


# BMJ Open Gut microbial dysbiosis in rheumatoid arthritis: a systematic review protocol of case-control studies

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## ABSTRACT

**Introduction** Rheumatoid arthritis (RA) has a huge societal impact due to the high prevalence, irreversible joint damage and systemic complications. Gut microbiota plays an important role in the pathogenesis and progression of RA by regulating the host immune system. Restoring intestinal homeostasis by altering the microbiota could be an attractive strategy for the prevention and treatment of RA. However, the signature features of microbial dysbiosis in RA are still controversial. Therefore, we aim to elucidate the characteristic change in the diversity and composition of gut microbiota in RA.

**Methods and analysis** We will systematically search through PubMed, EMBASE, Web of Science and Cochrane Library, as well as dissertations and conference proceedings. The reference lists of all included studies will be also reviewed to retrieve additional relevant studies. The case-control studies that reported either the relative abundance of bacteria at the phylum or genus level or at least one of the alpha-diversity, beta-diversity indexes in both RA and healthy controls will be included. Eligible studies will be screened independently by two reviewers according to the inclusion criteria. The Newcastle-Ottawa Quality Assessment Scale will be used to assess the quality of the included studies. Data extraction, qualitative and quantitative analysis will be performed within the gut microbial dysbiosis in RA. The expected outcomes will be the identification of the specific changes in composition and diversity of the gut microbiota in patients with RA. The quality of evidence will be assessed by the Grading of Recommendations Assessment, Development and Evaluation framework.

**Ethics and dissemination** Ethical approval is unnecessary as this review does not address the data and privacy of patients. The results will be published in a peer-reviewed scientific journal and conference presentations.

**PROSPERO registration number** CRD42021225229.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease characterised by persistent synovitis, inflammatory and autoantibody changes.<sup>1</sup> The prevalence of RA is about 1% globally, and 1.02% in China.<sup>2</sup> The prevalence of RA in women is 2–3 times higher than that in men.<sup>3</sup> Delays in diagnosis and treatment are associated with worse outcomes, including

## Strengths and limitations of this study

- This systematic review will identify the characteristic changes in the composition and diversity of gut microbiota in patients with RA, a significant but controversial clinical issue.
- The relative abundances of phyla and/or genus levels in the gut microbiota will be used in this meta-analysis.
- The Web Plot Digitizer will be used to digitise and extract data from graphs and plots, which may lead to biased results.
- This systematic review will only include studies written in English, which may limit available data or result in language bias.

irreversible joint destruction, disability and disease-related non-articular outcomes such as reduced life span.<sup>4 5</sup> In China, 77.6% of RA patients had disabilities, among which moderate and severe disabilities accounted for about 39%, seriously affecting the quality of life of patients.<sup>6</sup> The gradual deterioration of RA leads to a sharp increase in the cost of the disease, which imposes a heavy societal and economical burden on individuals and the country.<sup>7–9</sup>

RA is a lifelong condition and currently no cure for most patients.<sup>10 11</sup> European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) recommend that the purpose of RA treatment should be to enable each patient to achieve the goal of continuous remission or low disease activity.<sup>12</sup> Although the prognosis of RA has improved with advances in diagnosis and treatment in recent decades, the exact aetiology and pathogenesis of RA are not fully understood. In order to develop more effective treatment strategies for RA, it is essential to explore its underlying aetiology and pathogenesis.

