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Relationship between periodontitis and COVID-19: A bidirectional two-sample Mendelian randomization study

Jukun Song[1] | Yadong Wu[1] | Xinhai Yin[2] | Junmei Zhang[1]

[1]Department of Oral and Maxillofacial Surgery, the Affiliated Stomatological Hospital of Guizhou Medical University, Guiyang, China

[2]Department of Oral and Maxillofacial Surgery, Guizhou Provincial People's Hospital, Guiyang, China

Correspondence
Junmei Zhang, Department of Orthodontics, the Affiliated Stomatological Hospital of Guizhou Medical University, Guizhou 550002, China.
Email: zjm46688@126.com

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Abstract

Background and Aims: Coronavirus disease (COVID-19) is a major danger to world health and has been linked to periodontitis in a number of epidemiological observational studies. However, it is unclear whether COVID-19 causes periodontitis. COVID-19's causal influence on periodontitis was determined using bidirectional Mendelian randomization (MR).

Methods: Large-scale COVID-19 and periodontitis genome wide association study data were analyzed. Inverse variance weighting, MR-Egger, weighted median, and MR-PRESSO were used to estimate causal effects. Sensitivity studies were conducted using the Cochran's Q test, the MR-Egger intercept test, the MR-PRESSO, and the leave-one-out (LOO) analysis. Further investigation of potential mediating factors was performed using risk factor analysis.

Results: The MR presented no causal relationship between periodontitis and hospitalization for COVID-19 (odds ratio [OR] = 0.97, 95% confidence interval [CI] 0.78–1.20; $p = 0.76$), vulnerability to COVID-19 (OR = 1.04, 95% CI 0.88–1.21; $p = 0.65$), COVID-19 disease severity (OR = 1.01, 95% CI 0.92–1.11; $p = 0.81$). Meanwhile, a noncausal effect of genetic hospitalization for COVID-19, illness severity, and vulnerability to periodontitis was detected. Other MR methods yielded identical results to inverse variance weighting. According to sensitivity analysis, horizontal pleiotropy is unlikely to affect causal estimation.

Conclusion: Periodontitis had no link to the risk of COVID-19 hospitalization, susceptibility, or severity. However, the substance in COVID-19 that is responsible for this effect must be studied further.

KEYWORDS
COVID-19, Mendelian randomization, periodontitis

1 | INTRODUCTION

During Coronavirus Disease 2019 (COVID-19), individuals all over the world were infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] WHO declared COVID-19 a pandemic due to its rapid spread worldwide in March 2020.[3,4] In 2019, COVID-19, initially discovered in Wuhan, China, quickly spread over the globe, causing over 160 million cases and nearly 2,000 deaths by May 25, 2021.[1] A public health emergency burdens healthcare systems worldwide, threatening individuals' well-being

and disrupting economies.[5,6] The key to treating and managing COVID-19 is to understand how serious COVID-19 is linked to other health issues. Several studies have found that serious COVID-19 is linked to being older, being male, and having a number of other health problems, such as obesity, type 2 diabetes, heart disease, and high blood pressure.[7–12]

Periodontitis is a bacterial infection of the periodontal tissues that causes bone resorption and tooth loss in the oral cavity.[13] This chronic inflammatory noncommunicable disease, the sixth most prevalent globally, affects approximately 50% of adults. Periodontitis affects approximately 11% of the population.[14,15] Public health and socioeconomic problems remain a major concern due to periodontitis' high prevalence and consequences.[16] Several consequences can arise from periodontitis, including tooth loss and disability, affecting the patient's quality of life and overll-being.[17,18] In addition to diabetes, cardiovascular disease, and increased mortality, severe periodontitis is associated with other systemic diseases.[19,20] Periodontitis was considered aggressive periodontitis (AgP) in 1999, whereas chronic periodontitis (CP) is a slower-progressing form of periodontitis.[21]

A link between periodontitis and COVID-19 has long been recognized.[22–24] Innate immune system activation and the creation of inflammatory cytokines such interleukin-6 and tumour necrosis factor play an important role in both disorders.[25] Several observational studies have also demonstrated a link between COVID-19 and periodontitis.[25–27] A causal link between periodontitis and COVID-19 must be established to understand periodontitis and COVID-19 pathogenesis better. Thus, we hypothesize that COVID-19 could be caused by periodontitis progression. With the emergence of Mendelian randomization (MR) and large-scale genome wide association study (GWAS), it is now feasible to establish a causal relationship between complex characteristics and illnesses. MR, a novel epidemiological approach, may be considered conceptually as natural RCTs because allocating genotypes from parent to offspring is random. In contrast to observational studies, the use of genetic variations as instrumental variables (IVs) in MR is an efficient way to prevent the effects of confounding factors such measurement error, reverse causality, and underlying bias. Therefore, we investigate the causal link between COVID-19 and periodontitis using MR analysis with genetic variation as an IVs.[28] In addition, we employ reverse MR to examine the bidirectional causal effect of COVID-19 on periodontitis.

