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ORIGINAL RESEARCH

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Examining the link between gut microbiota and periodontitis in East Asians using Mendelian randomization

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Abstract

Objective: This study explores the possible connection between periodontitis and gut microbiota in East Asians, a relationship that has been largely unexplored until now.

Methods: Using publicly available genome-wide association study (GWAS) data, we performed Mendelian randomization (MR). We analyzed GWAS summary statistics to assess if gut microbiota could causally influence periodontitis risk. We applied methods such as MR-Egger, weighted median, inverse variance weighting, and simple MR, and conducted sensitivity analyses to confirm our findings.

Results: Utilizing the Inverse-Variance Weighted approach, we identified potential causal relationships between 17 host-genetically influenced gut microbiota characteristics and periodontitis, including *Granulicatella adiacens*, *Bilophila wadsworthia*, and *Thermosinus*. Specifically, *G. adiacens* was linked to an increased risk of periodontitis (odds ratios [OR] 1.07, 95% confidence interval [CI] 1.02–1.15, $p = 0.0004$), while *B. wadsworthia* was linked to a decreased likelihood of tooth loss (OR 0.98, 95% CI 0.96–0.99, $p = 0.0005$). No evidence of pleiotropy or heterogeneity was observed across sensitivity analyses.

Conclusion: This study reveals a causal relationship between specific microorganisms and periodontitis in the Asian population, shedding light on the influence of gut microbiota on periodontitis.

KEYWORDS

causal relationship, gut microbiota, Mendelian randomization, periodontitis

1 | INTRODUCTION

Periodontitis (PD) is a long-term inflammatory condition that affects the tissues surrounding and supporting the teeth, marked by the breakdown of the periodontal ligament, loss of alveolar bone, and the formation of periodontal pockets, ultimately leading to tooth mobility and, in severe cases, tooth loss. The development of periodontitis results from the complex interplay between pathogenic bacteria and the body's immune response, with various risk factors such as inadequate oral hygiene, smoking, and genetic predisposition contributing to its onset.[1,2] Current evidence suggests that periodontitis ranks as the sixth most prevalent disease worldwide.[3] In this respect, by 2019, it was estimated that between 20% and 50% of the global population would be affected by periodontal disease, making it

the second most widespread oral disorder worldwide.[4] Besides, periodontitis contributes to a loss of approximately 7.09 million Disability-Adjusted Life Years, equating to 1 year of overall health.[5] Additionally, individuals with multiple missing teeth may appear older, experience reduced chewing function, and encounter difficulties with pronunciation.[6] Furthermore, an increasing amount of evidence demonstrated a connection between periodontitis and systemic diseases. Numerous studies have established links between periodontal inflammation and different disorders such as Cardiac disorders,[7] metabolic disorders,[8] pulmonary conditions,[9] and unfavorable pregnancy outcomes.[10] Therefore, gaining a comprehensive understanding of the factors that either promote or mitigate periodontitis is of utmost importance. Recent research has suggested that the link between gut microbiota and periodontitis may be attributed to a two-way communication pathway known as the "gut-oral-axis," which exists between the gastrointestinal tract and the oral environment.[11,12] This axis involves bidirectional communication between the gut and oral microbiota. Mechanisms include the transfer of oral bacteria to the gut and the impact of gut microbiota on the oral microbiota through immune responses and systemic inflammation. Oral pathogens and their byproducts can also migrate to other parts of the body, including the gut, influencing immune responses and systemic inflammation. During gut dysbiosis, microbiota may affect the oral microbiota and contribute to oral diseases.[13–15] However, the current understanding of this axis remains limited, warranting further research on specific microbial species, metabolites, their role in diseases, and potential therapeutic interventions.

The existing literature suggests a connection between periodontitis and the gut microbiota.[16–18] Studies have indicated that changes in the oral microbiota, particularly microbial dysbiosis, can play a role in the onset and progression of periodontitis.[19] Oral pathogens can enter the bloodstream through gum tissues, potentially impacting the composition and function of the gut microbiota. However, it is worth noting that the authors of these studies did not explicitly emphasize the significant role of oral microbial dysbiosis in the etiology of periodontitis. Indeed, an exploration of the interplay between oral and gut microbiota would provide further insights into the disease's pathogenesis. Additionally, a comprehensive understanding of the host response and other contributing factors would enhance our comprehension of the development and progression of periodontitis.