Environmental factors are considered to play an important role in RA.<sup>13</sup> The gut microbiota is considered an important

environmental factor in the development of RA.<sup>14</sup> Almost all studies on autoimmune rheumatic diseases show abnormal microbial community structure (ie, dysbiosis).<sup>15</sup> Dysbiosis not only affects the proinflammatory and anti-inflammatory process of the intestinal mucosa, but also affects the distal joint through the intestinal-joint axis.<sup>16–18</sup> The studies have found dysbiosis in both RA patients and high-risk individuals, indicating that the imbalance of intestinal flora could have occurred before the onset of RA.<sup>14 19</sup> Dysbiosis has been involved in the pathogenesis of RA in the decade before its diagnosis.<sup>20</sup> The intestinal flora imbalance also appeared in the initial peak and relapse stage of RA.<sup>21</sup> Dysbiosis is related to the inflammatory response and disease activity of RA, which can be partially recovered by effective treatment.<sup>22–24</sup> As a first-line treatment for RA, methotrexate may act in part by modulating the human gut microbiota.<sup>24</sup> The results of animal experiments suggest that interventions targeting intestinal microbiota may have the potential to prevent RA in the preclinical stage.<sup>25</sup> Probiotics supplementation as adjunctive therapy improves the inflammatory state of RA in human and animal studies.<sup>26–29</sup> Therefore, gut microbiota plays an important role in the development of RA, and may be a new therapeutic target.<sup>30 31</sup> Gut microbiome studies of RA are essential to elucidate aetiology and pathophysiological mechanisms and to develop potential therapeutic strategies. Regulating the gut microbiota to slow the progression of the disease, especially in the preclinical phase of RA, may be a promising approach for the treatment of RA in the future.<sup>32 33</sup>

Although numerous studies have shown that dysbiosis of the gut microbiome is a key hallmark of RA, the distinct composition of the gut microbiome in RA patients remains controversial. The abundance of *Prevotella* increased in patients with early RA, which hurt the development and prognosis of RA.<sup>14 34–37</sup> However, it has been reported that the abundance of *Prevotella* did not significantly change in RA patients.<sup>38</sup> Moreover, *P. copri* and *P. histicola* of *Prevotella* have different effects on RA.<sup>14</sup> *Bacteroidetes* were enriched in female patients with RA, while *Actinomycetes* and *Collinsella* were enriched in healthy subjects.<sup>38</sup> However, the abundance of *Bacteroides* and *Bifidobacterium* was found to be reduced in RA patients and animal experiments.<sup>23 39</sup> It follows that the results of studies on the gut microbiota of RA patients are contradictory. The identification of specific microbial profiles and patterns that may contribute to the pathogenesis of RA remains a major challenge due to the inconsistent results of studies on the gut microbiota. The conflicting results may stem from inter-study batch effects, such as various biological factors influencing gut microbiome composition, different data processing and analysis methods.<sup>40 41</sup> The differences in demographics of the study cohorts (eg, sex, age, ethnicity, geography and diet) also have an important influence on the variability of the results of the gut microbiome study. Through a quantitative review of the existing literature, the changes of RA gut microbiota can be understood more clearly and

comprehensively. Recently, several meta-analyses of gut microbiota have identified specific microbial biomarkers associated with disease.<sup>42–47</sup> However, there has been no systematic review and meta-analysis focusing on the characteristic dysbiosis of gut microbiota in RA to date. Therefore, we will perform a systematic review and meta-analysis to identify characteristic alterations in the gut microbiota of RA patients.

## OBJECTIVE

The purpose of this protocol is to outline a systematic review and meta-analysis, which evaluates the changes in the diversity of gut microbiota and the relative abundance of bacterial phyla or genera in patients with RA.

## METHODS

### Study design

We plan to conduct a systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions Version 6.1,<sup>48</sup> Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA),<sup>49</sup> and PRISMA-Protocols (PRISMA-P) 2015,<sup>50</sup> as well as the Newcastle-Ottawa Quality Assessment Scale (NOS).<sup>51</sup> The PRISMA-P 2015 checklist is shown in [table 1](#). This protocol has been registered at PROSPERO (registration number: CRD42021225229).

