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Causal relationship between gut microbiota and dental caries

A Mendelian randomization analysis

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Abstract

The onset of dental caries is associated with multiple factors, including oral microbiota, dietary sugars, the defensive mechanisms of saliva and teeth, oral hygiene practices, and socioeconomic factors. However, its relationship with the gut microbiota remains to be further explored. It remains crucial to establish a definitive causal link between the gut microbiota and the development of dental caries. This study aimed to investigate the causal relationship between gut microbiota and the risk of dental caries, focusing on identifying specific microbial communities potentially implicated in its pathogenesis. Gut microbiota data from genome-wide association studies (GWAS) conducted by the MiBioGen consortium were utilized as the exposure variable, with dental caries as the outcome variable. A Mendelian randomization (MR) approach was employed, leveraging comprehensive, publicly available GWAS summary data from European populations. The primary analytical method was the inverse variance weighted method, supplemented by additional techniques such as the weighted median model, MR-Egger, simple mode, and weighted mode, to ensure the robustness of the results. Heterogeneity was evaluated using Cochran *Q* test, and potential pleiotropy was assessed through MR-Egger regression. Sensitivity analyses were performed using the leave-one-out method to further validate the findings. The results revealed that a higher relative abundance of Christensenellaceae, FamilyXIII, Ruminococcaceae, and Senegalimassilia was associated with a reduced risk of dental caries. In contrast, a higher relative abundance of Erysipelotrichia, Erysipelotrichales, Pasteurellales, Erysipelotrichaceae, Pasteurellaceae, Methanobrevibacter, Roseburia, and Terrisporobacter was linked to an elevated risk of dental caries. This study provides compelling evidence for a causal relationship between gut microbiota and the development of dental caries, offering novel insights into the potential role of specific gut microbial communities in the pathogenesis of dental caries.

Abbreviations: GWAS = genome-wide association studies, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, SNPs = single nucleotide polymorphisms, WHO = World Health Organization.

Keywords: dental caries, gut microbiota, GWAS, Mendelian randomization, the causal association

1. Introduction

Dental caries represents a significant global public health concern, affecting approximately 2.4 billion individuals worldwide. It not only undermines individual health and quality of life but also imposes a substantial socioeconomic burden on healthcare systems and society at large.[1] According to the World Health Organization, the prevalence of dental caries ranges from 60% to 80% among children and approaches nearly 100% in the adult population, highlighting the widespread nature of this condition across all age groups.[2] The occurrence of dental caries is driven by a combination of factors, primarily including the presence of oral bacteria, the consumption of dietary sugars, the protective mechanisms of saliva and tooth enamel, oral hygiene practices, socioeconomic status, and genetic susceptibility. These factors collectively contribute to the complexity of caries development, influencing individual risk and disease progression.[1] The oral microbiota plays a critical role in the development of dental caries. Recent research has suggested the potential existence of an oral-gut axis, whereby microorganisms in the oral cavity may influence the gut microbiota through the digestive system, and vice versa. This bidirectional interaction underscores the complex interplay between microbial communities in different regions of the body, with potential implications for both oral and systemic health.[3,4] However, there is limited research on the role of the gut microbiota in the pathogenesis of dental caries. Consequently, further investigation

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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is needed to determine whether the gut microbiota is linked to the onset and progression of dental caries, and to identify the specific microbial communities that may contribute to its development.

The human microbiome, residing in distinct anatomical regions, is fundamental to numerous physiological processes. It plays a vital role in nutrient absorption, maintaining the integrity of epithelial barriers, detoxifying harmful substances, regulating immune and inflammatory responses, and providing defense against pathogenic microorganisms. These microbial communities are essential for sustaining homeostasis and overall health.[5,6] Recent advancements in next-generation sequencing technologies have significantly expanded our knowledge of the human microbiome, particularly the gut microbiome, which is primarily dominated by the phyla Bacteroidetes and Firmicutes. These technological innovations have provided deeper insights into the composition, diversity, and functional roles of microbial communities, paving the way for more sophisticated analyses of their impact on human health.[7] A healthy gut microbiota produces short-chain fatty acids (SCFAs) through the fermentation of dietary fibers, which are essential for maintaining gut pH, supporting the proliferation of beneficial bacteria, inhibiting pathogen colonization, and promoting epithelial regeneration. As a result, a well-balanced gut microbiome plays a critical role in reducing the risk of chronic inflammation, obesity, metabolic syndrome, and cancer-related diseases.[8]

