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A Mendelian Randomisation Analysis Reveals No Relationship Between Periodontitis and Coronary Atherosclerosis

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ABSTRACT

Objectives: Growing evidence appears to intimate a profound connection between periodontitis and coronary atherosclerosis (CA), yet the existence of a causal relationship remains unclear. Through the implementation of Mendelian randomization analysis, we further evaluated the potential causal link between chronic/acute periodontitis (CP/AP) and CA.

Methods: Utilizing genome-wide association study (GWAS) summary statistics, we incorporated periodontitis data derived from European samples (n1 = 198,441; n2 = 195,762) and CA data from 61,194 cases. We conducted a 2 sample, bidirectional Mendelian randomization (MR) analysis using the inverse-variance weighted (IVW) method as the main analytical approach. Supplementary analyses were executed through MR Egger, Weighted median (WM), IVW, Simple mode, and Weighted mode approaches.

Results: The IVW analysis revealed no significant causal relationship between CA and periodontitis (CA-CP: OR = 2.110, 95% CI = 0.208-21.317, *P* = .527; CA-AP: OR = 0.414, 95% CI = 0.051-3.384, *P* = .644). Similarly, the bidirectional analysis did not identify impact of periodontitis on CA (OR = 1.000, 95% CI = 0.999-1.001, *P* = .953). The supplementary analyses corroborated these findings.

Abbreviations: CA, Coronary atherosclerosis; MR, Mendelian randomization; GWAS, Genome-wide association studies; IVW, Inverse-variance weighted; CI, Confidence interval; OR, Odds ratio; WM, weighted median; CP/AP, Chronic / Acute periodontitis; CRP, C-reactive protein; OS, Oxidative stress; CKD, Chronic kidney disease; PD, Periodontal disease; SNP, Single nucleotide polymorphism; SE, Standard errors; EA, Effect allele; OA, Other allele; EAF, Effect allele frequency; PWV, Pulse wave velocity; FMD, Flow-mediated dilation; cIMT, carotid intima-media thickness; IBD, Inflammatory bowel disease

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Conclusions: While studies highlighting a correlation between periodontitis and CA, our comprehensive analysis does not corroborate a causal association between periodontitis and CA. Further research is needed to elucidate other potential shared mechanisms and causal evidence between periodontitis and CA.

Introduction

As common knowledge dictates, periodontitis is a prevalent oral health condition that impacts around 50% of the general population and 11% of the global population,[1,2] making it one of the most common human diseases. It can be classified into acute and chronic forms (AP/CP), both of which impose a significant burden on patients, severely impacting their quality of life and overall well-being.[3]

Coronary atherosclerosis (CA), a principal contributor to global mortality,[4] continues to claim approximately 17.8 million lives annually[5] despite advancements in therapeutic interventions and preventative strategies. Acknowledged conventional risk factors encompass aging, cholesterol, hypertension, or dyslipidemia.[6-9] However, the implications of inflammatory disease as a pivotal driver in the onset and progression of CA has become gradually recognized.[10]

A substantial accumulation of evidence substantiates an critical correlation between severe periodontitis and several systemic diseases.[11-14] In fact, severe periodontitis has been independently and indubitably linked with all-cause and cardiovascular mortality across diverse cohorts,[15-17] especially coronary atherosclerosis. Proposed mechanisms involve bacteraemia and its resultant systemic inflammatory consequences,[13] such as elevated C-reactive protein (CRP) levels, as well as oxidative stress (OS). Among populations beset with multiple comorbidities,[18-21] such as chronic kidney disease (CKD) concurrent with diabetes and periodontitis, periodontitis has been significantly correlated with diminished all-cause and cardiovascular mortality rates. As such, periodontal disease (PD), especially periodontitis emerges as a potentially modifiable non-conventional risk factor for CA

Numerous studies have demonstrated the positive association between periodontitis and the risk of developing atherosclerotic disease.[22] Epidemiological evidence suggests that patients with periodontitis exhibit notable endothelial dysfunction,[6] as evidenced by impaired flow-mediated dilation (FMD), increased arterial stiffness (such as PWV - pulse wave velocity), augmented carotid intima-media thickness (cIMT), and elevated arterial calcification scores. Cohort studies have also shown a correlation between periodontitis and higher coronary atherosclerosis mortality rates.[23] Some hypotheses propose that dysregulated oral microbiota from periodontitis may indirectly or directly trigger systemic diseases by disseminating into the cardiovascular system.[13] At the same time, current biological experiments cannot validate these hypotheses nor establish periodontitis as the key cause of atherosclerosis.

