BMC Oral Health

RESEARCH

Open Access

From teeth to bone: dental caries has causal effects on osteoporosis and osteoporotic fracture

Gongzi Zhang[1,3†], Juan Zheng[1†], Ying Zhou[1†], Ming Zhou[1], Jiali Zhang[1,2], Yangxiaoxue Liu[1,2], Yuhan Geng[1], Wenxin Wang[1,2], Min Xin[1,2], Bo Yang[4], Lihai Zhang[3*] and Liping Huang[1*]

Abstract

Objectives Evidence from observational studies suggested oral diseases (periodontitis (PD) and dental caries) may increase susceptibility to bone loss. However, inherent confounding of observational studies limits causal interpretation. We aimed to conduct Mendelian randomization (MR) analysis to estimate the causal effect of oral diseases on osteoporosis (OP), bone mineral density (BMD) and fracture risk.

Methods We used summary-level GWAS meta-analysis data from the GLIDE consortium to identify 7 and 17 single-nucleotide polymorphisms (SNPs) for periodontitis and DMFS (the sum of Decayed, Missing, and Filled tooth Surfaces) as the instrumental variables. MR analyses of these instruments were performed on European individuals for the association with BMD of forearm, femoral neck and lumbar spine; and individuals from FinnGen consortium for OP, OP with pathological fracture, postmenopausal OP with pathological fracture, and site-specific fractures. We performed single-variable Mendelian randomization (SVMR) and multivariable Mendelian randomization (MVMR) to simultaneously assess independent causal effects of PD and DMFS on different outcomes. The estimates were primarily derived using inverse variance weighted (IVW) methods. Sensitivity analyses included weighted median, MR-egger, and Leave-one-out test.

Results In MVMR, after adjusting for PD, DMFS has a positive causal effect osteoporosis (OR = 1.165, [95% CI 1.020 to 1.331, $P = 0.025$]) and postmenopausal OP with pathological fracture (OR = 1.422, [95% CI 1.027 to 1.969, $P = 0.034$]). However, these causal relationships were not observed in the single-variable Mendelian randomization (SVMR) analysis. The causal associations were robust in various sensitivity analyses.

Conclusions In conclusion, dental caries causally increases the risk of OP and postmenopausal OP with pathological fracture, suggesting the existence of teeth-bone axis. Proactive osteoporosis screening in patients with severe dental caries may be warranted for clinical consideration.

Keywords Dental caries, Osteoporosis, Fracture, Mendelian randomization, Oral diseases

†Gongzi Zhang, Juan Zheng and Ying Zhou contributed equally to this work.

*Correspondence:
Lihai Zhang
zhanglihai74@qq.com
Liping Huang
huangliping301@163.com
Full list of author information is available at the end of the article

Background

Oral diseases are among the most prevalent diseases globally, causing a significant health and economic burden [1]. Approximately 3.5 billion people worldwide suffer from poor oral health conditions, mainly including tooth loss, pulpitis, and decreased chewing power [2]. Oral diseases are chronic and progressive in nature, affecting the teeth and mouth, mainly including dental caries (tooth decay), periodontal (gum) disease [3]. At present, a number of studies have shown that dental caries and periodontitis are closely associated with dementia, cardiovascular diseases, rheumatoid arthritis and other systemic diseases [4–6]. With multiple shared risk factors and links in biologically mechanisms, there has been consistent attention focused on the association between oral diseases and osteoporosis (OP). Similar to oral disease, osteoporosis is characterized by chronic skeletal disorders, including low bone mineral density (BMD), microarchitectural deterioration, and an increased fracture risk. OP is also highly prevalent, affecting approximately 6.3% of men and 21.2% of women aged 50 and older [7, 8].