The gut microbiota generally exists in a state of symbiotic balance with its host, contributing to overall health and physiological homeostasis. However, this delicate equilibrium can be disrupted by a range of factors, including medication use, obesity, dietary patterns, physical activity levels, and genetic predispositions. Such disturbances may compromise microbial diversity and function, leading to adverse health outcomes.[8] Intestinal dysbiosis, characterized by a loss of diversity and stability in the gut microbiota, can lead to the overgrowth of pathogenic bacteria and the production of harmful metabolites. This microbial imbalance impairs normal immune and metabolic functions and has been linked to a wide range of disorders, including inflammatory bowel disease, diabetes, obesity, metabolic syndrome, and cancer.[9] Recent studies have suggested the potential existence of an oral-gut axis, wherein the gut microbiota can influence oral microorganisms through the digestive system, and conversely, oral microorganisms may affect the gut microbiota via the same pathway.[3,10] However, there is currently no consensus on the relationship between the gut microbiota and the risk of dental caries, nor is it clear which gut microbial communities may be harmful or beneficial in the context of dental caries development. The existing evidence remains inconclusive, underscoring the need for further research to elucidate this potential association and the underlying mechanisms involved.

Mendelian randomization (MR) is a research method that utilizes genetic variants, particularly single nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS), as instrumental variables (IVs) to assess causal relationships between exposures and disease outcomes. By relying on the random allocation of genetic variants at conception, this approach mitigates biases such as confounding and reverse causation, offering more reliable evidence for causality in epidemiological research.[11] Therefore, to further investigate the potential association between gut microbiota and the risk of dental caries, we conducted a MR study. This analysis utilized gut microbiota data from GWAS conducted by the MiBioGen consortium as the exposure variables, with dental caries serving as the outcome variable. The primary objective of this study was to evaluate the causal relationship between gut microbiota composition and the risk of developing dental caries.

2. Materials and methods

The study design and methodology are outlined in the flowchart (Fig. 1).

2.1. Study population and data sources

Genetic summary statistics for dental caries were obtained from a GWAS including 2110 cases and 372,016 controls of European ancestry. The original data were sourced from the UK Biobank, a large-scale prospective cohort study encompassing over half a million participants from the United Kingdom. The UK Biobank dataset offers extensive phenotypic and genetic data, including genome-wide genotyping, and has been made publicly available to facilitate research endeavors.[12,13] Genetic summary data for gut microbiota were obtained from the MiBioGen consortium. A comprehensive overview of the data sources used in this study is provided in Table 1. All data consist of publicly available GWAS summary statistics that have undergone prior ethical approval, eliminating the need for an independent ethics application for the present analysis.

2.2. Selection of IVs

Gut microbiota was selected as the exposure variable in our analysis. Initially, we excluded 15 bacterial traits lacking specific nomenclature, retaining a total of 196 bacterial traits for further investigation. These traits encompass 9 Phyla, 16 Classes, 20 Orders, 32 Families, and 119 Genera. SNPs significantly associated with gut microbiota were selected as IVs for this study. To ensure an adequate number of SNPs with appropriate statistical significance, we applied a genome-wide significance threshold of $P < 5 \times 10^{-5}$ for exposure selection. SNPs exhibiting linkage disequilibrium were excluded based on an r^2 threshold of <0.001 and a distance of >10,000 kb. Additionally, palindromic SNPs, SNPs with allele mismatches between the exposure and outcome datasets (e.g., A/G vs A/C), and SNPs with $P < .05$ in the outcome data were removed to ensure proper alignment of allele effects between the exposure and outcome variables.[14] To further evaluate the validity of the IVs, we calculated the R^2 and F-statistics for each SN using the following formulas: $R^2 = 2 \times \beta^2 \times EAF \times (1 - EAF)$; $F = (N - K - 1) \times R^2/(1 - R^2)$, where "EAF" represents the minor allele frequency of the SNPs used as IVs, "R^2" denotes the proportion of variance in the exposure explained by the IVs, "N" is the sample size, and "K" represents the number of IVs used in the analysis. SNPs with F>10 were retained for further analysis, ensuring that the selected SNPs exhibited strong predictive power for the exposure variable and thereby reducing the potential bias from weak instruments in the study.[15]

