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ORIGINAL RESEARCH

Gut-joint axis in knee synovitis: gut fungal dysbiosis and altered fungi–bacteria correlation network identified in a community-based study

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ABSTRACT

Objectives Knee synovitis is a highly prevalent and potentially curable condition for knee pain; however, its pathogenesis remains unclear. We sought to assess the associations of the gut fungal microbiota and the fungi–bacteria correlation network with knee synovitis.

Methods Participants were derived from a community-based cross-sectional study. We performed an ultrasound examination of both knees. A knee was defined as having synovitis if its synovium was ≥4 mm and/or Power Doppler (PD) signal was within the knee synovium area (PD synovitis). We collected faecal specimens from each participant and assessed gut fungal and bacterial microbiota using internal transcribed spacer 2 and shotgun metagenomic sequencing. We examined the relation of α-diversity, β-diversity, the relative abundance of taxa and the interkingdom correlations to knee synovitis.

Results Among 977 participants (mean age: 63.2 years; women: 58.8%), 191 (19.5%) had knee synovitis. β-diversity of the gut fungal microbiota, but not α-diversity, was significantly associated with prevalent knee synovitis. The fungal genus *Schizophyllum* was inversely correlated with the prevalence and activity (ie, control, synovitis without PD signal and PD synovitis) of knee synovitis. Compared with those without synovitis, the fungi–bacteria correlation network in patients with knee synovitis was smaller (nodes: 93 vs 153; edges: 107 vs 244), and the average number of neighbours was fewer (2.3 vs 3.2).

Conclusion Alterations of gut fungal microbiota and the fungi–bacteria correlation network are associated with knee synovitis. These novel findings may help understand the mechanisms of the gut-joint axis in knee synovitis and suggest potential targets for future treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Knee synovitis, a potentially modifiable pathological lesion, can cause knee pain, impair function and accelerate the progression of knee osteoarthritis. The pathogenesis of knee synovitis remains poorly understood. The dysbiosis of the gut fungal microbiota and the related alteration of the fungi–bacteria correlation network may trigger systemic inflammation involving the knee joints. No available research has assessed the associations of the gut fungal microbiota and the fungi–bacteria correlation network with knee synovitis.

WHAT THIS STUDY ADDS?

⇒ Using data collected from a large general population-based cohort study, we found that the gut fungal microbiota composition was altered in participants with knee synovitis. The fungal genus *Schizophyllum* was inversely correlated with the prevalence and activity of knee synovitis. Compared with those without synovitis, the fungi–bacteria correlation network in patients with knee synovitis was smaller, and the average number of neighbours was fewer, suggesting a disrupted interface interaction of the fungi–bacteria network in patients with knee synovitis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ The results suggest that the gut-joint axis may be involved in joint pathology through gut fungi and fungi–bacteria correlation network and emphasise the importance of maintaining the stability of gut fungi and bacteria in human health. Our study suggests potential targets for future treatment of knee synovitis.

INTRODUCTION

Knee synovitis is a prevalent and recurrent pathological condition, with the prevalence ranging from 18.1% to 23.9% in the middle-aged and older community population.[1 2] Synovitis can cause knee pain, impair function and accelerate the progression of knee osteoarthritis.[3 4] Previous studies suggest that targeting knee synovitis may potentially

alleviate symptoms and modify structural changes of knee osteoarthritis.[5–7] However, the pathogenesis of knee synovitis remains poorly understood, hindering the development of effective prevention and treatment strategies.

The gut microbiota is the largest reservoir of microbes in the human body and is closely related to host health.[8] Previous studies have shown that gut microbiota can contribute to developing and maintaining joint diseases via immunity and metabolism, namely the 'gut-joint axis'.[9–11] While several studies suggested the role of bacteria in the gut-joint axis,[12–14] to our knowledge, few if any, studies have evaluated the relation of gut fungi and fungi–bacteria interactions to the risk of joint synovitis. The fungal gut microbiota, another key component of the microbiota in the human body, has been shown to contribute significantly to pathophysiological mechanisms by regulating host homeostasis and physiological processes.[15 16] Fungi–bacteria interactions can weave a complex and dynamic fungi–bacteria correlation network, which may play roles in disease.[16–18] In addition, the dysregulation of fungi and fungi–bacteria interactions can also disrupt the normal 'running' of the immune system and increase the production of proinflammatory agents, such as TNF-α, IFN-γ and IL-17.[9 19–22] Thus, the dysbiosis of gut fungal microbiota and the related alteration of the fungi–bacteria correlation network woven by the fungi–bacteria interactions may trigger systemic inflammation in the knee joints. Unravelling associations between gut fungal dysbiosis, altered fungi–bacteria correlation network, and knee synovitis could bring a fresh perspective on knee synovitis and expand the framework of the gut-joint axis.

To fill this knowledge gap, we performed the internal transcribed spacer 2 (ITS2) and shotgun metagenomic sequencing analyses to profile gut fungal and bacterial community structure among the participants in the Xiangya osteoarthritis study (XO study).[2 14] We assessed the relation of dysbiosis of gut fungal and bacterial microbiota and the altered fungi–bacteria correlation network to ultrasound-detected knee synovitis.