2 | METHODS

2.1 | Data sources

Data from the GLIDE consortium's most recent meta-analysis of GWAS of gene-lifestyle interactions were used to summarize the findings for periodontitis (https://data.bris.ac.uk/data/dataset/2j2rqgzedxlq02oqbb4vmycnc2). The data set included 12,289 clinically identified cases and 22,326 controls with European ancestry.[29] Seventeen IV SNPs were identified as having a p value > 5×10^{-6}, as used in other literature.[30]

A GWAS meta-analysis conducted previously for COVID-19, Round 5, was used to obtain genetic statistics for the COVID-19 phenotype (https://www.covid19hg.org/results/).[31] A total of 2,586,691 European-ancestry participants participated in the study. Three phenotypes, including susceptibility, hospitalization, and severe clinical consequences, were linked to COVID-19. The diagnosis of SARS-CoV-2 infection was made through a laboratory confirmation, electronic health records, patient-reported COVID-19 infection, or a physician diagnosis of COVID-19. COVID-19 patients (N = 112,612) and disease-free population controls were compared to determine susceptibility. According to WHO guidelines, patients hospitalized for COVID-19-related symptoms or a confirmed SARS-CoV-2 infection were considered hospitalized COVID-19 patients. The study compared COVID-19 hospitalization outcomes between two groups: those with COVID-19 (N = 24,274) and those without. Severe COVID-19 patients were characterized as those who needed respiratory support while in the hospital, including interventions such as Bilevel positive airway pressure, continuous external negative pressure, intubation, continuous positive airway pressure, or high-flow nasal cannulation. The number of severe cases was 8779 for COVID-19 severity.[32,33] IV SNPs were identified with the $p > 5 \times 10^{-8}$.

2.2 | MR analyses

To ensure that the genetic IVs met the three key MR assumptions, we applied the following criteria: (i) a GWAS-related p value less than 5×10^{-6}, ii) a linkage disequilibrium [LD] r2 < 0.001, and iii) a proximity of <1 MB from the index variant. The potential effects of variance heterogeneity and pleiotropy were assessed using three different MR methods: inverse variance weighting (IVW), MR Egger, and weighted median.[34,35] The main analysis involved applying standard IVW estimates, which integrated the Wald ratios of each SNP of the outcome and calculated summary causal estimates. If only one SNP was available, the causality of the outcome exposure was estimated using the Wald ratio. Additional MR analyses were conducted using several methods, such as MR-Egger regression, weighted median, and MR-PRESSO (MR-PESO) to strengthen the MR results. An empirical distribution was considered in the weighted median method, with each variant receiving a weight corresponding to the inverse of the variance of the ratio estimate.[36] MR-Egger regression offers the advantage of being able to examine for unbalanced multi-effects and significant heterogeneity, though it needs a larger sample size to detect similar under-exposure variation.[37] The weighted median technique revealed that horizontal pleiotropy contributed at least 50% of the weighted variance.[36]

2.3 | Sensitivity analysis

Horizontal pleiotropy is characterized by genetic variations that are linked to the exposure of interest and impact the outcome (i.e., severe COVID-19) via other pathways beyond the hypothesized

exposure. To evaluate the robustness of the results and detect potential pleiotropy, several tests were conducted, including Cochran's Q statistic, funnel plots, leave-one-out (LOO) tests, and MR-Egger intercept tests. In the Cochran's Q test, a p value less than 0.05 suggest the presence of heterogeneity. Additionally, horizontal pleiotropy in MR-Egger regression was calculated using the intercept term. LOO analysis was performed, in which each exposure-associated SNP was removed separately to determine whether any single SNP was responsible for the causal estimate.