### Eligibility criteria

The studies, written in English as eligible, will be selected and screened based on PECOS steps (Population, Exposure, Comparator, Outcomes and Study design).<sup>52 53</sup> The data items will be extracted as follows:

#### Types of participants (P)

The population of interest of the eligible studies should be adults ( $\geq 18$  years old) diagnosed with RA according to a standardised diagnostic classification system (EULAR/ACR 2010 or ACR 1987 criteria).<sup>54 55</sup>

#### Type of exposure (E)

Trials were applied to assess the gut microbiota. Quantitative synthesis of microbiota in faecal samples was performed by using metagenomic shotgun sequencing, 16s rRNA sequencing techniques and/or real-time polymerase chain reaction (rt-PCR).

#### Comparison (C)

Only healthy adults will be considered eligible for the control group.

#### Type of outcomes (O)

The primary outcome of the study will be the identification of the composition of the gut microbiome and the relative abundance of bacteria in RA. The secondary outcomes will be considered: changes in the gut microbiota diversity (alpha-diversity, beta-diversity), the effects

**Table 1** PRISMA-P 2015 checklist

Section and topic	Item no	Checklist item	Reported on page #
<b>Administrative information</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	1-2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators and outcomes (PICO)	2,4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4-5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any preplanned data assumptions and simplifications	5
Outcomes and prioritisation	13	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5

Continued

Table 1 Continued

Section and topic	Item no	Checklist item	Reported on page #
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

of different gender and region on the relative abundance of gut microbiota.

#### Type of studies (S)

We will only include studies with the case-control design, written in English and published in the original peer-reviewed journals. The animal studies, reviews, case reports and the full text unachieved will be excluded from the qualitative and quantitative synthesis.

#### Data sources and search strategies

We conduct the search using the databases Embase, PubMed, Web of Science and Cochrane Library in the English language published up to September 2020. After reading several documents, a search strategy combining Medical Subject Headings (MeSH) terms and free words was developed: ('Arthritis, Rheumatoid' OR 'Rheumatoid arthritis' OR 'RA') AND ('Gastrointestinal Microbiome' OR 'Gastrointestinal Microbiomes' OR 'Microbiome, Gastrointestinal' OR 'Gut Microbiome' OR 'Gut Microbiomes' OR 'Microbiome, Gut'). The search strategy for the Embase database is shown in figure 1. To prevent the omission of the article, two researchers (DWW and XTP) will search the above database independently. Using the snowball method, we manually search for all references contained in the article.

#### Screening procedures of eligible studies

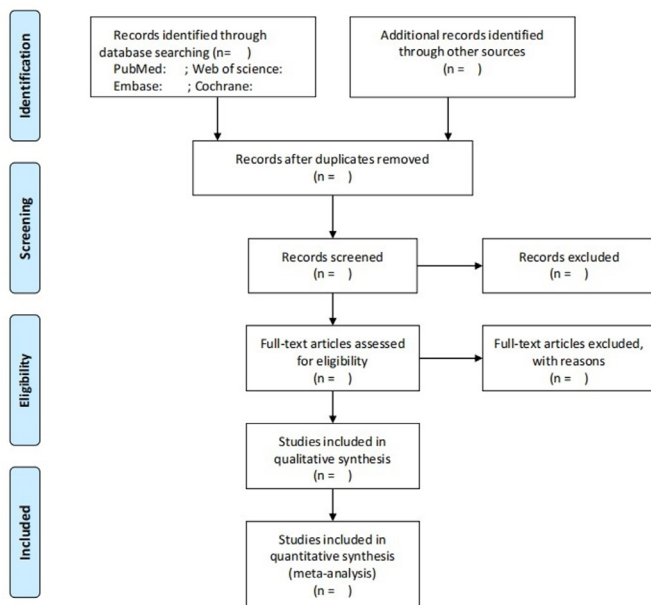
Once the search is complete, the literature will be managed using EndNote X9 (Clarivate Analytics (US) LLC). Duplicates will be identified and deleted according to literature title. Then, the titles and abstracts of the literature will be screened independently by two reviewers (XTP and YFL) according to the inclusion criteria. Retrieval of the full text will be based on the eligible of titles and abstracts, and the literature meeting all the inclusion criteria will be independently assessed. In case of disagreement, a third reviewer (ZLS) will be consulted. To measure inter-rater agreement, the kappa coefficients will be both calculated

for the processes of titles/abstract selection and full-text screening. The criteria for judging the scope of the agreement between the evaluators are as follows: 0.00–0.20 = slight agreement, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial and 0.81–1.00 = almost perfect

