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INVESTIGATING THE POTENTIAL GENETIC ASSOCIATION OF SALIVARY AND TONGUE MICROBIOTA WITH PERIODONTITIS: A MENDELIAN RANDOMIZATION STUDY

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Abstract

Chronic periodontitis (CP) is characterized by subgingival microbial dysbiosis and demonstrates distinct microbial profiles; however, clear causal relationships with microbiomes from separate oral regions remain poorly defined. Genome-wide association study (GWAS) data for CP and oral microbial communities were obtained from a large European cohort and the China National GeneBank DataBase (CNGBdb), respectively. Using single-nucleotide polymorphisms (SNPs) as genetic instruments, Mendelian randomization (MR) analyses were performed via the inverse-variance weighted (IVW) method. Analytical procedures were executed using the 'TwoSampleMR' package (version 0.6.4) in R. Sensitivity analyses were conducted to confirm result robustness and limit horizontal pleiotropy.

The MR analysis identified three salivary bacterial taxa associated with reduced CP risk: Neisseria meningitidis (OR = 0.67, 95% CI: 0.49–0.98), Streptococcus vestibularis (OR = 0.74, 95% CI: 0.56–0.98), and Lancefeldella unclassified (OR = 0.68, 95% CI: 0.52–0.91) ($p<0.05p<0.05$). In contrast, three tongue microbial

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taxa were linked to increased CP risk: Solobacterium unclassified (OR = 1.45, 95% CI: 1.04–2.04), Fusobacterium sp000235465 (OR = 1.40, 95% CI: 1.02–1.94), and Haemophilus parainfluenzae (OR = 1.56, 95% CI: 1.12–2.18) ($p<0.05p<0.05$). No significant heterogeneity or directional pleiotropy was detected.

This study underscores associations between specific salivary and tongue microbial taxa and CP, providing mechanistic insight into their potential roles. Certain microbial taxa may serve as biomarkers for risk-stratified prevention and as targets for precision prebiotic or therapeutic interventions.

Keywords: Mendelian randomization, Oral microbiome, Periodontitis, Tongue microbiota.

1. Introduction

Chronic periodontitis (CP) is a widespread chronic inflammatory condition with non-communicable disease attributes. In 2019, severe periodontitis affected approximately 1.1 billion individuals globally, accounting for 10.6% of the population; age-standardized prevalence increased by 8.4% from 1990 to 2019 (Wu et al., 2022). Clinical hallmarks include microbial dysbiosis, periodontal pocket formation, connective tissue degradation, and alveolar bone loss, ultimately threatening tooth retention and quality of life (Kwon et al., 2021; Agnese et al., 2024). Established risk factors include smoking, alcohol use, and inadequate oral hygiene, yet underlying etiological mechanisms remain incompletely understood (Lasica et al., 2024).

The oral cavity hosts a complex microbial ecosystem, second in diversity only to the gut, and is intimately linked to oral and systemic diseases (Gopinath et al., 2020). Dysbiosis of oral microbial communities is recognized as a key driver in CP pathogenesis (Deng et al., 2017). Although microbial composition varies across oral niches (e.g., supragingival, subgingival), lifestyle, systemic health,