METHODS

Study participants

Participants were from the XO study, a population-based cohort study of the natural history and the risk factors of osteoarthritis. Participants aged 50 years or older living in Longshan County of the Hunan Province, China (ClinicalTrials.gov identifier: NCT04033757). Details of the XO Study are described elsewhere.[2 14] The XO study consisted of three subcohorts of a randomly selected sample of residents. Participants of subcohort I (n=1469), subcohort II (n=1271) and subcohort III (n=1340) were recruited in 2015, 2018 and 2019, respectively. The current analyses included participants from subcohort II and III who had knee ultrasound examinations and provided stool samples at baseline.

Assessment of knee synovitis

An ultrasonographer (TJ, with more than 10 years of experience in musculoskeletal ultrasonography) performed all ultrasound examinations and graded the ultrasound images on both knees without knowing the participants' clinical data or the results of other examinations. All ultrasounds were conducted on a Philips ultrasound machine (CX30) with a 4–12 MHz linear transducer. Power Doppler (PD) examination (a pulse repetition frequency of 400 Hz) was used to detect vascular flow in the synovial membrane. The suprapatellar bursa was examined with the participant supine and the knee in 30° flexion according to the Outcome Measures in Rheumatology atlas.[23] We measured the maximal synovial thickness and effusion depth in millimetres along the longitudinal axis. The presence of synovial hypertrophy (synovial thickness ≥4 mm) and joint effusion (depth of effusion ≥4 mm) was defined according to the European League Against Rheumatism study.[24] Based on a semiquantitative grading system (0: absent, 1: mild, 2: moderate, 3: marked or severe), the PD signal was assessed in the synovial membrane in both longitudinal and transverse planes.[25] It represents the activity of synovitis. Both the intra-rater and inter-rater reliability were excellent for synovial hypertrophy (range of intraclass correlation coefficients 0.94–0.99) and PD signal (range of weighted Kappa statistics 0.82–1.00).[2]

PD synovitis was defined as the presence of a PD signal within the knee synovium area. We defined a participant as having knee synovitis if synovial hypertrophy and/or PD synovitis were present in either knee. Since PD reflects the inflammatory activity of synovitis,[26] knee synovitis activity was divided into three categories: control, synovitis without PD signal and PD synovitis. We defined a participant as having knee effusion if this feature was present in either knee. The prevalence of effusion in the XO study was as high as 46.6%.[2] To improve the precision of synovitis classification, participants (n=360) with isolated joint effusion, but no synovial hypertrophy, were excluded from the analyses.

Stool sample collection and DNA extraction

Stool samples from participants were collected at the recruitment site. Collected stool samples were frozen immediately, transported on dry ice within 20 min, and stored at −80°C until DNA extraction. For ITS2 sequencing (fungi), following the manufacturer's protocol, total genomic DNA samples were extracted using the OMEGA Soil DNA Kit (M5635-02) (Omega Bio-Tek, Norcross, Georgia) and stored at −20°C before further analysis. The quantity and quality of extracted DNAs were measured using a NanoDrop NC2000 spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts) and agarose gel electrophoresis, respectively. For shotgun metagenomic sequencing (bacteria), 200 mg of stool was used for DNA extraction using the Magen HiPure Soil DNA Kit (Magen, Guangzhou, China). DNA sample extraction procedure has been detailed elsewhere.[27]

