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Causal Association Between Microbiome and Oral-Oropharyngeal Cancer: A Mendelian Randomization Study

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ABSTRACT

Introduction and aims: This study aimed to examine the causal link between oral microbiome and the risk of oral and oropharyngeal squamous cell carcinoma (OOPSCC) using Mendelian randomization (MR).

Methods: Utilizing single nucleotide polymorphisms as instrumental variables, we applied the MR inverse-variance weighted approach to assess the impact of salivary and tongue microbiome on OOPSCC. The data were obtained from the CNGBdb database and the UK Biobank, and analytical procedures were performed using the R package 'TwoSampleMR'. To ensure the robustness of our findings, we conducted sensitivity studies, which included the MR-Egger intercept test, to establish strong correlations and eliminate the phenomenon of horizontal pleiotropy.

Result: Our large-scale MR study revealed a genetically predisposed causal relationship between 13 microbial taxa, each from saliva and tongue, with OOPSCC. Notably, microbial taxa from six genera, including *Prevotella, Neisseria, Veillonella, Granulicatella, Treponema,* and *Streptococcus*, in both salivary and tongue microbiomes, showed this relationship. Conversely, several taxa, including *Hemophilus, Solobacterium, Campylobacter,* and *Porphyromonas*, predominantly demonstrated an inverse relationship, suggesting a protective effect. The robustness of our findings was further confirmed through sensitivity analyses, providing additional confidence in our results.

Conclusion: Our MR study indicates that the oral microbiota has a significant causal impact on the risk of oral and oropharyngeal cancers. The microbial biomarkers we identified, which are linked to OOPSCC, have the potential to uncover the underlying mechanisms and pave the way for new therapeutic approaches for targeted treatment of these malignancies.

Introduction

Oral and oropharyngeal squamous cell carcinoma (OOPSCC) is one of the most common kinds of cancer globally and is linked to high rates of morbidity.[1,2] Approximately 60% of cases of

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oral malignancies are detected in a late stage, leading to a survival probability of fewer than 50% during a 5-year period.[1,2] Established risk factors implicated in the development of OOPSCC include tobacco use, excessive alcohol consumption, betel nut chewing, and human papillomavirus, especially for SCC of the oro-pharynx.[3] However, there has been a rise in the incidence of OOPSCC cases without these conventional risk factors in recent years.[4] Hence, it is essential to promptly uncover the additional risk factors that may substantially influence the prognosis in patients with these malignancies and enable early detection and prevention.

The oral microbiome is a highly significant and intricate collection of microorganisms within the human body. It is considered one of the top five areas of focus in the human microbiome project, alongside the nasal cavity, vagina, intestine, and skin.[5,6] Mounting data substantiates the correlation between the oral microbiota and human systemic disorders.[7] The correlation between these two factors can be ascribed to the capacity of several oral microorganisms to impact the inflammatory microenvironment. Extensive data over the past two decades has conclusively demonstrated a strong correlation between bacteria and the development of tumours.[8,9] Several pathogens have been implicated in the development of various types of cancer. For instance, *Helicobacter pylori* with gastric cancer, *Chlamydia pneumoniae* with lung cancer, *Salmonella typhi* with gallbladder cancer, *Streptococcus bovis* and *Bacteroides fragilis* with unspecified types of cancer, and *Fusobacterium nucleatum* (*F. nucleatum*) with colon cancer.[10,11] Moreover, numerous studies have suggested that oral bacteria might play a role in carcinogenesis through both direct and indirect mechanisms.[12,13]

Microbial dysbiosis, defined as the imbalance in the microbial equilibrium, has been suggested to play a significant role in the development of OOPSCC; notable changes in the diversity of specific genera or species have been reported by several studies in OOPSCC.[8,14] These investigations have indicated the potential involvement of several bacteria in the development of OOPSCC, and the subsequent research findings offer some evidence to substantiate this hypothesis. Nevertheless, the makeup of oral bacterial populations varies depending on the saliva and specific locations within the mouth cavity.[15] In addition, the established etiological factors, including betel quid chewing, tobacco, and alcohol, can potentially affect the population of oral microorganisms, which makes the relationship more complicated.[16] Thus, the observational research in this particular area is impeded by confounding factors and reverse causality. Considering the growing data suggesting that the human microbiome might cause cancer, exploring the role of oral microbial dysbiosis in OOPSCC may help explain why some individuals who are not exposed to established risk factors nevertheless develop cancer. Further, clarifying the potential cause-and-effect relationship between the oral microbiome and OOPSCC is crucial to improving the prevention and prognosis.