In recent studies, increasing evidence supports osteoporosis or decreased BMD may be considered a risk factor for suboptimal oral health [9–11]. Studies also revealed that the number of teeth was negatively associated with fractures and a decreased bone mineral density, while periodontal disease was positively associated with osteoporosis and a decreased bone mineral density [12, 13]. Work from many laboratories has demonstrated that, periodontitis can cause bone loss in many parts of the body by promoting an inflammatory response [14, 15]. Meanwhile, the microbiota might act as a potential mediator linking oral and bone health. The gut microbiota has a crucial regulatory factor in bone metabolism and plays an essential role in the pathological progression of bone loss in ovariectomized (OVX) animal models [16]. Analogously, the oral microbiome-the gastrointestinal tract's primary microbial reservoir-exhibits comparable regulatory potential and can aggravate bone loss [17]. Periodontitis was even considered as a local manifestation of systemic "pre-senile osteoporosis" [18]. However, studies on the impact of dental caries on osteoporosis or fractures are currently lacking. And because of the inherent limitations of observational studies which are susceptible to confounding or reverse causation, whether oral diseases are the causal effect of osteoporosis, lower BMD or higher incidence of osteoporotic fracture is unclear.

Mendelian randomization (MR) analysis can elucidate causal associations between exposure and outcome by using genetic variants as instrumental variables (IVs), thus accounting for observational bias [19]. It relies on the principle of independent assortment of alleles during meiosis, yielding a random distribution of genetic variants at birth. The natural randomization process is analogous to the randomization used in randomized controlled trials (RCTs) [20]. MR analysis also has been well utilized to explore the causal effect of BMD on periodontitis [19]. So, we conducted a MR study using genome-wide significant single-nucleotide polymorphisms (SNPs) from large-scale genome-wide association studies (GWAS) as IVs to assess the causal effect of oral diseases (periodontitis and dental caries) on osteoporosis, site-specific BMD and fractures. Specifically, our study employed the DMFS (the sum of Decayed, Missing and Filled tooth Surfaces) index as the measurement for dental caries. The DMFS index can capture an individual's cumulative experience of past and present dental caries, both untreated or treated.

Methods

Study design

All identified data sets involved in this study were publicly available, ethical approval is not required. The main objective of this study was to investigate the causal effects of genetic predictors of oral diseases, specifically periodontitis and dental caries, on osteoporosis, BMD and fractures. For this purpose, we selected single nucleotide polymorphisms (SNPs) as genetic instruments for PD and DMFS, following three core assumptions: (1) IVs must be robustly related to PD and DMFS; (2) IVs should not be associated with potential confounding factors; (3) IVs must influence the outcomes in patients only via the oral diseases. This MR study was designed following the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization statement [21].

Data sources

Data sources for periodontitis and DMFS

For exposure, the summary level GWAS data were obtained from the European-ancestry participants from the latest meta-analysis the Gene-Lifestyle Interaction in the Dental Endpoints (GLIDE) Consortium (Genome-wide analysis of dental caries and periodontitis combining clinical and self-reported data). This meta-analysis of GWAS contains 17,353 periodontitis cases and 28,210 controls, as well as 26,792 participants who were clinically assessed for the DMFS [22]. For periodontal status, participants were classified as having (cases) or not having (controls) clinical symptoms of periodontitis, based on definitions applied by each participating cohort: Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) [23], dental examination by trained dental personnel at recruitment (defined as two or more tooth surfaces with probing

Table 1 Details of the GWAS included in the Mendelian randomization

Trait	No. of cases	No. of controls	Population	Atribute	GWAS
PD	17,353	28,210	European/Hispanic/Latino	exposure	GLIDE consortium
DMFS	26,792	——	European/Hispanic/Latino	exposure	GLIDE consortium
Osteoporosis	10,461	473,264	European	outcome	FinnGen
FN-BMD	32,735	——	European	outcome	GEFOS Consortium
LS-BMD	28,498	——	European	outcome	GEFOS Consortium
FA-BMD	8,143	——	European	outcome	GEFOS Consortium
Osteoporosis with Pathological Fracture	2429	374,317	European	outcome	FinnGen
OSTPOPATFRCTURE_POSTEMENO	2001	279,785	European	outcome	FinnGen
FRACT-FEMUR	12,229	476,877	European	outcome	FinnGen
FRACT-FOREA	27,907	462,982	European	outcome	FinnGen
FRACT-LUMBAR-SPINE-PELVIS	9,061	481,639	European	outcome	FinnGen

