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Dissecting the causal association of periodontitis with biological aging and its underlying mechanisms: findings from Mendelian randomization and integrative genetic analysis

Yu Cao [1], George Pelekos [2], Lijian Jin [2], An Li [3], Mi Du [4], Shixian Hu [5], Zuyun Liu [6,*], Ke Deng [2,*]

[1]Department of Psychiatry, The University of Hong Kong, Hong Kong SAR, China
[2]Division of Periodontology and Implant Dentistry, Faculty of Dentistry, The University of Hong Kong, Hong Kong SAR, China
[3]Department of Periodontology, Stomatological Hospital, School of Stomatology, Southern Medical University, Guangzhou, China
[4]School and Hospital of Stomatology, Cheeloo College of Medicine, Shandong University & Shandong Provincial Clinical Research Center for Oral Diseases, Jinan, China
[5]Institute of Precision Medicine, The First Affiliated Hospital of SunYat-Sen University, Sun Yat-Sen University, Guangzhou, China
[6]Center for Clinical Big Data and Analytics of the Second Affiliated Hospital, and Department of Big Data in Health Science School of Public Health, The Key Laboratory of Intelligent Preventive Medicine of Zhejiang Province, Zhejiang University School of Medicine, Hangzhou, China

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***Correspondence:**
Ke Deng
Division of Periodontology and Implant Dentistry, Faculty of Dentistry, The University of Hong Kong, 34 Hospital Road, Hong Kong SAR 999077, China.
Email: cdeng@hku.hk
Tel: +852-28590251
Fax: +852-28587874

Zuyun Liu
Center for Clinical Big Data and Analytics of the Second Affiliated Hospital, and Department of Big Data in Health Science School of Public Health, the Key Laboratory of Intelligent Preventive Medicine of Zhejiang Province, Zhejiang University School of Medicine, 866 Yuhangtang Road, Xihu District, Hangzhou 310058, China.
Email: zuyunliu@zju.edu.cn
Tel: +86-(0571)87077127
Fax: +86-(0571)87077120

ABSTRACT

Purpose: Chronic low-grade inflammation is linked to the biology of aging; however, evidence supporting a causal relationship between periodontitis—a dysbiotic biofilm-initiated inflammatory disease—and accelerated aging remains limited. This study investigated the causality between periodontitis and biological aging and identified potentially shared genomic loci, genes, and pathways.
Methods: We conducted a 2-sample Mendelian randomization (MR) analysis to explore the causality of periodontitis on age acceleration measures (DNAm PhenoAge acceleration, GrimAge acceleration, Hannum age acceleration, and intrinsic epigenetic age acceleration) using a dataset from genome-wide association studies of European ancestry populations. Independent genetic variants associated with each trait were used as instrumental variables. The inverse variance-weighted (IVW) method served as the primary MR approach, supplemented by sensitivity testing. We also performed additional statistical genetic analyses to identify pleiotropic loci, shared functional genes, and potential biological pathways, integrating large-scale expression quantitative trait loci data from blood samples.
Results: The MR analysis indicated a causal relationship between periodontitis and DNAm PhenoAge acceleration (IVW β=0.308; 95% confidence interval, 0.056–0.561; *P*=0.017), a finding corroborated by sensitivity analyses. There was a significant genetic overlap between periodontitis and age acceleration. Pleiotropic analysis revealed 24 shared SNPs associated with 242 genes, predominantly involved in immune functions and pathways related to cellular processes. Further integration analysis showed that 91 of these pleiotropic genes were causally linked to both conditions, with C6orf183 identified as a potential mediator.

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ORCID iDs
George Pelekos
https://orcid.org/0000-0003-1917-1988
Lijian Jin
https://orcid.org/0000-0002-5340-9710
Shixian Hu
https://orcid.org/0000-0002-1190-0325
Zuyun Liu
https://orcid.org/0000-0001-6120-5913
Ke Deng
https://orcid.org/0000-0003-1308-0399

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
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Conclusions: This study presents compelling genetic evidence supporting a causal relationship between periodontitis and accelerated aging. Further research is required to validate these findings and investigate the underlying mechanisms.

Keywords: Periodontitis; Biological aging; Causality; Molecular epidemiology

INTRODUCTION

The magnitude of the global aging crisis is substantial, as evidenced by a recent report predicting that 1 out of every 6 people worldwide will be 60 years of age or older by 2030. Additionally, the population aged 80 years or older is expected to reach 426 million by 2050 [1]. This demographic shift has profound societal implications, as age-related disabilities and functional declines significantly increase the vulnerability to premature mortality.