2.3. MR analysis

The analysis relies on 3 core assumptions: the IVs are strongly associated with the exposure of interest; the IVs are independent of the outcome, except through their influence on the exposure, and are not affected by confounding factors; and the IVs affect the outcome exclusively through their impact on the exposure, without any direct effect on the outcome itself. To explore the causal relationship between gut microbiota and dental caries, 5 regression models were employed: inverse variance weighted (IVW) method, weighted median estimation, MR-Egger regression, the simple mode method, and the weighted mode method. The IVW method was utilized as the primary analytical tool, while the other 4 models were applied as complementary approaches to validate and support the findings. The IVW method estimates the predictive value of genetic instruments influencing the exposure-outcome relationship, expressed through the effect size (β). It calculates the causal effect by combining estimates

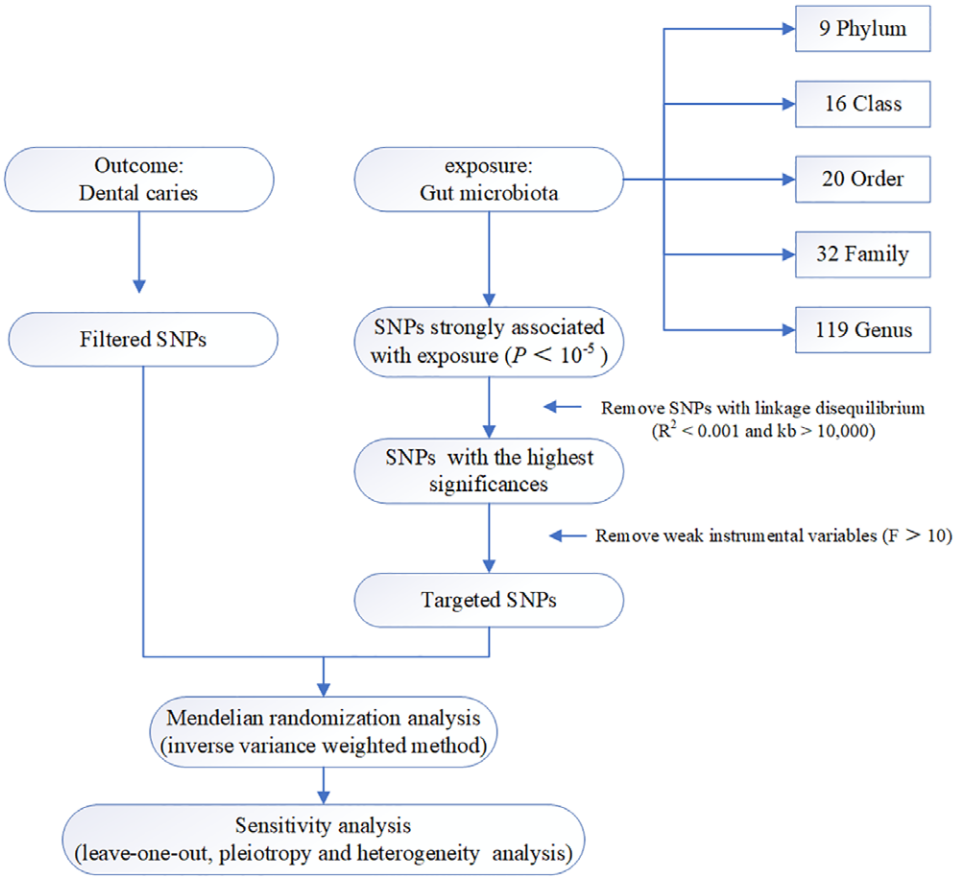

Figure 1. Flow chart of this study.

Table 1

Details of the GWAS datasets in the study.

Exposure/outcome	ID	Sample size	Population	Portal website
Human gut microbiome		18,340 participants	Mixed	https://mibiogen.gcc.rug.nl
Dental caries	ukb-d-K02	2110 cases and 361,194 controls	European	https://gwas.mrcieu.ac.uk/

Abbreviation: GWAS = genome-wide association studies.

from multiple genetic instruments, where each estimate is derived using the Wald ratio for individual instruments. This provides a robust aggregate estimate of the causal relationship between exposure and outcome. Following the primary analysis, we assessed the results of the MR study through several steps. First, the leave-one-out method was used to evaluate the sensitivity of the results by sequentially excluding individual SNPs. Next, heterogeneity in the IVW estimates was assessed using Cochran *Q* test. Finally, the potential for pleiotropy in the IVs was evaluated using the MR-Egger regression.