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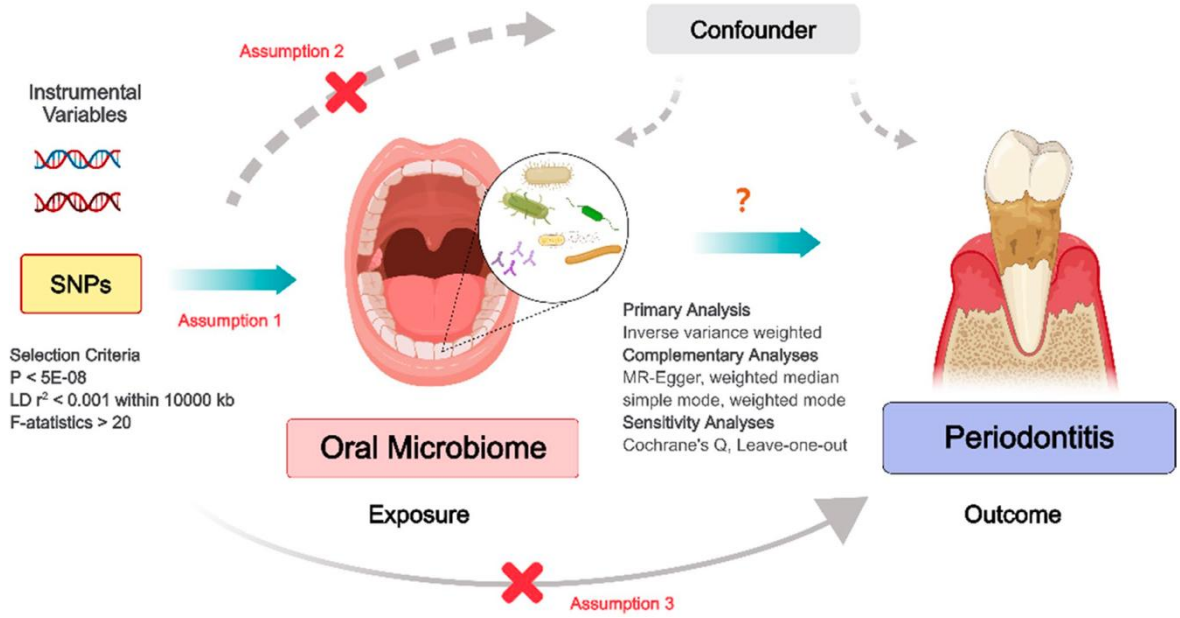
and hygiene practices further influence these communities (Li et al., 2022; Gopinath et al., 2022; Guo et al., 2024). Studying these relationships is challenging due to confounding and reverse causation.



Mendelian randomization (MR) uses genetic variants as instrumental variables to infer causality between exposures and outcomes, minimizing confounding and reverse causality (Davey Smith & Ebrahim, 2003). Prior research indicates host genetics shape oral microbiome composition (Goodrich et al., 2017; Dennmitt et al., 2017), and GWAS have identified genetic regulators of oral microbial structure (Awany et al., 2019; Liu et al., 2024). However, causal links between non-subgingival oral microbiota and CP are underexplored.

This study employed bidirectional two-sample MR to examine causal relationships between salivary/tongue microbiota and CP using GWAS data. We hypothesize that host genetics influence heritable microbial taxa in saliva and tongue, which in turn affect CP susceptibility. Findings may establish a causal

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framework for microbiome-mediated periodontitis and guide targeted interventions.

2. Methods

2.1 Study Design and Data Sources

A two-sample MR design was implemented. Oral microbiome GWAS summary data were sourced from CNGBdb (Liu et al., 2021). CP data were obtained from the FinnGen consortium (dataset "finn-b-K11_PERIODON_CHRON"), comprising 3,046 cases and 195,395 controls of European ancestry, classified using ICD-8, ICD-9, and ICD-10 criteria.

The study complied with ethical standards for secondary data analysis and followed STROBE-MR reporting guidelines.

2.2 Oral Microbiome Profiling and Bioinformatics

The analysis included 2,017 tongue and 1,915 salivary metagenomes (total N = 3,984). Quality control included genotype missingness < 2%, sequencing coverage > 20×, HWE > 10^{-5}, and exclusion of population outliers and related individuals. Taxonomic assignment and data normalization were performed for cross-cohort comparability.

2.3 Instrumental Variable Selection

SNPs associated with microbial taxa ($p<5\times10-8p<5\times10-8$) were selected as instruments. Linkage disequilibrium clumping ($r2<0.001r2<0.001$, window = 10,000 kb) and MR-PRESSO outlier removal were applied. Three core IV assumptions were verified:

1. **Relevance:** Strong SNP–exposure association.
2. **Independence:** No SNP–confounder association.
3. **Exclusion restriction:** SNP–outcome effect mediated only via exposure.