Mendelian randomization (MR) offers a method to explore potential causal connection between exposures and outcomes using instrumental variables (IVs). Previous MR studies have identified connections between gut microbiota and various disorders.[20–23] Nevertheless, these MR analyses did not specifically examine the causal link between gut microbiota and periodontitis. Therefore, this study sought to examine potential link between gut microbiota and the risk of periodontitis in the East Asian population. We employed MR, utilizing genome-wide association study (GWAS) data sets from a previous investigation.[24]

2 | MATERIALS AND METHODS

2.1 | Design of the study

Figure 1 presents a comprehensive synopsis of the study design. To investigate the relationship between periodontitis and gut microbiota influenced by host genetics, a two-sample MR approach was employed. single nucleotide polymorphisms (SNPs) for each MR study instrument were selected according to these criteria: (i) the association assumption, indicating SNPs were linked to exposure levels; (ii) the independence assumption, asserting SNPs are unassociated with confounders of both exposure and outcome; and (iii) the exclusion restriction assumption, stating SNPs influence outcomes exclusively through exposure.

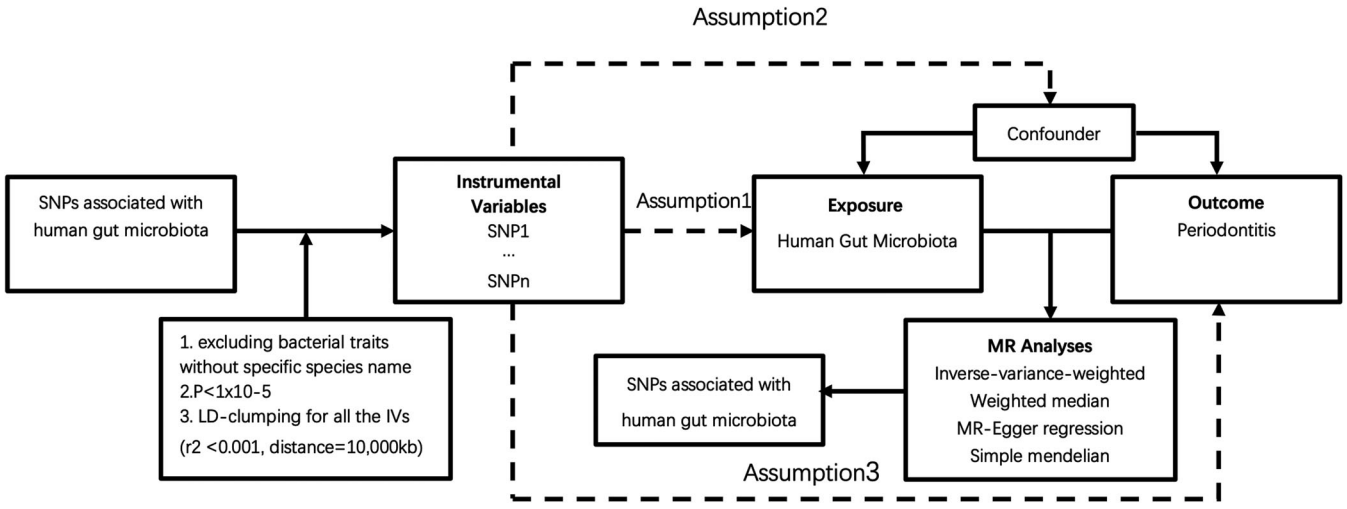

FIGURE 1 Illustrates the study design of the current MR investigation on the connections between gut microbiota and periodontitis. MR, Mendelian randomization.

2.2 | Summary statistics from genome-wide association studies

The exposure data were derived from summary statistics of the microbiota GWAS from recently conducted research. The GWAS data included 2002 Chinese individuals with 1539 fecal samples.[24] Using an MGIEasy kit, feces were collected, and stool DNA was extracted according to the MetaHIT technique. According to recent studies, relevant SNPs were identified with a p Value below 1×10^{-5}.[25–28]

Compiling the summary data for periodontitis was based on the most recent meta-analysis of GWAS carried out by the BBJ collaboration. This study comprised 9560 cases and 169,166 controls.[29] In the revised International Classification of Diseases (ICD-10) code, cases of periodontitis were identified as K05.30 and K05.31.