2.4. Statistical analysis

MR analysis was performed using the "TwoSampleMR" package in R (version 4.30). $P < .05$ was employed to determine statistical significance in the interpretation of the results.

3. Results

3.1. IVs selection

Fifteen bacterial traits lacking specific nomenclature were excluded, resulting in a final dataset comprising 196 bacterial traits. A total of 2601 SNPs associated with these 196 gut microbiota traits were identified through a selection criterion for IVs with a significance threshold of $P < 1.0 \times 10^{-5}$, an $r^2 < 0.001$, and $k > 10{,}000$. This gut microbiota included 124 SNPs from 9 phyla, 223 SNPs from 16 classes, 279 SNPs from 20 orders, 444 SNPs from 32 families, and 1531 SNPs from 119 genera. All selected SNPs had *F*-statistics exceeding the threshold of 10, ensuring the robustness of the IVs and minimizing the risk of weak instrument bias in the analysis.

3.2. Causal effects of gut microbiota on dental caries

Mendelian randomization analysis was performed on 196 bacterial taxa using the IVW method, applying a significance threshold of $P < .05$ for SNP selection. We identified 142 SNPs across 12 bacterial taxa that demonstrated a causal relationship with dental caries (Table 2). The identified gut microbiota was classified into 1 class (13 SNPs), 2 order (30 SNPs), 5 family (64 SNPs), and 4 genus (35 SNPs), specifically including Erysipelotrichia, Erysipelotrichales, Pasteurellales, Christensenellaceae, Erysipelotrichaceae, FamilyXIII, Pasteurellaceae, Ruminococcaceae, Methanobrevibacter, Roseburia, Senegalimassilia, and Terrisporobacter. Our

Table 2

The associations between genetically determined 12 bacterial traits with the risk of dental caries.

Gut microbiota	Types	Number of SNPs	OR (95% CI)	*P*
Erysipelotrichia	Class	13	1.0024 (1.0003–1.0044)	.0218
Erysipelotrichales	Order	13	1.0024 (1.0003–1.0044)	.0218
Pasteurellales	Order	17	1.0012 (1.0001–1.0023)	.0483
Christensenellaceae	Family	11	0.9981 (0.9962–0.9999)	.0481
Erysipelotrichaceae	Family	13	1.0024 (1.0003–1.0044)	.0218
FamilyXIII	Family	12	0.9978 (0.9958–0.9998)	.0320
Pasteurellaceae	Family	17	1.0012 (1.0001–1.0023)	.0483
Ruminococcaceae	Family	11	0.9980 (0.9961–0.9999)	.0461
Methanobrevibacter	Genus	8	1.0014 (1.0002–1.0026)	.0213
Roseburia	Genus	16	1.0018 (1.0001–1.0034)	.0429
Senegalimassilia	Genus	6	0.9981 (0.9962–0.9999)	.0392
Terrisporobacter	Genus	5	1.0028 (1.0008–1.0047)	.0048

Abbreviations: CI = confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

result revealed that higher abundances of Erysipelotrichia (OR: 1.0024, 95% confidence interval (CI): 1.0003–1.0044, $P = .0218$), Erysipelotrichales (OR: 1.0024, 95% CI: 1.0003–1.0044, $P = .0218$), Pasteurellales (OR: 1.0012, 95% CI: 1.0001–1.0023, $P = .0483$), Erysipelotrichaceae (OR: 1.0024, 95% CI: 1.0003–1.0044, $P = .0218$), Pasteurellaceae (OR: 1.0012, 95% CI: 1.0001–1.0023, $P = .0483$), Methanobrevibacter (OR: 1.0014, 95% CI: 1.0002–1.0026, $P = .0213$), Roseburia (OR: 1.0018, 95% CI: 1.0001–1.0034, $P = .0429$), and Terrisporobacter (OR: 1.0028, 95% CI: 1.0008–1.0047, $P = .0048$) were significantly associated with an increased risk of dental caries. In contrast, higher genetically predicted levels of Christensenellaceae (OR: 0.9981, 95% CI: 0.9962–0.9999, $P = .0481$), FamilyXIII (OR: 0.9978, 95% CI: 0.9958–0.9998, $P = .0320$), Ruminococcaceae (OR: 0.9980, 95% CI: 0.9961–0.9999, $P = .0461$) and Senegalimassilia (OR: 0.9981, 95% CI: 0.9962–0.9999, $P = .0392$) were significantly associated with a decreased risk of dental caries (Table 2 and Fig. 2A–L).