Mendelian randomization (MR) is a flexible tool that employs whole-genome sequencing data to investigate causal correlations in epidemiology.[17,18] Genetic variants strongly linked to the exposure are used as instrumental variables (IVs) in MR to establish causality and reduce the impact of confounding biases.[19-21] In previous studies, scientists have demonstrated the influence of human genetics on the composition of microorganisms in the mouth. A study on the oral microbiome in twins showed that the oral microbiome is inherited, with more than 50% of the microbiome traits showing heritability.[22] Despite limited understanding, earlier genome-wide association study (GWAS) investigations have found specific genetic loci linked to the composition and stability of the oral microbiome, highlighting the influence of host genetics.[23] However, our understanding of the causal influence of oral microbiota and cancers is still in its early developmental phases.[24] The presence of such research gaps not only restricts our comprehension of the correlation between the oral microbiome and cancer but also obstructs the identification of possible preventative and therapeutic approaches. In this study, we performed a two-sample MR analysis to examine the causal link between salivary and tongue microbiome with OOPSCC using publicly available GWAS summary statistics.

Methods

Study design and data sources

This two-sample MR analysis utilized a previously published GWAS focused on the oral microbiota of East Asian individuals – CNGBdb database.[25-27] This GWAS is notable for being the first large-scale study within this population, targeting 2017 tongue dorsum samples and 1915 salivary samples, utilizing high-depth whole-genome sequencing (PMID: 34873157). For summary statistics, we used the publicly available ieu-b-4962 dataset that includes OOPSCC genetic data from a large European cohort.

Oral microbiota data collection and processing

The study dataset included tongue dorsum microbiomes (N = 2017) and salivary microbiomes (N = 1915) (Table S1). Samples were subjected to rigorous inclusion criteria to ensure data quality, including a variant calling rate of at least 98%, a mean sequencing depth of over 20×, absence of population stratification in principle component analysis, and the exclusion of related individuals based on pairwise identity by descent estimates. Additional stringent criteria were applied, such as a minimum mean depth of 8×, Hardy–Weinberg equilibrium values greater than 10^ to 5, and a genotype calling rate above 98% for analysed variations. Following these stringent quality control protocols, a comprehensive cohort of 2984 participants was established, comprising 2017 individuals with tongue dorsum samples and 1915 individuals with salivary samples. This dataset included approximately 10 million variants, covering common and low-frequency variants with a minor allele frequency of at least 0.5%, maintained for further analysis. Raw sequencing data were processed to generate operational taxonomic units, which were then taxonomically classified using reference databases. Data standardization and normalization procedures were implemented to ensure comparability across different datasets and sequencing platforms.

Genetic data and IV selection

Genetic data for both datasets were obtained from GWAS. Single nucleotide polymorphisms (SNPs) significantly associated with oral microbiota taxa ($P < 5 \times 10^{-7}$) were selected as IVs for the MR analyses. These SNPs were chosen based on their relevance to the microbial taxa of interest and their availability in both datasets. To ensure the validity of the IVs, we excluded SNPs with pleiotropic effects unrelated to the microbiota.

MR analyses

We employed the inverse-variance weighted (IVW) method as the primary analysis, complemented by MR-Egger regression, weighted median, simple median, and weighted mode methods to account for potential pleiotropy and provide robust estimates. The IVW method combines the effect estimates of the IVs, assuming no pleiotropy, while complementary methods offer sensitivity analyses to detect and adjust for pleiotropy.

Heterogeneity and pleiotropy assessments

To assess the robustness of our findings, we performed heterogeneity and pleiotropy analyses. Cochran's Q test about IVW and Eggar methods was used to evaluate the heterogeneity among the selected SNPs, with significant heterogeneity indicating variability in the IV effects. The MR-Egger intercept test was employed to detect directional pleiotropy, where a significant intercept suggests the presence of pleiotropy. Additionally, the MR-PRESSO (Pleiotropy RESidual Sum and Outlier) test was used to identify and correct for outliers, further ensuring the reliability of the MR findings.[18,28,29] The Steiger analysis was used to detect the causal direction of the MR analysis between exposure OM and outcome OOPSCC.

Statistical analyses

All statistical analyses were performed using R software, with 'TwoSampleMR' and 'MR-PRESSO' packages specifically designed for MR analyses. The significance threshold for the MR analyses was set at $P < .05$. Results were visualized using forest and bubble plots to illustrate the effect sizes and confidence intervals (CI) of the associations between microbiota taxa and OOPSCC risk. These visualizations facilitate the interpretation of the findings and highlight the most significant associations.

