Review

The microbiota in axial spondyloarthritis: what have we learned from Mendelian randomisation studies?

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ABSTRACT

Objective. *It has been postulated that the gut microbiota plays an important role in the pathogenesis of spondyloarthritis (SpA). However, cross-sectional studies are limited in their ability to differentiate disease-driven microbial alterations from causative changes. Mendelian randomisation (MR) studies leverage existing genetic associations to investigate causality, offering insights into microbiota-disease associations.*

Methods. *We conducted a systematic review of all MR studies that evaluated the relationship between the microbiota and axial SpA. Eight studies were identified and reviewed. To look for genetic associations with the microbiota, all of them used the MiBioGen microbiota genome-wide association study (GWAS), with one also using the Dutch Microbiome Project. To find associations between the human genome and disease, various data sources were used, including the published GWAS in ankylosing spondylitis (AS), FinnGen, the UK Biobank, and the Integrative Epidemiology Unit (IEU) Open GWAS project.*

Results. *MR findings revealed predicted increased abundances of Ruminococcaceae NK4A214 and Verrucomicrobia among others, alongside decreased abundances of Lactobacillaceae, and Rikenellaceae families, as well as the Bacteroides genus. These findings largely support the results from cross-sectional studies of the microbiota in patients with SpA. They suggest that bacteria that disrupt gut barrier function may result in an increased risk of SpA, while the opposite may be true with bacteria such as Alistipes and Bacteroides that may have a protective role.*

Conclusion. *These results underscore the interplay of genetics, microbiota, and disease. Further research is needed to refine these findings and optimise therapeutic approaches.*

Introduction

Retrospective and cross-sectional studies are frequently designed to assess for an association between an exposure and an outcome of interest, an association which may in turn support a causal relationship. Regardless of the strength of the identified statistical association, these studies as recently summarised (1) have well-known limitations. Reverse causality may occur when the 'outcome' precedes and perhaps causes the 'exposure', and confounding can arise when a single event influences both. In the realm of microbiota studies, reverse causality is a substantial concern. Not only can intestinal inflammatory changes result in alterations in the microbiota (2), but so can many of the therapies used to treat rheumatologic diseases. Examples include non-steroidal anti-inflammatory drugs (NSAIDs) (3), proton pump inhibitors (3), (while not directly therapeutic, may be used to limit toxicities associated with NSAIDs or corticosteroids), methotrexate (4), sulfasalazine (5), and biologics (6). Patients with inflammatory conditions characterised by gastrointestinal symptoms may attempt dietary changes, which in turn can result in rapid changes in the contents of the microbiota (7). Finally, some inflammatory conditions are either treated with antibiotics or induce symptoms that may prompt empiric antibiotic use prior to diagnosis. Taken together, these factors suggest multiple factors that may bias microbiota studies involving patients with arthritis, blurring the line between disease-induced changes and treatment-related alterations in microbial composition.

An additional consideration with the interpretation of microbiota studies is that the microbiota at the time of disease onset may be less important than early-life microbiota alterations. While

studies using blood biobanks have shown serologic changes taking place years before the onset of diseases such as rheumatoid arthritis (8) or lupus (9), stool biobanks are less frequently used, although one study did show differences among 12 infants (10) who eventually developed juvenile idiopathic arthritis (JIA) compared to 1671 who did not. As reviewed, numerous studies have shown that early-life events, including mode of delivery, mode of feeding, and antibiotic use can influence future risk of development of JIA (11), with studies also linking SpA risk with duration of breastfeeding among both paediatric (12) and adult (13) patients. Since some of these changes, especially those associated with the mode of delivery (14), may not have long-lasting impacts on the intestinal microbiota, these findings raise the possibility that microbiota induced by early-life alterations may have an 'imprinting' effect on the development of the immune system. Indeed, studies using germ-free animal models have shown that the age of exposure to a microbiota impacts the presence and severity of certain diseases (15, 16).

Using genetic data, researchers can infer which microorganisms are likely to be enriched or depleted in individuals relative to the general population, offering an indirect means of assessing pre-disease microbiota. The MiBioGen genome-wide association study between the fecal microbiota and human genetics demonstrated numerous genetic variants that are associated with alterations in the abundance of specific organisms (17). Separately, studies have sought out genetic associations with rheumatologic conditions, including axial SpA (18). These studies have prompted the development of a branch of studies known as Mendelian randomisation (MR) studies, which use as input genomic associations between genetic variants and exposure and test the association between genetic variants and outcome only through exposure. The genetic variants (SNPs) act as a valid instrument variable (IV) for studying the causal relationship between the exposure and the outcome in an MR study. Thus, the selection of strong genetic variants is crucial for a successful MR study determining causality. There are three key assumptions of the MR study: 1. relevance (significantly and strongly associated with the exposure); 2. independence (genetic variants are independent of potential confounders that could influence the outcome), and 3. exclusion restriction (genetic variants affect the outcome through only exposure and not any other pathway (no pleiotropy). Any violation of the assumptions can lead to a biased conclusion of the causality in the MR study. Figure 1 depicts the MR study pictorial with assumptions.

