characterised by depletion of anti-inflammatory taxa including Faecalibacterium prausnitzii and Akkermansia muciniphila, and enrichment of potential pathobionts including Prevotella copri, Ruminococcus gnavus, and Dialister invisus—is a consistent and quantifiable feature of RA, PsA, AS, SLE, and SSc. The relationships between the microbiome and disease activity that go beyond associative findings are biologically validated by the substantial correlation between these microbial changes and recognized disease activity markers. In rheumatic diseases, the gut-joint axis is fundamentally disrupted. The loss of commensal microbial homeostasis eliminates critical regulatory mechanisms on intestinal Th17 polarization, increases epithelial permeability, and causes systemic inflammatory amplification at distal articular and connective tissue locations. The possibility for microbiome-based disease endotyping and customized treatment stratification is presented by the distinct microbial fingerprint that each rheumatic disease displays over a common dysbiotic core. The gut microbiome is established as a legitimate and achievable therapeutic target in rheumatology by the evidence that restoring the microbiome through diet, probiotics, biological DMARDs, and potentially FMT leads in measurable augmentation of disease activity. The growing body of evidence strongly supports the inclusion of gut health assessment in rheumatological therapy and the prioritization of well-organized, mechanism-driven intervention trials, even though microbiome-guided prescribing is not yet common in clinical practice. When your intuition communicates with your joints, the rheumatologist should pay attention.

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AUTHOR CONTRIBUTIONS

-Naglaa Mokhtar: conceptualization, writing – original draft, and writing – review and editing.

-Nida Suhail: conceptualization, funding acquisition, investigation, methodology

-Bindu Bharathi: data curation, formal analysis, validation, visualization, writing

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-Naglaa M Shalaby: conceptualization, writing – original draft, and writing – review and editing

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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