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ARTICLE

Unraveling the Gut-Oral Axis: A Mendelian Randomization Analysis of Gut Microbiota Impact on Periodontitis via Circulating Inflammatory Proteins

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Abstract

Aims/Background Gut microbiota (GM) dysbiosis may exacerbate periodontitis by impairing intestinal barrier integrity and inducing systemic inflammation. However, the causal relationships and mediating roles of inflammatory proteins remain unclear. This study aimed to clarify these causal pathways and mediating mechanisms.

Methods Two-sample and multivariable Mendelian randomization (MR) analyses were conducted to evaluate the causal association between GM and periodontitis using publicly available genome-wide association study (GWAS) data and FinnGen repository. Causal estimates were obtained through inverse-variance weighted (IVW), weighted median, MR-Egger, simple mode, and weighted mode approaches. Additionally, MR-Egger regression and Cochran's Q-test were applied to detect and correct for potential pleiotropy and heterogeneity.

Results Significant causal relationships were identified between GM genetics and periodontitis risk. Protective effects were observed for the class *Actinobacteria* (odds ratio [OR]: 0.726, 95% confidence interval [CI]: 0.574–0.918; $p = 0.007$), the genus *Collinsella* (OR: 0.655, 95% CI: 0.456–0.941; $p = 0.022$), the genus *Ruminococcus 1* (OR: 0.692, 95% CI: 0.497–0.964; $p = 0.029$), the genus *Sutterella* (OR: 0.697, 95% CI: 0.541–0.897; $p = 0.005$), and the phylum *Actinobacteria* (OR: 0.712, 95% CI: 0.551–0.921; $p = 0.010$), whereas the genus *Alistipes* was identified as a risk factor (OR: 1.682, 95% CI: 1.240–2.280; $p = 0.001$). Furthermore, fractalkine potentially mediated 13.37% of the association between the phylum *Actinobacteria* and periodontitis. No evidence for reverse causation was found between periodontitis risk and the aforementioned six gut microbiota in the bidirectional MR analysis.

Conclusion Specific GM taxa and fractalkine exert causal effects on periodontitis, supporting the existence of a gut-oral axis mediated by systemic inflammation. These findings suggest potential therapeutic strategies targeting GM dysbiosis and inflammatory pathways.

Key words: gut-oral axis; Mendelian randomization; gut microbiota; periodontitis; circulating inflammatory proteins

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Introduction

Periodontitis is recognized as the second most prevalent oral condition and the 12th most common pathology worldwide (Nocini et al, 2020), with a combined prevalence of approximately 62% among dentate adults (Trindade et al, 2023). This microbiome-driven inflammatory disease is characterized by progressive degradation of periodontal tissues, often leading to tooth loss and compromised masticatory function (Cai et al, 2024). The complexity of periodontitis, arising from bacterial and immune factors, poses treatment challenges, and conventional approaches such as scaling and root planing, with or without antimicrobials, may not be effective for all patients. This highlights its significance as a major public health and economic concern, with costs estimated at $154.06 billion in the USA and €158.64 billion in Europe (Botelho et al, 2022). Furthermore, epidemiological evidence has linked elevated systemic inflammatory levels to the prevalence of periodontitis, while therapeutic interventions targeting periodontitis have been shown to reduce systemic inflammation and biomarkers associated with related comorbidities (Kurushima et al, 2023; Li et al, 2021).

The gut microbiota (GM) constitutes the largest microbial community in the human body, comprising a complex ecosystem of approximately 100 trillion microorganisms (Ley et al, 2006). A balanced gut microbiome is characterized by high taxonomic variability, extensive microbial genetic diversity, and the capacity to maintain homeostasis (Bock et al, 2024). Disruption of this delicate balance by external stimuli can initiate a series of dysregulated physiological responses, leading to pathological manifestations (Hou et al, 2022). Recent studies have increasingly suggested that gut microbiota dysbiosis may promote the onset and progression of periodontitis (Han et al, 2023; Wang et al, 2023). The phylum *Actinobacteria* contributes to carbohydrate metabolism, short-chain fatty acids (SCFAs) production, and maintenance of intestinal barrier integrity. Imbalance within *Actinobacteria* population can indirectly influence oral inflammation through the Th17 response (Alexander et al, 2022). Additionally, periodontal changes in children with type 1 diabetes (T1D) may be influenced by the presence of *Ruminococcus* in the oral cavity (Moskovitz et al, 2021). Although *Collinsella* primarily colonizes the intestine, alterations in its abundance or metabolic activity may also impact oral microbiota composition (Rajasekaran et al, 2024).

The oral and gut microbiota exert bidirectional influences, whereby dysbiosis in one site can impact the other. Consequently, emerging research has explored strategies to inhibit the progression of periodontitis and its associated risk factors by targeting the "gut-oral axis" (Yuan et al, 2023). For instance, Sato et al (2021) transplanted fecal microbiota from high-fat diet-fed mice into those fed a normal diet, inducing periodontitis and demonstrating that microbiota imbalance exacerbated alveolar bone loss through elevated serum uric acid levels. Collectively, these findings underscore the critical role of GM in periodontitis pathogenesis, though its underlying mechanisms still need to be further clarified.