2.4 | Risk factors

Several potential co-variables that could affect the genetic relationship between periodontitis and COVID-19 were explored further. Additionally, the PhenoScanner platform, which provides comprehensive information on genotype-phenotype associations, was utilized to check whether any of the SNPs used in the analysis were linked to potential risk factors such as body mass index, obesity, smoking, drinking, and hypertension.[38] Any SNPs found to be associated were removed from the analysis to prevent confounding and ensure the validity of the results.

2.5 | Statistical analysis

The MR analysis findings were presented as odds ratios (OR) with accompanying 95% confidence intervals (CI). Each standard deviation (SD) increment in COVID-19 risk caused an estimate of the relative periodontitis risk. This study was conducted using TwoSampleMR (version 4.25) and MR-PRESSO (version 1.0) in R (version 3.6.1).[39]

2.6 | Ethical approval

This study's data were publicly available, and the studies from which they were obtained had previously obtained ethical approval and participant consent.[29,31,40]

3 | RESULTS

3.1 | The causal effect of periodontitis on COVID-19

This study used 17 SNPs to predict periodontitis genetically, with no genetic variant being palindromic or having intermediate allele frequencies. The genetic instrument used in the MR analysis had all F statistics greater than the typically recommended value of 10, indicating that it was a robust and strong instrument.[41]

Figure 1 and Table 1 present the MR estimates for the different methods. The genetically predicted periodontitis risk and the COVID-19 risk appeared unrelated. The increased risk of periodontitis due to MR was not statistically significant with increased COVID-19 risk (vulnerability to COVID-19: SNP: 3, odds ratio [OR] = 1.03, 95% CI: 0.79–1.34, p = 0.82; hospitalization for COVID-19: SNP: 4, OR = 1.34, 95% CI: 0.98–1.85, p = 0.07; the severity of COVID-19 illness: SNP: 2, OR = 1.01, 95% CI: 0.61–1.66, p = 0.97). However, MR-Egger, the Weighted Median, and the Weighted Mode demonstrated similar findings. Figure 2 illustrates a scatter plot of SNP effect sizes for periodontitis and COVID-19. The heterogeneity test revealed no heterogeneity among individual SNPs. An MR-Egger regression and MR-PRESSO test indicate that horizontal pleiotropy has not affected these findings (Table 2). LOO analysis revealed that no single SNP

Exposure	Outcome	Method	N.SNPs	P
PD	Susceptibility	MR Egger	3	0.672248545
PD	Susceptibility	Weighted median	3	0.716664126
PD	Susceptibility	Inverse variance weighted	3	0.823107972
PD	Susceptibility	Weighted mode	3	0.686386594
PD	Hospitalization	MR Egger	4	0.230866145
PD	Hospitalization	Weighted median	4	0.303887929
PD	Hospitalization	Inverse variance weighted	4	0.066875418
PD	Hospitalization	Weighted mode	4	0.606696048
PD	Severity	MR Egger	3	0.672248545
PD	Severity	Weighted median	3	0.716664126
PD	Severity	Inverse variance weighted	3	0.823107972
PD	Severity	Weighted mode	3	0.686386594
Susceptibility	PD	MR Egger	4	0.565164331
Susceptibility	PD	Weighted median	4	0.488812863
Susceptibility	PD	Inverse variance weighted	4	0.654838687
Susceptibility	PD	Weighted mode	4	0.434897916
Hospitalization	PD	Inverse variance weighted	1	0.756974991
Severity	PD	MR Egger	6	0.860163856
Severity	PD	Weighted median	6	0.681450166
Severity	PD	Inverse variance weighted	6	0.812557314
Severity	PD	Weighted mode	6	0.648079117

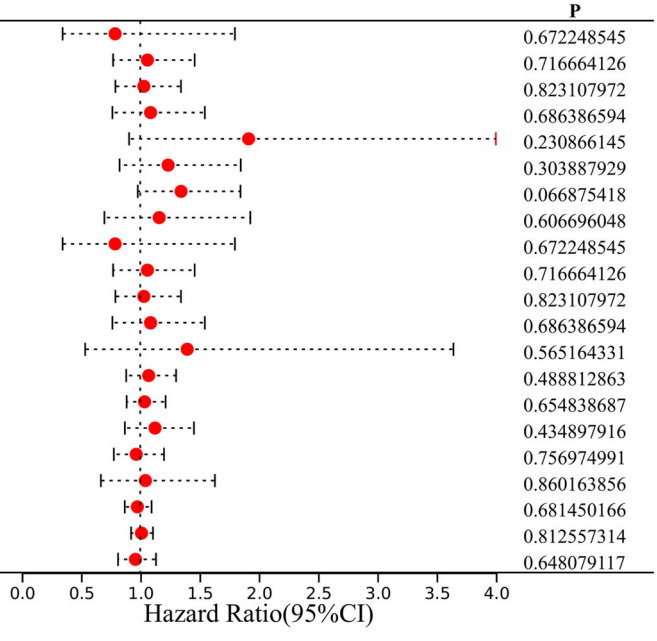

FIGURE 1 Estimated causal effects between periodontitis and COVID using different MR methods. MR, Mendelian randomization.