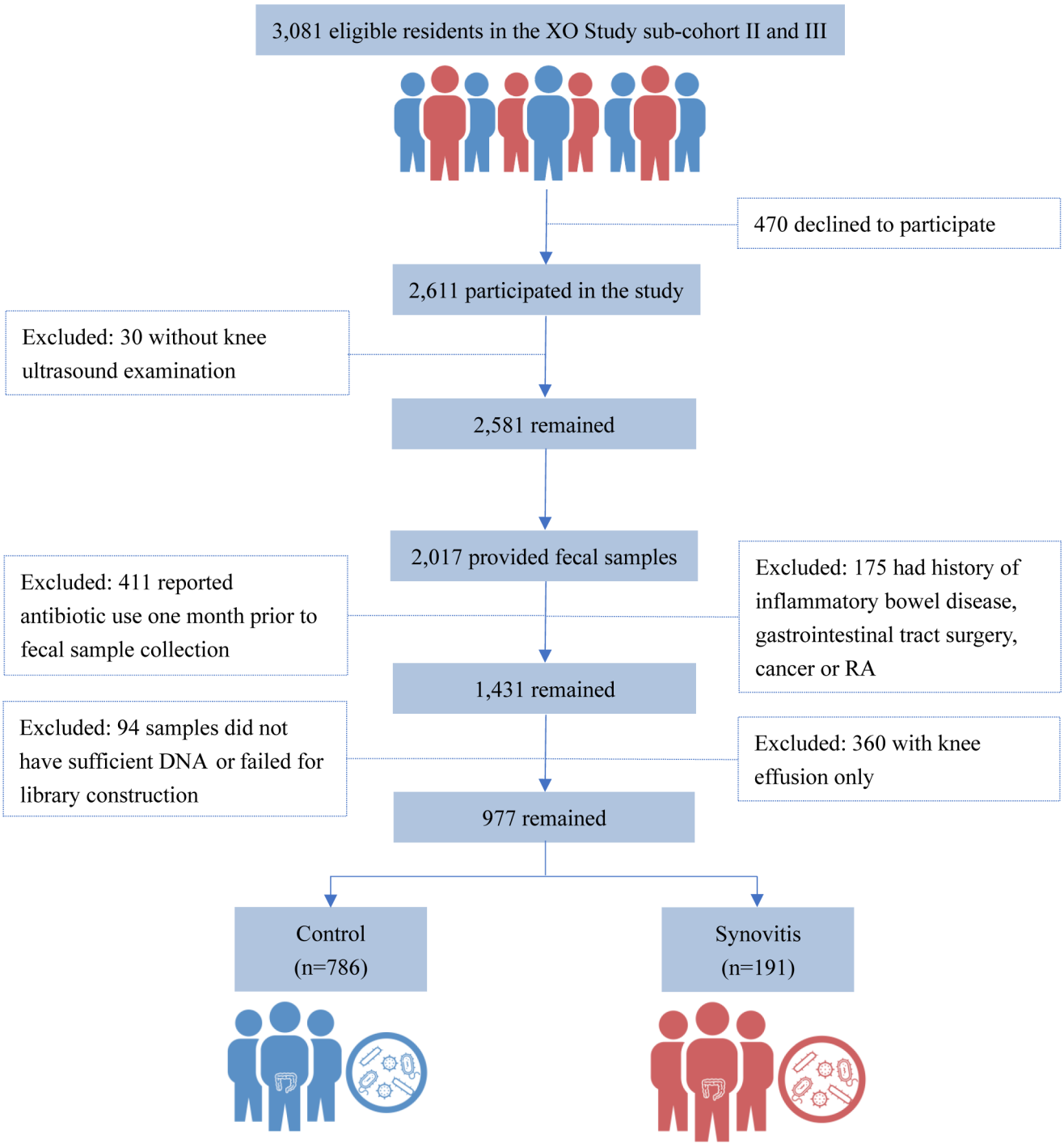


Figure 1 Selection process of the participants in the study. RA, rheumatoid arthritis.

ITS2 sequencing for gut fungi

We amplified the ITS2 based on a primer set specific (front primer: 5'-GTGARTCATCGAATCTTT-3' and reverse primer: 5'-GATATGCTTAAGTTCAGCGGGT-3') targeting the ITS2 hypervariable region, and DNA was sequenced with the NovaSeq 6000 SP Reagent Kit of Illumina NovaSeq platform. In brief, the selected fragments went through end repair, 3'adenylation, adapters ligation, PCR amplification and magnetic bead purification. Microbiome bioinformatics analysis was performed with QIIME2 2022.8 (https://qiime2.org/).[28] Raw sequence data were demultiplexed via the demux plugin, followed by primers cut with the cutadapt plugin. Then, the sequences were quality filtered, denoised, merged and chimaera removed by the DADA2 plugin.[29] Non-singleton amplicon sequence variants (ASVs) were aligned with mafft and used to construct a phylogeny with fasttree2.[30] Taxonomy was assigned to ASVs using the classify-sklearn naïve Bayes taxonomy classifier in the feature-classifier plugin against the UNITE Release V.8.0 Database.[31]

Table 1 Basic characteristics of included participants

	Knee synovitis	Control	P
N	191	786	–
Age, mean (SD), years	66.1 (9.0)	62.5 (9.1)	<0.001
Sex (%)			0.393
Male	44.0	40.6	
Female	56.0	59.4	
BMI, mean (SD), kg/m^2	24.0 (3.6)	23.9 (3.5)	0.689
Drinking status (%)			0.012
None	39.3	51.0	
Past	15.0	10.5	
Current	45.7	38.5	
Smoking status (%)			0.370
None	59.1	64.5	
Past	6.5	5.1	
Current	34.4	30.4	
Dietary intake of meat/eggs, mean (SD), times/week	3.3 (4.1)	3.1 (3.0)	0.198
Dietary intake of dairy products, mean (SD), times/week	0.3 (1.2)	0.2 (0.8)	0.938
Dietary intake of vegetables, mean (SD), times/week	11.0 (6.0)	10.3 (5.8)	0.147

BMI, body mass index; N, number.