GM influences systemic inflammation through multiple mechanisms. For instance, lipopolysaccharide (LPS) produced by bacteria can traverse the intestinal

barrier and enter the bloodstream, stimulating immune cells to release pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (Wang et al, 2024; Zhao et al, 2021). Conversely, short-chain fatty acids (SCFAs) produced by the intestinal microbiota exert anti-inflammatory effects by binding to receptors, regulating enzyme activity, and influencing immune cell functions (Gasaly et al, 2021; Golpour et al, 2023; Mann et al, 2024). The GM also helps maintain intestinal barrier integrity by strengthening epithelial junctions, thereby limiting the translocation of pathogenic microbes and bacterial components (Bao et al, 2022; Ghosh et al, 2021).

Epidemiological evidence has linked elevated systemic inflammatory levels to the prevalence of periodontitis (Guo et al, 2024; Muñoz Aguilera et al, 2021). Moreover, therapeutic interventions targeting periodontitis have been shown to reduce systemic inflammation and biomarkers of related comorbidities (Hajishengallis, 2022; Hajishengallis and Chavakis, 2021; Loos and Van Dyke, 2020). Although both GM and systemic inflammation play significant roles in the etiology of periodontitis, the precise mechanisms underlying these interactions remain incompletely understood. Elucidating these pathways is crucial for developing more effective treatment strategies for periodontitis, ultimately improving health outcomes and quality of life for affected individuals.

Randomized controlled trials (RCTs) remain the gold standard for establishing causal relationships between GM, inflammatory proteins, and periodontitis, yet their implementation poses significant practical challenges. Mendelian randomization (MR), an epidemiological approach, utilizes genetic variations as instrumental variables (IVs) to infer causality (Cao et al, 2025; Cao et al, 2024; Skrivankova et al, 2021). The random allocation of genetic variants at conception allows for the control of confounding variables and reduces reverse causation bias, thereby strengthening causal inference between exposures and outcomes (Czesnikiewicz-Guzik et al, 2019; Li et al, 2024; Smith and Ebrahim, 2024).

We hypothesized that circulating inflammatory proteins mediate the relationship between GM and the onset of periodontitis. Mediation analysis provided a framework to assess the indirect effects of an exposure on outcomes through intermediary variables. Accordingly, we performed MR with mediation analysis using genome-wide association study (GWAS) data to investigate how GM influences periodontitis through circulating inflammatory proteins. In addition, reverse causality analysis was conducted to examine whether genetic predisposition to periodontitis affects GM composition. Previous MR studies primarily examined the direct association between GM and periodontitis (Luo et al, 2023; Song et al, 2023; Ye et al, 2023) but largely overlooked the potential mediating role of systemic inflammation. This gap limits the in-depth understanding of molecular mechanisms linking GM to periodontitis.

To address this critical knowledge gap, we conducted a comprehensive MR study to investigate the causal relationship between GM and periodontitis, with a specific focus on quantifying the mediating effects of circulating inflammatory proteins. Our research not only verified the causal role of specific GM in the pathogenesis of periodontitis but also identified fractalkine as a key inflammatory mediator

within the gut-oral axis. This work provides genetic evidence supporting systemic inflammation as a mechanistic link, thereby opening a new direction for the development of targeted prevention and treatment strategies for periodontitis.

Methods

Study Design

This study utilized publicly available GWAS data to analyze the genetic association between GM and periodontitis. We employed the MR method, using single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs). This approach is based on three core assumptions: (1) IVs are strongly correlated with exposure factors, (2) IVs are independent of all confounding variables, and (3) IVs influence outcomes only through exposure factors. Satisfying these assumptions allows for the mitigation of confounding interference and a more reliable assessment of causal relationships.

We conducted two-sample MR and multivariate MR analyses to explore the causal relationship between GM and periodontitis, with particular attention on the mediating role of circulating inflammatory proteins. First, we estimated the causal effect of GM on periodontitis. Next, we examined how GM regulates circulating inflammatory protein levels and evaluated the role of these inflammatory proteins in periodontitis using a multivariate model. Considering the bidirectionality of the gut-oral axis, we also conducted reverse MR analyses to assess the potential impact of genetic predisposition to periodontitis on GM composition. All analyses were performed using publicly available genetic data, which had received ethical approval in their original studies. GM data in the IEU GWAS database [https://gwas.mrcieu.ac.uk/datasets/], inflammatory protein data in the GWAS Catalog [https://www.ebi.ac.uk/gwas/], and periodontitis data in the FinnGen repository [https://storage.googleapis.com/finngen-public-data-r11/summary_stats/finngen_R11_K11_PERIODON_CHRON_COMPL.gz]. Consequently, no additional ethical review was required for this work. The overall research design is shown in Fig. 1, and the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) checklist (**Supplementary Material**) was followed for the reporting of MR studies.

GWAS Sources

The Microbiome Genetics (MiBioGen) consortium provided a comprehensive GWAS dataset for the human GM (Kurilshikov et al, 2021). This dataset included 18,340 participants from 24 cohorts across various global regions. Through microbiota quantitative trait loci (mbQTL) mapping analysis, 211 taxonomic units associated with gut bacterial taxa were identified. After excluding 15 unclassified units, the dataset retained 196 bacterial taxonomic units, offering a robust foundation for further analysis.

