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No conflict of interest for any of the authors.

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ABSTRACT

Objectives
Systemic inflammatory factors have been implicated in symptomatic hand osteoarthritis (SHOA). Gut microbiome dysbiosis promotes systematic inflammation. The aim of the study was to examine the association between gut microbiome with the presence of SHOA in a population-based study.

Methods
Study participants were derived from the Xiangya Osteoarthritis (XO) Study, a community-based observational study. SHOA was defined as the presence of both symptoms and radiographic osteoarthritis in the same hand. The gut microbiome was analyzed using 16S ribosomal RNA sequencing from stool samples. We examined the relation of α diversity, β diversity, relative abundance of gut microbiome and potential bacterial functional pathways based on predictive metagenome profiling to SHOA.

Results
A total of 1,388 participants (women: 57.4%; mean age: 61.3 years; SHOA prevalence: 5.2%) were included. β diversity, but not α diversity, was significantly associated with SHOA (P=0.003). Higher relative abundance of genus Bilophila and Desulfovibrio as well as lower relative abundance of genus Roseburia were associated with SHOA. Most Kyoto Encyclopedia of Genes and Genomes pathways altered in participants with SHOA belonged to amino acid, carbohydrate and lipid metabolic pathways.

Conclusions
This large population-based study provides the first evidence that alteration of gut microbiome composition was observed among participants with SHOA, and low relative abundance of Roseburia but high relative abundance of Bilophila and Desulfovibrio at genus level were associated with prevalent SHOA. Our findings may help understand the role of microbiome in the development of SHOA and contribute to potential translational opportunities.
INTRODUCTION

Hand osteoarthritis (OA) is highly prevalent within the middle-aged and older population (1). People with hand OA may experience pain and stiffness and have structural joint damage, which may impair their ability to undertake activities of daily living (1). Previous studies have reported that symptomatic hand OA (SHOA) can have a comparable clinical burden to rheumatoid arthritis (RA) (2). Although the pathogenesis of hand OA remains largely unknown, systematic factors, including systemic inflammation, have been implicated as a potential risk factor for SHOA (1, 3).

Gut microbiome dysbiosis can lead to the dysregulation of the various important functions, such as producing small molecules that interact with the host, synthesizing essential amino acids and regulating fat metabolism, which can in turn contribute to the development of systematic inflammation (4). Over the past decades many studies have found that gut microbiome and its metabolites played important pathological roles in the development and progression of several systemic inflammatory diseases, including inflammatory bowel disease, inflammatory arthritis, multiple sclerosis and systemic lupus erythematosus (4). However, to our best knowledge, no study has examined the association between gut microbiome and hand OA. Elucidating this association would help understand the role of microbiome in the development of hand OA and contribute to potential translational opportunities for the prevention and treatment of this common condition.

To help fill this knowledge gap, we examined the association between gut microbiome and prevalent SHOA using data collected from the Xiangya Osteoarthritis (XO) Study, a population-based observational study conducted among the residents of the rural areas of China.

METHODS

Study participants

XO Study is a population-based longitudinal study of natural history and risk factors of OA in a rural area of China (NCT04033757) (5). Participants in the XO Study were a randomly selected sample of residents, aged 50 years or older from rural mountainous villages of Longshan County in Hunan Province. Specifically, we firstly adopted probability proportionate to size sampling method to select
fourteen communities. Then, all villages in the selected communities were listed in a random order. The village-to-village recruitment began from the first village in the first community until the number of participants in that community met the pre-determined quota. A total of 25 rural mountainous villages of Longshan County were eventually included in the XO Study. The XO study includes three sub-cohorts (i.e., sub-cohorts Ⅰ, Ⅱ and Ⅲ), and participants of each sub-cohort were recruited in 2015, 2018 and 2019, respectively.

**Hand OA assessment**

Participants in the XO Study underwent a posterior-anterior (PA) radiograph of both hands. Radiographs of the bilateral second to fifth distal interphalangeal (DIP), second to fifth proximal interphalangeal (PIP), first to fifth metacarpophalangeal (MCP), thumb interphalangeal (IP) and thumb base (carpometacarpal joint) joints were graded using a modified Kellgren-Lawrence (KL) scale for radiographic hand OA (RHOA) (6). A single musculoskeletal researcher (primary reader, TY, orthopedic surgeon) read all the hand radiographs. With each new batch of radiographs (n=50), we commingled five previously read radiographs to test intra-rater reliability. To assess the inter-rater reliability of the scoring, another reader (ADO, musculoskeletal imaging specialist) scored a selected subset of 30 films independently. Intra- and inter-rater reliabilities were assessed using kappa statistic and 95% confidence interval (CI). RHOA was defined as the presence of a KL grade ≥2 in any of the joints listed above in each hand. The intra-rater and inter-rater reliabilities for RHOA as a dichotomous variable expressed by the kappa statistic were 0.91 (95%CI:0.83-0.99) and 0.71 (95%CI:0.45-0.96), respectively.