Results

In the MR analysis considering saliva microbiota and tongue microbiota as an exposure, our study identified associations with one phylum, two classes, eight orders, 17 families, 15 genera, and 412 species. Regarding the saliva microbiota, we found associations with two phyla, 1 class, four orders, 13 families, 96 genera, and 424 species. With 9080 SNPs and 8661 SNPs with genome-wide significance were selected. The calculated *F*-statistics for the selected SNPs related to saliva microbiota and tongue microbiota exceeded the conventional threshold of 20 (Tables S2 and S3), indicating that these selected SNPs may be reliable representatives of saliva microbiota and tongue microbiota.

Associations between saliva microbiota and OOPSCC

The MR analyses revealed several significant associations between saliva microbiota taxa and oral cancer risk. Notably, *Veillonella* unclassified (pheno.1057) (odds ratios [OR] = 1.00125, 95% CI = 1.00012-1.00238, *P* = 0.03045), *Granulicatella* unclassified (pheno.1308) (OR = 1.00187, 95% CI = 1.00095-1.00278, *P* = .00006), *Streptococcus* unclassified (pheno.134) (OR = 1.00121, 95% CI = 1.00013-1.00229, *P* = .02753), *Streptococcus* sp000411475 (pheno.1435) (OR = 1.00083, 95% CI = 1.00003-1.00162, *P* = .04085), *Streptococcus* unclassified (pheno.1713) (OR = 1.00150, 95% CI = 1.00024-1.00277, *P* = .02012), *Streptococcus* unclassified (pheno.1771) (OR = 1.00247, 95% CI = 1.00094-1.00399, *P* = .00153), *Prevotella veroralis* (pheno.1822) (OR = 1.00152, 95% CI = 1.00025-1.00279, *P* = .01864), *Neisseria* unclassified (pheno.2211) (OR = 1.00136, 95% CI = 1.00021-1.00252, *P* = .02015), *Kingella* unclassified (pheno.2262) (OR = 1.00103, 95% CI = 1.00004-1.00201, *P* = .04092), *Haemophilus* unclassified (pheno.2373) (OR = 1.00127, 95% CI = 1.00001-1.00253, *P* = .04779), *Streptococcus* unclassified (pheno.2374) (OR = 1.00173, 95% CI = 1.00058-1.00289, *P* = .00330), *Streptococcus* unclassified (pheno.250) (OR = 1.00238, 95% CI = 1.00050-1.00426, *P* = .01290), and *Treponema vincentii* (pheno.2566) (OR = 1.00143, 95% CI = 1.00018-1.00268, *P* = .02513 were significantly associated with an increased risk of OOPSCC (Figure 1).

On the contrary, *Campylobacter* unclassified (pheno.1053) (OR = 0.99826, 95% CI = 0.99655-0.99997, *P* = .04578), *Aggregatibacter segnis* (pheno.1100) (OR = 0.99862, 95% CI = 0.99741-0.99984, *P* = .02600), *Prevotella* unclassified (pheno.1299) (OR = 0.99906, 95% CI = 0.99819-0.99994, *P* = .03679), *Streptococcus* unclassified (pheno.1388) (OR = 0.99850, 95% CI = 0.99710-0.99991, *P* = .03657), *Mogibacterium* unclassified (pheno.1415) (OR = 0.99892, 95% CI = 0.99787-0.99998, *P* = .04622), *Saccharimonadaceae* unclassified (pheno.1447) (OR = 0.99833, 95% CI = 0.99697-0.99969, *P* = .01613), *Campylobacter* unclassified (pheno.1972) (OR = 0.99842, 95% CI = 0.99695-0.99988, *P* = .03421), *Pauljensenia cellulosilytica* (pheno.2054) (OR = 0.99864, 95% CI = 0.99747-0.99982, *P* = .02357), *Solobacterium* unclassified (pheno.2178) (OR = 0.99880, 95% CI = 0.99781-0.99979, *P* = .01793), *Streptococcus* sinensis (pheno.2416) (OR = 0.99822, 95% CI = 0.99703-0.99941, *P* = .00343), and *Streptococcus* unclassified (pheno.2437) (OR = 0.99864, 95% CI = 0.99745-0.99983, *P* = .02506) was associated with an reduced risk (Figure 1). The detailed effect estimates (β), standard errors, OR, 95% CI, and *P* values for these associations of saliva microbiota are provided in Supplementary Table 2.