contributed significantly to periodontitis causal estimates. Figures 3 and 4 depict a funnel plot and a LOO analysis plot, respectively.

3.2 | Causal effects of COVID-19 on periodontitis

The 167, 637, and 550 SNPs with $p < 5 \times 10^{-8}$ were considered IV SNPs for COVID-19 hospitalization, susceptibility, and disease severity, respectively. Identifying any palindromes with moderate allele frequencies was impossible, and the average F values for COVID-19 hospitalization, susceptibility, and illness severity were 22.22, 21.32, and 23.15, respectively, with all genetic variations having F values higher than 10.

Figure 1 compares the MR estimates generated by the different methods. Genetically predicted periodontitis and COVID-19 risk were not causally associated. The IVW demonstrated no statistically significant link between COVID-19 and periodontitis (COVID-19 hospitalization: SNP: 1, OR = 0.97, 95% CI: 0.78–1.20, $p = 0.76$; vulnerability to COVID-19: SNP: 4, OR = 1.04, 95% CI: 0.88–1.21, $p = 0.65$), COVID-19 seriousness (SNP: 6, OR = 1.01, 95% CI: 0.92–1.11, $p = 0.81$). Meanwhile, the weighted median, the MR-Egger, and the weighted mode methods were similar. Figure 2 presents the scatter plots for periodontitis and COVID-19. The heterogeneity test revealed that the SNPs were not heterogeneous. Based on the results of the MR-Egger regression and MR-PRESSO tests, there is strong evidence to suggest that horizontal pleiotropy did not affect the causal relationship between periodontitis and COVID-19. (Table 2). LOO analysis indicated that no single SNP contributed significantly to causal estimates of periodontitis. Figures 3 and 4 illustrate the funnel plots and the LOO.

TABLE 1 Mendelian randomization estimates of the causal association between periodontitis and COVID-19.

Exposure	Outcome	OR (95% CI)	*p* Value
Periodontitis	Susceptibility	1.03 (0.79–1.34)	0.82
	Hospitalization	1.34 (0.98–1.85)	0.07
	Severity	1.01 (0.61–1.66)	0.97
Susceptibility	periodontitis	1.04 (0.88–1.21)	0.65
Hospitalization		0.97 (0.78–1.20)	0.76
Severity		1.01 (0.92–1.11)	0.81

