

## Medical Science

### To Cite:

Polkowska W, Kondratowicz M, Kałamarz K, Żmuda K, Świerczyna M, Czerniachowska M, Kaniewski M, Wojnowska M, Figzał A, Grabek M. Rheumatoid Arthritis and the Gut Microbiota: Findings from Recent Studies (2017-2025). *Medical Science* 2026; 30: e57ms3811 doi: <https://doi.org/10.54905/disssi.v30i169.e57ms3811>

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### Peer-Review History

Received: 21 August 2025  
 Reviewed & Revised: 07/September/2025 to 23/February/2026  
 Accepted: 03 March 2026  
 Published: 18 March 2026

### Peer-review Method

External peer-review was done through double-blind method.

Medical Science

pISSN 2321-7359; eISSN 2321-7367



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# Rheumatoid Arthritis and the Gut Microbiota: Findings from Recent Studies (2017-2025)

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## ABSTRACT

Rheumatoid arthritis (RA) is one of the most common autoimmune conditions, characterized by persistent joint inflammation. Recent studies have examined the gut microbiota in patients with RA and in individuals assessed before clinical symptoms appear. This review provides an overview of recent findings on alterations in gut microbiota in rheumatoid arthritis. Many studies report lower bacterial diversity and reduced numbers of short-chain fatty acid-producing bacteria compared with healthy individuals. Similar findings are also observed in some individuals before the onset of clinical disease. The review also discusses factors influencing gut microbiota composition, such as diet, antibiotic use, and genetic background, and reviews studies evaluating probiotic supplementation. Differences in gut microbiota are observed in individuals carrying HLA-DRB1 risk alleles. Some studies also report a poorer response to methotrexate in patients with lower bacterial diversity and fewer short-chain fatty acid-producing bacteria. Gut microbiota changes are common in RA, but they vary among patients. At this stage, this evidence helps explain disease mechanisms but has limited use in routine clinical practice.

**Keywords:** rheumatoid arthritis; gut microbiota; dysbiosis; short-chain fatty acids; intestinal barrier; probiotics

## 1. INTRODUCTION

Rheumatoid arthritis is a chronic disease recognized by persistent synovial inflammation and progressive joint damage (Smolen et al., 2016; McInnes & Schett, 2011). Despite existing therapies that have shown success, researchers continue to investigate the causes of rheumatoid arthritis. Immunological dysfunctions may appear before any clinical symptoms (Alpizar-Rodríguez et al., 2019; Rooney et al., 2024). As a result, more attention is now focused on the early stages of the disease.

There are many differences in the gut microbiota between patients with RA and healthy people. A few studies describe reduced bacterial diversity and lower levels of bacteria that produce short-chain fatty acids (Kishikawa et al., 2020; Jeong et al., 2019). Gut microbiota changes are also observed prior to the onset of clinical

symptoms, including in ACPA-positive individuals and first-degree relatives (Alpízar-Rodríguez et al., 2019; Rooney et al., 2024; Wells et al., 2020).

The presentation of these changes varies between populations. It appears to be influenced by factors such as diet, antibiotic use, and genetic background (Asquith et al., 2019; Sultan et al., 2019). In this review, we want to summarize current findings on gut microbiota changes in rheumatoid arthritis and discuss their possible clinical implications.

## 2. MATERIALS AND METHODS

### Study design and reporting standards

We designed this work as a systematic review of published literature. We prepared the review in line with the PRISMA 2020 recommendations for reporting systematic reviews. A separate review protocol was not registered.

### Search strategy

The literature search included PubMed, Scopus, Web of Science, and Google Scholar. We considered articles published between January 2017 and April 2025. The search used terms associated with rheumatoid arthritis and gut microbiota, such as intestinal microbiome, dysbiosis, short-chain fatty acids, intestinal permeability, molecular mimicry, probiotics, and microbial metabolites.

An example search strategy applied in PubMed was: (“rheumatoid arthritis” AND (“gut microbiota” OR “intestinal microbiome” OR dysbiosis)). Reference lists of relevant articles and reviews were also manually screened to identify additional eligible studies. References published outside the predefined search window were used only for background information. They were not included in the qualitative synthesis.

### Eligibility criteria

The review included original research papers. These comprised observational studies and clinical trials conducted in patients with rheumatoid arthritis, individuals at increased risk of disease (for example, ACPA-positive individuals), or relevant control groups. The studies examined gut microbiota composition, functional changes associated with it, and interventions targeting it. We excluded systematic reviews and meta-analyses in the qualitative synthesis, but they were screened for additional references.