Metagenomics sequencing for gut bacteria

DNA samples were randomly fragmented using Covaris. An average size of 200–400 base pairs of the fragmented DNA was selected using magnetic beads. The selected fragments underwent end repair, 3'adenylation, adapters ligation, PCR amplification and magnetic bead purification. Heat-denatured double-stranded PCR products were circularised by splint oligo sequences. The single-strand circular DNA was formatted as the final library and qualified. The qualified libraries were sequenced on the MGISEQ-2000 platform (BGI, Shenzhen, China) and paired end reads of 150-base pair nucleotides were generated.[32] The original sequencing reads were processed through a series of standardisation schemes to obtain clean data.[27] MEGAHIT was used to assemble high-quality reads after quality control.[33] Based on UHGG, Kraken2 was used to assess DNA reads for the taxonomic classification of human stool samples.[34]

Statistical analysis

We used the Shannon index to assess the richness and evenness (ie, α diversity) and the Bray-Curtis distance to evaluate the composition similarities (ie, β diversity) of the gut fungi and bacteria, respectively.[35] We compared the genetic and taxonomic differences in the Shannon index using generalised linear regression and the difference in Bray-Curtis distance using the permutation multivariate analysis of variance test combined with principal coordinates analysis between participants with and those without knee synovitis.[36]

The association between microbial taxa present in ≥10% of samples and the prevalence of knee synovitis was assessed using multivariate association with linear models (MaAsLin2 V.1.10.0), adjusting for age, sex, BMI, smoking history, alcohol drinking and frequency of dietary intake of meat/eggs, dairy products and vegetables.[37] The regression coefficient in MaAsLin represents the mean difference in the log-transformed relative abundances of taxa. We also examined the association of either fungal genus or bacterial species with the knee synovitis activity (ie, control, synovitis without PD signal and PD synovitis) using MaAsLin2.

The Spearman correlation algorithm was applied to construct the interkingdom correlations to explore the ecological links between gut fungi and bacteria, adjusting for the confounders mentioned above.[38] In this analysis, we only considered genera with relative abundance >0.001 and present in >70% of samples.[39] The network was visualised in Cytoscape (V.3.9.1). The relative connectedness of the network was calculated as the ratio between the number of significant interactions (edges) and the number of taxa (nodes) in the network.[38]

Finally, we conducted a sensitivity analysis of adjusting for the use of non-antibiotic drugs that affect the gut microbiota, physical activity, and diabetes when examining the association between gut microbiomes and knee synovitis.

P values <0.05 were considered statistically significant. Multiple testing with the Benjamin and Hochberg False discovery rate method was applied if necessary, and a corrected p value (Q value) <0.1 was considered statistically significant.[40]

RESULTS

Figure 1 shows the selection process for participants in the current analysis. Of 2611 participants recruited in subcohort II and III of the XO study, we excluded 30 participants who did not have knee ultrasound examination, 564 who did not provide faecal samples, 411 who reported antibiotic use within a month before faecal sample collection, 175 who had a history of inflammatory bowel disease gastrointestinal tract surgery, cancer or rheumatoid arthritis, 94 who did not have a sufficient amount of DNA or failed for library construction and 360 had knee joint effusion only. The basic characteristics of the remaining 977 participants are shown in table 1. Of them, 191 (19.5%) had knee synovitis, 14.9% (n=146) had synovitis but no PD signal and 4.6% (n=45) had PD synovitis. Compared with those without knee synovitis, participants with knee synovitis were older and had a slightly higher prevalence of alcohol drinkers. No difference was observed in other sociodemographic and lifestyle factors between the two comparative groups.