GWAS summary statistics for circulating inflammatory proteins were obtained from the GWAS Catalog (accession numbers between GCST90274758 and GCST 90274848). This dataset includes 91 inflammatory markers measured across 11

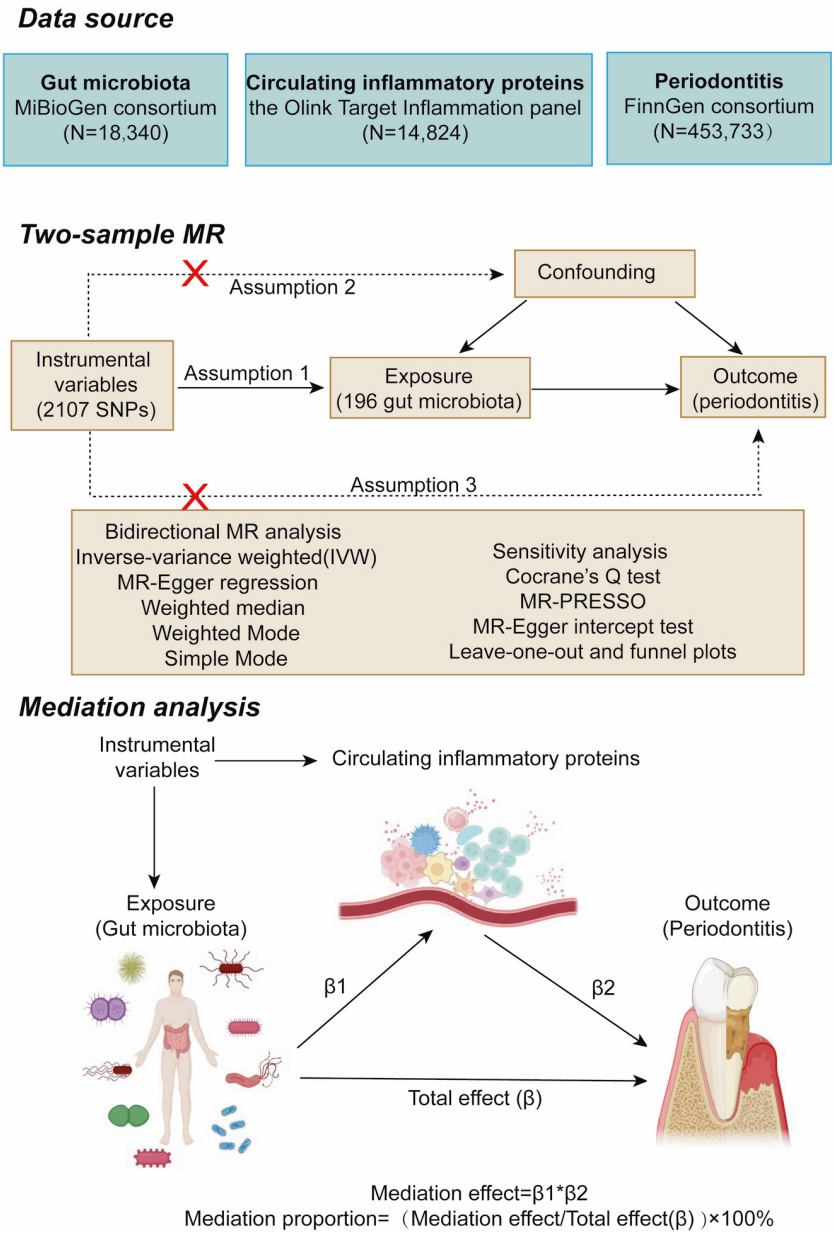

Fig. 1. Study design and analytical workflow. Total effect (β) represents the overall impact of GM on periodontitis; β_1 represents the MR effect of GM on circulating inflammatory proteins, while β_2, derived from multivariable MR, indicates the MR effect of circulating inflammatory proteins on periodontitis, accounting for genetically influenced GM. The figure was created using Adobe Illustrator 2020 (v2.12.0.25). SNPs, single-nucleotide polymorphisms; MR, Mendelian randomization; GM, gut microbiota; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

cohorts, comprising 14,824 individuals of European ancestry. The Olink Target-96 Inflammation immunoassay panel (https://olink.com/products/olink-target-96) was initially utilized to evaluate 92 proteins. However, brain-derived neurotrophic factor was excluded due to assay inconsistencies, ultimately retaining 91 proteins in this study (Zhao et al, 2023).

The FinnGen consortium R11 release provides an extensive genomic resource characterizing the genetic architecture of periodontitis through a robust comparison

between affected individuals and a large control population. This dataset is notable for its substantial sample size, comprising 3010 periodontitis cases and 450,723 controls, offering a strong foundation for genetic association analyses and the identification of novel genetic factors contributing to periodontitis susceptibility. A summary of the GWAS dataset used in the MR analyses is presented in **Supplementary Table 1**.

Genetic Instrumental Variable Selection

Initially, a stringent significance threshold of $p < 5 \times 10^{-8}$ was applied for the identification of IVs correlated with GM and the 91 circulating inflammatory proteins. However, due to the limited number of SNPs associated with GM genera and circulating cytokines at this threshold, the criteria were adjusted to $p < 1 \times 10^{-5}$ for GM and $p < 5 \times 10^{-6}$ for circulating inflammatory proteins. Relaxing these thresholds allowed for the inclusion of more genetic variation loci (SNPs) associated with GM, inflammatory proteins, and periodontitis, thereby expanding the scope of the analysis.

Subsequently, linkage disequilibrium (LD) analysis ($r^2 < 0.001$ within a 10,000 kb window) was performed to remove highly correlated SNPs. Palindromic SNPs were further excluded to ensure alignment between the genetic effect directions of the exposure and outcome variables. The strength of IVs was quantified through F-statistics, retaining only SNPs with $F > 10$ for downstream analyses (Burgess and Thompson, 2011). Detailed information on the selected IVs is provided in **Supplementary Tables 2,3**.