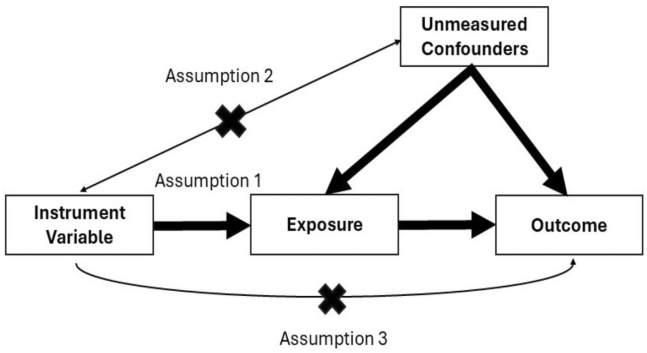

Fig. 1. The graph illustrates the core assumptions of Mendelian randomisation.
Assumption 1: The Instrument variable (IV) must be associated with the exposure of interest.
Assumption 2: The IV should be independent of other factors which affect the outcome.
Assumption 3: The IV should be independent of the outcome, given the exposure and all the confounders.

The implication of the finding of a limited set of genetic variants that are associated with both the exposure and the outcome is the possibility that these genes mediate the outcome by acting on the exposure. In the setting of MR studies involving the microbiota and rheumatologic diseases, this specifically means that the hypothesis is that the genes impact disease risk by acting on the microbiota.

Methods

Identification of articles

Since the publication of the MiBioGen genetic association study involving the microbiota (17), there has been a rapid increase in the publication of MR studies involving the microbiota, with PubMed searches identifying 21 in 2021, 43 in 2022, 368 in 2023, and 555 in 2024 at the time of this writing. For the current analysis, we conducted a systematic literature search in PubMed up to November 22, 2024 using the search terms 'Mendelian', 'randomization', and ('spondyloarthritis' or 'spondylitis' or 'axial spondyloarthritis') and ('microbiome or microbiota'). The analysis was limited to prospective studies limited to patients with axial SpA; all other diagnoses, including psoriatic arthritis and IBD-associated arthritis, were excluded. Studies involving subjects with more than one condition (*e.g.* SpA and rheumatoid arthritis) were included, provided that subjects with each condition were reported separately – which was the case in all instances. Review articles were excluded. This search identified 10 articles published between February 2023 and November 2024, of which 8 are reported herein (19-26); of the other two, one was a review article (27) and the other an erratum (28) (Table I).

Association of the microbiota with human genetics

All 8 of the included studies used the MiBioGen Consortium (17) to generate the instrumental variables (IVs), which is the list of single nucleotide polymorphisms (SNPs) significantly associated with the microbiota. The MiBioGen study included 18,340 healthy human subjects aged 4–88 years from 24 different cohorts based in multiple locations in the United States, Europe, the Middle East, and Asia who underwent 16S sequencing of the fecal microbiota as well as host DNA sequencing. Sequencing was done using various platforms, with data from 23 of 24 of the cohorts imputed using the Haplotype Reference Consortium panel through the Michigan Imputation Server (29). Additionally, one of the MR studies

Table I. Studies included in the systematic review.