#### Embase Session Results (22 Oct 2020)

No.	Query	Results
#45	#4 AND #43 AND [english]/lim	817
#44	#4 AND #43	838
#43	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR	77807
#42	'bacteria, enteric':ab,ti	20
#41	'enteric bacteria':ab,ti	3639
#40	'flora, intestinal':ab,ti	37
#39	'intestinal flora':ab,ti	5300
#38	'microflora, intestinal':ab,ti	27
#37	'intestine flora':ab,ti	18
#36	'microbiota, intestinal':ab,ti	135
#35	'intestinal microbiotas':ab,ti	28
#34	'intestinal microbiotas':ab,ti	9646
#33	'microbiome, intestinal':ab,ti	39
#32	'intestinal microbiomes':ab,ti	75
#31	'intestinal microbiome':ab,ti	2159
#30	'microbiome, gastric':ab,ti	0
#29	'gastric microbiomes':ab,ti	9
#28	'gastric microbiome':ab,ti	79
#27	'microflora, gastrointestinal':ab,ti	2
#26	'gastrointestinal microflora':ab,ti	306
#25	'microbial community, gastrointestinal':ab,ti	0
#24	'gastrointestinal microbial communities':ab,ti	31
#23	'gastrointestinal microbial community':ab,ti	27
#22	'microbiota, gastrointestinal':ab,ti	14
#21	'gastrointestinal microbiotas':ab,ti	2
#20	'gastrointestinal microbiotas':ab,ti	868
#19	'flora, gut':ab,ti	8
#18	'gut flora':ab,ti	2424
#17	'flora, gastrointestinal':ab,ti	6
#16	'gastrointestinal flora':ab,ti	365
#15	'microbiota, gut':ab,ti	605
#14	'gut microbiotas':ab,ti	103
#13	'gut microbiotas':ab,ti	24863
#12	'microflora, gut':ab,ti	10
#11	'gut microflora':ab,ti	1766
#10	'microbiome, gut':ab,ti	199
#9	'gut microbiomes':ab,ti	599
#8	'gut microbiome':ab,ti	10019
#7	'microbiome, gastrointestinal':ab,ti	2
#6	'gastrointestinal microbiomes':ab,ti	35
#5	'intestine flora'/exp	60763
#4	#1 OR #2 OR #3	283315
#3	ra:ab,ti	131504
#2	'arthritis, rheumatoid':ab,ti	625
#1	'rheumatoid arthritis'/exp	227296

Figure 1 Embase session results.



**Figure 2** Plan of study screening and selection process.

agreement.<sup>56</sup> The plan of study screening and selection is available in [figure 2](#).

### Assessment of risk of bias

The quality of the included studies will be assessed using NOS.<sup>51</sup> It is a tool mainly used to evaluate the quality of case-control and cohort studies. The parameters considered under each category are ① selection: case definition, representativeness of the cases, selection of controls and definition of controls; ② comparability: comparability of cases and controls based on the basis of the design or analysis; ③ exposure: ascertainment of exposure, the same method of ascertainment for cases and controls, non-response rate. There are 1–2 stars in each category, with a maximum of 9 stars for all. The number of stars is proportional to the mass of the study. The number of stars is directly proportional to the quality of the study. The standard of high quality will be NOS score  $\geq 7$  stars.

To ensure consistency in assessments, the two reviewers (HXG and HZ) will independently evaluate the eligible literature according to NOS and will be summarised in a table. When disagreements arise in the review, the third reviewer (ZLS) cooperates with the team to reach a consensus.