While chronological age progresses uniformly across individuals, the rate of biological aging varies among people. This discrepancy between chronological age and biological age within an individual is defined as age acceleration. Various metrics have been proposed to characterize the phenotypic, epigenetic, and molecular aspects of biological age. Phenotypic age (PhenoAge) is calculated using a combination of clinical biomarkers and chronological age to assess the risk of adverse health outcomes and age-related mortality [2]. Epigenetic age, also known as epigenetic clocks, is recognized as a reliable age predictor based on DNA methylation levels. These clocks include various cytosine-phosphate-guanine (CpG) sites that are integrated with mathematical algorithms for the DNA-based estimation of age [3]. The multiple established epigenetic clocks can be categorized into first-generation clocks, including the Hannum [4] and Horvath clocks [5], and their derivatives, such as the intrinsic epigenetic age acceleration (IEAA) [6], as well as second-generation clocks like the GrimAge clock [7]. DNAm PhenoAge is a specific type of epigenetic clock that integrates both DNA methylation data and phenotypic age-related markers to estimate biological age [8]. Notably, increasing evidence from animal models and human studies reveals that biological aging is influenced by low-grade chronic inflammation (inflammaging), environmental exposures, and lifestyle factors [9]. Despite the widespread acknowledgment of the concept of inflammaging-accelerated aging, the role of periodontitis in biological aging remains poorly understood.

Periodontitis is one of the most prevalent dysbiotic inflammatory diseases affecting the tooth-supporting structures. Its severe form is the sixth most common disease globally, impacting around 1 billion people [10]. Periodontitis extends beyond oral health, as it is closely associated with numerous systemic comorbidities outside the oral cavity. Consequently, periodontitis may act as a source of chronic inflammation during the aging process. If a causal link is established, periodontitis could significantly influence the global aging crisis. In this scenario, interventions aimed at reducing oral inflammation could play a crucial role in decelerating the aging process and preventing its associated complications. Recent epidemiological studies have indicated that periodontitis is linked with accelerated aging, characterized by the shortening of telomere length [11,12]. However, a comprehensive understanding of the relationship between periodontitis and biological aging is still lacking. This gap in knowledge is due to the absence of well-validated composite measures of aging, the lack of study designs that minimize potential biases, and insufficient exploration of the underlying biological mechanisms.

Mendelian randomization (MR) is an emerging approach in genetic epidemiology that examines the causal effects of exposures on outcomes, minimizing the influence of potential confounding factors and reverse causation [13]. In this study, we conducted an MR analysis to explore the potential causality between periodontitis and biological aging, utilizing datasets from large-scale genome-wide association studies (GWAS). We identified putative shared genomic loci, functional genes, and biological pathways to elucidate the underlying mechanisms.

MATERIALS AND METHODS

Study design

The study design flowcharts are depicted in **Figures 1** and **2**. We conducted a 2-sample MR assessment using a large-scale GWAS dataset from publicly accessible sources, focusing on European ancestry populations. Various statistical genetic methods were applied to uncover the shared molecular basis of the disease through integrative omics analysis. This study was conducted in accordance with the Guidelines for Performing Mendelian Randomization Investigations [14], and the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization statement [15]. Additional ethical approval and informed consent were not required for this analysis, as all included GWAS statistics from publicly available sources had previously received approval from the appropriate ethical review bodies.