Although periodontitis is associated with coronary atherosclerosis, the relationship remains unclear. Two-sample Mendelian randomization (MR) analysis is a statistical method aimed at inferring potential causal relationships from observed associations.[24] MR utilizes exposure-associated genetic variants as proxy indicators to evaluate the relationship between the potential indicators and outcomes.[24] Given the urgency to investigate the potential causal link between periodontitis and coronary atherosclerosis. Scholars have employed MR analysis to study the relationship between periodontitis and multiple non-oral diseases,[25-35] including arthritis, hypertension, psoriasis, Parkinson's disease, inflammatory bowel disease (IBD), etc. However, most studies have not provided strong supporting a significant causal relationship between the periodontitis and these diseases, suggesting that periodontitis may be a comorbid condition or that other shared disease mechanisms are yet to be explored.

We conducted a 2-sample, bidirectional Mendelian randomization analysis using genome-wide association study (GWAS) summary data to investigate the potential relationship between periodontitis and coronary atherosclerosis. By employing this rigorous approach, we aim to enhance our understanding of the intricate interplay between periodontal disease and cardiovascular disease. This research endeavour is expected to contribute valuable insights to the field, inform future investigations, and shed light on the underlying mechanisms linking these 2 conditions.

Materials and methods

Data assumption and preparation

The workflow of our study is depicted in Figure 1. We utilized statistical genetic data on periodontitis from the European sample FinnGen database (https://www.finngen.fi/en), including chronic periodontitis (finn-b-K11_PERIODON_CHRON, case: 3046, control: 195395) and acute periodontitis (finn-b-K11_PERIODON_ACUTE, case: 367, control: 195395). Data on coronary atherosclerosis from the OpenGWAS (https://gwas.mrcieu.ac.uk), a publicly accessible database with stringent quality control (ukb-d-I9_CORATHER, case: 14334, control: 346860), were also from a European sample. Local institutional review boards and ethical committees approved all studies contained in the 3 datasets.

Coronary atherosclerosis cases were selected per the International Classification of Diseases. The American Academy of Periodontology (AAP) defines periodontitis, apart from being broadly classified into acute and chronic forms, as cases assessed by comparable standards through probing depth or self-reported.

For the purpose of this study, periodontitis (whether acute or chronic) cases also can be categorized based on the following criteria: (1) Mild: ≥2 interproximal sites with attachment