### Study selection

We screened all identified records by title and abstract. We retrieved full-text articles for studies considered potentially eligible. We excluded articles that did not meet the inclusion criteria after full-text assessment. We resolved disagreements during the selection process through discussion.

### Data extraction

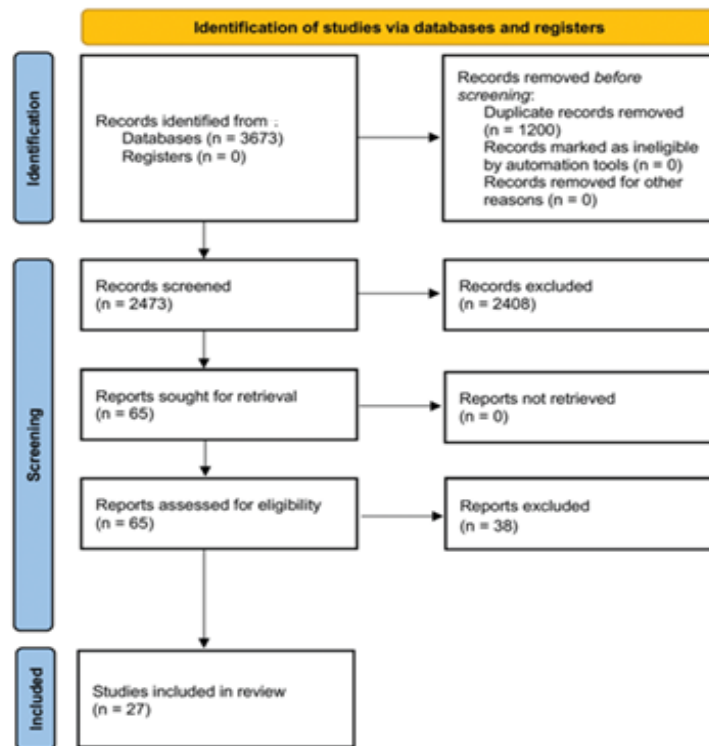
We reviewed each paper individually. For each study, we collected basic details on study design and participant characteristics. These data included the size of the study group and whether patients had early or established rheumatoid arthritis or belonged to an at-risk group. We also recorded how the gut microbiota was analyzed. Information on sequencing approaches, including 16S rRNA and metagenomic methods, was recorded. We also summarized the main microbial findings described by the authors and noted any reported links with clinical or immunological features.

### Quality assessment

Because the included studies differed widely in design and methodology, we did not apply a single quantitative risk-of-bias tool. Instead, we assessed study quality descriptively by considering sample size, sequencing approach, choice of control groups, and potential confounding factors.

### Study selection

The database search identified 3,673 records. After removing 1,200 duplicate records, 2,473 titles and abstracts were screened. Of these, we excluded 2,408 records. We conducted a full-text assessment of 65 reports and excluded 38 based on predefined eligibility criteria. The final qualitative synthesis included 27 studies. Figure 1 presents the PRISMA 2020 flow diagram of the study selection process.



**Figure 1.** PRISMA 2020 flow diagram of study selection.

### 3. RESULTS & DISCUSSION

#### Characteristics of included studies

The 27 included studies mainly involved adult patients with established rheumatoid arthritis. Fewer studies focused on early disease or on individuals considered at increased risk, such as ACPA-positive individuals and first-degree relatives. All included studies used an observational design, including cohort, case-control, and cross-sectional designs. Most studies assessed gut microbiota using 16S rRNA gene sequencing. Some studies used metagenomic methods to analyze functional aspects of the microbiome. Most studies used stool samples. Methods varied between studies in terms of sequencing platforms, data processing, and taxonomic resolution. Clinical data accompanying microbiome analyses usually included disease activity measures and serological markers, such as rheumatoid factor and anti-citrullinated protein antibodies.