2.3 | Identifying IVs

First, to validate the initial MR hypothesis, exposure-related SNPs needed to meet a genome-wide significance threshold of $p < 1 \times 10^5$. To confirm the independence of the SNPs,[30] we evaluated linkage disequilibrium by assessing r^2 values greater than 0.001 and clump distance exceeding 10,000 kb. To evaluate IV strength, the F statistic and the percentage of variation explained were calculated for each microbial taxa and imputed.

2.4 | Statistical analysis

In our study, we utilized four MR approaches to evaluate the correlation between gut microbiota and periodontitis. The findings from the IVs were regressed using the inverse variance weighting (IVW) approach for the primary analysis.[31] Furthermore, the MR-Egger technique and weighted median were incorporated. To assess individual variability, Cochran's Q statistic for IVW and the MR-Egger approach were employed.[32] Our findings predominantly relied on the IVW method, irrespective of heterogeneity. The MR-Egger intercept test evaluated the presence of pleiotropy in SNPs.[33] To test the reliability of the findings, a sensitivity analysis was performed.[34] The odds ratios (OR) for all MR estimates are displayed with 95% confidence intervals (CIs). To determine the robustness or fragility of IVs, we employed the following formula to calculate the F-statistic.[35]

$$R^2 = 2 \times \mathrm{EAF} \times (1\text{-}\mathrm{EAF}) \times \beta^2, F = R^2(N\text{-}2)/(1\text{-}R^2).$$

Where, N indicates the total number of exposure GWAS samples and the SNP impact size on exposure. Statistical analyses were implemented using the TwoSampleMR R package[36] (version 0.5.6).

3 | RESULTS

3.1 | Overview

All IVs related to the human gut microbiota exhibited F-statistics ranging from 21.43 to 36.45, exceeding the cutoff of >10, suggesting a minimal likelihood of weak instrument bias. Additional details can be found in Supporting Information S1: Table 1, which presents results regarding the associations between 500 bacterial traits and the risk of periodontitis. Notably, we identified the presence of 17 distinct types of gut bacteria (as detailed in Table 1 and Figure 2) were linked to susceptibility to periodontitis.

3.2 | The causal effect of gut microbes on periodontitis

The IVW method unveiled 17 different gut microorganisms that were linked to periodontitis, including *s_Granulicatella_adiacens*, *s_Bilophila_wadsworthia*, *g_Thermosinus*, *g_Granulicatella*, *s_Bifidobacterium_angulatum*, *s_Streptococcus_constellatus*, *g_Thermoanaerobacter*, *MF0095_propionate_production_III*, *MF0050_threonine_degradation_II*, *s_Bacteroides_uniformis*, *MF0003_pectin_degradation_I*, *MF0082_putrescine_degradation*, *g_Cronobacter*, *g_Leuconostoc*, *s_Prevotella_salivae*, *o_Campylobacterales*, and *s_Escherichia_albertii*. Detailed results are presented in Table 1 and Figure 2. Out of these gut microbiomes, six exhibited a negative correlation with the risk of periodontitis, while 11 demonstrated a positive correlation. Notably, 15 gut microbiota stayed significant after FDR adjustment.

As illustrated in Figure 2, our research unveiled a correlation between a higher susceptibility to periodontitis and the presence of *s_Granulicatella_adiacens*, *g_Thermosinus*, *g_Granulicatella*, and *s_Bifidobacterium_angulatum*, resulting in an increased risk (OR). Specifically, the OR was 1.07, with a 95% CI of 1.02−1.11 and a p Value of 0.0004 for *s_Granulicatella_adiacens*; OR of 1.04, 95% CI: 1.01−1.07, $p = 0.0007$ for *g_Thermosinus*; OR of 1.06, 95% CI: 1.02−1.10, $p = 0.0007$ for *g_Granulicatella*; and OR of 1.04, 95% CI: 1.01−1.08, $p = 0.0008$ for *s_Bifidobacterium_angulatum*. In contrast, *s_Bilophila_wadsworthia* was linked to a lower chance of developing periodontitis (OR: 0.98, 95% CI: 0.96–0.99, $p = 0.0005$).