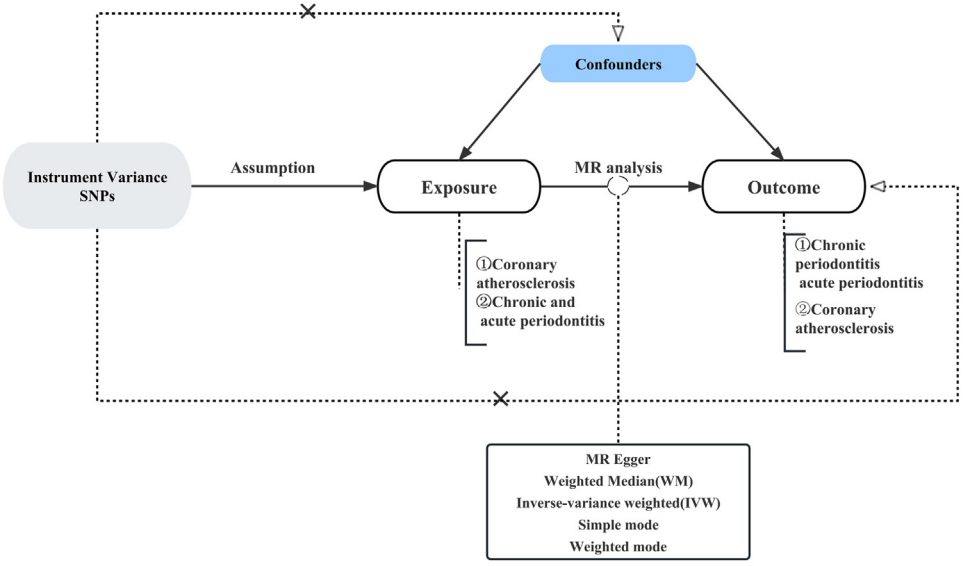

Fig. 1 – Schematic illustration of the 2-sample Mendelian randomization study investigating the relationship between periodontitis (chronic/acute) and coronary atherosclerosis. The depicted design proposes a bidirectional association between periodontitis and coronary atherosclerosis, accounting for potential confounding factors.

loss (AL) ≥3 mm and ≥2 interproximal sites with probing depth (PD) ≥4 mm (not on the same tooth) or 1 site with PD ≥5 mm. (2) Moderate: ≥2 interproximal sites with AL ≥4 mm (not on the same tooth) or ≥2 interproximal sites with PD ≥5 mm (not on the same tooth). (3) Severe: ≥2 interproximal sites with AL ≥6 mm (not on the same tooth) and ≥1 interproximal site with PD ≥5 mm. To facilitate analysis within our binary logistic model, we converted these 3 categories into 2 categories by combining mild and moderate periodontitis into a single category. This simplification was based on the observation that mild and moderate periodontitis share similar clinical characteristics and responses to treatment. Thus, the 2-category variable used in our analysis comprises (1) Mild/Moderate periodontitis and (2) Severe periodontitis. This binary classification enabled a clearer and more statistically robust analysis of the relationship between periodontitis severity and coronary atherosclerosis.

In this study, we conducted a bidirectional, 2-sample Mendelian randomization (MR) investigation to elucidate the potential causal association between acute / chronic periodontitis and coronary atherosclerosis.

Mendelian randomization and statistical analysis

Data analysis was conducted using R (version 4.2.1) with the 'TwoSampleMR (0.5.6)' and 'MR-PRESSO (1.0)' packages. Mendelian randomization (MR) utilizes genetic variants as instrumental variables (IVs) to estimate causal effects of risk factors on complex diseases. Various methods were employed to assess the potential causal relationship between periodontitis and coronary atherosclerosis (CA), with the primary analysis employing the inverse variance-weighted (IVW) method. Additional MR testing methods, including MR Egger, Weighted median (WM), IVW, Simple mode, and Weighted mode, were used for supplementary analyses to accurately evaluate causal effects and correct for horizontal pleiotropy. IVs were selected based on a threshold of $P < 5\times10^{-6}$. The association between periodontitis and CA risk was expressed as odds ratios (ORs) with 95% confidence intervals (CIs), which based on beta coefficients (β). Bonferroni correction was applied for multiple comparisons across different classification levels, and statistical significance was set at different *P*-values.

To examine heterogeneity among the selected single nucleotide polymorphisms (SNPs), Cochran's Q test was performed. If heterogeneity was detected ($P < .05$), the random-effects IVW method was employed; otherwise, the fixed-effects IVW method was used. Given that IVW results may be influenced by valid instruments and potential pleiotropy, sensitivity analyses were conducted to assess the robustness of the associations. Firstly, the weighted median method was utilized to estimate associations, as it provides reliable causal effect estimates even when effective instruments are limited, and it remains valid when less than 50% of the information is derived from invalid instruments. Secondly, MR-Egger regression was employed to test for potential horizontal pleiotropy, with a *P*-value of the intercept less than .05 indicating the presence of pleiotropy among the SNPs.

The IVW analysis assumes that all genetic variants are valid instrumental variables with strong causal inference capabilities. We harmonized the SNPs by removing incompatible alleles and palindromic SNPs with intermediate allele frequencies. Due to variations in experimental conditions, selected populations, and SNPs, heterogeneity may exist in 2-sample MR analysis, which can introduce bias to causal effect estimates. Therefore, heterogeneity tests were conducted for the primary IVW analysis and MR-Egger regression in this study, with *P*-values >.05 indicating no heterogeneity among the IVs. One assumption of MR analysis is that the instrumental variable affects the outcome solely through the

exposure, hence testing for horizontal pleiotropy is essential to understand the causal relationship between the exposure and outcome. The intercept value in MR-Egger regression is used to assess pleiotropy, with an intercept close to 0 indicating close similarity to IVW regression. The smaller the likelihood and significance of pleiotropy, the more the SNP is associated solely with the exposure and unrelated to other confounding variables. In this study, the *P*-value of the pleiotropy test was employed to evaluate the presence of pleiotropy. If the *P*-value is greater than .05, the influence of pleiotropy in the causal analysis is considered minimal or nonexistent, and its impact can be disregarded. Consistency of the results was assessed through a leave-one-out analysis.