Associations between tongue microbiota and OOPSCC

In addition, the tongue microbiota also demonstrated significant associations with OOPSCC. MR analysis illustrates these significant associations, highlighting the effect sizes (OR) and statistical significance for these associations across OOPSCC datasets and tongue microbiota types. *Prevotella veroralis*

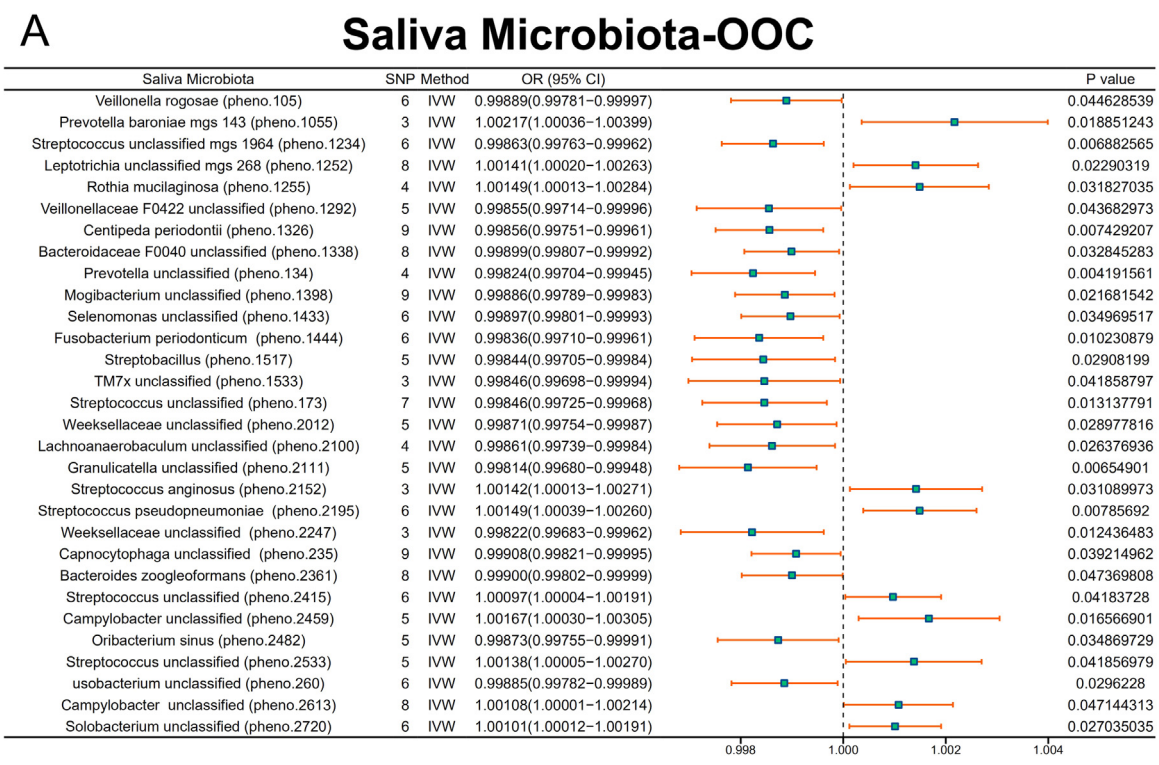

Fig. 1 – Primary MR analysis (IVW) of salivary microbiome associations with OOPSCC risk. This figure presents the effect estimates (odds ratios) and 95% confidence intervals for the associations between oral microbiota taxa and OOPSCC risk using MR-IVW methods across the ieu-b-4962 datasets.

(pheno.1822) (OR = 1.00152, 95% CI = 1.00025-1.00279, *P* = .01864) and *Treponema vincentii* (pheno.2566) (OR = 1.00143, 95% CI = 1.00018-1.00268, *P* = .02513) was positively associated with OOPSCC risk, while *Veillonella* unclassified (pheno.1057) (OR = 1.00125, 95% CI = 1.00012-1.00238, *P* = .03045), *Granulicatella* unclassified (pheno.1308) (OR = 1.00187, 95% CI = 1.00095-1.00278, *P* = .00006), *Streptococcus* unclassified (pheno.134) (OR = 1.00121, 95% CI = 1.00013-1.00229, *P* = .02753), *Streptococcus* sp000411475 (pheno.1435) (OR = 1.00083, 95% CI = 1.00003-1.00162, *P* = .04085), *Streptococcus* unclassified (pheno.1713) (OR = 1.00150, 95% CI = 1.00024-1.00277, *P* = .02012), *Streptococcus* unclassified (pheno.1771) (OR = 1.00247, 95% CI = 1.00094-1.00399, *P* = .00153), *Neisseria* unclassified (pheno.2211) (OR = 1.00136, 95% CI = 1.00021-1.00252, *P* = .02015), *Kingella* unclassified (pheno.2262) (OR = 1.00103, 95% CI = 1.00004-1.00201, *P* = .04092), *Haemophilus* unclassified (pheno.2373) (OR = 1.00127, 95% CI = 1.00001-1.00253, *P* = .04779), *Streptococcus* unclassified (pheno.2374) (OR = 1.00173, 95% CI = 1.00058-1.00289, *P* = .00330), *Streptococcus* unclassified (pheno.250) (OR = 1.00238, 95% CI = 1.00050-1.00426, *P* = .01290), showed similar patterns (Figure 2).