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2.4 Mendelian Randomization Analyses

Primary analysis used IVW meta-analysis. Sensitivity analyses included MR-Egger, weighted median, contamination mixture, and mode-based methods to assess robustness and pleiotropy.

2.5 Heterogeneity and Pleiotropy Assessments

Cochran's Q statistic evaluated heterogeneity. MR-Egger intercept and MR-PRESSO tested directional pleiotropy. Steiger filtering confirmed causal directionality.

2.6 Statistical Analysis

Analyses were conducted in R v4.3.1 using 'TwoSampleMR' and 'MRPRESSO'. Multiple testing correction applied Benjamini–Hochberg FDR ($q<0.05q<0.05$). Results were visualized with forest plots, volcano plots, and circular heatmaps.

3. Results

MR analysis identified taxon-specific causal associations across multiple phylogenetic levels. A total of 28,715 SNPs met instrument strength criteria (F-statistic > 20). Reverse MR yielded no significant results, supporting unidirectional causality from microbiome to CP.

3.1 Associations Between Saliva Microbiota and CP

Three salivary taxa were inversely associated with CP risk:

- Neisseria meningitidis (OR = 0.67, 95% CI: 0.49–0.98, $p=0.037p=0.037$)
- Streptococcus vestibularis (OR = 0.74, 95% CI: 0.56–0.98, $p=0.034p=0.034$)
- Lancefeldella unclassified (OR = 0.68, 95% CI: 0.52–0.91, $p=0.008p=0.008$)

3.2 Associations Between Tongue Microbiota and CP

Three tongue taxa were positively associated with CP risk:

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- Solobacterium unclassified (OR = 1.45, 95% CI: 1.04–2.04, p=0.031p=0.031)
- Fusobacterium sp000235465 (OR = 1.40, 95% CI: 1.02–1.94, p=0.040p=0.040)
- Haemophilus parainfluenzae (OR = 1.56, 95% CI: 1.12–2.18, p=0.009p=0.009)

3.3 Heterogeneity and Pleiotropy Analysis

Cochran's Q tests indicated no significant heterogeneity. MR-Egger intercepts were non-significant, suggesting absence of directional pleiotropy.

4. Discussion

This MR study provides evidence for causal roles of specific salivary and tongue microbiota in CP. Salivary taxa (Neisseria meningitidis, Streptococcus vestibularis, Lancefeldella) exhibited protective effects, while tongue taxa (Solobacterium, Fusobacterium, Haemophilus parainfluenzae) were associated with increased risk.

Saliva's functions in cleansing, digestion, and immune modulation may explain protective microbial roles. Conversely, the tongue's papillary structure shelters biofilm-embedded pathogens that may interact with subgingival plaque to promote dysbiosis.

Mechanistically, Neisseria meningitidis may modulate immune responses; Streptococcus vestibularis may support homeostasis via metabolic activities; Lancefeldella likely plays context-dependent roles. Tongue-associated Solobacterium produces volatile sulfur compounds linked to tissue toxicity; Fusobacterium and Haemophilus parainfluenzae are recognized pro-inflammatory agents.

The use of MR overcomes limitations of observational studies, though several constraints remain: heterogeneity in CP definitions across datasets, ancestry-

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specific genetic effects, potential unmeasured confounding, and limited SNP counts for some taxa. Future experimental studies are needed to validate mechanisms.

Clinically, these findings suggest potential for microbiome-targeted diagnostics, risk stratification, and precision interventions such as probiotics or antimicrobials prior to disease manifestation.

5. Conclusion

This study offers novel MR-based evidence for causal relationships between salivary/tongue microbiota and CP. Specific microbes may exert protective or pathogenic influences, informing future strategies for microbiome modulation in periodontal disease prevention and treatment.

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