The presence of hand symptoms was ascertained by a response of “yes” to the question, “On most days, do you have pain, aching, or stiffness in your left/right hand?” (7). SHOA was defined as the presence of both self-reported symptoms and radiographic OA in the same hand. Participants were defined as having SHOA if they had SHOA in at least one hand (7).

**Stool sample collection and DNA extraction**

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Stool samples from the participants collected at the recruitment cite were immediately frozen and transported on dry ice within 20 minutes. Samples were stored in -80°C freezers until analysis. 200 mg of stool was used for DNA exaction using a Magen Hipure Soil DNA Kit according to the manufacturers’ protocol, and the subsequent DNA samples were quantified using a Qubit 2.0 Fluorometer.

**16S rRNA gene sequencing**
The 16S rRNA gene was amplified using the 341F/806R primer set targeting the V3-V4 hypervariable region and the DNA sequenced using the Illumina MiSeq platform. Microbiome bioinformatics were performed with QIIME 2 2019.10. Raw sequence data were demultiplexed and quality filtered using the q2-demux plugin followed by denoising with DADA2 (via q2-dada2). All amplicon sequence variants (ASVs) were aligned with mafft (via q2-alignment) and used to construct a phylogeny with fasttree2 (via q2-phylogeny). α diversity metrics, β diversity metrics, and Principle Coordinate Analysis (PCoA) were estimated using q2-diversity after samples were rarefied (subsampled without replacement) to the minimal number of reads per sample. Taxonomy was assigned to ASVs using the q2-feature-classifier classify-sklearn naïve Bayes taxonomy classifier against the Greengenes 13_8 99% OTUs reference sequences. The 16S rRNA sequencing data of this study are available for downloading (European Nucleotide Archive, https://www.ebi.ac.uk/ena/browser/home, PRJEB33926).

**Statistical analysis**
The similarities of gut microbiome composition between participants with SHOA (i.e., SHOA group) and those without SHOA (i.e., control group) were compared using α diversity measured by Shannon index and β diversity measured by unweighted Unifrac distance. We performed Wilcoxon rank sum test for the difference of α diversity and permutation multivariate analysis of variance (PERMANOVA) test for the difference of β diversity between the two comparison groups. To gain more insight into which gut microbiome taxonomies drive the association with SHOA, we performed multivariate linear regression analysis (MaAsLin) adjusting for age, sex, body mass index (BMI), alcohol consumption, and dietary intake frequency of meat/eggs, dairy and vegetables on phylum,
family and genus levels, respectively. Specifically, we removed microbiome taxa present in < 20% of samples and compared the difference in relative abundance of phylum, family and genus levels between SHOA and control groups. Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) software package was used to impute bacterial metagenomes from 16S sequencing microbial DNA data, and functional annotation was applied using the Kyoto Encyclopedia of Genes and Genomes (KEGG) catalogue. Then, we performed the MaAsLin to assess difference in KEGG level 3 pathways (present in more than 20% of samples) between participants with and without SHOA, adjusting for age, sex, BMI, alcohol consumption, and dietary intake frequency of meat/eggs, dairy and vegetables. P values were corrected for multiple testing with the Benjamin & Hochberg False discovery rate method and a corrected P value (Q value)<0.1 was considered as statistically significant. Moreover, three sensitivity analyses were performed to assess the robustness of our study findings. First, to minimize potential residual effect of antibiotic use, we compared the difference in relative abundance of genus level between SHOA and control group after excluding individuals who reported antibiotic use two or three months prior to the stool sample collection. Second, we conducted a matched case-control study in which up to four controls were matched to a case by age, sex and BMI. We compared the difference in relative abundance of microbiome genera and KEGG level 3 pathways between the case and the control groups using MaAsLin adjusting for alcohol consumption and dietary intake frequency of meat/eggs, dairy and vegetables. Third, we performed a sex-specific analysis to explore the potential sex interaction between microbiome and SHOA. Detailed information of methods and analysis code are described in Supplementary Methods.

Results
The flowcharts depicting the selection process of participants are shown in Figure 1A. Baseline characteristics of the remaining 1,388 participants are shown in Supplementary Table 1. Participants with SHOA (n=72) were older (70.9 vs. 62.8 years, P<0.001) and more likely to be women (75% vs. 57%, P=0.003) than those without SHOA (n=1,316).