### Data extraction

Data from each eligible article will be extracted and compiled using a standardised excel sheet. Items required for extraction will be obtained using the PECOS steps. The following data will be extracted for eligible studies: first author's surname, year of publication, country, classification criteria for RA, number of cases and controls, age and sex, disease duration, antibody positive of RA, 28-joint disease activity score, medication, assessment methods of faecal microbiota, alterations in gut microbial

abundance, alpha-diversity indexes (OTUs, Shannon Index and Chao 1 Index) and beta-diversity.

To conduct the meta-analysis, we involve trials that have available and sufficient data to calculate the standardised mean difference (SMD) with 95% CI in RA patients and healthy controls in the analysis of the pooled data set. If additional data or data transformations will be required for analysis, we will download the publicly available raw data from online repositories or links provided in the original publications. If there is no relevant data in the original literature, we will acquire it after personal communication with the authors of the manuscripts. If the authors do not reply, we will use Web Plot Digitizer (v.4.42) to digitise and extract sufficient data from graphs and plots in the articles.<sup>45 57</sup>

To ensure the accuracy of the extracted data, we will randomly select two eligible pieces of literature to be independently extracted by two reviewers (FQC and RZ). Kappa will be applied to compare the consistency of data extraction from the two literatures by the two reviewers. If there is an almost perfect agreement between the two reviewers (kappa value  $\geq 80\%$ ), the remaining literature will be extracted by one of the two reviewers.

### Data synthesis and analysis

When the number of studies for a single bacterium is five or more, we will conduct the meta-analysis by R language Version 3.4.3 to compare the abundance level of gut microbiota in RA patients with healthy controls. We will adopt SMD with 95% CI of microbiota abundance as summary statistics when gut microbiota was detected by different techniques in the included studies.<sup>58–60</sup> The included studies will be analysed at the phylum or genus levels for consistency. The forest plots will be used to visualise the results. We will assess heterogeneity between studies using the Higgin  $I^2$  statistic. In relative terms,  $I^2$  values are proportional to heterogeneity:  $I^2$  values of 25%, 50% and 75% means low, moderate and high heterogeneity, respectively.<sup>61</sup> Data analysis will be performed by a random-effect model when there is substantial heterogeneity ( $I^2 > 50\%$ ); otherwise, a fixed-effects model will be used.<sup>47</sup> Additionally, we will conduct subgroup analysis of different genders (man/woman) and regions (east/west) included in the studies.

If meta-analysis is not feasible, we will conduct narrative synthesis to summarise the relevant evidence between RA and gut dysbiosis. The quantitative narrative synthesis will be conducted according to the Synthesis Without Meta-analysis guideline checklist.<sup>62</sup> In order to define the characteristics of the gut microbiota in RA, we will perform compositional analysis based on the abundance, diversity, and specific bacterial detection of gut microbiota in RA patients and healthy controls.

### Assessment of publication bias

We will apply funnel plot and Egger's test to assess publication bias.<sup>59</sup> If funnel plots present asymmetry, we will use Egger's test to statistically examination.<sup>63 64</sup>

## Assessment of evidence quality

We will conduct an appraisal of the quality of evidence by applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.<sup>65</sup> Two reviewers (YF and RZ) will assess five domains including limitations of design, inconsistency, indirectness, imprecision and publication bias. The GRADE classifies the quality of evidence as four levels: high, moderate, low and very low. Disagreement on the assessment will be resolved by a third reviewer (ZLS). The GRADE Evidence Profiles will be generated using GRADEpro GDT (<https://www.gradepro.org/>).

## PATIENT AND PUBLIC INVOLVEMENT

No patient or public involved.

**Contributors** DWW and XTP drafted the manuscript and contributed equally to this manuscript as joint first authors. YFL provided the materials. HXG and HZ collected and assembled the data. FQC, RZ and YF analysed and interpreted the data. ZLS conceived the study and critically revised the draft. All authors assisted in manuscript editing and approved its contents.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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