Result

Causal effects of coronary atherosclerosis on chronic and acute periodontitis

For the Mendelian randomization (MR) analysis, a total of 60 single nucleotide polymorphisms (SNPs) were identified, with Coronary Atherosclerosis (CA) considered as the exposure and periodontitis (chronic/acute) as the outcome. Among these SNPs, 31 were excluded as their alleles did not meet the specified criteria. Consequently, 29 SNPs were retained for further MR analysis.

The results for CA and chronic periodontitis demonstrated that MR-egger (OR = 0.032, 95% CI = 0.000-7.423, *P* = .226), WM (OR = 0.679, 95% CI = 0.025-18.250, *P* = .818), IVW (OR = 2.110, 95% CI = 0.208-21.313, *P* = .527), Simple mode (OR = 0.567, 95% CI = 0.001-228.643, *P* = .854), and weighted model (OR = 0.285, 95% CI = 0.003-28.281, *P* = .597) demonstrated no impact of CA on chronic periodontitis (Table 1). Forest plots of the causal effect of CA on chronic periodontitis, estimated individually for each SNP using the Wald ratio, showed the same trend (Figure 2A). Sensitivity analysis demonstrated the robustness of the current 2-sample MR analysis (Figure S1), indicating the absence of instrumental variable bias in the causal inference. The Cochrane Q test did not reveal heterogeneity among these IVs (*P* = .8547, I^2 = 0.382034). The heterogeneity test displayed the impact of coronary atherosclerosis on the risk of chronic periodontitis (Table 2): Egger regression intercept = 0.032, Standard error = 0.015, Directionality *P*-value = .0433. The absence of heterogeneity among these instrumental variables (IVs) was indicated, as there was no significant heterogeneity detected. Scatter plots depicting the effect sizes of single nucleotide polymorphisms (SNPs) for chronic periodontitis and coronary atherosclerosis are presented (Figure 2C). Funnel plot analysis also corroborated these results (Figure S1), revealing that direction and horizontal pleiotropy were insignificant, and the evidence for directional pleiotropy was markedly insufficient.

The results of CA and acute periodontitis demonstrated MR-egger (OR = 1.614, 95% CI = 0.417-6.255, *P* = .510), WM (OR = 0.661, 95% CI = 0.050-8.730, *P* = .948), IVW (OR = 0.414, 95% CI = 0.051-3.384, *P* = .644), Simple mode (OR = 0.600, 95% CI = 0.053-6.837, *P* = .404), and weighted median (OR = 0.028, 95% CI = 0.001-0.769, *P* = .645); CA had no impact on acute periodontitis (Table 1). Forest plots of the causal effect of exposure on outcome using Wold's ratio estimated separately for each SNP show the same trend although with a slight horizontal bias (Figure 2B).The Cochrane Q report did not show heterogeneity among these IVs (*P* = .3522, I^2 = 0.073768). The heterogeneity test demonstrated the impact of coronary atherosclerosis on the risk of acute periodontitis (Table 2): Egger regression intercept = -0.043, Standard error = 0.045, Directionality *P*-value = .35. The analysis yielded results that indicate the absence of heterogeneity among these instrumental variables (IVs), suggesting a consistent pattern. Scatter plots illustrating the effect sizes of single nucleotide polymorphisms (SNPs) for acute periodontitis and coronary atherosclerosis are presented for visual representation (Figure 2D). The funnel plot analysis confirmed these results (Figure S2), indicating that horizontal pleiotropy was insignificant. Moreover, no high-impact points were detected in the leave-one-out analysis (Figure S2).