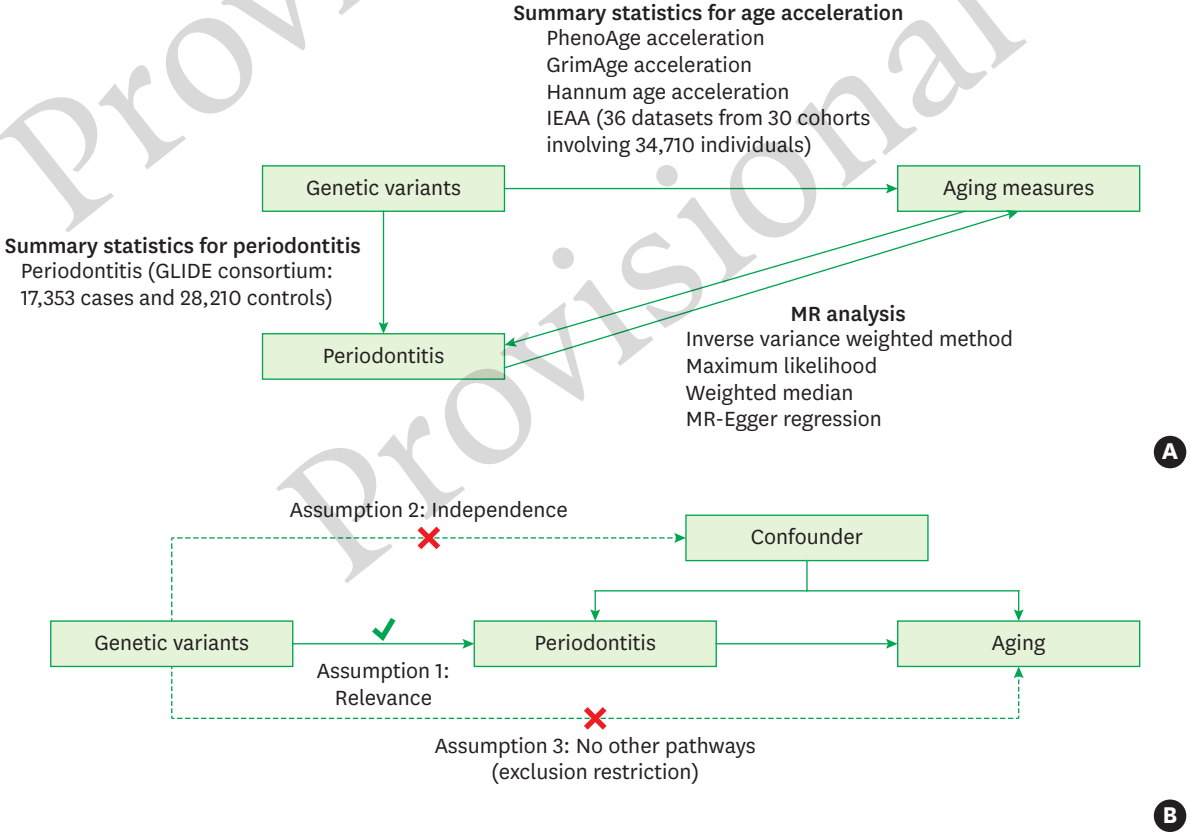

Figure 1. A schematic representation of MR analysis. (A) A 2-sample MR framework was used, where the exposure and the outcome are measured in large-scale GWAS summary statistics. (B) MR relies on 3 pivotal assumptions for the genetic variants to be valid instruments.
MR: Mendelian randomization, GWAS: genome-wide association studies, IEAA: intrinsic epigenetic age acceleration, GLIDE: Gene-Lifestyle Interactions in Dental Endpoints.

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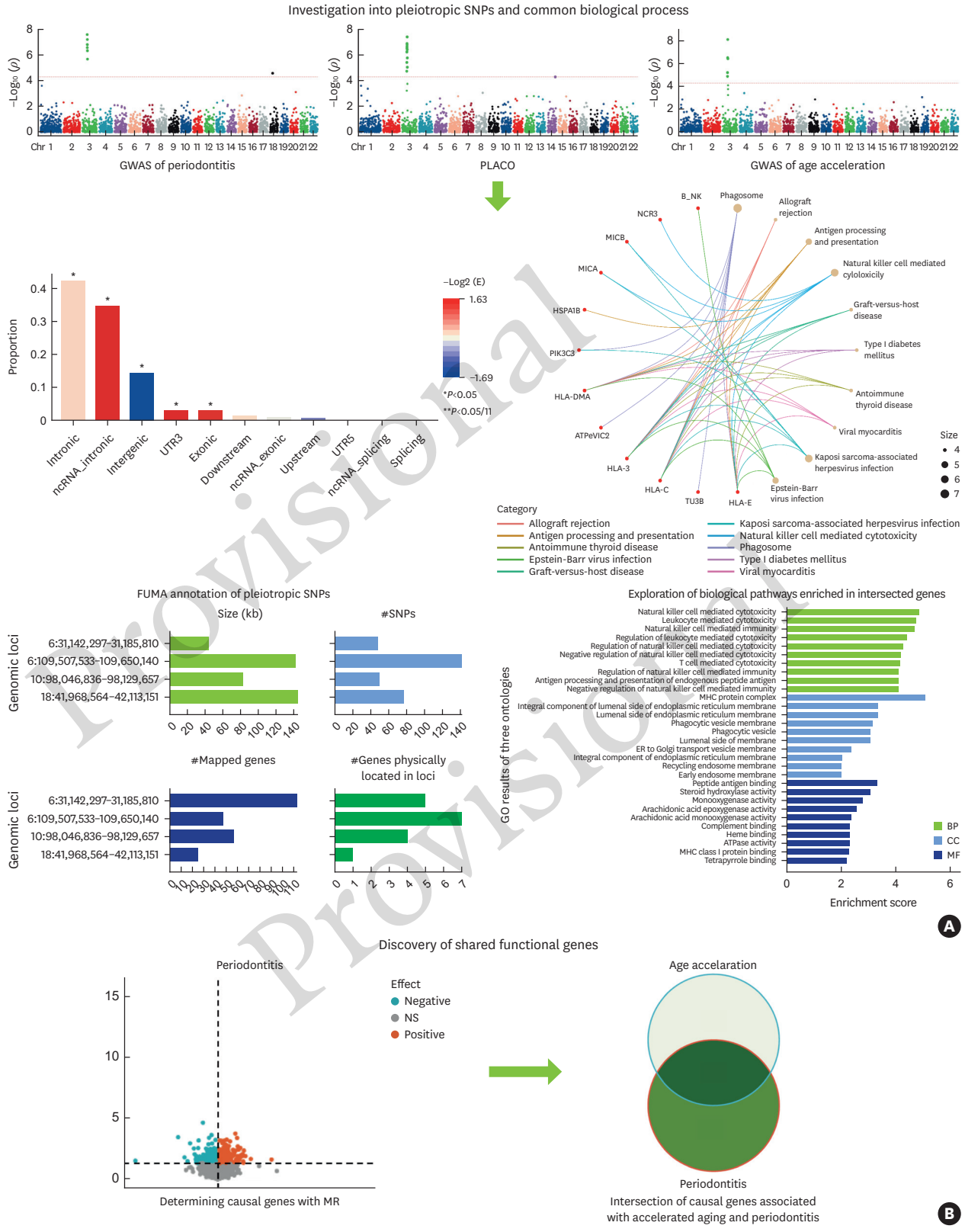

Figure 2. Workflow of the integrative genetic analysis to identify shared genetic determinants between periodontitis and age acceleration. (A) Investigation into pleiotropic SNPs and common biological process. (B) Discovery of shared functional genes.
SNP: single nucleotide polymorphism, GWAS: genome-wide association studies, PLACO: pleiotropic analysis under composite null hypothesis, FUMA: functional mapping and annotation, MR: Mendelian randomization.