However, *Porphyromonas asaccharolytica* (OR = 0.712, 95% CI = 0.541-0.936, *P* = .015) from the ieu-b-4962 dataset was negatively associated with OOPSCC risk. Additionally, *Centipeda noxia* (OR = 0.406, 95% CI = 0.194-0.852, *P* = .017), *Clostridia* (OR = 0.389, 95% CI = 0.177-0.855, *P* = .019), *Gemella* unclassified (OR = 0.415, 95% CI = 0.190-0.905, *P* = .027), *Haemophilus* unclassified (OR = 0.494, 95% CI = 0.256-0.952, *P* = .035), *Lachnoanaerobaculum saburreum* (OR = 0.518, 95% CI = 0.303-0.885, *P* = .016), *Lachnoanaerobaculum* unclassified (OR = 0.455, 95% CI = 0.212-0.976, *P* = .043), and *Veillonella rogosae* (OR = 0.385, 95% CI = 0.175-0.843, *P* = .017) showed similar patterns (Figure 2). The circos plot, which displays the complex relationships between different microbiota taxa and OOPSCC risk, providing a comprehensive overview of the microbiota's influence on OOPSCC across various datasets, is provided in Figure 3. The detailed effect estimates (β), standard errors, OR, 95% CI, and *P* values for these associations of tongue microbiota are provided in Supplementary Table 3.

Heterogeneity and pleiotropy analyses

To ensure the robustness of our findings, we performed heterogeneity and pleiotropy analyses. The results of Cochran's Q test, which indicated no significant heterogeneity across most associations, supporting the consistency of the IVs used in the analyses, are presented in Supplementary Tables S4 and S5. Additionally, the MR-Egger intercept tests did not show significant evidence of directional pleiotropy for the significant associations. This suggests that the results are unlikely to be biased by horizontal pleiotropy (Supplementary Tables S6 and S7).

Discussion

This study utilized primary MR analyses (IVW) to investigate the causal relationships between microbiota from the oral cavity (saliva and tongue) and oral and oropharyngeal cancer (OOPSCC), employing comprehensive datasets. The analyses