MR Analysis and Mediation Analysis

In this study, bidirectional MR was applied to evaluate the causal relationship (total effect, β) between GM and periodontitis, and the mediating role of circulating inflammatory proteins was further assessed using mediation analysis (Carter et al, 2021). First, the effect of GM on inflammatory proteins (β_1) was estimated through two-sample MR analysis. Next, multivariate MR was used to identify inflammatory proteins (β_2) that maintained an independent association with periodontitis after adjusting for the effect of GM. The mediating effect value was calculated as $\beta_1 \times \beta_2$, and the direct effect (β') was obtained as the total effect (β) – ($\beta_1 \times \beta_2$). The mediating ratio (mediating effect/total effect $\times$ 100%) was then derived to quantify the proportion of the GM effect on periodontitis mediated by circulating inflammatory proteins (Chen et al, 2023; Shen et al, 2024). This analytical framework effectively distinguishes the direct impact of GM on periodontitis from the indirect pathways mediated by inflammatory proteins.

Sensitivity Analysis

A multifaceted MR analytical approach was employed, incorporating inverse-variance weighted (IVW), MR-Egger, simple mode, weighted median, and weighted mode methods (Bowden et al, 2015). The IVW method was chosen as the primary approach due to its high statistical power and capacity to produce unbiased estimates in the absence of pleiotropy, achieved by combining Wald ratios with a fixed

intercept of zero. MR results were presented as odds ratios (ORs) with 95% confidence intervals (CIs), with statistical significance defined as $p < 0.05$ for the IVW method.

The weighted median method enhances the robustness of the analysis, yielding credible estimates even when up to 50% IVs are invalid due to pleiotropy or other biases (Burgess et al, 2017). The weighted mode method provides valid results if the majority of IVs with similar causal estimates are robust, even if some fail to meet MR assumptions (Hartwig et al, 2017). The simple mode method is straightforward, focusing on the SNP with the strongest exposure association, making it suitable for preliminary analyses or when only a few strong IVs are available. When β values across alternative approaches were consistent and the IVW method produced statistically significant results ($p < 0.05$), causal inference was considered reliable. Conversely, the absence of significant differences across alternative methods suggested no evidence of pleiotropy or heterogeneity (Sekula et al, 2016).

To further assess pleiotropy, the MR-Egger intercept test was used to identify directional pleiotropy via the regression intercept and assess the overall pleiotropic impact of genetic variants used as IVs (Hajishengallis and Chavakis, 2021). Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) was employed to detect and correct outliers potentially influencing results through pleiotropic effects undetected by alternative approaches. Heterogeneity in SNP effect estimates was evaluated using Cochran's Q-test ($p < 0.05$) (Greco et al, 2015). Moreover, a "leave-one-out" sensitivity analysis was conducted to determine whether any single SNP disproportionately influenced the overall causal effect.

All MR analyses were performed using R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria) with the "TwoSampleMR" (version 0.6.2), "MR-PRESSO" (version 1.0), and "MVMR" (multivariable Mendelian randomization) (version 0.4) packages.

Fig. 2. Forest plot of MR estimates for the association between GM and periodontitis. OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted.

Results

Causal Relationship Between GM and Periodontitis

Using the IVW method, six GM taxa (including one phylum, one class, and four genera) were identified as significantly associated with periodontitis ($p < 0.05$) (Figs. 2,3). Fig. 2 presents the causal effects of GM on periodontitis estimated us-

ing IVW as the primary approach. The genus *Alistipes* (IVW, OR: 1.682, 95% CI: 1.240–2.280; $p = 0.001$) significantly increased the risk of periodontitis. Conversely, five GM taxa were associated with a reduced risk of periodontitis, including the class *Actinobacteria* (IVW, OR: 0.726, 95% CI: 0.574–0.918; $p = 0.007$), the genus *Collinsella* (IVW, OR: 0.655, 95% CI: 0.456–0.941; $p = 0.022$), the genus *Ruminococcus 1* (IVW, OR: 0.692, 95% CI: 0.497–0.964; $p = 0.029$), the genus *Sutterella* (IVW, OR: 0.697, 95% CI: 0.541–0.897; $p = 0.005$), and the phylum *Actinobacteria* (IVW, OR: 0.712, 95% CI: 0.551–0.921; $p = 0.010$). The full results are provided in **Supplementary Table 4**. In the scatter plots, the slope of each line represents the causal estimates derived from different MR methods. Each point with vertical and horizontal error bars reflects the influence of individual SNPs on the outcome and exposure, respectively (**Supplementary Fig. 1**).