The study included a substantial sample size of 198,441 individuals with chronic periodontitis, 195,762 individuals with acute periodontitis, and 361,194 individuals with

Table 1 – The relationship between genetically instrumented coronary atherosclerosis (CA) and chronic/acute periodontitis (CP/AP) was estimated using Mendelian randomization.

Outcome	Exposure	MR method	nSNP	Beta	SE	OR	95% CI	*P* value
Chronic periodontitis	Coronary atherosclerosis	MR Egger	29	−3.456	2.786	0.032	0.000-7.423	.226
		WM	29	−0.3867	1.679	0.679	0.025-18.250	.818
		IVW	29	0.7467	1.18	2.110	0.208-21.317	.527
		Simple mode	29	−0.5674	3.061	0.567	0.001-228.643	.854
		Weighted mode	29	−1.254	2.345	0.285	0.003-28.281	.597
Acute periodontitis	Coronary atherosclerosis	MR Egger	29	0.479	0.691	1.614	0.417-6.255	.510
		WM	29	−0.4145	1.317	0.661	0.050-8.730	.948
		IVW	29	−0.882	1.072	0.414	0.051-3.384	.644
		Simple mode	29	−0.51	1.241	0.600	0.053-6.837	.404
		Weighted mode	29	−3.579	1.692	0.028	0.001-0.769	.645
Coronary atherosclerosis	Periodontitis	MR Egger	5	−0.001467	0.003447	0.999	0.992-1.005	.699
		WM	5	0.000282	0.0004831	1.000	0.999-1.001	.559
		IVW	5	0.00002859	0.0004805	1.000	0.999-1.001	.953
		Simple mode	5	0.000684	0.000707	1.001	0.999-1.002	.388
		Weighted mode	5	0.0006446	0.0007783	1.001	0.999-1.002	.454

Beta(β), Beta coefficient; OR, odds ratio (beta); SE, Standard Error (beta); 95%CI, confidence interval (OR, beta).