PD Periodontitis, *DMFS* the sum of Decayed, Missing, and Filled tooth Surfaces, *FN-BMD* femoral neck bone mineral density, *LS-BMD* lumbar spine bone mineral density, *FA-BMD* forearm bone mineral density, *OSTPOPATFRCTURE_POSTEMENO* Postmenopausal osteoporosis with pathological fracture, *FRACT-FEMUR* fracture of femur, *FRACT-FOREA* fracture of forearm, *FRACT-LUMBAR-SPINE-PELVIS* fracture of lumbar spine and pelvis, *GLIDE consortium* Gene-lifestyle Interactions in Dental Endpoints Consortium, *GEFOS consortium* The GEnetic Factors for OSteoporosis Consortium

depth ≥ 5 mm, or at least four tooth surfaces with probing depth ≥ 4 mm, or probing depth ≥ 5.5 mm in 2 or more sextants) [24], or the individual's self-reported status. DMFS in each included cohort is derived from clinical dental records.

Data sources for BMD

To obtain a more comprehensive and reliable conclusion of the causal relationship between oral diseases and osteoporosis, we selected the largest GWAS published to date for BMD.

For the outcomes, the summary level BMD GWAS data of European participants were retrieved from the Genetic Factors for Osteoporosis Consortium (GeFOS, http://www.gefos.org/), including femoral neck BMD (FN-BMD, 32,735 participants), lumbar spine BMD (LS-BMD, 28,498 participants), forearm BMD (FA-BMD, 8,143 participants) [25, 26]. Measurement of BMD was recommended utilizing dual-energy X-ray absorptiometry.

Data sources for osteoporosis and fractures

The data used in our study are publicly available, and the participants of the GWAS studies are of European descent for all variables. OP (n = 483,725), OP with pathological fracture (n = 376,746), postmenopausal OP with pathological fracture (n = 281,786), fracture of femur (n = 489,106), fracture of forearm (n = 490,889) and fracture of lumbar spine and pelvis (n = 490,700) were retrieved from large-scale GWAS and meta-analyses of European populations in the FinnGen consortium [25]. Fractures of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist) have long been regarded as the quintessential osteoporotic fractures [27].

SNP selection/genetic instrumental variables

To uncover the causal relationship between oral diseases (periodontitis and dental caries) and osteoporosis, site-specific BMD and fractures, index SNPs was used representing periodontitis and DMFS (listed in Supplementary Table S1). In order to satisfied the assumptions of linearity and the absence of statistical interaction, we selected genetic instruments based on the following criteria: 1) Since there were not enough SNPs with p-value less than 5×10^{-8} for PD and DMFS, we broadened the threshold to 5×10^{-6} to select eligible instrumental variables; and 2) a linkage disequilibrium [LD] r2 < 0.0001, and within 1 MB distance from the index variant [28]. We then utilized the resource at http://www.phenoscanner.medschl.cam.ac.uk/ to exclude SNPs that were correlated with potential confounders, including smoking, alcohol intake, and Vitamin D insufficiency. Following this, we harmonized the exposure and outcome SNPs to ensure alignment of effect alleles, eliminating any palindromic or incompatible SNPs. Additionally, Radial Inverse Variance Weighted (IVW) test was then conducted to identify inconsistencies between genetic associations of different genetic variants and to calculate the F-statistics. Any genetic variants identified as outliers were subsequently excluded. The F-statistic, which quantifies the strength of the relationship between the instrumental variables and the exposure, is calculated using the formula $[(N-k-1)/k]\times R^2/(1-R^2)$, where R^2 represents the variance of oral diseases explained by the genetic instrumental variables, and N represents the sample size [29]. An F-statistic value of ≥ 10 for the SNPs indicated that the selected instruments had adequate power and were unlikely to introduce bias into the MR estimates [30]. Detailed information on each data source was presented in Table 1.