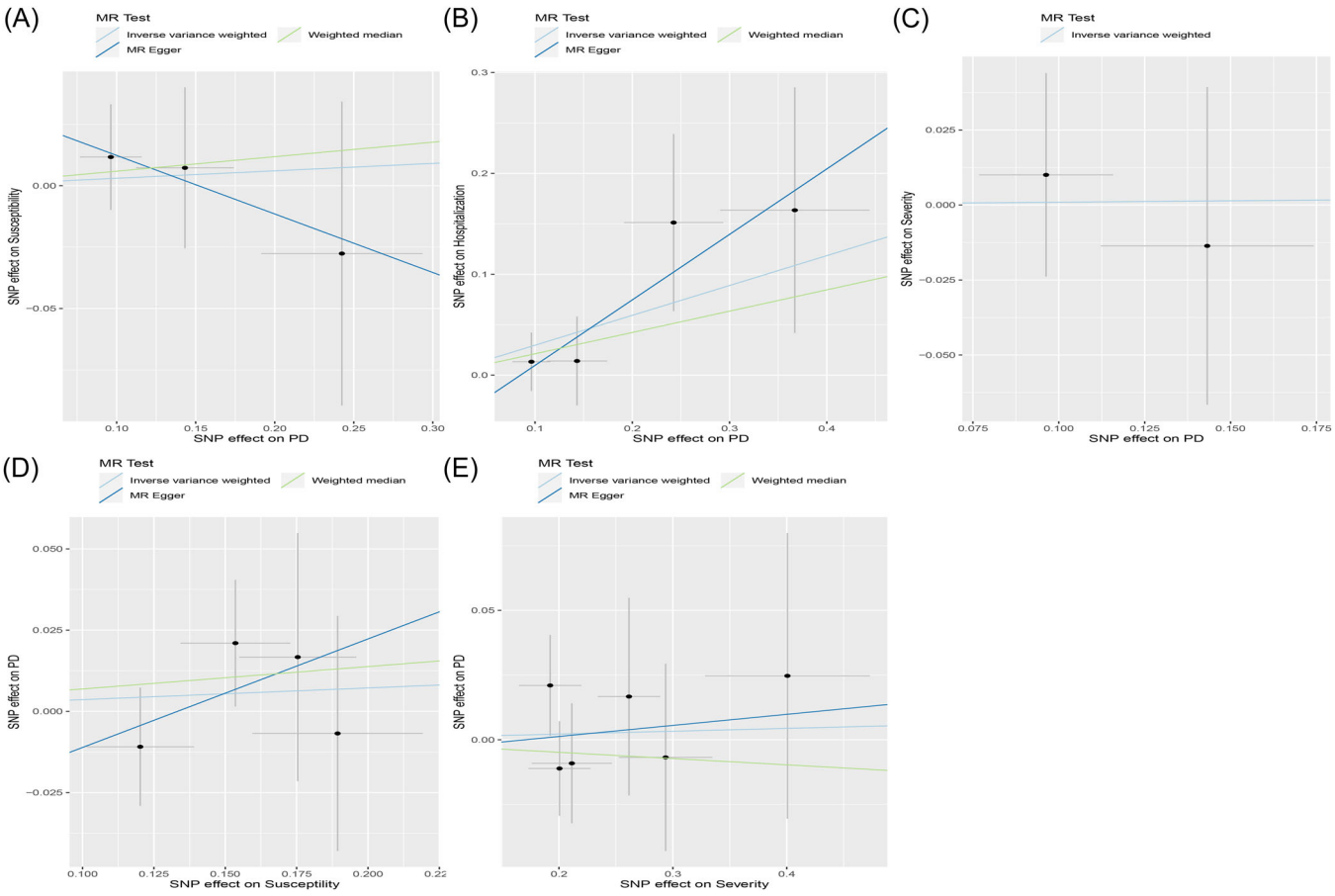

FIGURE 2 Scatter plot of the causal relationships between periodontitis and COVID using different MR methods. (A) Causal estimates for periodontitis on COVID susceptibility. (B) Causal estimates for periodontitis on COVID hospitalization. (C) Causal estimates for periodontitis on COVID severity. (D) Causal estimates for COVID susceptibility on periodontitis. (E) Causal estimates for COVID severity on periodontitis. MR, Mendelian randomization.

TABLE 2 Sensitivity analysis of the causal association between periodontitis and the risk of COVID-19.

Exposure	Outcome	Cochrane Q test		MR-Egger		MR-PRESSO *p* value
		Q value	*p*	Intercept	*p*	
Periodontitis	Susceptibility	0.49	0.78	0.036	0.62	0.52
	Hospitalization	1.71	0.63	−0.055	0.41	0.71
	Severity	0.15	0.69	NA	NA	NA
Susceptibility	Periodontitis	1.54	0.67	−0.044	0.59	0.55
Hospitalization		NA	NA	NA	NA	NA
Severity		2.05	0.84	−0.007	0.89	0.53