Study	Database of microbial GWAS	Database of AS GWAS	Increased bacteria	Decreased bacteria
Yang *et al*., 2023[24]	MiBioGen[17]	FinnGen[31]	*G. Streptococcus, F. Lachnospiraceae*	*G. Bacteroides, P.* Proteobacteria,
Chen *et al*., 2023[19]	MiBioGen[17]	IGAS Consortium[18]	*G. Ruminococcaceae NK4A214 group*	*F. Lactobacillaceae, F. Rikenellaceae, G. Howardella, G. Anaerotruncus*
Wang *et al*., 2023[23]	MiBioGen[17]	UK Biobank[32]	*F. Defluviitaleaceae, G. Butyricicoccus, G. Coprococcus 3, G. Defluviitaleaceae UCG011,*	*G. Anaerotruncus, RuminococcaceaeUCG002*
Lu *et al*., 2024[25]	MiBioGen[17]	FinnGen[31]	C. Actinobacteria, *F. Streptococcaceae, G. Enterorhabdus, G. Ruminococcaceae NK4A214 group*	*F. Lactobacillaceae, F. Rikenellaceae, G. Anaerotruncus, G. Howardella, G. Oscillibacter*
Tang *et al*., 2024[22]	MiBioGen[17]	FinnGen[31]	C. Actinobacteria, O. Bacillales, *G. Enterorhabdus, G. Ruminococcaceae NK4A214 group*	*F. Lactobacillaceae, F. Rikenellaceae, G. Anaerotruncus, G. Howardella, G. Oscillibacter*
Du *et al*., 2024[20]	MiBioGen[17]	IEU database[33]	C. Actinobacteria, *G. Ruminococcaceae NK4A214 group*	*F. Lactobacillaceae, F. Rikenellaceae, G. Howardella*
Jiang *et al*., 2024[21]	MiBioGen[17], DMP[30]	FinnGen[31]	P. Verrucomicrobia, C. Verrucomicrobiae, O. Bacillales, O. Burkholderiales, O. Verrucomicrobiales, *F. Alcaligenaceae, F. Verrucomicrobiaceae, G. Akkermansia, G. Erysipelato clostridium, G. Holdemania, S. Bacteroides vulgatus, S. Paraprevotella xylaniphila, S. Sutterella wadsworthensis, S. Haemophilus parainfluenzae*	O. Mollicutes RF9, *G. Dialister, G. Howardella, G. Oscillibacter, G. Oscillospira, S. Barnesiella intestinihominis, S. Eubacterium hallii*
Pan *et al*., 2024[26]	MiBioGen[17]	FinnGen[31]	C. Actinobacteria, O. Bacillales, P. Verrucomicrobia	*F. Bacteroidaceae, G. Bacteroides, G. Oscillospira*

AS, ankylosing spondylitis; DMP, Dutch Microbiome Project; GWAS, genome-wide association study; IEU, Integrative Epidemiology Unit, IGAS, International Genetics of Ankylosing Spondylitis.

(21) also used the Dutch Microbiome Project (30) (DMP), combining the two datasets to generate IVs. The DMP analysed the gut microbiota of 7,738 participants aged 8–84 years using shotgun metagenomic sequencing. For generating SNPs, genotyping was performed using the Infinium Global Screening Array MultiEthnic Diseases, and the data were imputed using the Haplotype Reference Consortium panel. Both MiBioGen and the DMP used a genome-wide association study (GWAS) approach to assess the association between gut microbiota composition and human genetic variation.

Association of axial spondyloarthritis with human genetics

A variety of sources were used to evaluate genetic associations between AxSpA and the IVs identified from the microbial GWAS data. Specifically, five of the studies (21, 22, 24-26) used data from the FinnGen Consortium (31), a national cohort study involving approximately 500,000 Finnish participants. FinnGen integrates genetic data from biospecimens with clinical information, which is continuously updated as new diagnoses are made. The data are made available to outside investigators, permitting integrated data analyses. One study (19) used data from the International Genetics of Ankylosing Spondylitis Consortium (18), a landmark study of 10,619 individuals with ankylosing spondylitis (AS) and 15,145 controls of mostly European ancestry. Another study (23) used data from the UK Biobank (32), a large UK cohort study similar to FinnGen in its cohort size, the availability of genetic and clinical data, and its open-access model for researchers. Finally, one study (20) used data from the Integrative Epidemiology Unit (IEU) Open GWAS project (33). Developed by the Medical Research Council IEU at the University of Bristol, this serves as a comprehensive resource providing access to a vast array of GWAS summary datasets, including public datasets such as the above and private datasets.

Evaluation of the MR studies

Recently, guidelines for performing MR studies have been proposed (34). We investigated whether the MR studies on AS follow the proposed guidelines using appropriate methods. Supplementary Table S1 provides information on AS MR studies methods, including 1. selection of strong independent genetic variants (pruning and clumping to avoid possible pleiotropy and also F-values >10 for SNPs to avoid weak instrument bias); 2. removing possible confounding due to association of SNPs and outcome through phenotypes other than exposure, using PhenoScaner v. 2.0 (a database for genotype-phenotype association) (35); 3. appropriate primary method of MR and supplementary methods to test concordance and direction of the findings from primary method; (4) MR-Egger or any other method to test for horizontal pleiotropy using intercept model; (5) Cochran Q-test for heterogeneity; (6) pleiotropy global test using MR-PRESSO to test pleiotropy and outlier detection; (7) leave-one-out

Table II. The MR results from all 8 studies with *p*-value ≤0.05.