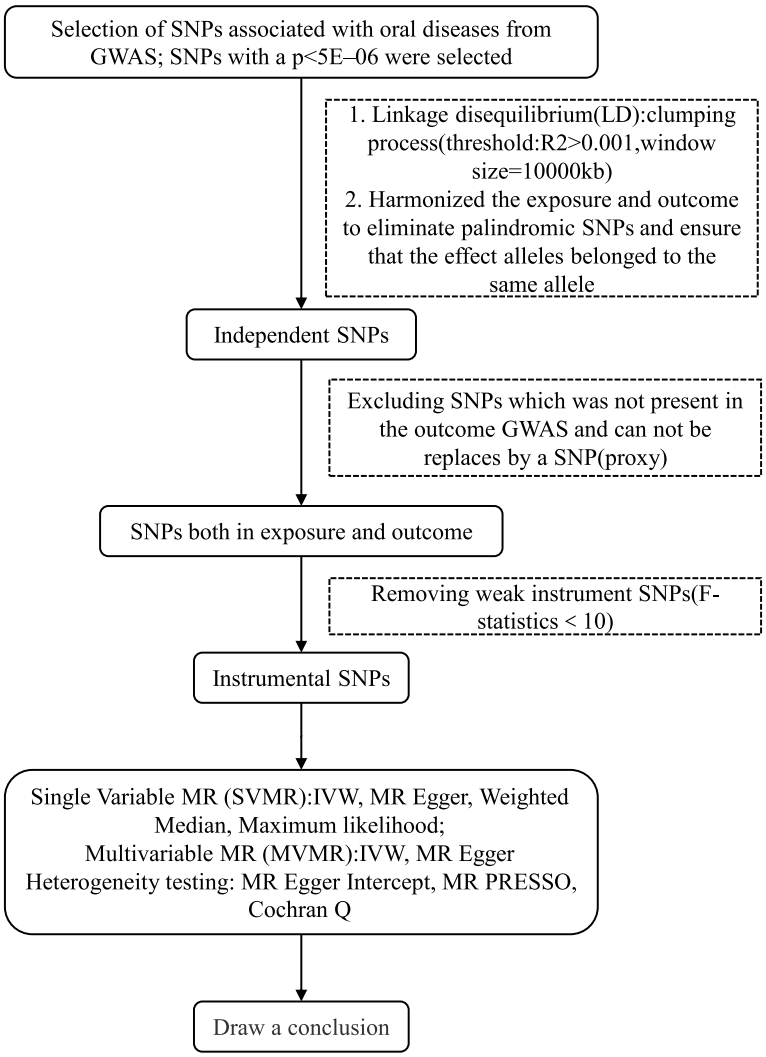

Fig. 1 Study flow chart of the Mendelian randomization analysis. GWAS, genome-wide association study: IVW, inverse variance weighted; MR, Mendelian randomization: MVMR, multivariable Mendelian randomization; SNP, single nucleotide polymorphism; SVMR, single-variable Mendelian randomization

MR analysis

We applied multiple complementary MR approaches to calculate the causal relationship between oral diseases and osteoporosis. Figure 1 illustrates the process of Mendelian randomization analysis in this study. For single-variable Mendelian randomization (SVMR), we employed inverse-variance weighted (IVW), MR-Egger, weighted median (WM), and maximum likelihood (ML). Among these, the IVW method was identified as the primary MR analysis [31]. To improve the IVW estimates, MR-Egger and weighted median methods was employed, which could offer more reliable estimates in a broader set of scenarios. The MR-Egger regression model provided a relatively robust estimate regardless of the validity of the instrumental variables; however, it was sensitive to outliers, which could reduce precise and statistical power [32]. For multivariable Mendelian randomization (MVMR) analysis, we utilized an expanded version of the IVW Mendelian randomization method, performing multivariable-weighted linear regression (assuming uncorrelated genetic variants and applying a random-effects model), with the intercept term fixed at zero. *P* value thresholds are given as graded measures of evidence, from "little or no evidence" to "very strong evidence" [33].

To correct weak instrument bias in our analysis, we employed the bias correction methods in both single-variable Mendelian randomization (SVMR) and multivariable Mendelian randomization (MVMR). For SVMR, we used the MR-RAPS (Mendelian Randomization using the Robust Adjusted Profile Score) method, while

for MVMR, we employed Debiased Inverse Variance Weighting (IVW) method [34].