A total of 90,608,388 raw sequence reads (mean reads per sample: 65,279) were generated from all stool samples of eligible participants. After quality filtering and removal of contaminants, there
were 61,294,662 high-quality reads that were used for analysis (mean reads per sample: 44,160). Of all samples, 31,355 different ASVs were discovered. Shannon index was not statistically significantly different between the two groups (Figure 1B, P=0.095). However, PCoA plot constructed by unweighted UniFrac distances showed that the structure and composition of gut microbiome differed significantly between the two groups (Figure 1C, P=0.003). In both groups, the profile of gut microbiome appeared to be dominated by Firmicutes and Bacteroidetes at the phylum level (Supplementary Figure 1), by Lachnospiraceae, Bacteroidaceae, Prevotellaceae and Ruminococcaceae at the family level (Supplementary Figure 2), and by Bacteroides, Prevotella, Faecalibacterium and Roseburia at the genus level (Supplementary Figure 3), consistent with the usual composition of the human gut microbiome.

The associations between microbiome taxonomies and SHOA are shown in Figure 2. After adjusting for age, sex, BMI, alcohol consumption, and dietary intake frequency of meat/eggs, dairy and vegetables, there was no apparent difference in microbiome taxa at phylum level between subjects with and without SHOA. However, at family level, individuals with SHOA had higher relative abundance of Christensenellaceae (P<0.001, Q<0.001, Figure 2A), Desulfovibrionaceae (P=0.001, Q=0.008, Figure 2B) and Mogibacteriaceae (P=0.010, Q=0.053, Figure 2C), but lower relative abundance of Lachnospiraceae (P=0.020, Q=0.092, Figure 2D) than those without. The statistically significant differences of gut microbiome were also observed at the genus level, where individuals with SHOA had higher relative abundances of Bilophila (P=0.001, Q=0.006, Figure 2E) and Desulfovibrio (P=0.012, Q=0.064, Figure 2F) but a lower relative abundance of Roseburia (P=0.011, Q=0.062, Figure 2G) compared with those without SHOA. Full summary statistics of associations of microbiome taxonomies with SHOA adjusting for age, sex, BMI, alcohol consumption, and dietary intake frequency of meat/eggs, dairy and vegetables using MaAsLin are presented in Supplementary Table 2-4. After excluding individuals who reported antibiotic use two or three months prior to the stool sample collection, the results remained statistically significant (Supplementary Table 5-6). Sensitivity analysis of age-sex-BMI matched case-control study (68 SHOA vs. 234 control) showed similar results (Supplementary Table 7). The sex-specific analysis undertaken in the 54 women with SHOA gave results consistent with the primary analysis (i.e.,
Bilophila: coefficient=0.008, P=0.003, Q=0.031; Desulfovibrio: coefficient=0.011, P=0.026, Q=0.148; Roseburia: coefficient=-0.046, P=0.006, Q=0.049). However, although an analysis confined to the 18 men with SHOA gave similar findings (i.e., relative abundance of genera Bilophila and Desulfovibrio increased and genera Roseburia decreased in men with SHOA), the associations were not statistically significant.

The functional analysis, performed by reconstructing metagenomes using PICRUSt, identified fifteen KEGG level 3 pathways to be altered in association with SHOA (Figure 3). Most KEGG pathways related to amino acid (amino acid metabolism, tyrosine and lysine degradation, and cyanoamino acid metabolism), carbohydrate (starch, sucrose, amino sugar and nucleotide sugar, butanoate and propanoate metabolisms) and lipid (sphingolipid metabolism) metabolisms were significantly altered in SHOA individuals compared with control. Full summary statistics of associations of KEGG level 3 pathways with SHOA adjusting for age, sex, BMI, alcohol consumption, and dietary intake frequency of meat/eggs, dairy and vegetables using MaAsLin are presented in Supplementary Table 8. Similar results were observed in the age-sex-BMI matched case-control study (Supplementary Table 9).

DISCUSSION
Several studies have reported that patients with inflammatory arthritis had decreased relative abundance of genus Roseburia (8), and there was a strong positive correlation between genus Desulfovibrio and inflammatory blood biomarkers in the general population (9). In accord with those findings, our results suggest that high relative abundance of genus Desulfovibrio but low relative abundance of genus Roseburia may play a role in SHOA. Furthermore, previous work has shown that metabolic pathways, namely those affecting branched chain amino acids, arginine and phosphatidylcholine to lysophosphatidylcholine metabolism, were significantly associated with the pathogenesis of OA (10). Similarly, our results based on PICRUSt also identified altered KEGG pathways related to the amino acid, lipid and carbohydrate metabolisms in association with SHOA. Taken together, our findings suggest that metabolic dysfunction of gut microbiome may play a key...
role in the state of systematic inflammation of SHOA by affecting the host metabolite levels, which warrants further investigation.