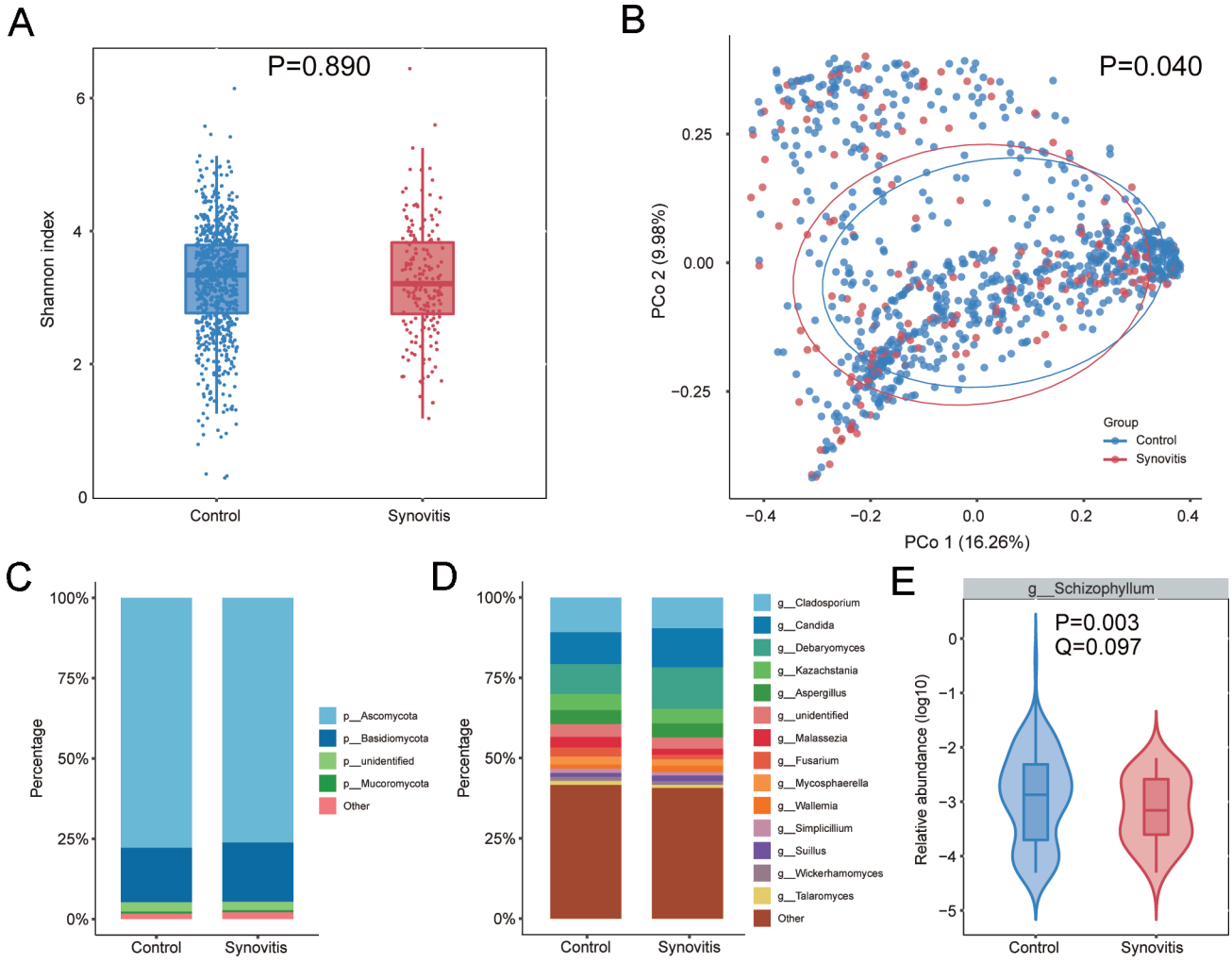


Figure 2 Comparison of fungal diversity and composition between participants with synovitis and controls. (A) Box plots comparing the α-diversity measured by the Shannon index between participants with synovitis and controls. (B) Principal coordinates analysis (PCoA) plots compared β-diversity measured by the Bray-Curtis distance between participants with synovitis and controls. Mycobiome composition at the phylum (C) and genus (D) levels. (E) Relative abundance of differential fungal genus between participants with synovitis and controls identified by multivariate linear regression analysis adjusting for age, sex, body mass index, drinking status, smoking status and frequency of dietary intake of meat/eggs, dairy products, and vegetables.

Gut fungal microbiota and knee synovitis

After quality filtering and removal of contaminants, 91 184 562 high-quality reads from gut fungi were used for analysis (mean reads per sample: 93 331). There was no significant difference in the richness and evenness (ie, α-diversity) of gut fungi (difference in Shannon index, p=0.890) between participants with and those without knee synovitis (figure 2A). However, there was a significant difference in the similarities of gut fungi composition (ie, β-diversity) of gut fungi (difference in Bray-Curtis distance, p=0.040) between the two groups (figure 2B).

In both the knee synovitis and control groups, the profile of gut fungi was dominated by Ascomycota and Basidiomycota at the phylum level (figure 2C) and by *Cladosporium*, *Candida*, *Debaryomyces*, *Kazachstania* and *Aspergillus* at the genus level (figure 2D), the findings were consistent with the usual composition of the human gut fungal microbiota. However, compared with those without knee synovitis, participants with knee synovitis had lower relative abundances of Schizophyllaceae (p=0.004, Q=0.091) and Metschnikowiaceae (p=0.002, Q=0.058) at the family level and *Schizophyllum* (p=0.003, Q=0.097) at the genus level (figure 2E). In addition, there was a significant inverse association between *Schizophyllum* and the activity of knee synovitis (p=0.002, Q=0.092) (table 2). The sensitivity analysis of further adjustment of the use of non-antibiotic drugs that affect the gut microbiota, physical activity and diabetes did not change the relation of gut fungi to knee synovitis materially (online supplemental table S1).

Gut bacterial microbiota and knee synovitis

There was no significant difference in either the richness and evenness (ie, α-diversity) of gut bacteria (the difference in Shannon index, p>0.05) (figure 3A–C)

Table 2 Associations of gut fungi and bacteria with knee synovitis

	Prevalence of knee synovitis	Activity of knee synovitis
Fungi		
g__Schizophyllum		
β coefficient*	−1.509	−0.658
P value	0.003	0.002
Q value	0.097	0.092
Bacteria		
s__Veillonella_tobetsuensis		
β coefficient*	1.021	0.428
P value	0.004	0.002
Q value	0.100	0.079
s__Lawsonibacter_sp000177015		
β coefficient*	0.473	0.153
P value	0.001	0.001
Q value	0.053	0.072
s__CAG-110_sp003525905		
β coefficient*	−0.642	−0.259
P value	0.002	0.002
Q value	0.071	0.083

*Adjusted for age, sex, body mass index, drinking status, smoking status and frequency of dietary intake of meat/eggs, dairy products and vegetables.