#### Gut microbiota composition in rheumatoid arthritis

Across RA cohorts, microbial findings are rarely similar to each other. Some studies emphasise one group of organisms, others highlight entirely different shifts. Several consistent findings appear across independent studies, with one of them being the drop in butyrate-producing genera - *Faecalibacterium*, *Roseburia*, and related taxa (Kishikawa et al., 2020; Koh et al., 2023; Wells et al., 2020). Other studies found higher levels of bacteria, including *Prevotella copri*, *Collinsella aerofaciens*, and *Eggerthella lenta*. This shows that changes in the gut microbiome in rheumatoid arthritis are not the same in every study (Kishikawa et al., 2020; Alpízar-Rodríguez et al., 2019; Jeong et al., 2019; Koh et al., 2023; Rooney et al., 2024; Nii et al., 2023; Wells et al., 2020). Metagenomic data also reveal decreased genetic capacity for SCFA production and enhanced amino-acid fermentation and oxidative-stress pathways (Kishikawa et al., 2020; Nii et al., 2023; Krautkramer et al., 2021; Gong et al., 2024).

#### Gut microbiota findings before clinical arthritis

Some studies looked at people before they developed arthritis and found early changes in their gut bacteria. These changes were seen in people with ACPA, in close relatives of patients with rheumatoid arthritis, and in those considered at higher risk of the disease

(Alpizar-Rodríguez et al., 2019; Asquith et al., 2019; Rooney et al., 2024; Wells et al., 2020). What is noteworthy these microbial differences were evident even in the absence of joint symptoms.

Increased representation of *Prevotella* species has been reported in several preclinical cohorts, at times preceding the clinical manifestation of rheumatoid arthritis by many years (Kishikawa et al., 2020; Alpizar-Rodríguez et al., 2019; Rooney et al., 2024). Earlier research did not identify consistent taxonomic changes but instead noted a decline in the stability of the gut microbiota over time (Table 1). Individuals who later progressed to rheumatoid arthritis showed much larger shifts in their microbiota between sequential samples than those who remained symptom-free (Rooney et al., 2024).

**Table 1.** Gut microbiota changes in rheumatoid arthritis

Reported finding	Change	Disease stage	Notes
Overall microbial diversity	Lower	Established RA	Not observed in all populations
Butyrate-producing bacteria	Lower	RA/ at-risk	Includes <i>Faecalibacterium</i> and <i>Roseburia</i> ; functional role
<i>Prevotella copri</i>	Higher	At-risk/ early RA	Not observed in all populations
Microbiota stability	Lower	At-risk individuals	Reported in longitudinal studies
SCFA-related metabolic pathways	Reduced activity	RA	Based on metagenomic analyses

### Gut microbiota findings in rheumatoid arthritis

Several papers reported significantly decreased microbiota differentiation and lower levels of bacteria capable of producing butyrate, but these changes were not observed in all groups (Kishikawa et al., 2020; Maeda et al., 2016; Jeong et al., 2019; Koh et al., 2023; Wells et al., 2020). An increased abundance of *Prevotella copri* was described mainly in at-risk individuals and during early disease stages, but other cohorts did not reproduce this finding. In patients who later developed rheumatoid arthritis, the gut microbiota showed greater temporal instability over time (Kishikawa et al., 2020; Alpizar-Rodríguez et al., 2019; Rooney et al., 2024). Several studies observed reduced activity of pathways involved in short-chain fatty acid production, despite substantial differences in bacterial molecular composition (Kishikawa et al., 2020; Nii et al., 2023; Krautkramer et al., 2021).

### Metabolic changes in the gut microbiota

Some studies reported reduced activity of pathways involved in the production of short-chain fatty acids (Kishikawa et al., 2020; Nii et al., 2023; Krautkramer et al., 2021; Gong et al., 2024). Reduced butyrate-producing capacity does not necessarily reflect loss of a single bacterial group. It may result from disrupted microbial interactions that support short-chain fatty acid synthesis, including cross-feeding processes within the gut microbiota (Kishikawa et al., 2020; Koh et al., 2023; Krautkramer et al., 2021). Not all studies focused directly on microbial metabolites. Sometimes, functional conclusions focused more on dysfunctional pathway activity rather than on short-chain fatty acid levels (Kishikawa et al., 2020; Nii et al., 2023; Gong et al., 2024).

### Early microbial changes

Changes in the gut microbiota have been reported in people before the onset of rheumatoid arthritis, including ACPA-positive individuals, first-degree relatives of patients with established disease, and other groups considered higher risk (Alpizar-Rodríguez et al., 2019; Asquith et al., 2019; Wells et al., 2020). In some studies, higher levels of *Prevotella* species (usually *Prevotella copri*) were observed during the very first stages of disease, before symptoms. Other cohorts did not show similar findings (Kishikawa et al., 2020; Alpizar-Rodríguez et al., 2019; Rooney et al., 2024). In individuals who later developed rheumatoid arthritis, the gut microbiota changed more over time than in participants who remained asymptomatic (Rooney et al., 2024).