Study	Group	Exposure	#SNPs	OR (95%CI)	*p*-value
Yang *et al*., 2023	Genus	*Bacteroides*	9	0.990 (0.621, 1.579)	0.965
	Genus	*Streptococcus*	14	1.120 (0.741, 1.692)	0.591
	Phylum	Proteobacteria	12	0.954 (0.525, 1.733)	0.877
	Family	*Lachnospiraceae*	16	1.073 (0.732, 1.574)	0.717
Chen *et al*., 2023	Family	*Lactobacillaceae*	9	0.696 (0.527, 0.919)	0.011
	Family	*Rikenellaceae*	19	0.680 (0.491, 0.942)	0.020
	Genus	*Ruminococcaceae NK4A214 group*	14	1.707 (1.190, 2.449)	0.004
	Genus	*Howardella*	9	0.802 (0.650, 0.991)	0.041
	Genus	*Anaerotruncus*	13	0.671 (0.454, 0.991)	0.045
Wang *et al*. 2023	Family	*Defluviitaleaceae*	11	1.001 (1.000, 1.003)	0.005
	Genus	*Anaerotruncus*	13	0.998 (0.997, 0.999)	0.019
	Genus	*Butyricicoccus*	8	1.002 (1.000, 1.003)	0.043
	Genus	*Coprococcus 3*	9	1.002 (1.000, 1.003)	0.046
	Genus	*DefluviitaleaceaeUCG011*	9	1.002 (1.001, 1.003)	0.004
	Genus	*RuminococcaceaeUCG002*	21	0.999 (0.998, 1.000)	0.038
Lu *et al*., 2024	Class	Actinobacteria	14	1.695 (1.217, 2.360)	0.002
	Family	*Lactobacillaceae*	8	0.671 (0.502, 0.898)	0.007
	Family	*Rikenellaceae*	16	0.661 (0.466, 0.937)	0.020
	Family	*Streptococcaceae*	11	1.567 (1.021, 2.403)	0.040
	Genus	*Anaerotruncus*	13	0.671 (0.454, 0.991)	0.045
	Genus	*Enterorhabdus*	6	1.736 (1.036, 2.908)	0.036
	Genus	*Howardella*	9	0.802 (0.650, 0.991)	0.041
	Genus	*Oscillibacter*	13	0.403 (0.168, 0.966)	0.042
	Genus	*Ruminococcaceae NK4A214 group*	13	1.695 (1.148, 2.503)	0.008
Tang *et al*., 2024	Class	Actinobacteria	14	1.862 (1.292, 2.685)	0.001
	Order	Bacillales	9	1.229 (1 .000, 1.509)	0.049
	Family	*Lactobacillaceae*	7	0.645 (0.475, 0.876)	0.005
	Family	*Rikenellaceae*	17	0.662 (0.471, 0.932)	0.018
	Genus	*Anaerotruncus*	13	0.671 (0.454, 0.991)	0.045
	Genus	*Enterorhabdus*	6	1.736 (1.036, 2.908)	0.036
	Genus	*Howardella*	9	0.802 (0.650, 0.991)	0.041
	Genus	*Oscillibacter*	12	0.382 (0.151, 0.962)	0.041
	Genus	*Ruminococcaceae NK4A214 group*	13	1.695 {1.148, 2.503)	0.008
Du *et al*., 2024	Class	Actinobacteria	16	1.724 (1.259, 2.360)	0.001
	Family	*Lactobacillaceae*	9	0.707 (0.536, 0.932)	0.014
	Family	*Rikenellaceae*	17	0.652 (0.463, 0.917)	0.014
	Genus	*Howardella*	9	0.802 (0.650, 0.991)	0.041
	Genus	*Ruminococcaceae NK4A214 group*	13	1.695 (1.148, 2.503)	0.008
Jiang *et al*., 2024	Phylum	Verrucomicrobia	12	1.37 (1.07, 1.74)	0.011
	Class	Verrucomicrobiae	13	1.31 (1.03, 1.65)	0.026
	Order	Bacillales	9	1.17 (1.01, 1.36)	0.035
	Order	Burkholderiales	12	1.43 (1.07, 1.90)	0.015
	Order	Mollicutes RF9	16	0.80 (0.66, 0.97)	0.022
	Order	Verrucomicrobiales	13	1.31 (1.03, 1.65)	0.026
	Family	*Alcaligenaceae*	19	1.43 (1.13, 1.82)	0.003
	Family	*Verrucomicrobiaceae*	13	1.31 (1.03, 1.65)	0.026
	Genus	*Akkermansia*	13	1.31 (1.03, 1.65)	0.026
	Genus	*Dialister*	12	0.68 (0.53, 0.88)	0.006
	Genus	*Erysipelato clostridium*	17	1.23 (1.02, 1.48)	0.033
	Genus	*Holdemania*	17	1.22 (1.02, 1.46)	0.033
	Genus	*Howardella*	10	0.84 (0.72, 0.97)	0.020
	Genus	*Oscillibacter*	15	0.76 (0.63, 0.91)	0.003
	Genus	*Oscillospira*	10	0.75 (0.59, 0.97)	0.026
	Species	*Bacteroides vulgatus*	8	1.55 (1.22, 1.95)	**2.55E-04**
	Species	*Barnesiella intestinihominis*	13	0.84 (0.71, 1.00)	0.047
	Species	*Paraprevotella xylaniphila*	11	1.13 (1.00, 1.28)	0.048
	Species	*Eubacterium hallii*	12	0.86 (0.74, 0.99)	0.030
	Species	*Sutterella wadsworthensis*	5	1.55 (1.19, 2.02)	0.001
	Species	*Haemophilus parainfluenzae*	6	1.19 (1.01, 1.41)	0.036
Pan *et al*., 2024	Class	Actinobacteria	15	1.254 (1.004, 1.566)	0.046
	Order	Bacillales	8	1.199 (1.030, 1.394)	0.019
	Phylum	Verrucomicrobia	12	1.288 (1.025, 1.619)	0.030
	Family	*Bacteroidaceae*	9	0.660 (0.466, 0.933)	0.019
	Genus	*Bacteroides*	9	0.660 (0.466, 0.933)	0.019
	Genus	*Oscillospira*	8	0.735 (0.564, 0.957)	0.022