or the similarities of gut bacteria composition (difference in Bray-Curtis distance, p>0.70) (figure 3D–F) at either genes, genus or species level between participants with knee synovitis and those without it. The gut bacterial microbiota in the two groups was consistent with the previously reported composition of the human gut bacterial microbiota (figure 3G–I). However, a higher relative abundance of the bacterial genus *Lactobacillus H* (p=0.004, Q=0.081) and species *Veillonella tobetsuensis* (p=0.003, Q=0.100), *Lawsonibacter sp000177015* (p=0.001, Q=0.053) and *MGYG-HGUT-01995* (p=0.001, Q=0.052), but a lower relative abundance of bacterial species *CAG-110 sp003525905* (p=0.002, Q=0.071) were significantly associated with prevalent knee synovitis (figure 3J). In addition, *Veillonella tobetsuensis* (p=0.002, Q=0.079), *Lawsonibacter sp000177015* (p=0.001, Q=0.072) and *CAG-110 sp003525905* (p=0.002, Q=0.083) were significantly associated with the activity of knee synovitis (table 2). In the sensitivity analysis, the correlation between *CAG-110 sp003525905* and prevalent knee synovitis became non-significant, after further adjusting for the use of non-antibiotic drugs that affect the gut microbiota, physical activity and diabetes (online supplemental table S1).

Fungi–bacteria correlation network and knee synovitis

The fungal and bacterial microbiota network at the genus level in patients with knee synovitis was significantly different from that in controls (figure 4). The network in patients with knee synovitis was smaller (nodes n=93; edges n=107; relative connectedness ratio=1.2) than in controls (nodes n=153; edges n=244; relative connectedness ratio=1.6). In addition, the fungi–bacteria correlation network in participants with synovitis (average number of neighbours n=2.3) was fewer than those without it (average number of neighbours n=3.2) (figure 4). Detailed correlations between fungi and bacteria in each group are reported in online supplemental file 1.

DISCUSSION

Principal findings

Using data collected from a population-based cross-sectional study, we showed that alterations in gut fungal microbiota were associated with ultrasound-detected knee synovitis. Knee synovitis-associated gut fungal dysbiosis was characterised by different structures and compositions at the genus level and decreased relative abundance of the genus *Schizophyllum*. Additionally, the fungi–bacteria correlations showed markedly reduced complexity in patients with knee synovitis, indicating an imbalance in the relations between faecal fungi and bacteria.

Comparison with previous studies

An animal study demonstrated that transferring gut microbiota from individuals with metabolic disorders to mice increased the severity of synovitis.[41] Another animal