3.3. Sensitivity analysis

Cochran *Q* test results revealed no significant heterogeneity among the selected IVs ($P > .05$), indicating consistency across the analyzed models. Additionally, MR-Egger regression analysis showed no evidence of horizontal pleiotropy within the assessed bacterial taxa ($P > .05$), suggesting that the causal estimates are unlikely to be biased by pleiotropic effects (Table 3). The robustness and reliability of the MR analysis were further supported by the leave-one-out sensitivity analysis, which identified no notable outliers among the selected IVs (Fig. 3A–L).

4. Discussion

Dental caries is a multifactorial, chronic, and progressive destructive disease. Its epidemiological trends show distinctive characteristics: in developed countries, the incidence of dental caries has generally been on the decline over the past few decades, whereas in developing countries and emerging economies, the prevalence of dental caries has been rising.[16] The development of dental caries is the result of the complex interplay of multiple factors. To date, no published studies have explored the genetic causal relationship between gut microbiota and the risk of dental caries. Furthermore, there remains no consensus on the nature of the association between gut microbiota composition and the risk of developing dental caries. This gap in the literature underscores the need for further research to clarify the potential role of gut microbial communities in the pathogenesis of dental caries. This study seeks to bridge the existing knowledge gap by exploring the potential genetic links between gut microbiota and susceptibility to dental caries. Using MR analysis based on GWAS data, we investigated the causal relationships between specific gut microbial and the risk of dental caries. Our analysis identified a significant positive association between the presence of Erysipelotrichia, Erysipelotrichales, Pasteurellales, Erysipelotrichaceae, Pasteurellaceae, Methanobrevibacter, Rosebur, and Terrisporobacter and an increased risk of dental caries. Conversely, Christensenellaceae, FamilyXIII, Ruminococcaceae and Senegalimassilia were negatively associated with caries risk, suggesting a potential protective role for these microbial taxa in the pathogenesis of dental caries.

Erysipelotrichia, Erysipelotrichales, and Erysipelotrichaceae are different taxonomic levels of the same group of bacteria within the gut microbiota, ranging from class to order to family.[17] Some studies have reported that they may promote the development and progression of diseases such as obesity, insulin resistance, nonalcoholic fatty liver disease, and colorectal cancer through certain mechanisms.[17–19] Pasteurellales and Pasteurellaceae represent different taxonomic levels of the same group of bacteria within the gut microbiota, from order to family. Although they are not dominant members of the gut microbiome, their role in disease pathogenesis is significant. These bacteria contribute to the development and progression of diseases through various mechanisms, including inducing inflammation, altering metabolic functions, and modulating host immunity. They have been implicated in promoting intestinal inflammation, metabolic disorders, cardiovascular diseases, and tumorigenesis.[20–22] Methanobrevibacter, Roseburia, and Terrisporobacter can act as harmful bacteria within the gut microbiota and contribute to the development and progression of various human diseases, such as colorectal cancer, intestinal inflammation, and metabolic disorders. These bacteria exert their pathogenic effects through multiple mechanisms, including disrupting intestinal barrier function, inducing chronic inflammation, altering energy metabolism, and producing toxic metabolites.[23–25] Christensenellaceae, Family XIII, Ruminococcaceae, and Senegalimassilia are 4 beneficial bacterial groups within the gut microbiota that play crucial roles in maintaining host health. They contribute to disease prevention and mitigation (e.g., intestinal inflammation, metabolic disorders, and cardiovascular diseases) through mechanisms such as producing SCFAs, regulating intestinal immune responses, maintaining gut barrier integrity, and improving metabolic health.[26–29] Prior to our study, no investigations have been reported that examine the association between these gut microbiota and dental caries. The harmful gut microbiota identified in this study (such as Erysipelotrichia, Pasteurellales, and Methanobrevibacter) may contribute to the development of