Several biological mechanisms linking gut microbiome to systemic inflammation have been proposed. Member in *Bilophila* was shown to produce lipopolysaccharides that promotes intestinal barrier dysfunction, bile acid dysmetabolism and inflammation in mice models (11). Besides, in vitro experiment, species belongs to *Bilophila* was able to converts taurine to the toxic metabolite hydrogen sulfide (H$_2$S), which plays an important role in systematic inflammation (12). Operational taxonomic units (OTUs) in *Desulfovibrio* has been strongly correlated with systemic and chronic inflammation in high-fat diet mice models, suggesting that OTUs in *Desulfovibrio* might influence the chronic inflammatory condition of the host in a way that relates to weight gain and glucose tolerance (13). Several species included in *Roseburia* was reported to serve an anti-inflammatory function by producing butyrate, which was the main source of energy for colonic epithelial cells and which inhibits mRNA expression of pro-inflammatory cytokines in the mucosa by inhibiting NF-κB activation (14).

Several strengths of our study are noteworthy. This was a population-based study, so the findings may be generalizable to the Chinese population with similar characteristics, This is supported by the prevalence of SHOA in our study (5.2%) which was similar to that reported in other parts of China (15). In addition, our results provided novel evidence linking gut microbiome composition to the prevalent SHOA. The significant associations of several genera with SHOA parallels observations previously observed in inflammatory arthritis studies, supporting the validity of our findings. Furthermore, we demonstrated that several altered KEGG metabolism pathways associated with SHOA. This information may contribute to translational opportunities for the identification and treatment of individuals with SHOA and warrants further studies in independent populations.

There are several limitations of our study. Firstly, the gut microbiomes were profiled by 16s ribosomal RNA gene sequencing. Although this technology can identify microbial taxonomies and composition, it has limitations in identifying genetically specific species and strains. Future studies...
using metagenomic approaches are needed to evaluate the relation of a specific bacterial gene(s) and its function to SHOA. Secondly, the current study was a cross-sectional study; thus, we can’t assess the temporal sequence between gut microbiome and occurrence of SHOA. Thirdly, the present results weren’t validated and reproduced in an independent cohort. Changes in specific microbiome genus may not be replicable in other populations given the heterogeneity of the gut microbiome in different geographical locations. Finally, although the main findings were shown to relate to women with SHOA there may have been insufficient power due to the relatively small number of men in the study to fully explore the potential sex interaction between microbiome and SHOA and this warrants further study.

CONCLUSION
This large population-based study provides the first evidence that alteration of gut microbiome composition was observed among participants with SHOA, and low relative abundance of *Roseburia* but high relative abundance of *Bilophila* and *Desulfovibrio* at genus level were associated with prevalent SHOA. Our findings may help understand the role of microbiome in the development of SHOA and contribute to potential translational opportunities.
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AUTHOR CONTRIBUTIONS
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Lei and Zeng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: JW, CZ, YZ, WZ, MD, CZ, GL.
Acquisition of data: JW, TY.
Analysis and interpretation of data: JW, YZ, WZ, GZ, ADO, HL, CZ.
Drafting or revising it critically for important intellectual content: JW, CZ, YZ, WZ, MD, TY, GZ, ADO, HL, CZ, GL
Administrative, technical, or material support: CZ, GL.

ETHICAL APPROVAL
XO study has been approved by the Research Ethical Committee of Xiangya Hospital, Central South University (201510506), and all participants gave informed written consent for their participation in the studies.

DISCLAIMER
The interpretation of these data is the sole responsibility of the authors.

TRANSPARENCY

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.
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Figure Legends

Figure 1. Xiangya Osteoarthritis (XO) Study microbiome cohort profile using 16S rRNA sequencing method. A, Selection process of included subjects in the XO Study. B, Box plots of Shannon index of microbial diversity (\(\alpha\) diversity). C, Principal Coordinates Analysis (PCoA) plot of \(\beta\) diversity, constructed by unweighted Unifrac distance.

Figure 2. Compositional significant differences in gut microbiota between individuals with symptomatic hand osteoarthritis (SHOA) and individuals without SHOA on family and genus levels after adjusting for age, sex, body mass index, alcohol consumption, and dietary intake frequency of meat/eggs, dairy and vegetables.

Figure 3. Difference of relative abundances of predicted functions (third level of the Kyoto Encyclopedia of Genes and Genomes [KEGG Ortholog [KO] hierarchy) based on phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt) data set between individuals with symptomatic hand osteoarthritis (SHOA) and individuals without SHOA.
3081 eligible residents in 30 healthy subcohorts (Panel A)

2011 participated in study

252 retained

1538 provided stool samples

266 included

180 stool samples underwent 16s rRNA sequencing (Córdova et al., 2016)

a) community antibiotic usage in the 6 months prior to stool sample collection
b) history of inflammatory bowel disease

c) stool sample for bacterial 16s rRNA sequencing

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