Fig. 2. Protective or risk factor of organisms on AS using the IVW method in at least two studies.
Green represents the protective effect; red represents the risk factor; and no colour means no significant effect was found with a *p*-value <0.05 in the study.
*Genus *Bacteroides* was not significant in Yang *et al*. with a *p*-value ≤0.05, however, it was statistically significant in Pan *et al*. 2024, with *p*-value ≤0.05.
**Also, the species *Bacteroides vulgatus* has the same direction and was significant (*p*-value=2.255E-04) with Bonferroni correction in the Yang *et al*. 2024 study.

analysis to test the influence of single SNP; (8) performed reverse MR; and (9) lastly correction for multiple testing. Supplementary Table S3 presents the Cochran's Q-test results for each of the eight studies.

Querying for HLA-B27

The following SNPs were used as genetic markers for the HLA-B27 gene: rs43439859 (36), rs116488202 (36), rs13202464 (36, 37).

Results

Overview of the MR studies

A total of 8 studies were identified (Table I), in all of which the disease studied was AS. Additional populations included in some of these studies were not included in this review. In all of these studies, the primary published output was not the specific genes associated with the organisms and the condition, but rather the organisms whose abundance was predicted to be increased or decreased based on the shared genetics between the exposure (microbiota) and outcome (AS). All 8 studies used a lenient cut-off of *p*-value $<1 \times 10^{-5}$ to select GWAS SNPs to ensure a sufficient number of genetic variants for initial screening. To select only mutually independent SNPs, 7 studies used $r^2<0.001$ in 10,000 kb around the index SNP to avoid the dependence caused by linkage disequilibrium (LD) between the SNPs. Chen *et al*. (19) used 500 kb intervals and $r^2<0.01$. All studies used F-values >10 for SNPs to avoid weak instrument bias (38). Furthermore, they harmonised the effect size of SNPs on exposure and outcome and removed palindromic SNPs. A few studies used PhenoScanner v. 2.0 (a database for genotype-phenotype association) to remove possible confounders due to the association of SNPs and outcomes through phenotypes other than exposure (35).

All studies used the TwoSampleMR package (33, 39) and the MR-PRESSO package (40) in R software for all MR analyses. Note that the TwoSampleMR package provides a complete pipeline for MR analysis including a choice of primary method, additional methods to estimate causal effects under different conditions (weighted median, MR Egger, simple mode, and weighted mode, etc.) to test concordance and directionality with primary method; Cochran's Q test to detect heterogeneity among instrumental variables (41); assess horizontal pleiotropy using MR Egger intercept (42); determine global horizontal pleiotropy and to correct for potential outliers using MR-PRESSO (40); the leave-one-out method to evaluate the degree of influence of a single SNP in causal association; and a reverse-direction MR analysis to determine whether there was a reverse-direction causal relationship. In addition, 7 studies performed the multiple test correction either globally using Bonferroni correction or using the number of GM taxa in five biological classifications of phylum, class, order, family, and genus. Jiang *et al*. also used species (21). One study by Yang *et al*. tested only 4 taxa (24) and they did not find any taxa significant with a *p*-value ≤0.05, therefore it was a null study. All studies performed primary analysis using the inverse variance weighted (IVW) method (43) and reported the taxa with a suggestive significance threshold of *p*-value ≤0.05.