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Data source

Genetic instruments for periodontitis were derived from the Gene-Lifestyle Interactions in Dental Endpoints (GLIDE) consortium [16], based on data from 17,353 cases and 28,210 controls. The largest published GWAS datasets [17] for age acceleration phenotypes, with pooled summary statistics from 30 cohorts involving 34,710 individuals, were selected to identify genetic instruments for age acceleration. Four traits that characterize biological aging—namely IEAA, Hannum age acceleration, DNAm PhenoAge acceleration, and GrimAge acceleration—were calculated using the Horvath epigenetic age calculator [5]. The detailed descriptive data are available in **Supplementary Table 1**.

Selection of genetic instruments

The genetic variants used as instrumental variables (IVs) for MR analysis must satisfy 3 key assumptions: 1) the genetic variants are significantly associated with periodontitis (the "relevance" assumption); 2) these variants are not linked to confounding factors (the "independence" assumption); and 3) they influence biological aging solely through their impact on periodontitis (the "exclusion restriction" assumption). Based on these criteria, we selected IVs as follows: 1) single nucleotide polymorphisms (SNPs) associated with periodontitis at a significance threshold of $P<5\times10^{-6}$ were deemed eligible [18]; 2) SNPs exhibiting linkage disequilibrium (LD) were excluded, and independent SNPs were selected based on an $r^2<0.01$ and a clumping window of 10,000 kB, using PLINK; and 3) the F statistics for each SNP were calculated to assess their instrumental strength. Only SNPs with F statistics greater than 10 were retained to minimize the influence of weak instrumental variables. A detailed flowchart describing the SNP selection process is available in **Supplementary Figure 1**. The SNPs used as instrumental variables are listed in **Supplementary Table 2**.

MR analysis

Ambiguous or palindromic SNPs were systematically excluded through data harmonization. The inverse variance-weighted (IVW) method was used as the primary approach, assuming no directional pleiotropy for SNPs. Several sensitivity assessments were conducted to evaluate the robustness of the IVW results, including the maximum likelihood (ML), MR Egger, and weighted median (WM) methods. The ML method is sensitive to violations of standard MR assumptions, such as heterogeneity or horizontal pleiotropy. When these conditions are met, this approach can provide unbiased results with potentially smaller standard errors compared to the IVW, especially when the number of genetic instruments is large [19]. MR-Egger allows unbalanced pleiotropy, accommodating situations where certain SNPs may influence the results via different pathways other than the exposure of interest, but at the cost of lower statistical power [20]. Additionally, the WM method can accurately estimate causality even when up to half of the IVs are invalid [21]. The heterogeneity of the IVs was assessed using Cochran's Q, while horizontal pleiotropy was tested using MR Egger regression and the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method.

Identification of pleiotropic loci and shared biological mechanism

The pleiotropic analysis under composite null hypothesis (PLACO) method was employed to identify potential pleiotropic loci between periodontitis and age acceleration [22]. Subsequently, significant SNPs were analyzed using the functional mapping and annotation (FUMA) of GWAS tool. This analysis provided insights into the biological mechanisms of these genetic associations and helped prioritize potential causal genes [23]. We identified

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independent significant SNPs and their surrounding loci based on LD structure, which allowed us to define lead SNPs and genomic risk loci. FUMA then offered a comprehensive functional annotation of these SNPs, assessing gene functionality, potential regulatory roles, and deleteriousness scores. Additionally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway functional analyses further clarified the biological functions of the genes mapped by FUMA.

Identification of shared functional genes

We utilized an expression quantitative trait loci (eQTL) dataset from the eQTLGen Consortium [24] to conduct MR aimed at identifying genes that causally relate to both periodontitis and age acceleration, thus uncovering shared functional genes between these traits. The eQTLGen dataset includes 16,987 genes from 31,684 blood samples, predominantly from healthy European individuals. We set a false discovery rate (FDR) threshold of $P<0.05$ and chose cis-eQTLs located within 5kb upstream or downstream of genes as IVs for the MR analysis. These IVs were clumped with an r^2 threshold of 0.01. The Wald Ratio method was employed for MR effect estimation to identify genes associated with a single eQTL, while the IVW method was used for genes associated with multiple eQTLs. Given the exploratory nature of this study, a value below 0.05 was considered indicative of potential functional genes. Separate MR analyses were performed using periodontitis and age acceleration as outcomes, and the intersection of their respective results revealed shared functional genes. A comparative analysis was conducted with FUMA-mapped genes. All data analyses were performed using R 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Causal effects of periodontitis on age acceleration

The associations between periodontitis and different aging metrics are shown in **Figure 3**. The IVW approach uncovered a significant causal relationship between periodontitis and DNAm PhenoAge acceleration (β=0.308; 95% confidence interval [CI], 0.056–0.561; P=0.017). The ML method also showed a consistent result (β=0.308; 95% CI, 0.035–0.581; P=0.027). However, no evidence was found to support causal associations between periodontitis and other aging metrics, such as GrimAge acceleration, Hannum age acceleration, or IEAA.