P-values from the Cochran Q approach were above 0.05, suggesting no heterogeneity (Supporting Information S1: Table 2). In sensitivity analyses, MR-Egger produced consistent findings (Figure 3). Moreover, MR-Egger regression revealed little to no evidence of directional pleiotropy in these microbial genera, with intercept p-values of 0.517 for *s_Granulicatella_adiacens*, 0.628 for *s_Bilophila_wadsworthia*, 0.875 for *g_Thermosinus*, 0.427 for *g_Granulicatella*, and 0.578 for *s_Bifidobacterium_angulatum* (Supporting Information S1: Table 3).

TABLE 1 It presents a summary of the connections between specific gut microbial genera and periodontitis using the IVW method.

Outcome	Exposure	nsnp	*b*	se	*p* Value	R^2	*F*	OR	lci	uci
Periodontitis	s_Granulicatella_adiacens	20	0.064757	0.02252	0.000403	0.211295	26.53562	1.0669	1.020831	1.115048
Periodontitis	s_Bilophila_wadsworthia	35	−0.02125	0.007572	0.000502	0.393555	36.45268	0.978978	0.964555	0.993616
Periodontitis	g_Thermosinus	9	0.03898	0.014398	0.000678	0.092669	22.60559	1.039749	1.010819	1.069509
Periodontitis	g_Granulicatella	22	0.057385	0.021286	0.000702	0.232195	27.20359	1.059063	1.015788	1.104183
Periodontitis	s_Bifidobacterium_angulatum	8	0.043313	0.016663	0.000834	0.081288	22.04271	1.044264	1.010711	1.078932
Periodontitis	s_Streptococcus_constellatus	9	0.039333	0.015224	0.003778	0.093456	22.8173	1.040116	1.009539	1.07162
Periodontitis	g_Thermoanaerobacter	14	−0.03122	0.01288	0.015345	0.144328	23.93932	0.96926	0.945098	0.99404
Periodontitis	MF0003_pectin_degradation_I	16	−0.14876	0.067368	0.027232	0.180645	27.35238	0.861776	0.755179	0.98342
Periodontitis	MF0082_putrescine_degradation	12	0.050169	0.022743	0.02739	0.13285	25.39332	1.051449	1.005608	1.099378
Periodontitis	g_Cronobacter	2	0.067017	0.030434	0.027659	0.020995	21.43452	1.069314	1.007395	1.135039
Periodontitis	MF0095_propionate_production_III	18	0.046192	0.019899	0.027659	0.205038	28.41446	1.047275	1.007215	1.088929
Periodontitis	g_Leuconostoc	10	0.028793	0.013144	0.028487	0.105736	23.54113	1.029211	1.003035	1.056071
Periodontitis	MF0050_threonine_degradation_II	21	−0.18816	0.082739	0.028487	0.236119	29.14412	0.828481	0.704455	0.974342
Periodontitis	s_Bacteroides_uniformis	11	0.042732	0.019227	0.038389	0.120334	24.74742	1.043658	1.00506	1.083738
Periodontitis	s_Prevotella_salivae	5	0.04201	0.020288	0.038389	0.051986	21.89103	1.042905	1.002248	1.085212
Periodontitis	o_Campylobacterales	23	−0.02718	0.013471	0.043649	0.24546	27.97669	0.973189	0.94783	0.999226
Periodontitis	s_Escherichia_albertii	10	−0.02767	0.013823	0.045298	0.10747	23.97382	0.972707	0.946706	0.999421

Abbreviations: lci, lower conferdence index; nsnp, number of included SNP; OR, odds ratio; ucl, upper conferdence index.