Findings from the MR studies

Table II provides the results of IVW MR analyses for all eight studies consisting of taxon, number of SNPs, odds ratio (OR), 95% confidence interval of OR, and corresponding *p*-values. 7 out of 8 studies showed suggestive significance (*p*-value ≤0.05), using the inverse-variance weighted (IVW) method, although some of the other supplementary methods failed to detect statistically significant associations with *p*-value ≤0.05 but revealed a similar effect size direction, except for Yang *et al*. which contained no significant taxa (24). Also, the sensitivity analyses showed no significant heterogeneity or horizontal pleiotropy in all studies implying the MR results were accurate and reliable (Suppl. Table S1). Leave-one-out and reverse MR were performed in most of the studies (Suppl. Table S1).

Our focus was on taxa that were found to be significant in at least two studies. The only exception here is *Bacteroides*. At the genus level, *Bacteroides* was sta-

tistically significant in Pan *et al*., 2024 with a *p*-value of ≤0.05 (26). Also, the species *Bacteroides vulgatus* had the same direction and was significant (*p*-value = 2.55E-04) with Bonferroni correction in the Jiang *et al*., 2024 study (21); therefore, Bacteroides was included in Table II and Figure 2.

Figure 2 depicts the common taxa in the studies with *p*-value of ≤0.05 with the colour green representing bacteria with protective effects and red representing those that are risk factors. Supplementary Table S2 contains the number of SNPs used in the study, effect sizes with ORs and 95% CIs, and corresponding *p*-values, for all common taxa. Notable findings include an increased abundance of organisms from within the Ruminococcaceae NK4A214 group in 4 studies, Actinobacteria class in four studies, Verrucomicrobia phylum in two studies, *Bacillales* order in three studies, the genus *Enterorhabdus* in two studies, and several organisms identified in one study each. Decreased abundance of the *Howardella* genus was identified in five studies, the Lactobacillaceae and Rikenellaceae families and the *Anaerotruncus* genus in four studies each, the *Oscillibacter* genus in three studies, and the *Oscillospira* genus in two studies. Additionally, as noted above, the *Bacteroides* genus was decreased in one study, and the *B. vulgatus* species in another. *B. vulgatus* with a *p*-value of 2.55×10^{-4} was significant with multiple test corrections in the Jiang *et al*. study (21). Finally, several organisms were identified as predicted to be decreased in one study each. In addition, we performed a meta-analysis for each taxon using a random-effects model if the taxon was found significant in at least two studies (Suppl. Table S2). Meta-analyses showed significant associations corresponding to most of the taxa except *G. Bacteroides* (*p*-value = 0.223; I^2 = 67.98) and *G. Anaerotruncus* (*p*-value = 0.059; I^2 = 0.00). For taxa with consistent associations (*e.g. F. Lactobacillaceae*, *F. Rikenellaceae*, *G. Howardella*, *G. Oscillibacter*, *G. Oscillospira*, *G. Bacteroides*, *G. Ruminococcaceae NK4A214 group*, *C. Actinobacteria*, *P. Verrucomicrobia*, *O. Bacillales*, and *G. Enterorhabdus*), the pooled effect sizes remained significant with low to moderate heterogeneity (I^2 <50%), supporting the robustness of the associations.

Neither of the two GWAS studies of the microbiota identified SNPs associated with HLA-B27 to be associated with microbial abundance; consequently, it was not used as an IV in any of the MR studies.

Discussion

Taken together, the MR findings provide insight into the pathogenesis of SpA that is supportive of prior work in the field and also identify potential limitations in cross-sectional studies of the microbiota. For the most part, the MR studies demonstrated an association between the Ruminococcaceae family and axial SpA (19, 20, 22, 25). This finding supports several studies demonstrating an increased abundance of *Ruminococcus gnavus* or unspecified *Ruminococcus* genera in adult patients with axial or peripheral SpA (44-48). In one study, the abundance of *R. gnavus* correlated with disease activity among patients with inflammatory bowel disease-associated SpA (44). One mechanism by which Ruminococcaceae family members could trigger SpA is that some of these are mucin-degrading organisms, which can in turn degrade the intestinal barrier (49). Of note, two of the MR studies also identified Verrucomicrobia as an associative phylum, one of which also specifically identified the *Akkermansia* genus (21, 26). The first-described and only known species in this phylum that resides in humans, *A. muciniphila*, was assigned its name based on its primary energy source: intestinal mucin (50). There are contradictory data regarding a potential role of this organism in the pathogenesis of SpA, with a paediatric study demonstrating increased abundance in a subset of subjects (51), while a study in adults with AS demonstrated depletion as compared to HLA-B27+ adult controls (52). We have speculated that early on in the disease course, an increased abundance of *A. muciniphila* may result in loss of the intestinal barrier, while the decreased abundance of *A. muciniphila* in patients with long-standing disease may reflect secondary decreases due to loss of mucin (53). Given the lengthy diagnostic delay in adults with SpA (54), even newly diagnosed and treatment-naïve patients have likely had inflammation ongoing for several years, underscoring the need to identify patients with early disease.