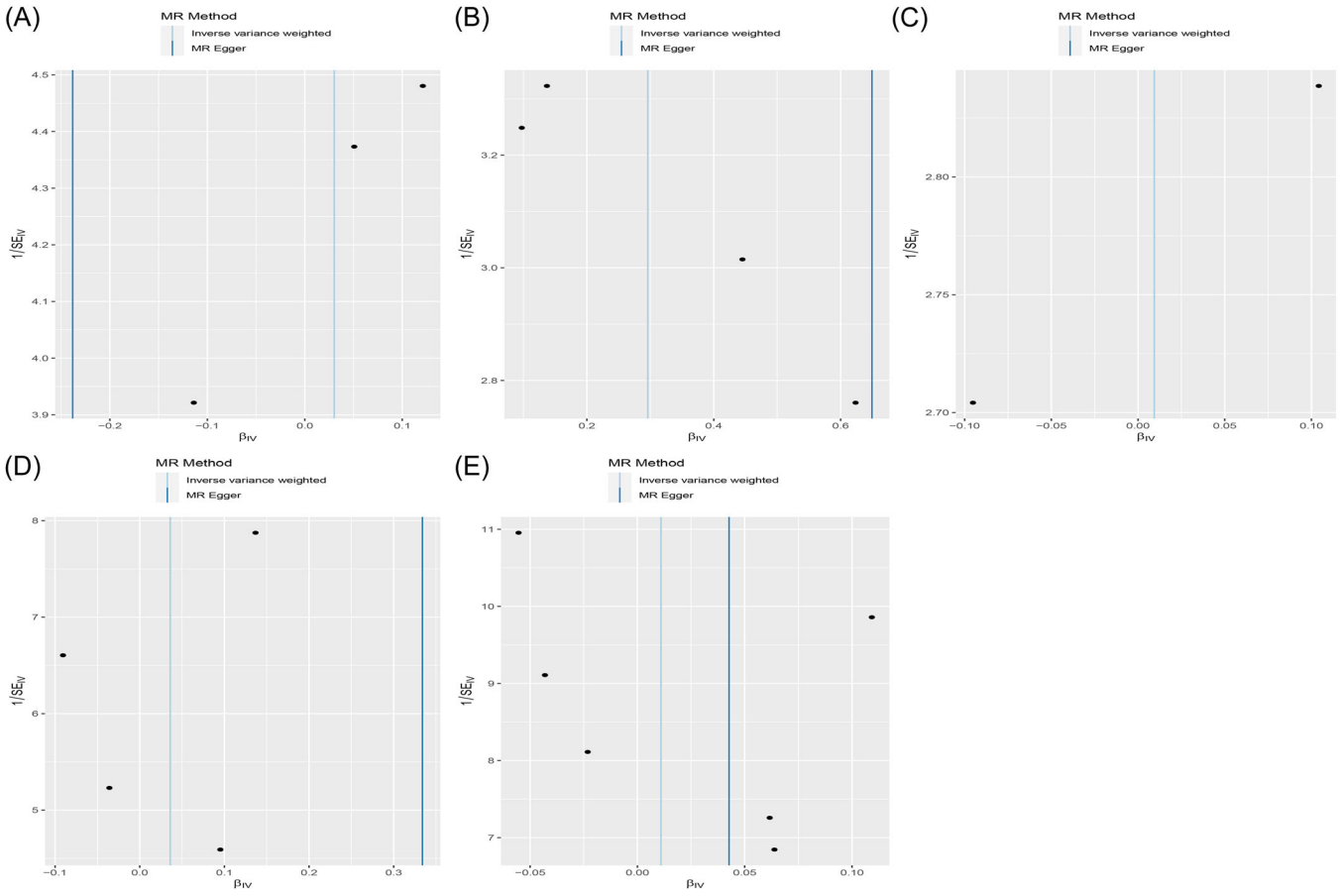

FIGURE 3 The funnel plots from genetically periodontitis on COVID-19 hospitalization, susceptibility and severity. (A) Causal estimates for periodontitis on COVID susceptibility. (B) Causal estimates for periodontitis on COVID hospitalization. (C) Causal estimates for periodontitis on COVID severity. (D) Causal estimates for COVID susceptibility on periodontitis. (E) Causal estimates for COVID severity on periodontitis.

4 | DISCUSSION

Oral health is impacted by broader health issues. Numerous studies have shown a connection between issues with dental health and systemic illnesses such diabetes, obesity, atherosclerotic heart disease, Alzheimer's disease, and the aftereffects of those illnesses.[42] Periodontitis is an inflammatory condition caused by physiological disruptions that elevate the host's inflammatory response[43] and lead to systemic disease.[44] Periodontitis has been associated with various diseases, including stroke,[45] cardiovascular disease,[46] malignant tumor,[47] and pneumonia.[48] "Cytokine storm," caused by cytokine release from host cells, has been linked to SARS-CoV-2 infection.[49] This association between periodontitis and systemic diseases is partially due to cytokines that stimulate bacteria and destroy tissues.[50] Consequently, purely observational studies cannot establish causality between periodontitis and COVID-19. Therefore, we investigated the causal link between periodontitis and COVID-19 using MR. We discovered no evidence that genetically predicted periodontitis in individuals of European descent is associated with COVID-19 in our two-sample MR analysis.