The results of Cochran's Q test revealed no significant heterogeneity among the genetic variants. Furthermore, the MR-Egger intercepts were centered around zero, indicating no evidence of uncorrelated pleiotropy. Similarly, the MR-PRESSO results showed no presence of horizontal pleiotropy (**Table 1**).

Table 1. Results of heterogeneity and horizontal pleiotropy tests

Age acceleration	Heterogeneity				Pleiotropy			
	MR Egger		IVW		MR Egger		MR-PRESSO	
	Cochran's Q	*P* value	Cochran's Q	P value	Egger intercept	*P* value	Rssobs	Global test *P* value
DNAm PhenoAge	4.412328	0.4916986	5.4489024	0.4876539	0.0318039	0.355327	7.602819	0.525
GrimAge	2.4790828	0.7796419	5.572498	0.472738	0.0423968	0.1389361	6.890101	0.55
HannumAge	1.5786386	0.9038204	6.8096617	0.338809	0.0548416	0.0709021	10.38605	0.325
IEAA	2.3504349	0.7988317	3.2590382	0.7757026	0.0235105	0.3842598	6.751484	0.61

MR: Mendelian randomization, IVW: inverse variance-weighted, MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier, Rssobs: residual sum of squares observed, PhenoAge: phenotypic age, IEAA: intrinsic epigenetic age acceleration.

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Outcome	No. SNPs	Beta (95% CI)	*P* value
DNAm PhenoAge			
IVW	7	0.308 (0.056 to 0.561)	0.017
ML	7	0.308 (0.035 to 0.581)	0.027
MR Egger	7	0.213 (−0.100 to 0.525)	0.240
WM	7	0.222 (−0.117 to 0.561)	0.199
GrimAge			
IVW	7	0.056 (−0.134 to 0.246)	0.563
ML	7	0.057 (−0.137 to 0.251)	0.562
MR Egger	7	−0.066 (−0.299 to 0.168)	0.606
WM	7	0.018 (−0.220 to 0.256)	0.881
HannAge			
IVW	7	0.085 (−0.112 to 0.281)	0.399
ML	7	0.089 (−0.105 to 0.284)	0.370
MR Egger	7	−0.068 (−0.294 to 0.158)	0.581
WM	7	0.030 (−0.215 to 0.274)	0.812
IEAA			
IVW	7	−0.063 (−0.254 to 0.128)	0.519
ML	7	−0.064 (−0.256 to 0.127)	0.511
MR Egger	7	−0.129 (−0.364 to 0.106)	0.330
WM	7	−0.165 (−0.402 to 0.073)	0.174

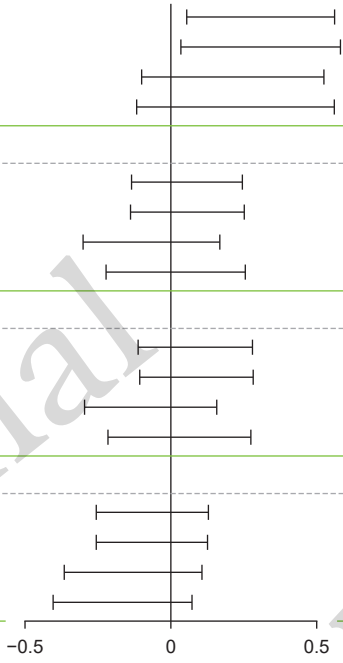

Figure 3. MR analysis of the association between periodontitis and age acceleration. The error bar plot depicts effect estimates (β) along with their corresponding 95% CIs.
MR: Mendelian randomization, CI: confidence interval, SNP: single nucleotide polymorphism, PhenoAge: phenotypic age, IVW: inverse variance-weighted, ML: maximum likelihood, WM: weighted median, IEAA: intrinsic epigenetic age acceleration.

Pleiotropic SNPs and shared biological mechanism

Supplementary Table 3 displays the shared SNPs between periodontitis and age acceleration. Using the PLACO method, we identified 24 significant SNPs as potential pleiotropic variants. Functional annotation was performed using FUMA, which mapped these SNPs to a total of 242 genes (**Supplementary Table 4**). This suggests a complex genetic architecture within the identified genomic risk loci. The distribution of pleiotropic SNPs assigned by ANNOVAR is presented in **Supplementary Figure 2**, showing a non-random distribution across genomic regions. A considerable portion of the SNPs was located in intronic regions, with intronic and specific noncoding RNA intronic regions together accounting for over 40% of the annotations. This is indicated by the red bars with a significant $-\log_2(E)$ enrichment score ($E<0.05$). The intronic region alone exhibited the highest proportion, suggesting statistical significance. Additionally, a significant number of SNPs were found within the 3′ untranslated regions (3′ UTRs). Therefore, these pleiotropic SNPs are primarily implicated in gene regulatory regions rather than protein-coding regions, as both intronic regions and 3′ UTRs are typically involved in gene regulation rather than directly coding for proteins.