It is challenging to assess the findings of increased predicted Actinobacteria class in patients with AS, given the large number of organisms falling within this class. The MR studies in this respect do validate two prior microbiota studies in patients with AS, which likewise showed an increased abundance of Actinobacteria in patients with the condition (55, 56). However, no single organism within Actinobacteria has been linked to the disease. Of interest, *Cutibacterium* (formerly known as *Propionobacterium*) a*cnes* has been postulated to be a causative organism in chronic non-bacterial osteomyelitis or synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, potentially through activation of the NLRP-3 inflammasome (57, 58). There is also a case report of suspected reactive arthritis triggered by *C. Acnes* in an HLA-B27-positive adolescent (59). Finally, echoing the findings with Verrucomicrobia, several members of this class are among the bacteria with enzymes capable of degrading mucin (60). There are mixed data with respect to some of the organisms within this class, particularly the *Bifidobacterium* genus, which various studies have found to be protective against (47, 61, 62) or a risk factor for (63, 64) SpA; these contradictory findings underscore the limitations of identifying patients at later stages of the disease process and as well underscore the limitations of identifying bacteria at higher phylogenetic levels.

Similar challenges underlie the assessment of potential mechanisms by which the Bacillales order may be linked to AS. The additional organism identified in two of the studies (22, 25), *Enterorhabdus*, was initially isolated from inflamed ileal tissue from TNF(ΔARE) mice, a model of inflammatory bowel disease and SpA caused by over-expression of tumour necrosis factor (TNF)

(65). Supporting a role for the microbiota in this model, transmission of the intestinal bacteria to wild-type germ-free mice can introduce inflammatory disease in recipient mice (66). However, little is known about this organism, and contradicting the findings from the present study, an MR study showed it to be predicted to be decreased in patients with IBD (67).

Among the organisms predicted to be decreased in patients with AS, the *Bacteroides* genus bears particular mention. This finding has been reported in multiple studies of adults with SpA (48, 52, 56, 63, 64, 68, 69), albeit it was also reported to be increased in paediatric patients (51, 62, 68, 70). Multiple studies have demonstrated that *Bacteroides* species, perhaps especially *B. fragilis* but also *B. vulgatus*, appear to have a regulatory effect through their impact on regulatory T cell *versus* Th17 balance in the intestines and draining lymph nodes (71-73). While the paediatric findings may reflect the impacts of early childhood microbiota abnormalities on immunologic maturation (11), it is likely that the decreased abundance of this genus observed in adults with SpA reflects a lack of the beneficial protective effect. Note that MR studies are likely to better reflect the impact of the microbiota on adult *versus* paediatric diseases due to the fact that the microbiota GWAS (17) was mostly conducted on adult subjects, and given rapid shifts in the microbiota throughout childhood especially (74) but not limited to (75) early childhood, MR studies cannot effectively capture associations with early-life microbiota.

There is not much literature on potential mechanisms by which the remainder of the genera shown to be decreased in patients with AS might have a protective effect on the disease. Yegerov *et al*. (2020) reported that the *Oscillibacter* genus was also decreased in patients with psoriasis (76), and Lee *et al*. (2016) demonstrated a decreased abundance of *Anaerotruncus colihominis* in patients with rheumatoid arthritis compared to osteoarthritis (77). *Oscillospora* has been shown to be a butyrate-producing organism (78), the significance of which will be discussed below. However, significant mechanistic data on these organisms are lacking.

It is more challenging to interpret the significance of altered organisms identified at the family level (Lactobacillaceae or Rikenellaceae). That said, the Lactobacillaceae family, which includes the *Lactobacillus* genus, is well-recognised for its regulatory properties. It includes several species, such as *L. rhamnosus*, *casei*, and *acidophilus*, which are frequently used in probiotic formulations. These bacteria are known for their ability to produce short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate (79). As recently reviewed (80), SCFAs augment intestinal barrier function through a variety of mechanisms including induction of antimicrobial peptides and enhancement of mucin production; and have a regulatory function on intestinal macrophages and T cells. *Lactobacillus* species furthermore appear to enhance intestinal barrier function by acting on tight junctions (81) and thus have a potential opposite impact of the bacteria predicted as being increased in patients with AS. With respect to the Rikenellaceae family, one of its members is the genus *Alistipes*. This genus is also known for its ability to produce SCFAs and is considered to have regulatory properties (82). Consistent with the genetic findings, recent studies have demonstrated decreased abundance of the *Alistipes* genus in patients with SpA (47, 48).