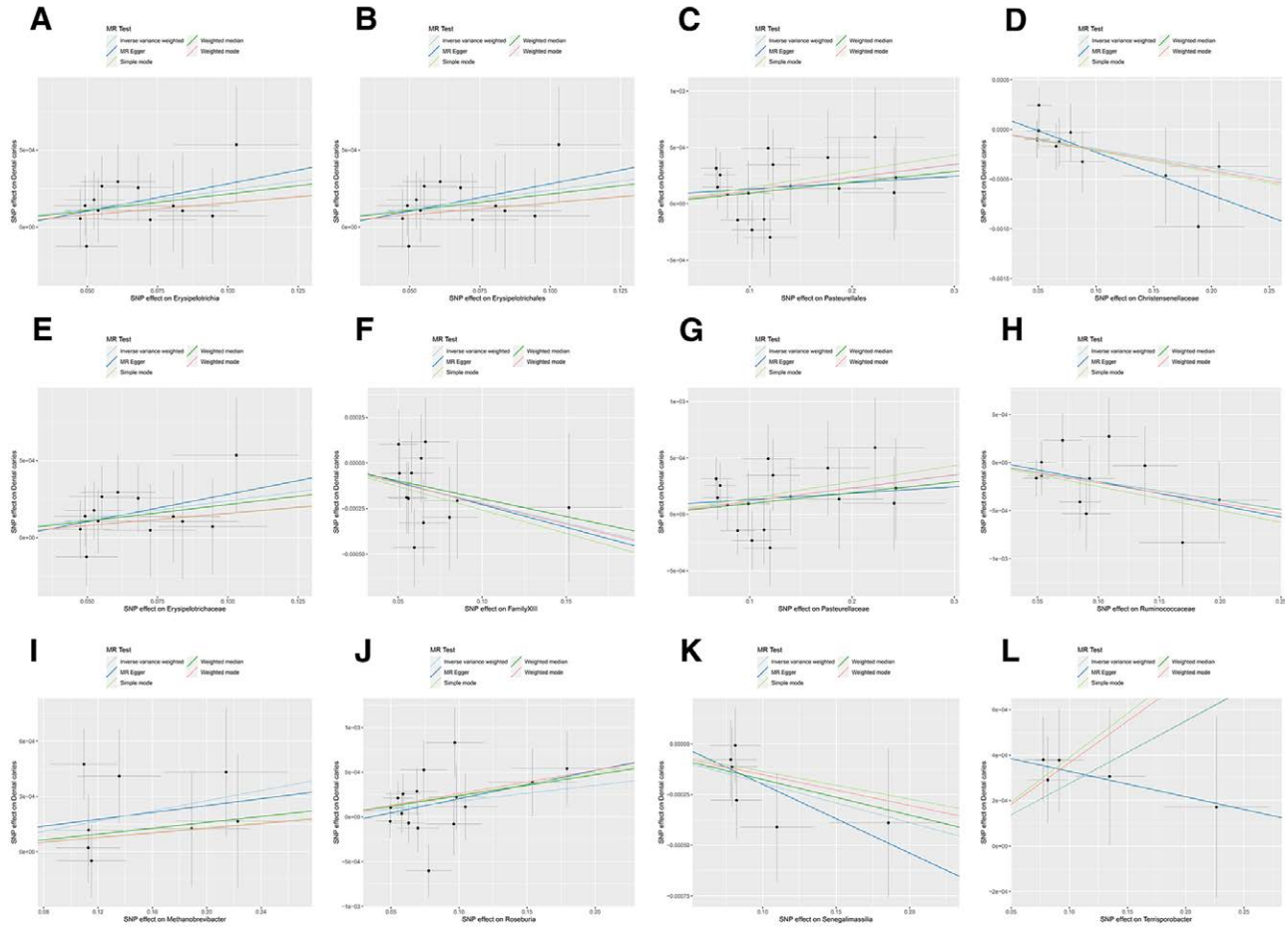

Figure 2. Scatter plots for causal SNPs effect of gut microbiota on dental caries. Each black point representing each SNP on the exposure (horizontal-axis) and on the outcome (vertical-axis) is plotted with error bars corresponding to each standard error. (A) Erysipelotrichia, (B) Erysipelotrichales, (C) Pasteurellales, (D) Christensenellaceae, (E) Erysipelotrichaceae, (F) FamilyXIII, (G) Pasteurellaceae, (H) Ruminococcaceae, (I) Methanobrevibacter, (J) Roseburia, (K) Senegalimassilia, and (L) Terrisporobacter. SNP = single nucleotide polymorphism.