### Diet, antibiotics, and genetics in relation to gut microbiota

Diet can distinctly affect how gut flora are comprised, and how one eats can also differ significantly based on the person that is being studied when conducting research. In persons with rheumatoid arthritis, compared with healthy persons, higher processed-food and saturated-fat diets tend to be associated with lower gut bacterial diversity and a continually declining number of bacteria that produce short-chain fatty acids. In contrast, a diet similar to the Mediterranean diet was associated with improvements in disease activity and inflammatory markers (Papandreou et al., 2023). Antibiotic use was more common in populations with a higher risk of rheumatoid

arthritis. In population-based studies, frequent or long-term antibiotic use was reported more often before the diagnosis of rheumatoid arthritis than in control groups (Sultan et al., 2019). Individuals with HLA-DRB1 shared-epitope alleles also showed differences in gut microbiota, even before the onset of any clinical symptoms (Asquith et al., 2019; Wells et al., 2020).

### **Gut microbiota and treatment response**

Studies regarding the supplementation of probiotics in rheumatoid arthritis showed little effect in clinical practice. A 2022 meta-analysis showed only small reductions in C-reactive protein levels and tender-joint counts (Zeng et al., 2022). Probiotic use did not correct the main gut microbiota changes described in rheumatoid arthritis, comprising reduced gut bacterial diversity and lower levels of short-chain fatty acid-producing bacteria.

Research has examined the gut microbiota and its effects on patient responses to certain therapies. In groupings exhibiting reduced bacterial diversity in their intestines and reduced levels of bacteria that produce short-chain fatty acids, the response to methotrexate was suboptimal (Koh et al., 2023; Artacho et al., 2021).

### **Gut microbiota and inflammatory processes in rheumatoid arthritis**

According to studies, there are many significant changes in gut barrier function in patients with rheumatoid arthritis, which cause inflammation (Tajik et al., 2020; Heidt et al., 2023). Reduced levels of short-chain fatty acids (for example butyrate) are the most important microbiota-related finding across studies and may weaken gut barrier function (Kishikawa et al., 2020; Koh et al., 2023; Krautkramer et al., 2021). Evidence for mimicking the molecular patterns comes mainly from experimental studies, and its relevance in clinical rheumatoid arthritis remains unclear (Maeda et al., 2016; Nii et al., 2023; Konig et al., 2016). Gut microbiota composition is also modulated by treatment and genetic background, making it difficult to separate cause from effect.

## **4. CONCLUSION**

Studies included in this review show that patients with rheumatoid arthritis have differences in gut microbiota composition compared with healthy individuals. These changes differ among patients and do not allow identification of a single, characteristic microbiota profile for rheumatoid arthritis. The most common findings include reduced gut bacterial diversity and fewer bacteria that produce short-chain fatty acids. Researchers have also identified similar changes in individuals studied before the first clinical symptoms of the disease appeared. Frequent or long-term antibiotic use and diets rich in highly processed foods and saturated fats are associated with a less favourable gut microbiota profile and higher disease activity. At present, these observations mainly help to improve understanding of rheumatoid arthritis mechanisms and may provide a starting point for further research on supportive treatment strategies.

### **Acknowledgments**

We thank the authors who contributed to the conduct of this study.

### **Authors' Contributions**

Wiktoria Polkowska- Conceptualization, review and editing, investigation, methodology

Maja Kondratowicz- Methodology, investigation, visualization, supervision

Kamila Kałamarz- Conceptualization, visualization, resources

Kinga Żmuda- Review, data curation, investigation

Maciej Świerczyna- Resources, writing- rough preparation, data curation

Maja Czerniachowska- Visualization, data curation, investigation

Marcin Kaniewski- Review, visualization, formal analysis

Martyna Wojnowska- Supervision, writing- rough preparation, data curation

Aleksandra Fizgał - Review and editing, formal analysis, supervision

Michał Grabek- Resources, writing- rough preparation, formal analysis

Project administration- Wiktoria Polkowska

### **Informed consent**

Not applicable.

**Ethical approval**

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

**Funding**

This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

**Conflict of interest**

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

**Data and materials availability**

All data associated with this work are present in the paper.

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