exposure	outcome	method	nsnp	b	se	pval	R2	F
s_Granulicatella_adiacens	PD	Inverse variance weighted	20	0.064757251	0.022520359	0.000403391	0.211295077	26.53562418
s_Bilophila_wadsworthia	PD	Inverse variance weighted	35	-0.021246143	0.007572464	0.000502058	0.393555016	36.45268415
g_Thermosinus	PD	Inverse variance weighted	9	0.038979813	0.01439765	0.00067818	0.09266907	22.60559353
g_Granulicatella	PD	Inverse variance weighted	22	0.057385006	0.021285863	0.000701943	0.232195454	27.20358543
s_Bifidobacterium_angulatum	PD	Inverse variance weighted	8	0.043312733	0.016662548	0.000833852	0.081288124	22.04271481
s_Streptococcus_constellatus	PD	Inverse variance weighted	9	0.039332725	0.015224019	0.003777605	0.093455843	22.81730352
g_Thermoanaerobacter	PD	Inverse variance weighted	14	-0.031222048	0.012879683	0.015345042	0.144327657	23.9393248
MF0003_pectin_degradation_I	PD	Inverse variance weighted	16	-0.148759985	0.067367759	0.027231887	0.180645274	27.35238303
MF0082_putrescine_degradation	PD	Inverse variance weighted	12	0.050168775	0.022742893	0.027390304	0.132849646	25.39332285
g_Cronobacter	PD	Inverse variance weighted	2	0.067017309	0.030433578	0.027659346	0.020995003	21.43452369
MF0095_propionate_production_III	PD	Inverse variance weighted	18	0.04619188	0.019899185	0.027659346	0.205038442	28.41445791
g_Leuconostoc	PD	Inverse variance weighted	10	0.028792924	0.01314436	0.02848687	0.105735758	23.54112838
MF0050_threonine_degradation_II	PD	Inverse variance weighted	21	-0.188161912	0.082739237	0.02848687	0.23611892	29.14411887
s_Bacteroides_uniformis	PD	Inverse variance weighted	11	0.04273167	0.019226577	0.038388979	0.120333756	24.7474205
s_Prevotella_salivae	PD	Inverse variance weighted	5	0.042010263	0.020288176	0.038388979	0.051986451	21.89102829
o_Campylobacterales	PD	Inverse variance weighted	23	-0.027176767	0.013470846	0.043648501	0.245459763	27.97669181
s_Escherichia_albertii	PD	Inverse variance weighted	10	-0.027672558	0.013823329	0.045298316	0.107470327	23.97381594

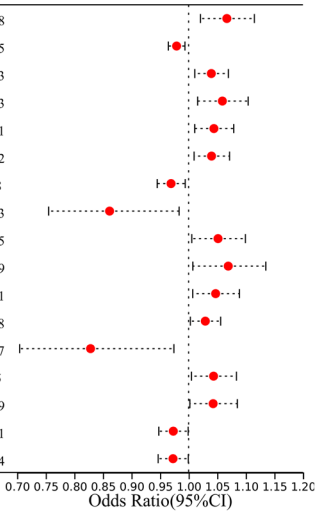

FIGURE 2 The impact of specific gut microbial genera on periodontitis was determined to be statistically significant ($p < 0.05$).

exposure	outcome	method	nsnp
s_Granulicatella_adiacens	PD	Inverse variance weighted	20
s_Granulicatella_adiacens	PD	MR Egger	20
s_Granulicatella_adiacens	PD	Weighted median	20
s_Granulicatella_adiacens	PD	Simple median	20
s_Bilophila_wadsworthia	PD	Inverse variance weighted	35
s_Bilophila_wadsworthia	PD	Weighted median	35
s_Bilophila_wadsworthia	PD	Simple median	35
s_Bilophila_wadsworthia	PD	MR Egger	35
g_Thermosinus	PD	Inverse variance weighted	9
g_Thermosinus	PD	Weighted median	9
g_Thermosinus	PD	Simple median	9
g_Thermosinus	PD	MR Egger	9
g_Granulicatella	PD	Inverse variance weighted	22
g_Granulicatella	PD	MR Egger	22
g_Granulicatella	PD	Weighted median	22
g_Granulicatella	PD	Simple median	22
s_Bifidobacterium_angulatum	PD	Inverse variance weighted	8
s_Bifidobacterium_angulatum	PD	Simple median	8
s_Bifidobacterium_angulatum	PD	Weighted median	8
s_Bifidobacterium_angulatum	PD	MR Egger	8