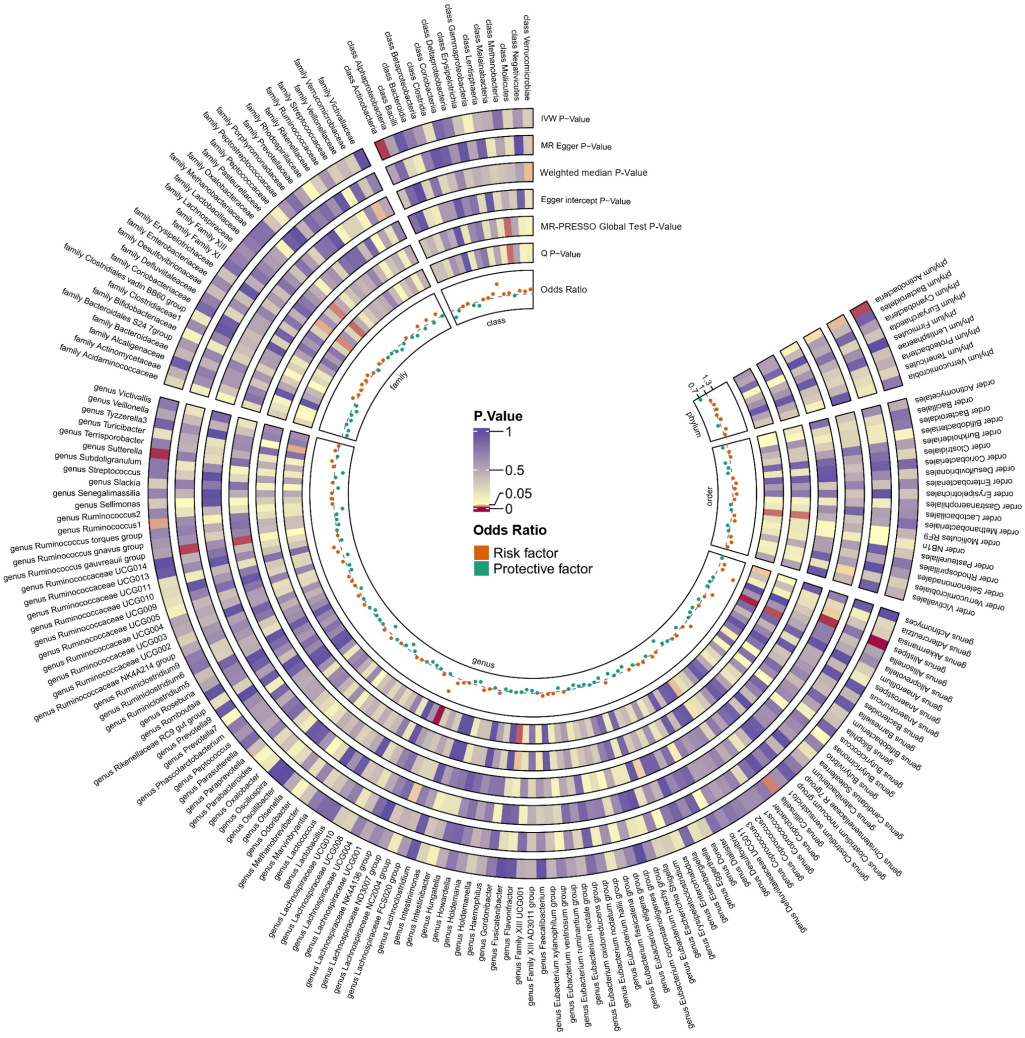

Fig. 3. Causal effects of GM on periodontitis based on MR analyses.

Sensitivity analyses revealed no significant heterogeneity ($p < 0.05$ in Cochran's Q-test), and MR-PRESSO results were consistent, further supporting the robustness of our findings (Fig. 3 and **Supplementary Table 5**). Moreover, the leave-one-out

analysis (**Supplementary Fig. 2**) confirmed that no single IV had an impact on any of the causative relationships that were found.

Causal Relationship Between 91 Circulating Inflammatory Proteins and Periodontitis Using MVMR

To evaluate the independent effects of circulating inflammatory proteins on periodontitis, we performed multivariable Mendelian randomization (MVMR) analysis. As illustrated in Fig. 4 and **Supplementary Tables 6,7**, 91 circulating inflammatory proteins were included as exposures using IVs that satisfied our predefined selection criteria.

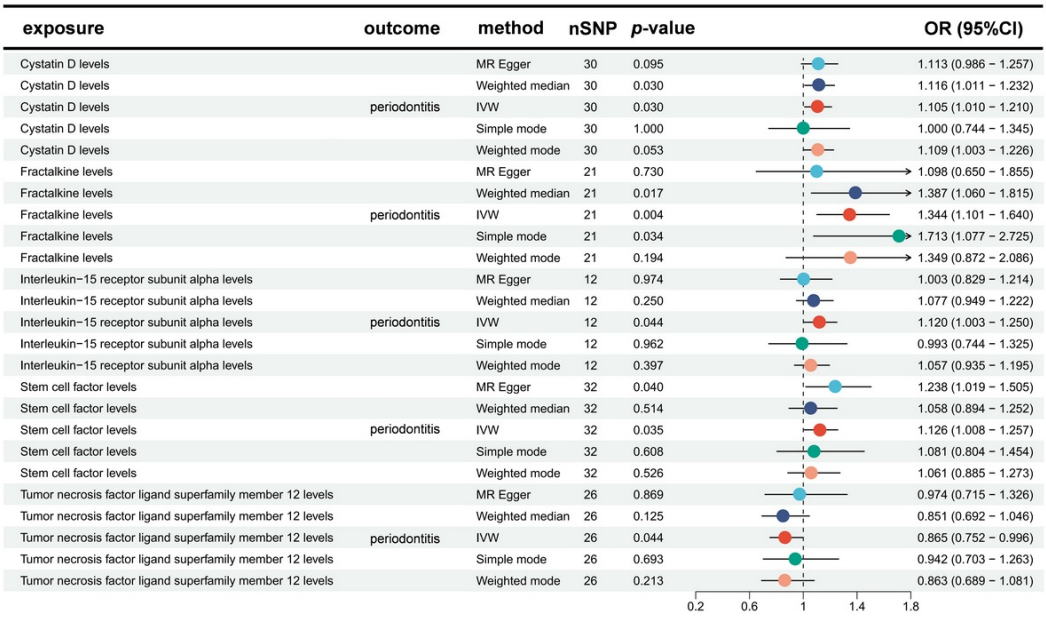

Fig. 4. MR estimates for the association between 91 circulating inflammatory proteins and periodontitis.