Sensitivity analysis

Sensitivity analysis is used to detect potential pleiotropy and heterogeneity in MR estimates and plays a crucial role in MR studies. The existence of horizontal pleiotropy could lead to a violation of the second and third assumption. So, MR-Egger regression analysis was used to assess the potential pleiotropic effects of instrumental SNPs. The intercept term in the MR-Egger regression can effectively indicate whether there is horizontal pleiotropy that influenced the results of the MR analysis. The MR-Egger intercept test with $P<0.05$ indicates the existence of horizontal pleiotropy [35]. In addition, the Cochran Q test was calculated to examine the heterogeneity among different genetic variations, and Cochran Q-derived $p<0.05$ would be regarded as considerable heterogeneity [36].

Finally, to distinguish whether MR estimates are influenced by a single SNP or suffer from bias, we conducted a "leave-one-out" test, examining each genetic variant one by one [37]. If the statistical significance of the causal relationship remains after excluding each SNPs, it provides stronger evidence of an association.

Results

Genetic instruments for dental caries and periodontitis

We incorporated 7 and 17 independent SNPs as IV for PD and DMFS respectively. None of them was associated with potential confounders by searching the PhenoScanner and GWAS Catalog. The proportion of variance (R^2) explained by these IVs for oral diseases was calculated using summary statistics, with values ranging from 0.298% for periodontitis to 1.402% for DMFS. The F-statistics for oral diseases—22.694 for periodontitis and 22.397 for DMFS—were all above the threshold of 10, suggesting a low likelihood of weak instrument bias in our Mendelian randomization (MR) analyses and ensuring compliance with the first assumption.

Causal effects of oral diseases on osteoporosis

In SVMR analyses, the outcomes of standard MR analysis across various methodologies are depicted in the Fig. 2. There was no discernible causal association between oral diseases and osteoporosis, with effect sizes for periodontitis and DMFS at 0.998 [95% CI 0.933 to 1.067, $P=0.950$] and 1.156 [95% CI 0.994 to 1.343, $P=0.059$], respectively.

However, when periodontitis and DMFS were examined together in MVMR, there was moderate evidence that DMFS was positively associated with osteoporosis risk (OR = 1.165, [95% CI 1.020 to 1.331, $P=0.025$]), suggesting that each increase in DMFS equal to a single standard deviation (SD) was associated with a 16.5% increased risk of osteoporosis.

Causal effects of oral diseases on BMD

Results of standard MR analysis of different methods were presented in Fig. 3. The results of IVW in SVMR showed moderate evidence that genetically predicted DMFS (β = 0.105 [95% CI 0.006 to 0.205], $P=0.037$) and periodontitis (β = 0.055 [95% CI 0.008 to 0.102], $P=0.023$) had casual effects on lumbar spine BMD (LS-BMD). In addition, the Maximum Likelihood method showed consistent results, while the Weighted Median, and the Weighted Mode methods did not.

In MVMR analyses, DMFS continued to demonstrate its positive association with LS-BMD (β = 0.105, [95% CI 0.011 to 0.199], $P=0.028$, moderate evidence), while periodontitis didn't (β = 0.047 [95% CI −0.002 to 0.096], $P=0.056$). No causal effect of oral diseases on FN-BMD and FA-BMD was found.

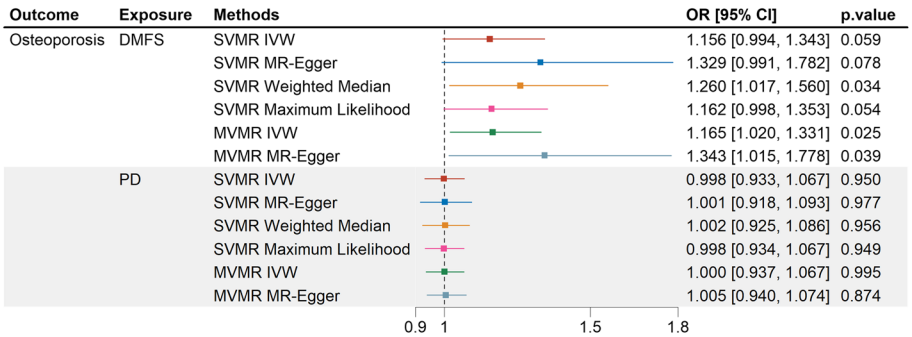

Fig. 2 Different methods for MR analyses of the causal effect of DMFS and periodontitis on osteoporosis. SVMR, single-variable Mendelian randomization; MVMR, multivariable Mendelian randomization; IVW, inverse variance weighted; OR, odds ratio; PD, periodontitis; DMFS, the sum of decayed, missing, and filled tooth surfaces