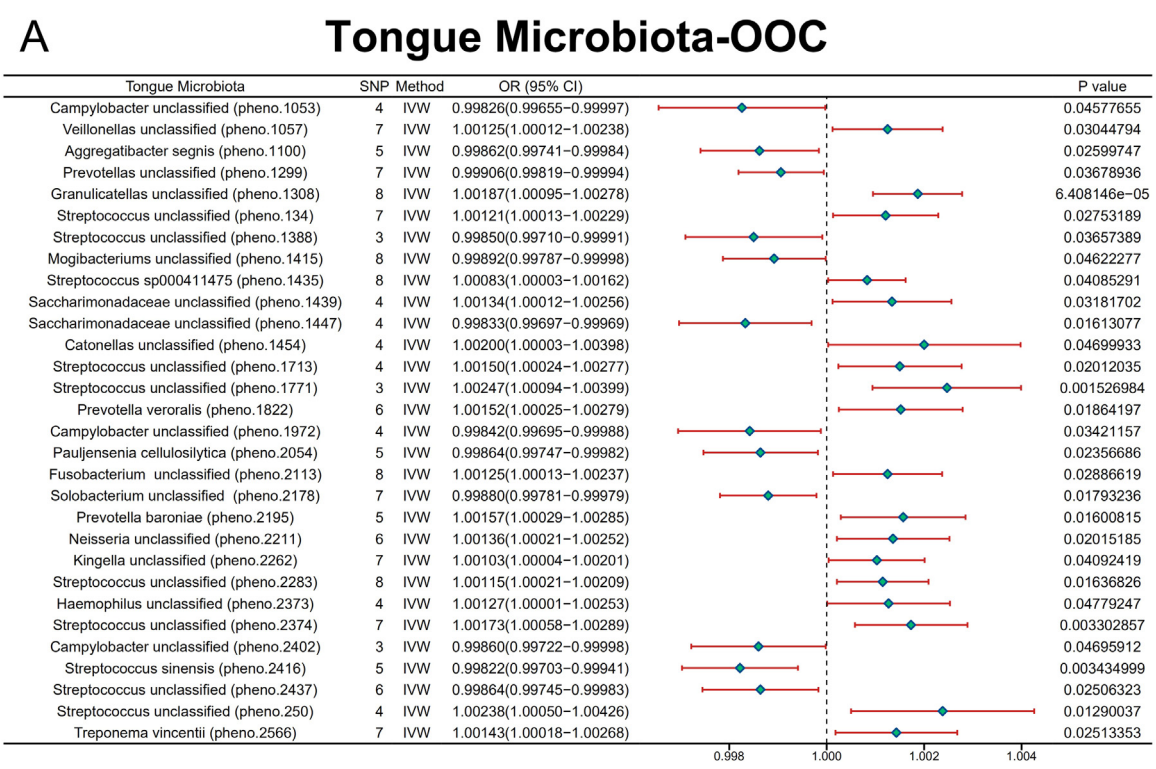

Fig. 2 – Primary MR analysis (IVW) of tongue microbiome associations with OOPSCC Risk. This figure presents the effect estimates (odds ratios) and 95% confidence intervals for the associations between oral microbiota taxa and OOPSCC risk using MR-IVW methods across the ieu-b-4962 datasets.

aimed to identify significant microbial taxa associated with OOPSCC risk across different microbiota and datasets, highlighting the integrated role. This large-scale MR study identified 13 microbial taxa each from saliva and tongue, showing a genetically predisposed causal relationship with OOPSCC.

Among the taxa associated with increased risk, several ones, including *Prevotella, Neisseria, Veillonella, and Treponema*, have already been implicated in cancer development. The correlation between *Prevotella* and oral carcinogenesis has been acknowledged for over two decades. In 2005, Mager et al[30] observed an elevated presence of *P. melaninogenica* in the saliva of individuals affected by the condition. More recently, Zhang et al[31] observed that oral squamous cell carcinoma (OSCC) tumour samples exhibit an increased presence of *Prevotella intermedia*. Torralba et al[32] also observed an elevation in the concentrations of *Prevotella* in certain patients with OSCC. Ganly et al[33] have also seen an increase in *Prevotella* levels in nonsmoking, human papillomavirus-negative OSCC patients, similar to *Alloprevotella*. Muto et al[34] demonstrated that the genus *Neisseria* exhibited exceptionally high ADH activity and generated substantial quantities of acetaldehyde in a laboratory setting. *Neisseria* has been proposed to serve as a local reservoir of carcinogenic acetaldehyde and thereby have a crucial function in the development of alcohol-related cancer in humans. It is widely believed that chronic inflammation and immunomodulation produced by *Treponema denticola (T. denticola*) may represent the underlying mechanism by which these bacteria contribute to developing oro-digestive cancers.[35,36] Invitro experiments have shown that *T. denticola* could promote the development of OSCC by activating the TGF-β pathway.[37]

A majority of taxa which was significantly associated with OOPSCC in our analysis belonged to the genus *Streptococcus*; they could not be identified at the species level because oral microbiome GWAS are still in their early stages since they have limited sample sizes, resulting in inadequate information at the species or strain level. Several species belonging to the genus *Streptococcus* have been previously implicated in having a role in cancers of the oral-gut axis. *Streptococcus anginosus* is more commonly discovered in esophageal cancer samples than oral cancer and is also higher in relative abundance.[38] One of the earlier reports by Tateda et al[39] documented the presence of *S. anginosus* in cancer samples collected from patients' oral and pharyngeal cavities. After 5 years, Sasaki et al[40] observed that *S. anginosus* is increased in patients with oral cancer but not in patients with other malignancies. In 2004, Narikiyo et al[41] documented that patients with esophageal cancer exhibited a predilection and high occurrence of *S. anginosus* and *S. mitis* infections. The study conducted by Rai et al[42] revealed an increased presence of *S. anginosus* in individuals with OSCC, underscoring the ongoing significance of this bacterium in the development of oral cancer. Another recent study suggested that *S. anginosus* could be used as a noninvasive biomarker for oropharyngeal cancer.[43] It has been suggested that *S. anginosus* induces the recruitment of neutrophils and monocytes, potentially disrupting epithelial cells and subsequent development of