Our analysis revealed that higher circulating levels of Cystatin D (IVW, OR: 1.105, 95% CI: 1.010–1.210; $p = 0.030$), fractalkine (IVW, OR: 1.344, 95% CI: 1.101–1.640; $p = 0.004$), interleukin-15 receptor subunit alpha (IVW, OR: 1.120, 95% CI: 1.003–1.250; $p = 0.044$), and stem cell factor (IVW, OR: 1.126, 95% CI: 1.008–1.257; $p = 0.035$) were significantly associated with increased periodontitis risk. In contrast, higher levels of tumor necrosis factor ligand superfamily member 12 (IVW, OR: 0.865, 95% CI: 0.752–0.996; $p = 0.044$) were associated with reduced risk of periodontitis. No significant evidence of pleiotropy or heterogeneity ($p > 0.05$) was observed, supporting the reliability of these causal inferences. Scatter plots and leave-one-out sensitivity analyses are shown in **Supplementary Figs. 3,4**.

Causal Relationship Between GM and 91 Circulating Inflammatory Proteins

Due to an insufficient number of effective IVs, *Alistipes* and *Collinsella* were excluded from the analysis evaluating the causal relationship between GM and 91 circulating inflammatory proteins. Among the four GM taxa previously associated

with periodontitis, only the phylum *Actinobacteria* (IVW, OR: 1.16, 95% CI: 1.00–1.33; p = 0.046) demonstrated a significant positive correlation with fractalkine levels in IVW analysis (Fig. 5). The selected IVs exhibited no notable heterogeneity or horizontal pleiotropy, as verified by MR-Egger regression intercept analysis and Cochran's Q-test (**Supplementary Tables 8,9**). Results from scatter plots and leave-one-out sensitivity analyses are presented in **Supplementary Figs. 5,6**.

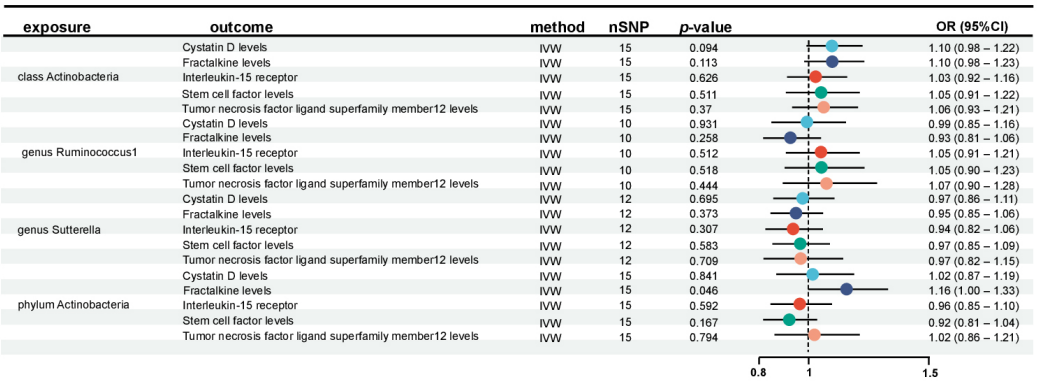

Fig. 5. MR estimates for the association between four GM taxa and five circulating inflammatory proteins.

Mediated MR Analysis

To explore the potential mechanisms underlying the onset and progression of periodontitis, we conducted a mediation analysis to investigate the causal pathway from GM to periodontitis, emphasizing the mediating role of circulating inflammatory proteins. This analysis focused on GM taxa and circulating inflammatory proteins previously identified as associated with periodontitis in the two-sample MR. As shown in Table 1, fractalkine levels significantly mediated the causal pathway from the phylum *Actinobacteria* to periodontitis, accounting for 13.37% of the total effect.

Table 1. The results of mediated MR analysis.

Exposure	Mediation	Outcome	Total effect (β)	β_1	β_2	Mediating effect	Percentage of the mediating effect
Actinobacteria (phylum)	Fractalkine levels	Periodontitis	0.34	0.15	0.303	0.045	13.37%

Reverse MR Analysis

In bidirectional MR analysis, we found no evidence of reverse causation between the six previously identified GM taxa and periodontitis risk: the class *Actinobacteria* (IVW, OR: 0.96, 95% CI: 0.91–1.11; p = 0.19), the genus *Alistipes* (IVW, OR: 0.97, 95% CI: 0.92–1.03; p = 0.32), the genus *Collinsella* (IVW, OR:

0.95, 95% CI: 0.89–1.01; p = 0.08), the genus *Ruminococcus 1* (IVW, OR: 1.03, 95% CI: 0.97–1.11; p = 0.345), the genus *Sutterella* (IVW, OR: 0.99, 95% CI: 0.91–1.06; p = 0.693), and the phylum *Actinobacteria* (IVW, OR: 0.97, 95% CI: 0.92–1.02; p = 0.205).

Conversely, reverse MR analysis revealed significant causal effects of periodontitis on six distinct taxa: the class *Mollicutes* (IVW, OR: 0.93, 95% CI: 0.87–0.99; p = 0.026), the genus *Actinomyces* (IVW, OR: 0.91, 95% CI: 0.84–0.99; p = 0.03), *Butyricicoccus* (IVW, OR: 0.95, 95% CI: 0.90–1.00; p = 0.044), *Intestinibacter* (IVW, OR: 0.89, 95% CI: 0.88–1.00; p = 0.043), *Olsenella* (IVW, OR: 0.89, 95% CI: 0.79–1.00; p = 0.046), and the phylum *Tenericutes* (IVW, OR: 0.93, 95% CI: 0.87–0.99; p = 0.026) (Fig. 6). No significant pleiotropy or heterogeneity was detected (**Supplementary Tables 10,11**). Scatter plot and leave-one-out analyses are presented in **Supplementary Figs. 7,8**.