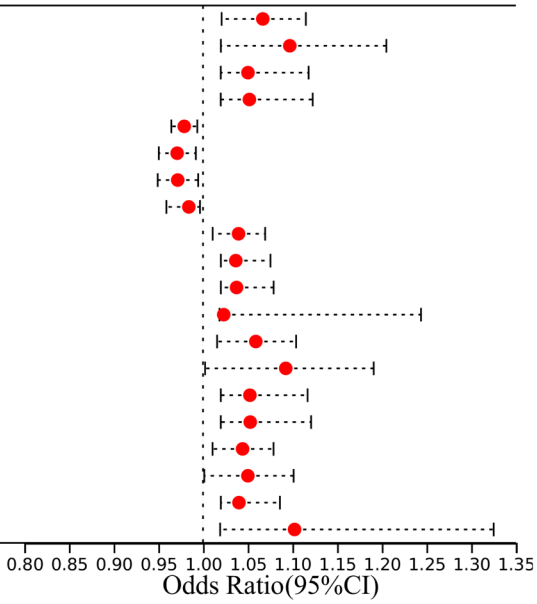

FIGURE 3 The risks of periodontitis are depicted in a forest plot showing the connections between genetically determined gut microbial genera.

3.3 | Multivariable MR analysis

To investigate the potential impact of horizontal pleiotropy on our findings, we conducted a multivariable MR analysis adjusting for BMI. Except for *s_Bilophila_wadsworthia*, no pleiotropic effects were identified after controlling for BMI (as shown in Figure 4). In models adjusted for BMI, the multivariate MR approach revealed a significant association between gut microbiota and periodontitis, consistent with the univariate analysis. Notably, the calculated causal effect for *s_Granulicatella_adiacens* on periodontitis was 1.08 (95% CI 1.01−1.21, *P* value for multivariable mendelian randomization (Pmvmr) = 0.032). Comparable findings were detected for *g_Thermosinus* on periodontitis (OR = 1.02, 95% CI 1.01−1.08, Pmvmr = 0.047), *g_Granulicatella* (OR = 1.04, 95% CI 1.01−1.09, Pmvmr = 0.025), and *s_Bifidobacterium_angulatum* (OR = 1.03, 95% CI 1.01−1.12, Pmvmr = 0.046). These findings indicate that BMI did not exert pleiotropic effects on the composition of gut microbial taxa or the development of periodontitis.

4 | DISCUSSION

Our research primarily aimed to examine the causal relationship between gut microbiota and periodontitis using a two-sample MR approach. Our findings provide compelling evidence supporting a

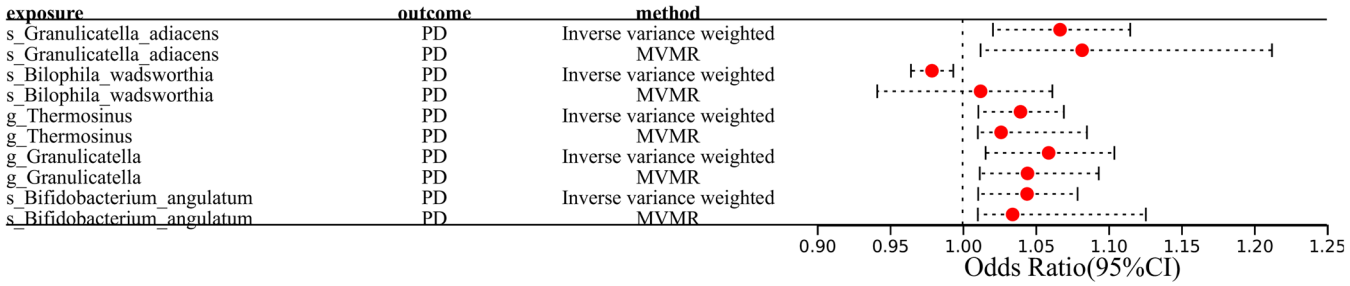

FIGURE 4 Using multivariable mendelian randomization, a forest plotwas generated to display the connections between gut microbial genera and the potential risks of periodontitis.