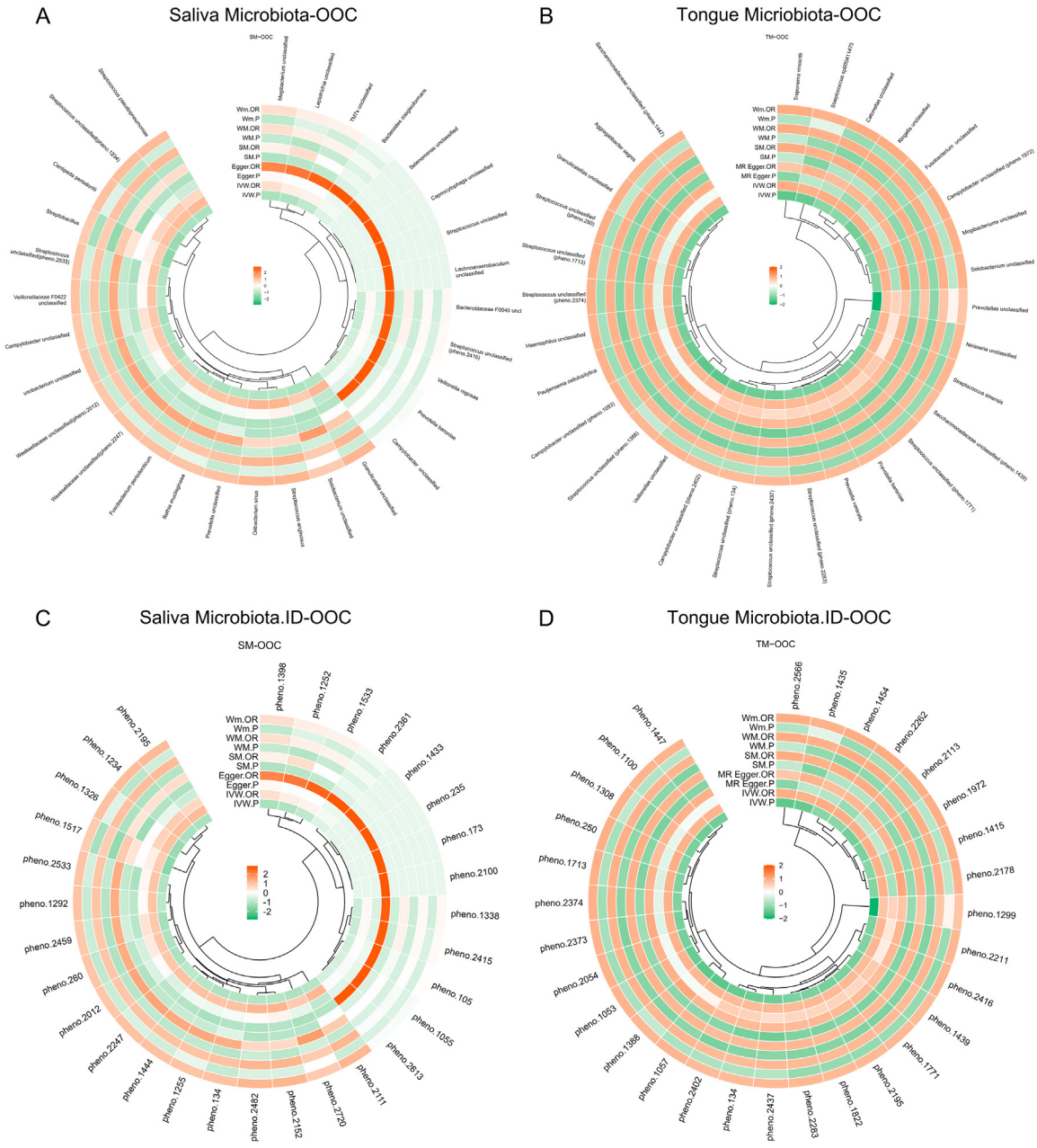

Fig. 3 – Mendelian randomization estimates (microbial taxa) visualised as Circos plot for Tongue microbiota (A) and Salivary microbiota (B). Mendelian randomization estimates (database ID of the microbes) visualised for Circos plot Tongue microbiota (C) and Salivary microbiota (D) *OOC: Oral and Oropharyngeal Cancer.