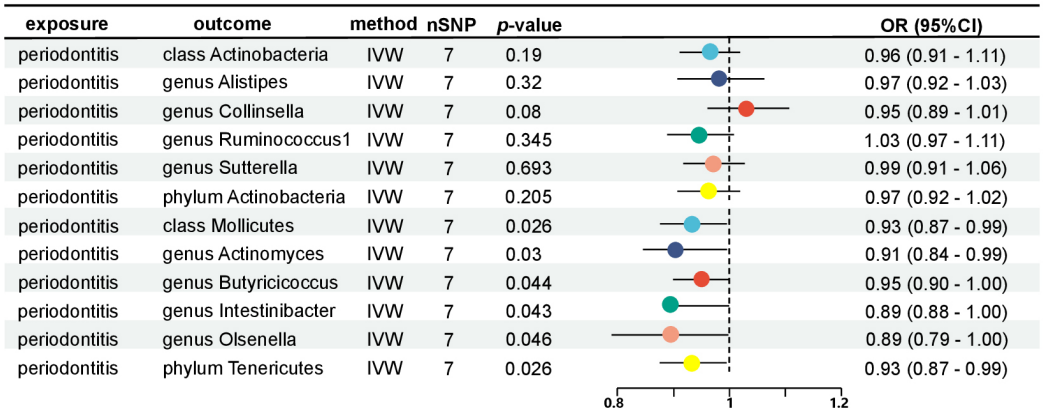

Fig. 6. Reverse MR estimates for the association between periodontitis and GM.

In summary, five GM taxa acted as protective factors against periodontitis, while one served as a risk factor. Among inflammatory proteins, four showed positive correlations and one exhibited a negative correlation with periodontitis. Notably, fractalkine significantly mediated the causal pathway between the phylum *Actinobacteria* and periodontitis.

Discussion

A growing number of studies highlight a close bidirectional connection between the oral cavity and the intestinal tract. Periodontal pathogenic bacteria can migrate from the oral cavity to the intestines, disrupting the native balance of the GM. GM dysbiosis can activate the immune system, initiating local and systemic inflammatory responses within the intestines, which may aggravate or even induce periodontitis (Cai et al, 2021). Notably, trimethylamine oxide (TMAO), a metabolite produced by GM, not only disrupts microbial and immune homeostasis but also aggravates intestinal inflammation. Elevated TMAO levels have been detected in patients with periodontitis, suggesting that changes in the intestinal microenvironment may influence periodontal inflammation through specific mechanisms (Wang

et al, 2023). These findings reveal the critical role of the "gut-oral axis" in overall health and underscore the need for more in-depth research on which specific GM exerts protective or damaging effects on periodontal health.

The phylum *Actinobacteria* is recognized as a protective factor for periodontal health due to its multifaceted functions. It regulates immune responses and maintains a balanced cytokine profile, thereby preventing inflammatory dysregulation, a key feature in the pathogenesis of periodontitis (Alam et al, 2020). *Actinobacteria* also support periodontal tissue integrity by promoting proteins that enhance tissue elasticity and by regulating osteoclast and osteoblast activity, helping to preserve bone homeostasis and prevent periodontitis-associated bone loss (Lu et al, 2021). Furthermore, *Actinobacteria* contribute to the function of the oral mucosal barrier, protecting against the invasion of harmful agents (Min et al, 2023), and play an essential role in oral nutritional metabolism, which impacts the overall health of the oral ecosystem (Sedghi et al, 2021).

Schulz et al (2019) reported that *Proteobacteria*, *Firmicutes*, and *Actinobacteria* are more prevalent in the oral cavity microbiota of healthy individuals, while pathogenic bacteria such as *Bacteroidetes*, *Spirochaetes*, and *Synergistetes* are more frequent in patients with periodontitis. Importantly, after periodontal treatment, the proportion of beneficial microbiota in the oral cavity significantly increases (Ko et al, 2020). These findings align with our study results, further confirming the close association between specific microbiota and periodontal health.

The progression of periodontitis is closely associated with the inflammatory response (Hajishengallis and Chavakis, 2021; Sczepanik et al, 2020). In the early stage of the disease, plaque accumulation at the gingival margin can trigger an acute inflammatory response (gingivitis), during which immune cells such as epithelial cells, fibroblasts, macrophages, and neutrophils, along with complement proteins and neuropeptides, participate in host defense. These cells release pro-inflammatory mediators, including TNF-α, IL-1, and IL-6, which recruit additional immune cells to the infected site (Pan et al, 2019). However, persistent inflammation increases Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) expression, leading to osteoclast activation and ultimately resulting in alveolar bone destruction (Nakao et al, 2021; Settem et al, 2021). Therefore, effective control of early inflammation is crucial for preventing the progression of periodontitis and mitigating tissue damage.