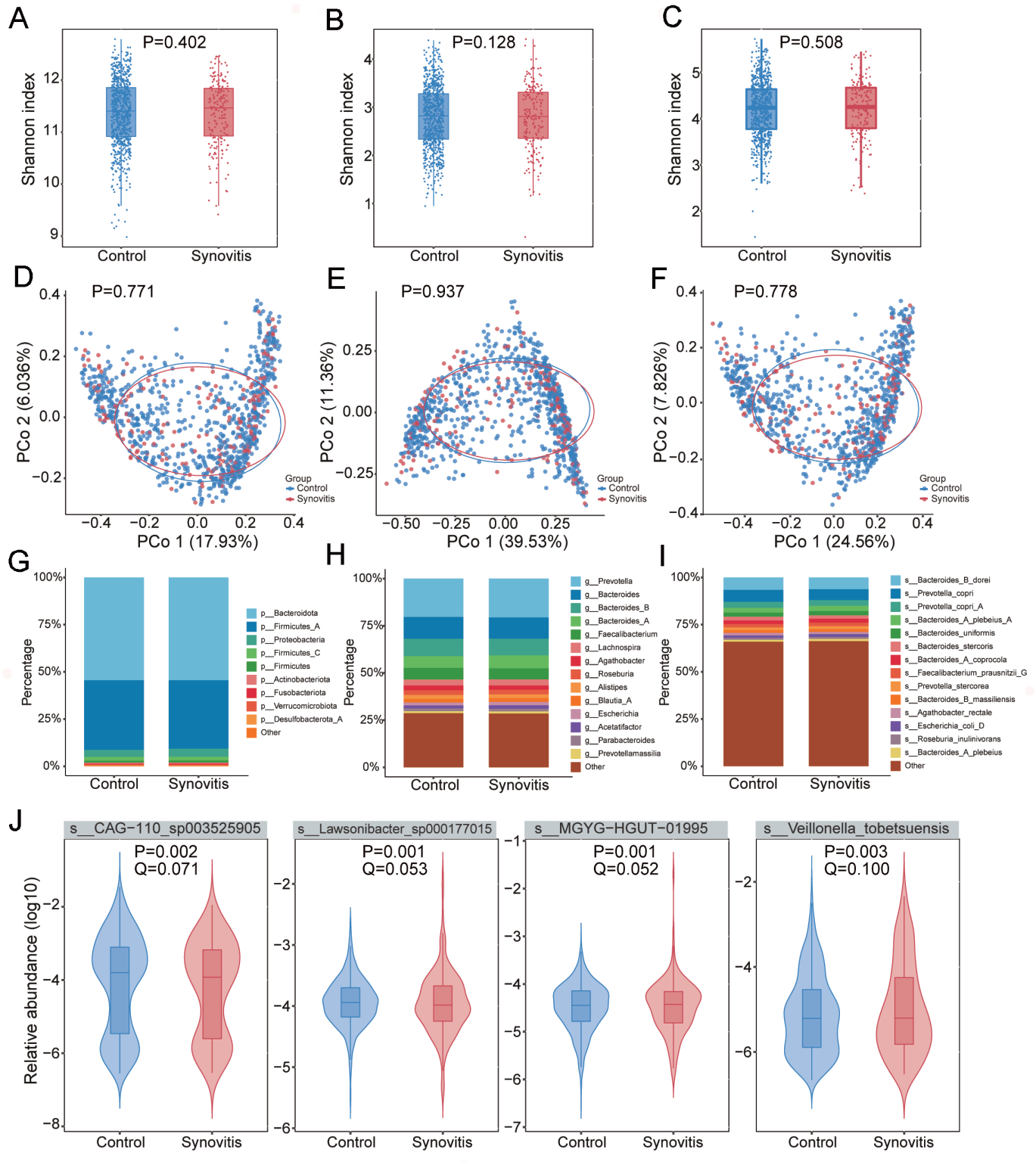
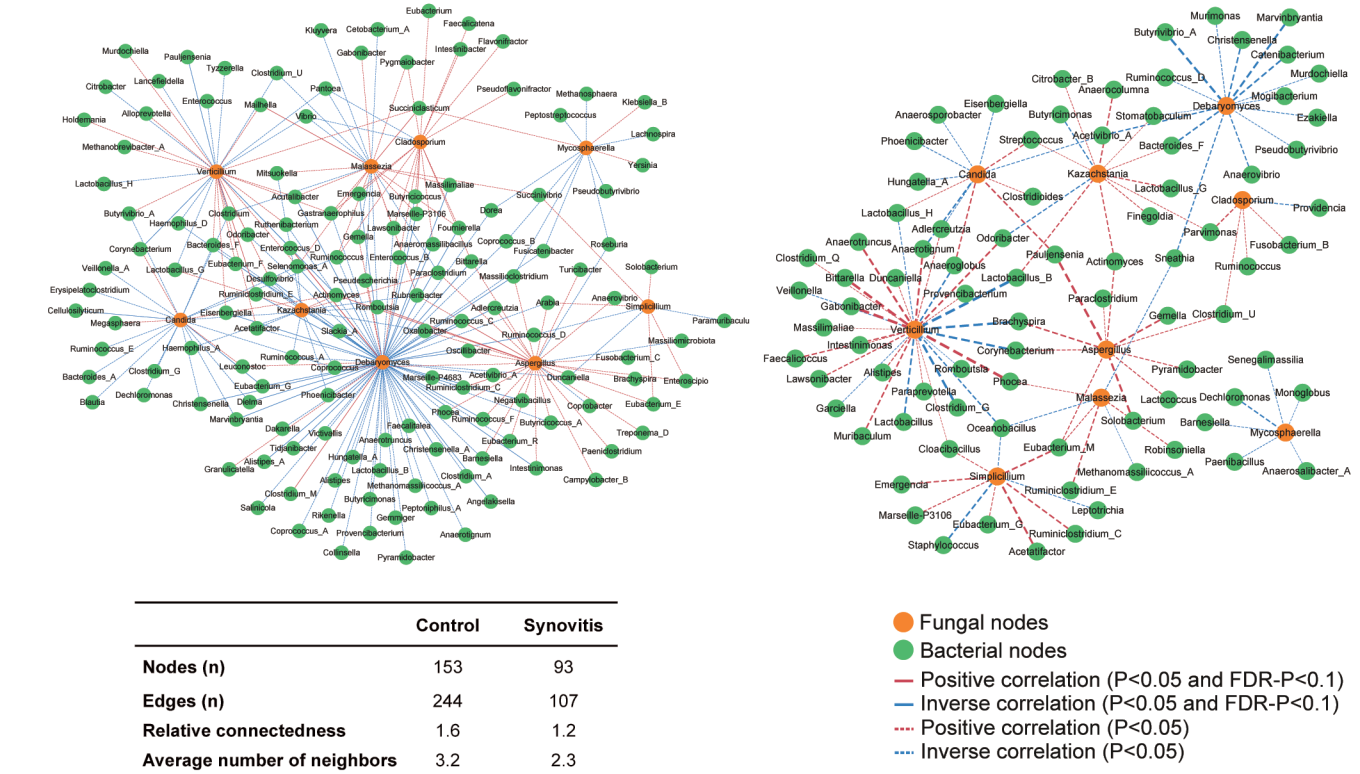


Figure 3 Comparison of bacterial diversity and composition between participants with synovitis and controls. (A) Box plots comparing the α-diversity measured by the Shannon index between participants with synovitis and controls at genes (A), genus (B) and species (C) levels. Principal coordinates analysis (PCoA) plots comparing the β-diversity measured by the Bray-Curtis distance between participants with synovitis and controls at genes (D), genus (E), and species (F) levels. Bacterial composition at the phylum (G), genus (H) and species (I) levels. (J) Relative abundance of differential bacterial species between participants with synovitis and controls identified by multivariate linear regression analysis adjusting for age, sex, body mass index, drinking status, smoking status and frequency of dietary intake of meat/eggs, dairy products and vegetables.