cancerous growths.[41] Furthermore, evidence supports the transformation of ethanol into acetaldehyde by *S. anginosus*.[44] Acetaldehyde is recognized to contribute to cancer development by causing DNA damage and generating point mutations that occur during its repair.[35,45] An increased presence of *S mitis*, another type of streptococci, has also been reported in patients with OSCC.[30] In recent years, there has been compelling evidence linking oral cancer to the following streptococci: *Streptococcus constellatus, Streptococcus salivarius, Streptococcus gordonii, and Streptococcus parasanguinis*.[46,47]

The present study also suggests that specific taxa belonging to the genus *Hemophilus*, may possess a mitigating or protective influence on the incidence of OOPSCC. One possible explanation for this phenomenon is their influence on safeguarding impact on the overall balance of oral microbiota. Previous studies have shown that *H. influenzae infection leads to increased expression of the NLRP3 inflammasome gene, thereby protecting the overall balance of gut microbiota and decreasing* the likelihood of colorectal cancer.[48] Exploring this connection is crucial in order to comprehend and evaluate the function of NLRP3 as a possible target for oncological protection against OOPSCC. Another species found to be protective is *P. asaccharolytica*, a Gram-negative, obligate anaerobic bacterium with black pigmentation, classified under the *Bacteriodaceae* family. Little is known about this species and its role in cancers. On the contrary, another species belonging to the same genus,

Porphyromonas gingivalis, is a pivotal pathogen involved in the development of periodontitis, which is marked by persistent inflammation and imbalance of microbiota. Several studies have highlighted the role of *P. gingivalis* in orodigestive cancers.[49]

One notable observation in our analysis is the absence of *F. nucleatum*, which has been previously linked to oral carcinogenesis by several microbiome studies.[50] The rationale for this could be explained by the fact that, specific taxa-associated carcinogenesis is uncommon in the general population and hence it may not be present in the GWAS of healthy individuals. On the contrast, increased microbial richness and diversity in microbiome studies do not always suggest taxonomic presence; it could also be because of the variation in methodology and the databases used for bioinformatic analysis in these studies.[51]

The human microbiome's composition is affected by several environmental influences.[14] Alterations in host nutrition influence oral microbiome communities both taxonomically and functionally.[52] Furthermore, the consumption of pharmaceuticals and antibiotics can influence the oral microbial flora.[53] These impacts of environmental influences on individuals will be influenced by their genotype and the distinct effects of both genotype and environmental factors. Simultaneously, the influence of genetic elements is also contingent upon environmental variables.[54] We employed the MR methodology to mitigate these certain confounders frequently encountered in epidemiological research.[55] Furthermore, our SNPs exhibited a robust correlation with microbiota and were analysed with various cancer databases. Another strength of this work lies in the use of extensive GWAS data that spans the salivary microbiome, tongue microbiome, and OOPSCC. This comprehensive data collection guarantees strong statistical power and produces many outcomes. Furthermore, this article utilized a meticulously crafted analytical framework to examine the causal connections, and the work utilizes several methods of MR analysis to establish causal relationships and performed sensitivity studies to guarantee the strength of the results, reducing the impact of horizontal pleiotropy and other variables.

The limitation of this study, which is inherent to several MR studies, is the assumption of linearity in the causal link between oral microbiome and OOPSCC. Nevertheless, this connection may be more complex, encompassing environmental elements and other genetic determinants. Although we have identified putative mediators of the causative association between tongue and salivary microbiome, it is essential to note that our analysis may not include all hypothetical mediation pathways due to the intricate biological processes involved. Given the unique nature of GWAS investigations, there is a shortage of covariate adjustment for the cohort from which, the data was initially obtained. Further, the study sample primarily comprises persons of European descent, potentially constraining the applicability of results to the general population. Moreover, the database we employed categorized oral and oropharyngeal malignancies under a single broad classification despite recent evidence highlighting their distinct risk factors, behaviours, and treatment outcomes.[3,56]

Our findings have provided plausible biomarkers that can be further explored as noninvasive biomarkers for diagnosis or intervention targets for the prevention of oral and oropharyngeal cancers.[57] Integrating our study results with what is currently known about the oral microbiome and cancer strengthens the microbiome's importance in cancer research and creates new interdisciplinary opportunities for comprehending and addressing disease. The comprehensive amalgamation of microbiological and conventional risk factors can enhance cancer prevention, diagnosis, and treatment methods, resulting in more individualized and efficient healthcare solutions.

Conclusion

While we have demonstrated the possible causative links between the oral microbiota and OOPSCC, we have also emphasized the necessity for further research to address the current knowledge gaps. Furthermore, future research should strive to investigate these correlations in varied populations and use longitudinal methodologies to comprehend the impact of temporal alterations in the microbiome on the risk and advancement of cancer.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.identj.2025.01.017.

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