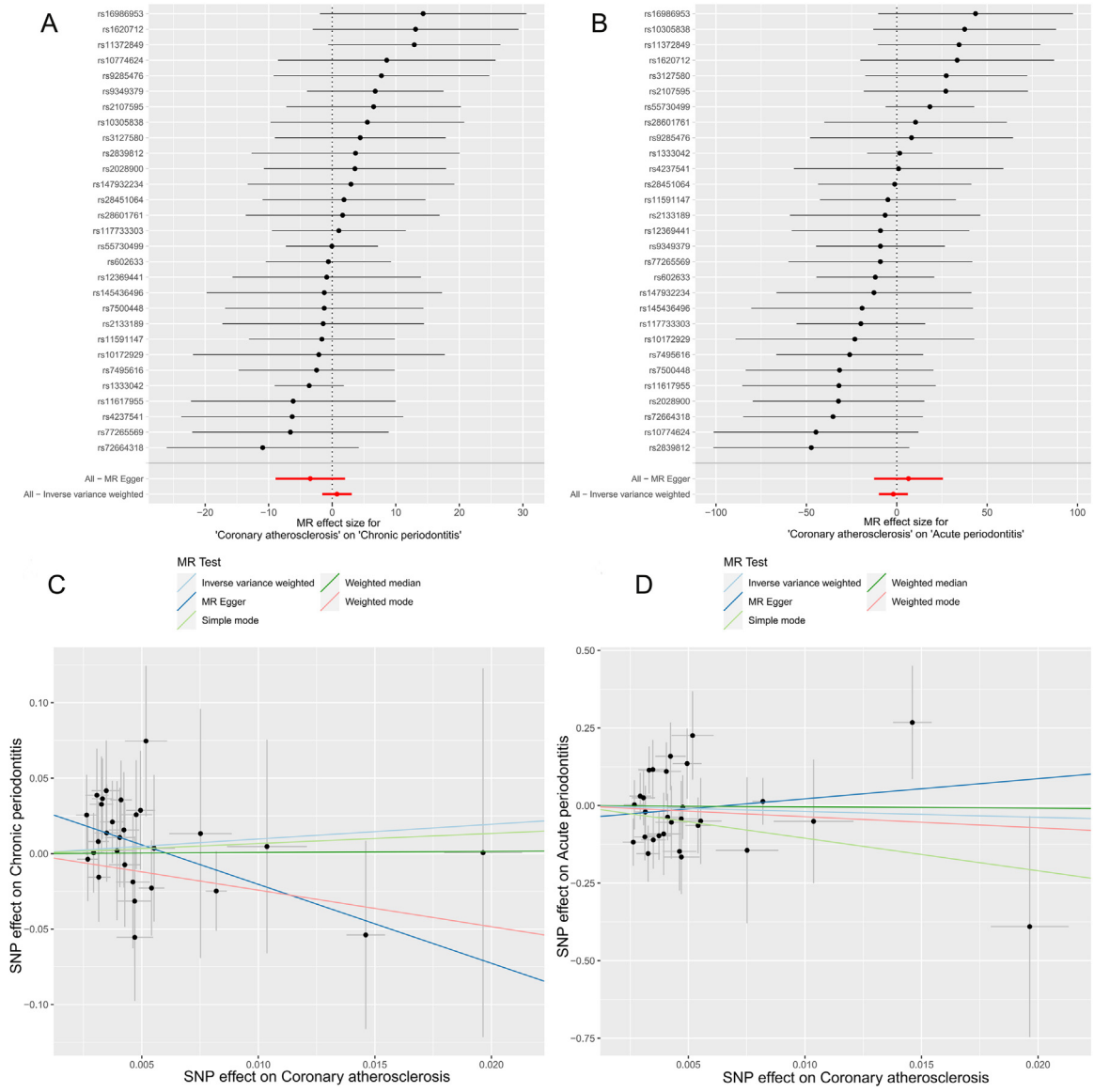

Fig. 2 – A and B. Forest plots depicting the causal influence of single nucleotide polymorphisms (SNPs) associated with coronary atherosclerosis on chronic periodontitis (A) and acute periodontitis (B). (The results calculated by Mendelian randomization using a single SNP are summarized and visualized. The red line below is the Mendelian randomization results including all SNPS. It can be seen that the results of a single SNP are positive and negative, indicating that the effect is not significant. The axis represents the effect size(β) of each SNP.) C and D. Scatter plots illustrate the genetic associations between coronary atherosclerosis, chronic periodontitis (C), and acute periodontitis (D). (Each point on the scatter plot represents an SNP, with the horizontal coordinate being the SNP's effect on exposure and the vertical coordinate being the SNP's effect on outcome. It is possible to observe whether the stronger the SNP effect on exposure, the stronger the SNP effect on outcome. At the same time, the scatter plot includes the analysis results of the 5 methods.)

Table 2 – Heterogeneity assessment of MR-Egger and IVW test for directional pleiotropy.

Outcome	Exposure	Heterogeneity	Q	Q_df	I^2	Q_P value
Chronic periodontitis	Coronary atherosclerosis	MR Egger	17.49	27	0.543739	.9183
		IVW	20.26	28	0.382034	.8547
Acute periodontitis	Coronary atherosclerosis	MR Egger	29.25	27	0.076923	.3488
		IVW	30.23	28	0.073768	.3522
Coronary atherosclerosis	Periodontitis	MR Egger	8.284	3	0.637856	.04049
		IVW	8.817	4	0.546331	.06584