The GO enrichment analysis (**Supplementary Figure 3**) revealed a significant overrepresentation of genes involved in immunological processes, particularly within the biological process category, which includes natural killer cell-mediated cytotoxicity and leukocyte-driven cytotoxicity. Additionally, the analysis highlighted shared pathways in antigen presentation and MHC protein complex interactions. In the cellular component category, there was notable enrichment in the integral component of the endoplasmic

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reticulum membrane and the luminal side of the endoplasmic reticulum. The molecular function category showed an enrichment of genes associated with enzymatic activities linked to metabolic processes, such as steroid hydroxylase activity and arachidonic acid monooxygenase activity.

The KEGG pathway analysis (**Supplementary Figure 4**) identified a network of gene associations linked to immune-related diseases. Additionally, connections between genes and pathways involved in allograft rejection, as well as antigen processing and presentation, were observed.

Shared functional genes

The MR analysis of GWAS and eQTL data identified 420 genes with a significant causal relationship to periodontitis. Regarding age acceleration, we identified 547 genes associated with GrimAge acceleration, 598 with Hannum age acceleration, 594 with IEAA, and 596 with DNAm PhenAge acceleration (**Figure 4A**, **Supplementary Table 5**). Notably, the *HOXB7* gene emerged as a common genetic link between periodontitis and all measures of age acceleration (**Figure 4B**). Furthermore, by categorizing genes into 2 groups—those related to periodontitis and those associated with age acceleration—we discovered 91 genes that were common to both categories (**Figure 4C**). This overlap suggests a shared molecular basis between periodontitis and age acceleration.

Finally, we conducted an intersectional analysis of pleiotropic SNPs that influence multiple traits, along with their corresponding genes, using the FUMA platform. The *C6orf183* gene emerged as a consistent point of interest, associated with both periodontitis and aging, as indicated by both the intersectional and eQTL analyses.

DISCUSSION

This study represents the first comprehensive assessment of the causal effects of periodontitis on the risk of accelerated aging, utilizing large-scale GWAS data. Notably, the MR analysis provided genetic evidence supporting a causal relationship between periodontitis and PhenoAge acceleration. Further comprehensive analyses offered insights into pleiotropic SNPs and loci, potentially shared functional genes, and biological pathways underlying both periodontitis and age acceleration.

Limited evidence has explored the association between periodontitis and biological aging, specifically characterized by the shortening of telomere length, yet these studies have been met with controversy. For instance, a Japanese study that included 20 patients with aggressive periodontitis and 51 healthy controls found no link between the disease status and telomere erosion [25], corroborating the findings of a cohort study of 734 adults in New Zealand [26]. In contrast, recent analyses of the National Health and Nutrition Examination Survey dataset in U.S. adults revealed a significant association between the presence and severity of periodontitis and telomere length shortening [11,27]. Additionally, a recent MR study indicated a reverse causal relationship, suggesting that shorter telomere lengths might increase the risk of periodontitis, rather than periodontitis leading to the shortening of telomere lengths [28]. However, these studies are inherently limited by their cross-sectional designs, which prevents the establishment of causality. Moreover, they typically relied on a single marker of cellular aging, which may not fully capture the complexity of the aging