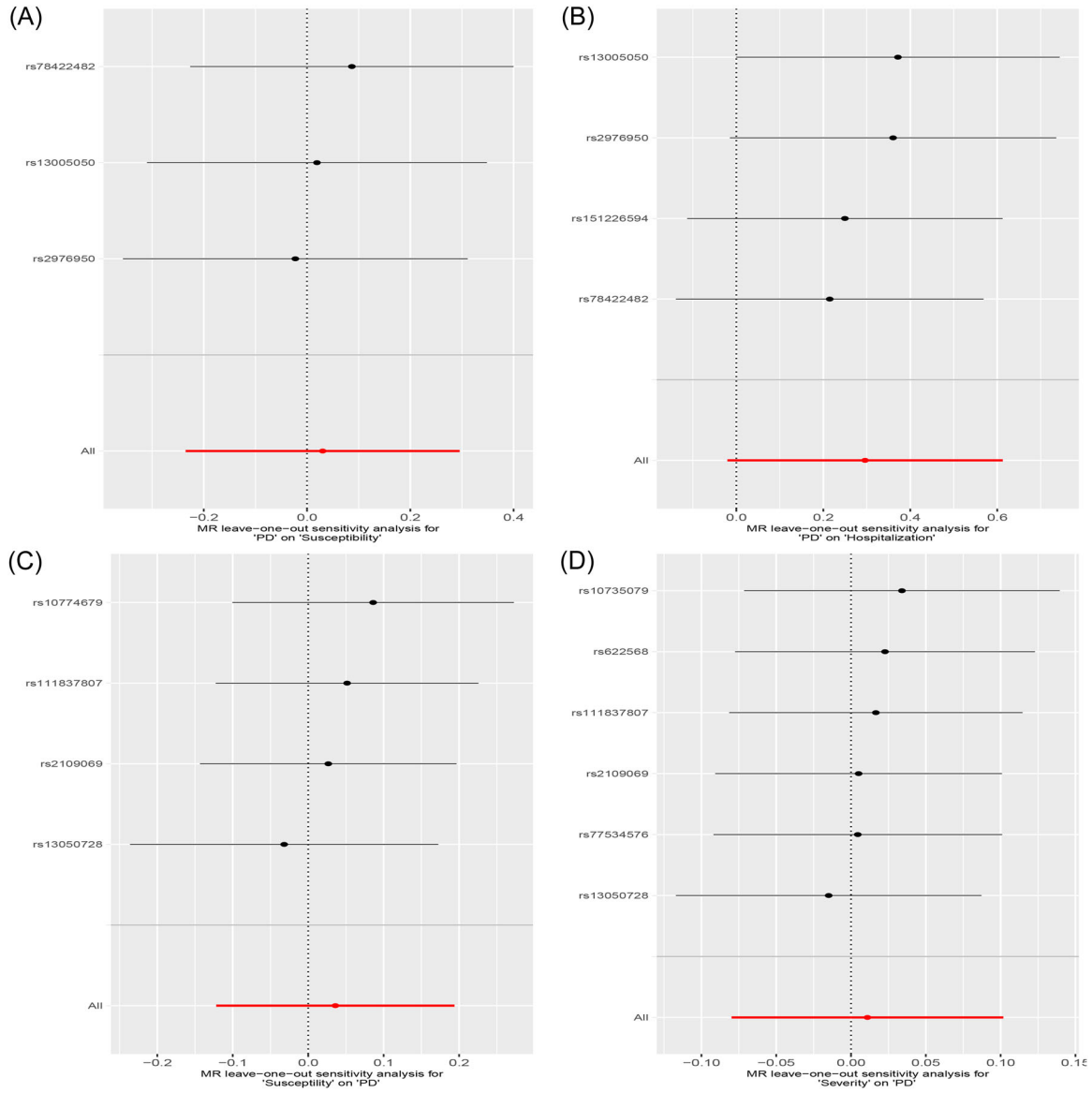

FIGURE 4 The leave-one-out analysis plots between periodontitis and COVID. (A) Causal estimates for periodontitis on COVID severity. (B) Causal estimates for periodontitis on COVID susceptibility. (C) Causal estimates for COVID susceptibility on periodontitis. (D) Causal estimates for COVID severity on periodontitis.