Table 3

Sensitivity analysis of the gut microbiota on dental caries.

		Heterogeneity test		
Gut microbiota	**Types**	**IVW Q_*P*-value**	**MR-Egger Q_*P*-value**	**Horizontal pleiotropy test (*P*)**
Erysipelotrichia	Class	.9858	.9757	.7924
Erysipelotrichales	Order	.9858	.9757	.7924
Pasteurellales	Order	.7774	.8191	.6619
Christensenellaceae	Family	.8469	.9156	.2280
Erysipelotrichaceae	Family	.9858	.9757	.7924
FamilyXIII	Family	.8363	.7701	.9377
Pasteurellaceae	Family	.7774	.8191	.6619
Ruminococcaceae	Family	.7654	.6886	.8042
Methanobrevibacter	Genus	.5696	.4571	.8438
Roseburia	Genus	.4669	.4213	.5426
Senegalimassilia	Genus	.8793	.8115	.6852
Terrisporobacter	Genus	.6320	.9852	.2176

Abbreviation: IVW = inverse variance weighted.

dental caries through mechanisms including disruption of intestinal barrier function, induction of chronic inflammation, and alteration of host energy metabolism. Furthermore, Pasteurellales and Pasteurellaceae may indirectly influence the oral environment by modulating host immune responses and metabolic functions. In contrast, protective microbiota (such as Christensenellaceae and Ruminococcaceae) improve gut health by producing SCFAs (e.g., butyrate), maintaining immune homeostasis, and potentially reducing caries risk through systemic effects. These mechanisms provide new perspectives on the systemic-local pathological connections in dental caries.