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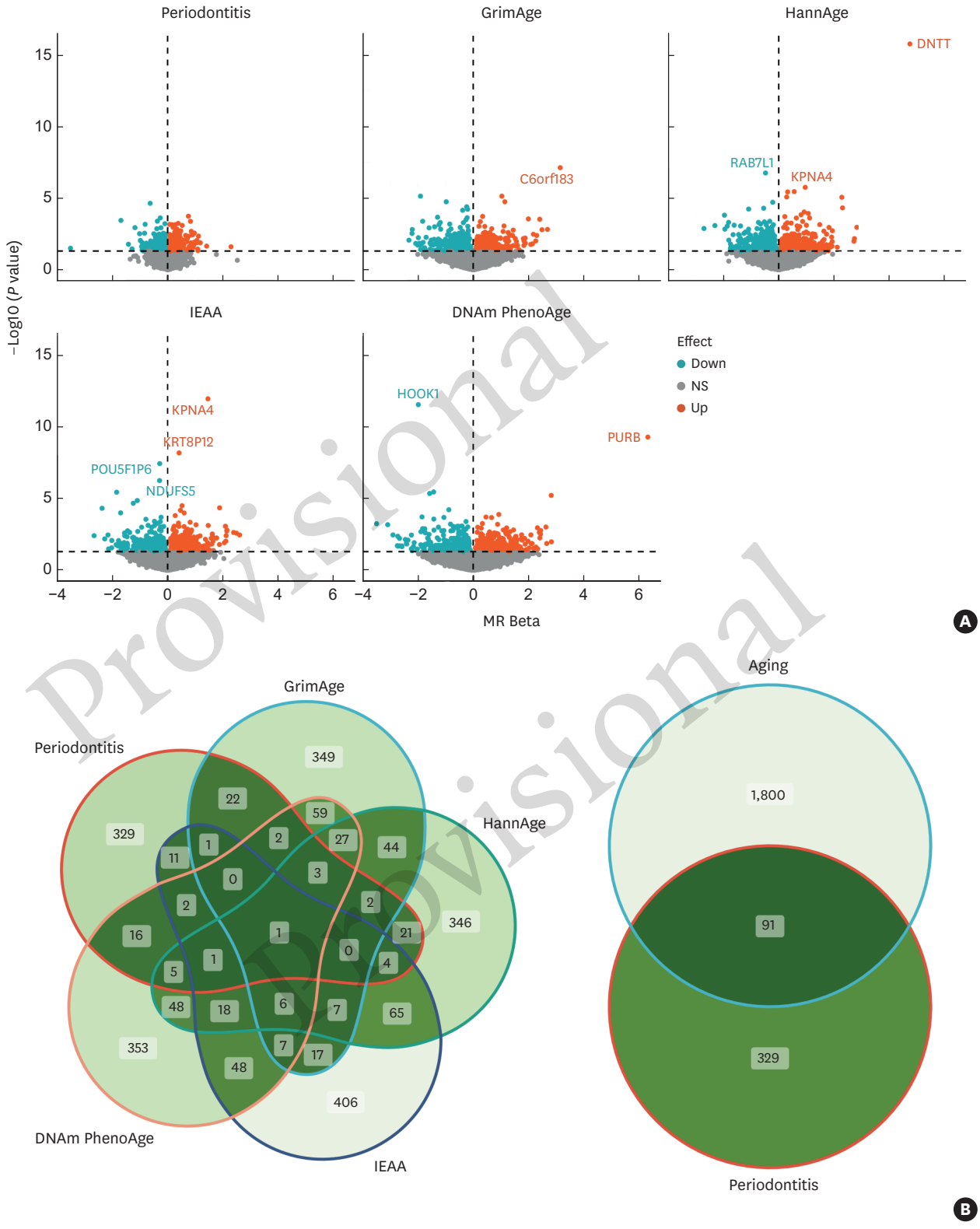

Figure 4. Mendelian randomization analysis of gene expression levels associated with periodontitis and age acceleration. (A) Identification of gene expression levels causally linked to periodontitis and age acceleration from the MR analysis. (B) Genes associated with all traits. (C) Overlapping genes associated with both periodontitis and age acceleration. Blue dot: negative causal relationship between gene expression and the traits; orange dot: positive causal relationship between gene expression and the traits.
MR: Mendelian randomization, IEAA: intrinsic epigenetic age acceleration, NS: not significant, PhenoAge: phenotypic age.

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process. Furthermore, the existing studies often had relatively small sample sizes and did not adequately address potential confounders, resulting in insufficient statistical power to draw definitive conclusions. Our study builds on these findings by employing well-validated aging measures, robust statistical assays, and minimizing bias.

In the present study, both the IVW and ML approaches demonstrated a significant causal relationship between periodontitis and DNAm PhenoAge acceleration. In contrast, the non-significant results from the MR Egger and WM methods may be attributed to their lower statistical power [29]. The inconsistency among different MR approaches is particularly noteworthy given that the actual causal effect of periodontitis on accelerated aging could be modest, and the number of genetic variants used as instrumental variables in this study is relatively limited. However, the IVW method remains the most robust for detecting causality when all instrumental variables are valid [30]. Interestingly, periodontitis was associated with an increased risk of DNAm PhenoAge acceleration among all aging measures examined. This finding suggests that the impact of periodontitis on biological aging may be more specifically related to the pathways or mechanisms captured by DNAm PhenoAge acceleration. Indeed, different epigenetic clocks, such as GrimAge, Hannum age, and IEAA, are linked to various health outcomes and reflect distinct facets of the biological aging process [31]. Epigenetic clocks such as GrimAge, Hannum age, and IEAA provide a more direct understanding of the molecular mechanisms of aging by focusing on aging-related epigenetic modifications in methylation levels [32]. However, they may not capture the full extent of the physiological changes associated with periodontitis. On the other hand, DNAm PhenoAge integrates the advantages of phenotypic age measures with molecular data provided by DNA methylation. This unique combination makes DNAm PhenoAge a robust indicator of various age-related conditions, including periodontitis [8]. DNAm PhenoAge might detect the systemic impact of periodontitis more accurately due to its comprehensive nature, capturing both phenotypic and molecular aspects of aging. It is important to note that the association between periodontitis and DNAm PhenoAge does not negate the relevance of other epigenetic clocks. Rather, it highlights the multifaceted nature of biological aging and the need for a variety of measures to capture its complexity. In future research, it would be interesting to explore in greater detail why certain epigenetic clocks are more sensitive to periodontitis than others, which may provide further insight into the biological mechanisms linking periodontitis and aging.