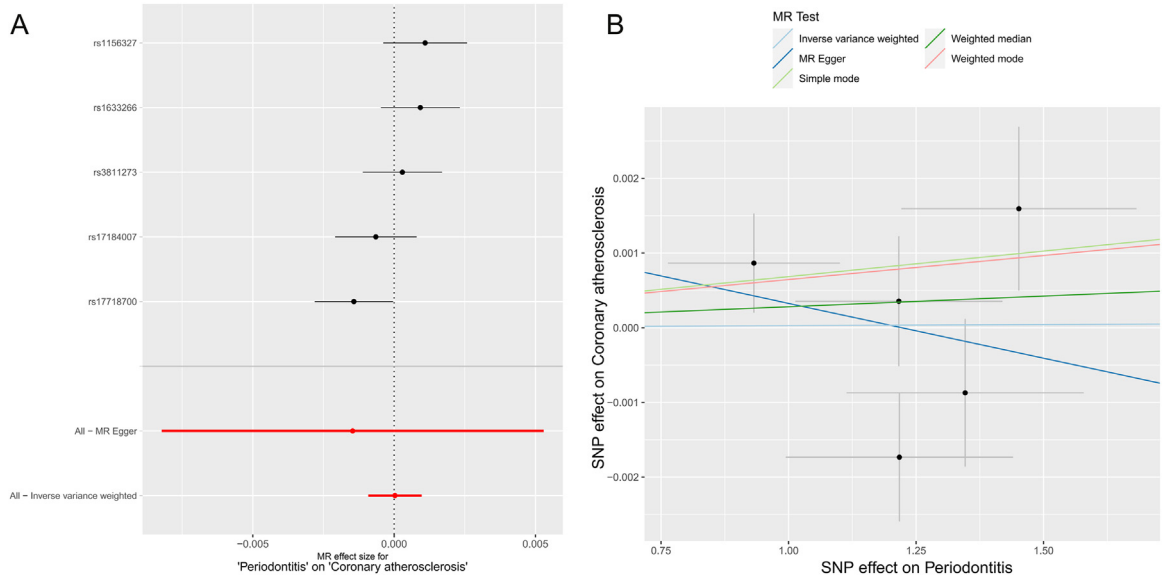

Fig. 3 – A. The forest plot illustrates the causal impact of single nucleotide polymorphisms (SNPs) associated with periodontitis on coronary atherosclerosis. (It can be seen that the results of a single SNP are positive and negative, indicating that the effect is not significant.) B. Genetic association between periodontitis and coronary atherosclerosis. There was no finding that the stronger the SNP effect on exposure, the stronger the SNP effect on outcome.

coronary atherosclerosis. The strength of the instrumental variables was assessed by calculating $R^2$and F-statistics using the Effector Allele Frequency (EAF) and effect estimate (BETA). The F-statistic values exceeded 10 in all cases (Table S1), with an average value of 66.1 (range: 29.94-312.83), indicating strong instrumental variables and no significant observable instrumental variable bias. However, the relatively lower R^2 values suggested challenges in fully explaining the extent of exposure through the instrumental variables.

Causal effects of periodontitis on coronary atherosclerosis

Due to insufficient exposure data for periodontitis, we merged the CA of the 2 cohorts, keeping the control group unchanged. Taking periodontitis as the exposure and coronary atherosclerosis as the outcome, we extracted 6 SNPs, with 1 SNP being discarded due to the need for corresponding outcome data. Ultimately, 5 SNPs were chosen for the following MR analysis. The results showed MR-egger (OR = 0.999, 95% CI = 0.992-1.005, *P* = .699), WM (OR = 1.000, 95% CI = 0.999-1.001, *P* = .559), IVW (OR = 1.000, 95% CI = 0.999-1.001, *P* = .953), Simple mode (OR = 1.001, 95% CI = 0.999-1.002, *P* = .388), and Weighted mode (OR = 1.001, 95% CI = 0.999-1.002, *P* = .454). No significant association between periodontitis and coronary atherosclerosis was observed, as evidenced by the results presented (Table 1 and Figure 3).

All F-statistic values exceeded 10, with an average F-statistic value of 949.2, indicating strong instrumental variables and a lack of observable horizontal pleiotropy (Table S1). The MR-Egger analysis also provided no evidence of horizontal pleiotropy when examining the impact of periodontitis on the risk of coronary atherosclerosis (Table 2): Egger regression intercept = 0.0018, Standard error = 0.0041, Directionality *P*-value = .69). The leave-one-out analysis yielded no remarkable deviations or anomalies (Figure S3). Consequently, our findings do not support the existence of a bidirectional genetic relationship between periodontitis and coronary atherosclerosis (Figure 3).

Furthermore, the Cochrane Q test revealed no significant heterogeneity among the estimates of the included SNPs (*P* = .06584, I^2 = 0.546331). A funnel plot observation revealed no significance in directionality and horizontal pleiotropy (Figure S3). Finally, the F statistics (F > 10, range 29.83-39.59) did not exhibit any significant instrumental variable bias (Table S2).

Discussion

This study employed a bidirectional, 2-sample MR analysis to investigate the potential causal association between periodontitis and coronary atherosclerosis. Although numerous clinical data suggest that periodontitis is a high-risk factor for cardiovascular disease, the results from the MR study did not support the evidence of a significant influence of periodontitis on coronary atherosclerosis, and vice versa.