	Control	Synovitis
Nodes (n)	153	93
Edges (n)	244	107
Relative connectedness	1.6	1.2
Average number of neighbors	3.2	2.3

Figure 4 Fungi–bacteria correlation networks at the genus level. (A) Fungi-bacteria correlation network in the control group. (B) Fungi-bacteria correlation network in the knee synovitis group. Only genera with relative abundance>0.001 and present in>70% of samples were considered. Dashed lines indicate significant correlations (p<0.05) between fungal and bacterial genera, whereas solid lines indicate FDR-p<0.1 and p<0.05, with line width indicating correlation magnitude. The red and blue edges denote positive and inverse correlations, respectively. The relative connectedness of the networks was calculated as the ratio between the number of significant interactions (edges) and the number of taxa (nodes) in the network. FDR, false discovery rate.

experiment showed that certain gut microbiota, such as live *Lactobacillus*, can improve monosodium iodoacetate-induced synovial inflammation in rats.[42] To our knowledge, no study has examined the relation of gut fungi or bacteria microbiota to knee synovitis in human beings. In this study, we demonstrated that the β-diversity of gut bacterial microbiota did not differ between participants with knee synovitis and those without. However, the relative abundances of a few bacterial genera and species were associated with the prevalence and activity of knee synovitis. On the contrary, the β-diversity of the gut fungal microbiota was significantly associated with knee synovitis.

Potential mechanisms

In the current study, we found that the genus *Schizophyllum* was negatively correlated with the prevalence and activity of knee synovitis. Schizophyllan, an important product of the *Schizophyllum*, has been shown to have anti-inflammatory effects. First, Schizophyllan increases the production of short-chain fatty acids (SCFAs) in mice by regulating the intestinal flora.[43] SCFAs are recognised for their anti-inflammatory effect and are vital metabolites for maintaining intestinal homeostasis.[44 45] Second, Schizophyllan can upregulate IL-10, reduce the number of macrophages and increase the M2 polarisation of macrophages, which may prevent the development of synovitis.[46] As a result, the up-regulated abundance of *Schizophyllum* genus level could increase the production of Schizophyllan, which may potentially suppress knee synovitis development.

Fungi and bacteria coexist in the gut microenvironment and interact with each other. Gut fungi–bacteria interactions are important in maintaining mucosa homeostasis.[47] Many pathogenic fungi are 'pathobionts', acting as commensals in our bodies that cause no harm under normal conditions but have a pathogenic effect (ie, inflammatory) when the symbiotic relationship is disrupted.[48] Our study found that nodes, edges and relative connectedness of correlation network in patients with knee synovitis were smaller, and the average number of neighbours was fewer compared with those without synovitis, suggesting that a disrupted interface interaction of fungi–bacteria network may play a role in knee synovitis. Alterations in fungal biodiversity are associated with novel interkingdom interactions, possibly involving inflammatory processes.[49 50] Whether this would provide

favourable conditions for the occurrence of knee synovitis warrants further indepth investigations.

Strengths and limitations

Several characteristics of our study are worth noting. First, our findings were derived from a large population-based study; thus, it minimised the effect of interperson variation in microbiome distribution and improved the stability of the results. Second, the findings were independent of major confounding variables, enhancing the robustness of the results. Finally, our study provided novel evidence linking gut microbiota composition (ie, gut fungal microbiota) to knee synovitis, revealing a promising research avenue for synovitis. However, our study also has some limitations. First, this study was cross-sectional; therefore, we could not establish a temporal relationship between gut microbiota and the development of knee synovitis and adjust for time-varied covariates (ie, BMI and lifestyle factors). Second, all participants were residents of a single rural area of China, and the findings may not be generalised to other populations with different characteristics. Further studies are needed to confirm these findings in other cohorts. Third, future studies are warranted to verify our findings and to investigate the potential mechanism of the genus *Schizophyllum* in the development of synovitis. Also, although we controlled several potential confounders, unmeasured confounding cannot be completely ruled out in an observational study.

Clinical and research implications

To our knowledge, this is the first study to show gut fungal microbiota is associated with knee synovitis. The results suggest that the gut-joint axis may be involved in joint pathology through gut fungi and fungi–bacteria correlation network. While the implications of these findings have yet to be clarified, our study findings suggest that gut fungi may play a role in knee synovitis. In addition, our results emphasise the importance of maintaining the stability of gut fungi and bacteria in human health.

In conclusion, our study identified the disruption of gut fungal community homeostasis and the altered fungi–bacteria correlation network in patients with knee synovitis. These findings may offer a potential treatment target for knee synovitis.

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