Periodontitis and COVID-19 have previously been linked in epidemiological studies. Evidence suggests that COVID patients have a higher risk of developing periodontitis. COVID-19 has been linked to severe periodontitis[25] and a higher risk of serious COVID-19 complications.[51–53] A cross-sectional clinical study by Gupta et al. indicated that COVID-19 pneumonia and hospitalization increased with periodontitis realities.[26] A recent meta-analysis found that while COVID-19 was not significantly linked to periodontal symptoms (OR = 1.1; 95% CI, 0.73–1.65) or mortality among patients with periodontitis (OR = 2.71; 95% CI, 0.64–11.51), there was an observed link between COVID-19 severity and the presence of periodontal disease (OR = 3.18; 95% CI, 1.81–5.58).[54] In Qatar, a case-control study involving 568 patients examined COVID-19 complications and the presence of periodontitis.[25] Another study of 137 COVID-19 patients (aged 20 to 65) revealed that patients with signs of oral disease were more likely to be infected by COVID-2019 than those without oral disease.[55]

Aging, obesity, diabetes, hypertension, and cardiovascular disease are associated with COVID-19 severity[56,57] and are also significantly associated with periodontitis.[16,46] Due to this uncertainty, it is unknown if periodontitis increases the severity of Coronavirus through comorbidities or if particular mechanisms or pathways are involved.[58,59] The included research suggested a link between COVID-19 infection and periods of poor oral health. However, there are several causes of poor dental health, including COVID-19-related stress and/or emotional responses, intubation, medications, and immunological problems.[60,61] Therefore, whether the oral health problem is produced directly by SARS-CoV-2, is

connected to antibiotic therapy, or if an immunity to COVID-19 has been badly impaired is unknown.[62] It has been hypothesized that symptoms of oral lesions may suggest that immune storm-related damage has persisted after the eradication of SARS-CoV-2, and SARS-CoV-2-related inflammatory markers may have been upregulated during this period.[60] COVID-19 patients treated with antibiotics are often prophylactic and therapeutic measures. Several infectious agents, including SARS-CoV-2, were detected in the oral cavity, suggesting a potential co-infection. As a result, antibiotic therapy may raise the risk of oral health issues by altering the oral microbiota because it is difficult to confirm a causal relationship.[63] The SARS-COV-2 pathogenesis and its direct role in oral homeostasis, the effects of antibiotics or other treatments on these processes, and the impact of the inflammatory response must be considered. More research is required to determine whether COVID-19 infection causes oral health problems. Therefore, we performed a reverse MR to determine whether COVID-19 also causally affects periodontitis in the opposite direction.

Several strengths can be identified in the current bidirectional MR. First, Using the MR design, our investigation may mimic a randomized controlled trial in an observational situation. Randomized control features are widely accepted in the study of causality but are costly, expensive, and frequently impractical. However, MR studies can effectively avoid confounding bias in assigning SNPs randomly at conception. In contrast to other observational studies, MR also avoids reverse causality effects. Second, we analyzed the biggest GWAS data of periodontitis to determine the causal association between COVID-19 and periodontitis. Our study supports the causal link between periodontitis and COVID-19.

This MR analysis has some flaws that need to be considered when interpreting the results. Firstly, the study population was of European ancestry, so the findings may not be generalizable to other populations from different regions. Secondly, the IVs used in the analysis were selected based on SNPs with p values less than 5×10^{-6} in GWAS data of periodontitis. This threshold is lower than the commonly accepted threshold of 5×10^{-8} and may have affected the statistical power of the causal estimates. Therefore, caution is required when interpreting the results, and further research is needed to validate the findings and confirm their generalizability to different populations.

In summary, our study demonstrated that the risk of COVID-19 is not causally related to genetic periodontitis and did not genetically predict COVID-19 susceptibility and hospitalization on periodontitis, except for COVID-19 severity.

AUTHOR CONTRIBUTIONS

Jukun Song: Conceptualization; data curation; software; writing—original draft. **Yadong Wu**: Formal analysis; investigation; methodology. **Xinhai Yin**: Methodology; project administration; validation. **Junmei Zhang**: Software; visualization; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data can be downloaded from the 'GLIDE' database (https://data.bris.ac.uk/data/dataset/2j2rqgzedxlq02oqbb4vmycnc2) and COVID19-hg GWAS meta-analyses round 5 (https://www.covid19hg.org/results/).

ETHICS STATEMENT

The present study was a secondary analysis based on publicly available data. Informed consent was obtained for all the participants according to the original GWAS protocol, and ethical approval for GWAS was obtained from the original GWAS authors.

TRANSPARENCY STATEMENT

The lead author Junmei Zhang affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Jukun Song http://orcid.org/0000-0003-2542-9340

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