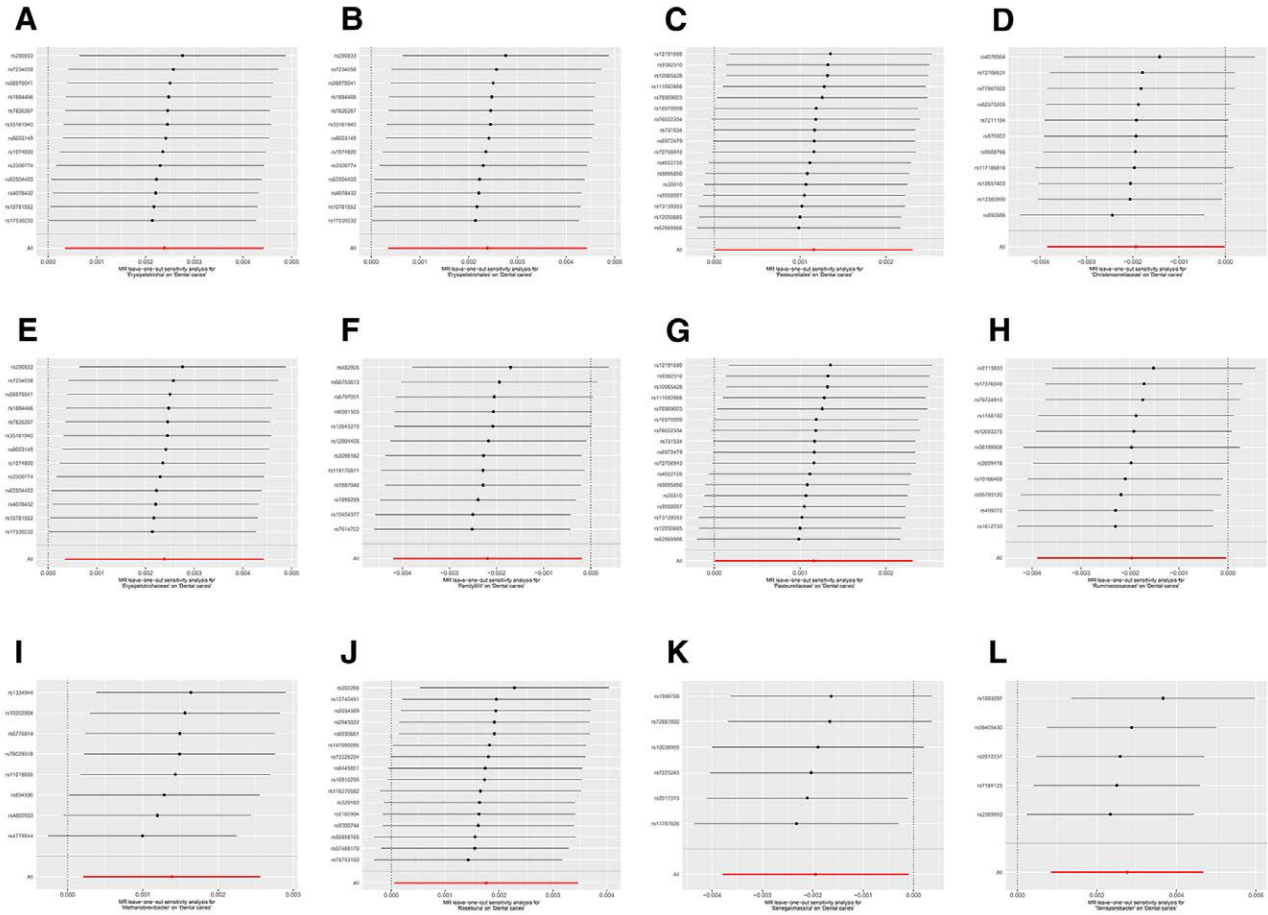

Figure 3. Forest plots of leave-one-out analyses for causal SNP effect of gut microbiota on dental caries. The error bars indicate the 95% confidence interval. (A) Erysipelotrichia, (B) Erysipelotrichales, (C) Pasteurellales, (D) Christensenellaceae, (E) Erysipelotrichaceae, (F) FamilyXIII, (G) Pasteurellaceae, (H) Ruminococcaceae, (I) Methanobrevibacter, (J) Roseburia, (K) Senegalimassilia, and (L) Terrisporobacter. SNP = single nucleotide polymorphism.

This study is the first to reveal a significant association between 12 gut microbiota and the risk of dental caries, with their roles potentially mediated through various biological mechanisms, including inflammation regulation, metabolic modulation, and immune function control. Although the causal relationship is relatively weak, this study provides critical insights and a foundation for future investigations into the pathophysiology of dental caries. Firstly, this study highlights that gut microbiota may influence the risk of dental caries through systemic metabolic and immune pathways, providing a theoretical basis for personalized caries prevention strategies. Secondly, the identification of harmful and protective microbiota offers potential targets for future microbial interventions, such as probiotic therapies or dietary modifications. For instance, adjusting dietary patterns or supplementing specific probiotics (e.g., Christensenellaceae) may simultaneously improve gut microbiota composition and reduce caries risk. Lastly, these findings open new avenues for exploring the interconnected mechanisms between gut and oral diseases, supporting the implementation of comprehensive health management approaches.

However, our study also has certain limitations. The primary limitation lies in the reliance on GWAS summary data from European populations, with limited inclusion of gut microbiota data from other ethnic groups. This lack of diversity may influence the generalizability and precision of our findings across different populations. Additionally, dental caries is a complex, multifactorial disease influenced by interactions between genetic and environmental factors, including gut microbiota composition. Consequently, potential confounding effects arising from gene-diet and gene-environment interactions cannot be entirely ruled out. To further explore the functional roles of these identified microbiota, future research should focus on animal models, which will be crucial to evaluate the therapeutic potential of targeting these microbiotas in the prevention and treatment of dental caries.

5. Conclusion

In summary, this study provides a comprehensive analysis of the potential causal relationship between gut microbiota and dental caries. We identified twelve gut microbiota that are associated with the risk of developing dental caries. These findings offer novel insights and open new avenues for future strategies in the prevention and treatment of dental caries.

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Author contributions

Data curation: Yongyuan Jiang, Xuan Zhu.
Methodology: Huan Jin.
Writing – original draft: Xuan Zhu.
Writing – review & editing: Qian Liang.

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