We posit that both periodontitis and cardiovascular disease are multifactorial disorders, manifesting in individuals exposed to risk factors over many years.[15,22] The connection between the 2 diseases is likely far more complex than a simple causal relationship, with other significant associations still present. For instance, oral microbiota represents a crucial link between periodontitis and coronary atherosclerosis. Moreover, other risk factors, (including detrimental habits, smoking, and so on), are prominent shared.[1,6]

In general, the outcomes of our Mendelian randomization (MR) analysis diverge from the findings of prior observational studies. Our findings fail to substantiate a causal association

between periodontitis and cardiovascular disease, therefore cautioning against prioritizing periodontitis treatment as a means to mitigate the risk of stroke and coronary artery disease. There may be coincidences or confounding by some unknown factors. Furthermore, most current observational studies cannot determine the causal relationship between periodontitis and coronary atherosclerosis,[13,16,23] only establishing a co-occurrence or association. However, the nature of this association has yet to be deeply researched, merely elucidating a comorbidity phenomenon. Many periodontitis patients often present with a range of systemic issues, as do patients with coronary atherosclerosis. Hence, the presence of shared pathophysiological mechanisms between these conditions may potentially establish a connection between periodontitis and coronary atherosclerosis, thereby warranting further investigation in future studies.

Multiple sensitivity analyses were employed to reinforce the robustness of our findings. The instrumental variable-weighted (IVW), weighted median, and MR-Egger methods were utilized to explore the causal relationship between periodontitis and coronary atherosclerosis. However, none of these approaches provided evidence supporting a causal association. The consistent outcomes obtained through these diverse methods lend credibility to our study's findings.

Moreover, our study possesses several notable strengths. Firstly, only single nucleotide polymorphisms (SNPs) that exhibited significant associations with clinically-defined periodontitis at the genome-wide level and were replicated in independent cohorts were included as instrumental variables (IVs). This stringent criterion ensures the validity and reliability of our genetic instruments. Additionally, we integrated exposure data from multiple periodontitis cohorts, augmenting the likelihood that all selected periodontitis-associated SNPs genuinely capture the relationship with coronary atherosclerosis.

This MR study has limitations. Firstly, the population selected for the study represents only European groups, not entirely capturing the absolute causal relationship between the 2 diseases in the global population. Moreover, larger data sets are needed to seek associations further. Lastly, the disease characteristics of periodontitis and coronary atherosclerosis at different stages may not fully reflect the association between the two, particularly for acute periodontitis, which has a rapid onset and recovery, its impact on coronary atherosclerosis might be minimal, whereas chronic periodontitis, a long-term chronic disease, may present higher clinical risks due to constant systemic inflammatory impact.

In conclusion, the findings of this study do not provide substantial evidence supporting a causal relationship between periodontitis and coronary atherosclerosis, as well as the reverse association. This result contrasts with observational studies and requires further research for validation to achieve a more reasonable and robust conclusions. Future studies should elucidate other potential shared mechanistic interactions and causal evidence between periodontitis and coronary atherosclerosis. The primary objective of this research was to comprehensively investigate the causal association between periodontitis and coronary atherosclerosis, offering valuable insights to clinicians. By enhancing the understanding of the connection between periodontitis and coronary atherosclerosis, this study contributes to the exploration of potential links between periodontitis and systemic diseases, thereby providing valuable references for future investigations in this field.

Ethics approval and consent to participate

Not applicable.

Informed consent

Not applicable.

CRediT authorship contribution statement

Zhengrui Li: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Qi Wang:** Investigation, Methodology, Visualization, Writing – original draft. **Xufeng Huang:** Conceptualization, Data curation, Visualization. **Yinteng Wu:** Data curation, Formal analysis. **Rao Fu:** Formal analysis. **Xutao Wen:** Formal analysis. **Ji'An Liu:** Visualization. **Yuanguo Chen:** Resources, Writing – review & editing. **Ying Liu:** Conceptualization, Resources, Supervision. **Ling Zhang:** Resources, Supervision, Writing – review & editing.

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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 paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.identj.2024.01.027.

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