genetically predicted association between gut microbiota and periodontitis among individuals in the East Asian population. Specifically, we observed that several bacteria, including *Granulicatella adiacens*, *Thermosinus*, *Granulicatella*, and *Bifidobacterium angulatum*, were linked to an increased risk of periodontitis (OR 1.07, 95% CI 1.02−1.11, $p = 0.0004$ for *G. adiacens*; OR 1.04, 95% CI 1.01−1.07, $p = 0.0007$ for *Thermosinus*; OR 1.06, 95% CI 1.02−1.10, $p = 0.0007$ for *Granulicatella*; and OR 1.04, 95% CI 1.01−1.08, $p = 0.0008$ for *B. angulatum*), while *Bilophila wadsworthia* was linked to a reduced risk of periodontitis (OR 0.98, 95% CI 0.96-0.99, $p = 0.0005$ for *B. wadsworthia*). These findings were consistent across sensitivity analyses. It is worth noting that previous studies have reported associations between *G. adiacens* and inflammation[37] and cancer risk.[38,39] Additionally, *B. wadsworthia* has been linked to inflammation, intestinal barrier dysfunction, and dysregulation of bile acid metabolism, which can contribute to glucose dysmetabolism and hepatic steatosis.[40] The presence of these bacteria in the gut microbiota and their potential impact on periodontitis underscore the complex relationship between oral and systemic health.[41]

It is now understood that the gut microbiome, composed of various microbial communities from our environment, plays a crucial role in our physical and mental development, as well as overall well-being.[42,43] It is involved in immune and metabolic functions and can influence conditions affecting the central nervous system, including movement, neurodegenerative, behavioral, neuroimmune-mediated disorders, and strokes.[44] A recent epidemiological study has revealed a link between gut microbiota and periodontitis. In comparison to mice with germ-free microbiota, animals colonized with commensal gut microbiota exhibit reduced trabecular shape and experience greater loss of alveolar bone.[45,46] This underscores the bidirectional regulation between gut and oral pathologies. It is widely acknowledged that gut physiology or disease can be influenced by the transmission of oral infections to the gut through both the alimentary canal and hematogenous routes.[47] The correlation between the oral microbiome and gastrointestinal disorders suggests that oral inflammation significantly impacts gut health. However, the precise mechanisms by which the gut microbiota within the "gut-oral" axis exerts control over dental health remain unclear.

MR analysis represents an effective approach to exploring causality between exposure and outcome while accounting for potential confounding factors. The MR analysis employed in our study offers several distinct advantages, providing hitherto undocumented evidence on the cause-and-effect relationship between gut microbiota and periodontitis, thereby providing a theoretical foundation for future investigations into the regulatory mechanisms of specific bacterial strains on periodontal disease. Moreover, as it relies on readily available extensive GWAS summary statistics, MR analysis offers a cost-effective way to extract reliable genetic information. Nevertheless, our study does come with certain drawbacks. The statistical power of MR analysis is inherently constrained due to the limited number of genetic loci identified in gut microbiota GWAS, largely attributable to the small sample size. Furthermore, conducting MR analysis solely based on a single independent variable may yield less robust results, potentially complicating the interpretation of our findings.

Conclusively, our MR study established a causal link between the gut microbiome and periodontitis in East Asians. This finding paves the way for innovative therapies that target the microbiome, underscoring its critical role in the interaction between oral and systemic health. By focusing on microbiome-based strategies, our research highlights its potential as a key target for personalized prevention and treatment.

AUTHOR CONTRIBUTIONS

Yu Xia: Writing—original draft. **Yadong Wu**: Formal analysis; validation; visualization. **Xinhai Yin**: Data curation; investigation; methodology; software. **Jukun Song**: Validation; writing—original draft; writing—review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Supporting data are available from the corresponding author upon request. Data can also be accessed from Human Gut Microbiome (https://ftp.cngb.org/pub/CNSA/data2/CNP0000794/) and Japanese Periodontitis (https://pheweb.jp/downloads). Original contributions are

available in the article/Supporting Information Materials, with further inquiries directed to Jukun Song, the corresponding author.

ETHICS STATEMENT

This study belongs to the secondary data mining analysis. The ethics were approved by the institute of the authors,[24,29] And all methods were performed in accordance with the Declaration of Helsinki.

TRANSPARENCY STATEMENT

The lead author Jukun Song affirms that this 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 (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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