One observation in this review that bears clarification is the varied findings in the MR studies, despite being based on similar data inputs. Specifically, all eight studies used the MiBioGen database (17), one of which also used the Dutch Microbiome Project (30), for the GWAS linking human genetics to the microbiota. Additionally, five of the studies (21, 22, 24-26) used the FinnGen database for the ankylosing spondylitis GWAS, whereas three other studies (18-20) each used a separate database. While we provided a structured summary of studies with consistent associations (Suppl. Table S2), it is important to note that although the number of SNPs used was often similar, the actual SNPs varied across studies. This variability may contribute to differences in effect estimates, yet the reproducibility of associations across independent analyses suggests robustness in the observed relationships. To address variability across studies, we conducted a formal meta-analysis for each taxon using a random-effects model. For taxa with consistent significant associations (*e.g*. Lactobacillaceae, Rikenellaceae), the pooled effect sizes remained significant with low to moderate heterogeneity (I^2 <50%), supporting the robustness of the associations. Beyond these differences, statistical approaches within the individual MR studies may also account for the varied findings, including the threshold for selecting SNPs as instrumental variables, the use of sensitivity analyses; and multiple test correction. Furthermore, the variation in our findings is unlikely due to methodological differences as all studies followed a uniform MR approach including SNP selection at genome-wide significance ($p<5 \times 10^{-8}$), use of Inverse Variance Weighting (IVW) as the primary MR method, with MR-Egger, weighted median, and MR-PRESSO applied as sensitivity analyses in most studies. Given this methodological consistency, the variations in reported associations likely reflect biological and population-level factors. Possible sources of variability may include differences in study populations where variations in genetic ancestry, environmental exposures, and dietary habits could influence gut microbiota composition and its relationship with axial SpA. Also, there could be differences in microbiota measurement techniques. Although all studies used GWAS-derived microbiota traits, variations in sequencing methods and taxonomic classification may have led to inconsistencies in taxa-specific findings. Additionally, the FinnGen, UK Biobank, and IEU are evolving databases, so the differences may reflect the data present in the respective biobank at the time it was accessed.

Limitations

While this systematic review provides a genetic perspective on gut microbiota and axial spondyloarthritis (axSpA), several limitations should be acknowl-

edged. The small number of MR studies, with only eight meeting the inclusion criteria, limits the ability to draw definitive conclusions. Larger MR studies incorporating multi-ancestry GWAS data will be essential for validation. Additionally, biobank data from sources like the IEU, FinnGen, and UK Biobank evolve over time, meaning that variations in results may reflect differences in data availability at the time of access rather than true biological differences. Finally, despite MR methods accounting for pleiotropy, some SNPs may still influence inflammation independently of microbiota changes.

An important limitation to all MR studies is the possible presence of pleiotropy, or the ability of genes to have multiple impacts on the host. Should there be one function that directly impacts inflammation and another that alters the microbiota without significant impact on inflammation, then the gene may be identified in an MR study, yet ultimately the microbiota changes would in this scenario be a confounder. As an illustration, although the SNPs associated with HLA-B27 (36, 37) (rs4349859, rs116488202, rs13202464) were not linked to changes in specific organisms in the two microbiota GWAS (17, 30), targeted studies have shown that HLA-B27 influences the overall composition of the microbiota (62, 83), yet some of the specific changes associated with HLA-B27 (*e.g.* increased *F. prausnitzii* (52, 84) would not likely contribute directly to the disease. Thus, while HLA-B27 is unquestionably linked to AS pathogenesis (85), its mechanism is likely to be independent of impacts on the microbiota. This may as well be the case with some of the genes identified in the microbiota GWAS studies, despite attempts by the authors of the MR studies to correct for pleiotropy.

Novel contributions

Despite these limitations, this review makes an important contribution to the field as the first systematic review of MR studies examining gut microbiota and axSpA. These studies have several important implications. First, they demonstrate the value of genetic approaches to assess predicted microbiota. Obtaining samples at the time of disease fails to capture information about microbial changes that may precede disease development, an important limitation given that early childhood events modulate the risk of juvenile arthritis and likely adult SpA as well (11, 12). Despite this, the MR studies have partially corroborated the cross-sectional studies with respect to the abundance of organisms in the Ruminococcaceae, Lactobacillaceae, and Rikenellaceae families, as well as the *Bacteroides* genus, providing a rationale for direct modulation of these bacteria as a therapeutic approach. Finally, these studies lend support to considerations of gut barrier integrity as a pathogenic feature of SpA and provide support to the use of markers of intestinal inflammation and integrity as a research target as well as an outcome measure in this population. However, since microbiota-targeted therapy in patients with SpA has not yet borne fruit (86), much more work is needed on the optimisation of microbiota-targeted therapy as a complementary tool in patients with SpA. Ultimately, clinical trials will be needed to demonstrate the role of the microbiota and its alterations in the pathogenesis of inflammatory arthritis (87).

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