To address the research gap in understanding how periodontitis may increase the risk of accelerated aging, we conducted various statistical genetic analyses to explore the shared genetic architecture. We identified a significant number of shared pleiotropic SNPs and functional genes between periodontitis and age acceleration, suggesting potential interconnected biological pathways between these 2 conditions. Notably, the pleiotropic genes were predominantly enriched in immunological processes and were involved in immune-related diseases. The *HOXB7* and *C6orf183* genes emerged as shared genetic links between periodontitis and age acceleration. Specifically, the *HOXB7* gene, a member of the homeobox family of transcription factors, plays a critical role in regulating various functions in cancer cells [33]. Although *HOXB7* has been primarily associated with tumor growth, evidence suggests that its expression may be epigenetically regulated in periodontitis [34]. Conversely, the function of *C6orf183*, a protein-coding gene located on chromosome 6, remains largely uncharacterized. These findings collectively indicate that pleiotropic SNPs, especially those affecting genes like *HOXB7* and *C6orf183*, could be pivotal in linking periodontitis with age acceleration, potentially through shared immunological and inflammatory processes. In light of these findings, it is crucial to acknowledge the

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shared biology between periodontitis and age acceleration, which encompasses chronic inflammation, senescence-associated secretory phenotypes (SASPs), oxidative stress, immune system dysregulation, altered matrix degradation and tissue remodeling, and epigenetic modifications [35]. Those potential biological mechanisms can explain the interconnection between periodontitis and biological aging. Firstly, human aging is often accompanied by a chronic, low-grade inflammatory state known as "inflammaging." This condition is believed to set the stage for most known age-related diseases, including periodontitis [35]. Second, periodontitis is an age-related, chronic inflammatory disease associated with dysbiosis and is closely linked with many systemic comorbidities beyond the oral cavity, possibly even aging itself. This connection is probably due to the direct spread of periodontal pathogens to other organs, which triggers immune responses that release inflammatory mediators and induce the expression of the SASPs into the bloodstream, consequently accelerating the onset of aging [36,37]. A recent study showed that the inflammatory periodontal tissue microenvironment can trigger senescence-like alterations and expression of various SASP markers [38]. Thirdly, proinflammatory environments can increase levels of reactive oxygen species, inducing oxidative stress which can damage cells, proteins, and DNA. This damage can influence numerous cellular processes linked to aging and the development of age-related diseases [39]. Therefore, further research is necessary to elucidate the underlying mechanisms and potential clinical implications.

Our study holds significant clinical relevance and public health implications. It suggests a potential link between periodontitis and accelerated aging, underscoring the importance of early detection, prevention, and treatment of periodontitis to potentially slow the aging process, reduce the risk of age-related health issues, and ultimately extend lifespan. Recognizing the shared genetic architecture, developing interventions that target these common genetic risk factors could represent a promising strategy for the effective prevention and improved treatment of both periodontitis and aging-related issues.

The key strengths of this study include its pioneering evidence on the causal relationship between periodontitis and age acceleration, its initial exploration of underlying genetic mechanisms, the use of reliable aging measures, extensive genetic data, multiple sensitivity analyses, and the control of pleiotropic effects, all of which enhance the robustness and reliability of the findings. Nevertheless, there are certain limitations that need to be addressed. First, our study only included participants of European ancestry, which limits the generalizability of the results to other ethnic groups worldwide. Second, the selection of epigenetic clocks did not encompass the full spectrum of the complex aging process. Therefore, future studies should incorporate various cellular, phenotypic, and epigenetic aging metrics. Lastly, while horizontal pleiotropy is a common issue in MR analysis and cannot be entirely ruled out, the MR-Egger intercepts showed no indication of pleiotropy, suggesting that it is unlikely to significantly impact the association estimates.

In conclusion, this MR study presents the first evidence of a causal relationship between periodontitis and accelerated aging, underscoring the importance of proactive prevention and early intervention strategies to improve oral and periodontal health. Such measures are crucial for promoting healthy aging and potentially extending lifespan. Further research involving larger sample sizes and diverse ethnic groups is needed to confirm these findings and to explore the underlying mechanisms and clinical implications.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Description of included GWAS studies in the MR analysis

Supplementary Table 2
List of the genetic variants used as instrument variables for periodontitis in the Mendelian randomization studies

Supplementary Table 3
Pleiotropic SNPs between periodontitis and age acceleration identified by PLACO method

Supplementary Table 4
Information about genes linked to pleiotropic SNPs identified through the FUMA analysis

Supplementary Table 5
Significant causal genes identified by MR analysis for each trait

Supplementary Figure 1
Flowchart demonstrates the process of genetic instruments selection in the MR analysis.

Supplementary Figure 2
Functional distribution of SNPs on genes.

Supplementary Figure 3
GO enrichment analysis results of FUMA mapped genes.

Supplementary Figure 4
KEGG enrichment analysis results of FUMA mapped genes.

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