Recent studies demonstrate that specific probiotics offer unique advantages in managing periodontitis. *Lactobacillus gasseri* SBT2055 effectively combats periodontal tissue destruction caused by *Porphyromonas gingivalis*, primarily by reducing the levels of key pro-inflammatory factors TNF-α and IL-6 (Kobayashi et al, 2017). Clinical evidence indicates that combining *Bifidobacterium lactis* HN019 lozenges with standard periodontal therapy significantly improves the clinical adhesion levels, reduces periodontal pocket depth, and simultaneously lowers the number of periodontal pathogenic bacteria and the expression of inflammatory factors IL-8 and IL-1β (Invernici et al, 2018). Notably, the intestinal probiotic *Akkermansia muciniphila* exhibits multiple protective effects in animal models: it inhibits alveolar bone resorption, regulates macrophage function, promotes secretion of the

anti-inflammatory cytokine IL-10, and enhances the expression of junctional proteins in gingival epithelial cells, thereby strengthening the tissue barrier (Huck et al, 2020). These findings provide new insights into the gut-oral microbiota interplay and establish a theoretical foundation for the development of novel probiotic-assisted therapeutic strategies for periodontitis.

This study focused on elucidating the key role of the inflammatory mediator fractalkine (CX3CL1) in periodontitis. Fractalkine not only promotes angiogenesis but also recruits osteoclast precursors, contributing to bone resorption (Balci et al, 2021; Yilmaz et al, 2021). This chemokine activates multiple intracellular signaling pathways, including Mitogen-Activated Protein Kinase (MAPK), Phospholipase C (PLC), and Nuclear Factor kappa-B (NF-κB), by binding to the C-X3-C Motif Chemokine Receptor 1 (CX3CR1) on monocytes and macrophages (Rodriguez et al, 2024). Activation of these signaling pathways promotes the synthesis of pro-inflammatory cytokines and regulates cellular growth, differentiation, proliferation, and metabolism (Pandur et al, 2022). Lipoteichoic acid (LTA), a key component of the cell wall of *Actinobacteria*, plays a central role in this process. LTA activates endothelial cells through the Toll-Like Receptor 2 (TLR2) signaling pathway, inducing the expression of fractalkine in endothelial cells, recruiting CX3CR1-expressing lymphocytes to periodontal lesions, and amplifying the inflammatory response. Both *Streptococcus mutans* LTA and *Staphylococcus aureus* LTA can induce the production of fractalkine, suggesting that LTA from different bacterial sources may activate endothelial cells through this pathway (Hosokawa et al, 2005). Blocking the LTA-TLR2 or CX3CL1-CX3CR1 axis may therefore represent a promising therapeutic strategy to inhibit the progression of periodontitis. It is noteworthy that elevated fractalkine levels are not only seen in periodontitis but also have similar manifestations in chronic inflammatory conditions such as diabetes and rheumatoid arthritis (Alarcón-Sánchez et al, 2024; Germano et al, 2024), suggesting potential shared molecular mechanisms between local oral inflammation and systemic inflammatory responses. Future research should further clarify the precise mechanism of fractalkine at different stages of periodontitis.

This study has several limitations: First, the analysis relied solely on European GWAS data, limiting the generalizability of the findings. Broader studies involving diverse populations are essential to enhance the universality of these results. Second, the dichotomous categorization of periodontitis status may introduce significant heterogeneity and biases, as our source data lacked information on disease severity, precluding assessment of the relationship between GM and the intensity of periodontitis. Third, consistent with prior microbiota MR studies, a lenient *p*-value threshold was applied in the selection of genetic instruments due to the limited number of variants associated with GM composition, which may introduce weak instrument bias. Lastly, while the MR technique is a powerful tool for assessing causality between exposure factors and health outcomes, these findings require validation through additional experimental and clinical research.

Conclusion

Our findings highlight the substantial influence of GM and circulating inflammatory proteins in the development and progression of periodontitis. Blocking the pathway from fractalkine to periodontitis may enhance the protective effect of *Actinobacteria* against disease progression. These findings indicate that therapies aimed at modifying GM composition could potentially alter the host inflammatory profile, thereby reducing the risk of periodontitis. This research provides a fundamental framework for understanding the mechanisms underlying the gut-oral axis and offers new directions for the development of microbiome-targeted therapies and cytokine-focused interventions in periodontitis. Nevertheless, additional comprehensive experimental and clinical investigations are necessary to validate and expand upon these findings.

Key Points

- Periodontitis is the second most prevalent oral disease and the 12th most common pathology worldwide, affecting approximately 19% of adults globally.
- Gut microbiota dysbiosis may significantly promote the development of periodontitis, though the underlying mechanisms remain unclear.
- The phylum *Actinobacteria* and chemokine fractalkine causally influence periodontitis, revealing a gut-oral axis mediated by systemic inflammation.
- This study proposes novel strategies for developing GM-targeted therapies and cytokine-based interventions for the treatment of periodontitis.

Availability of Data and Materials

The datasets analyzed in this study are publicly available in the following repositories: GM data in the IEU GWAS database [https://gwas.mrcieu.ac.uk/datasets/], inflammatory protein data in the GWAS Catalog [https://www.ebi.ac.uk/gwas/], and periodontitis data in the FinnGen repository [https://storage.googleapis.com/finngen-public-data-r11/summary_stats/finngen_R11_K11_PERIODON_CHRON_COMPL.gz]. All data included in this study are available from the corresponding authors upon reasonable request.

Author Contributions

Conceptualization, YYT and SYG; Data curation, YYT and WWL; Methodology, YYT and YQW; Project administration, YX and JQM; Software, SYG, YQW, SYJ and YYW; Visualization, WWL; Writing—original draft, YYT and SYG; Writing—review & editing, YX and JQM. All authors made substantial contributions to design. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2025.0447.

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