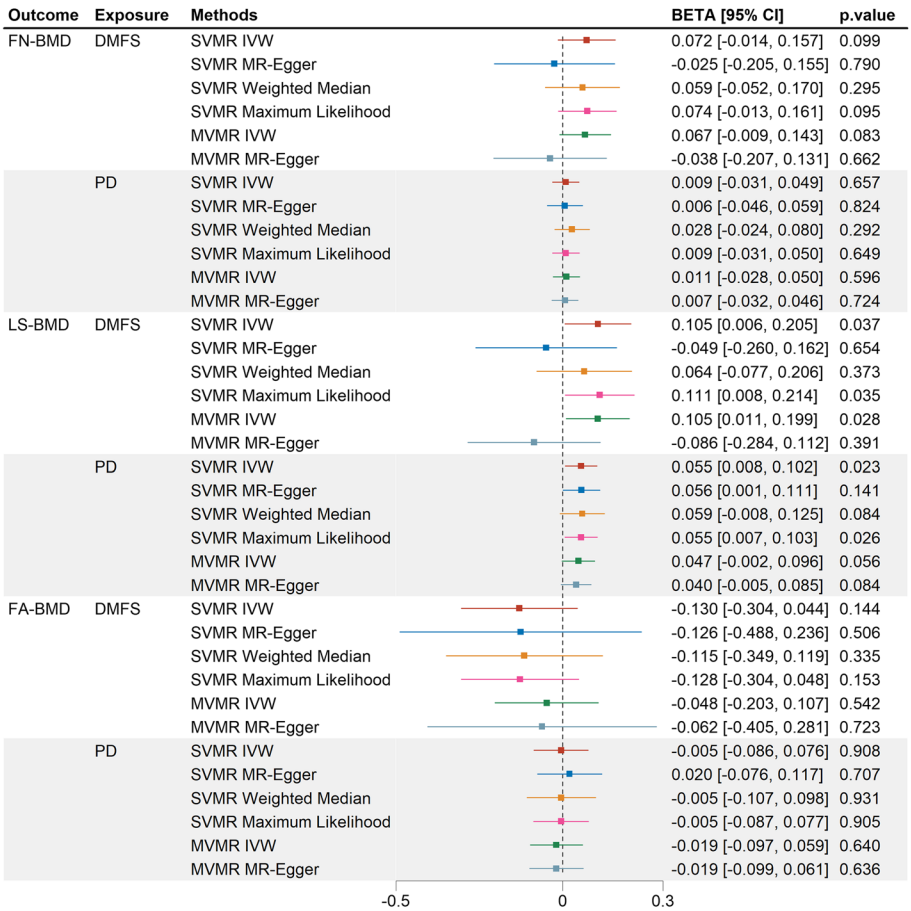

Fig. 3 Different methods for MR analyses of the causal effect of DMFS and periodontitis on BMD. SVMR, single-variable Mendelian randomization; MVMR, multivariable Mendelian randomization; IVW, inverse variance weighted; PD, periodontitis; DMFS, the sum of decayed, missing, and filled tooth surfaces; BMD, estimated bone mineral density; FN-BMD, femoral neck bone mineral density; LS-BMD, lumbar spine bone mineral density; FA-BMD, forearm bone mineral density

Causal effects of oral diseases on fractures

According to IVW analyses in SVMR (Fig. 4), oral diseases showed no MR association with postmenopausal osteoporosis with pathological fracture, osteoporosis with pathological fracture, fracture of forearm, fracture of femur, fracture of lumbar spine and pelvis. These results were all confirmed by the weighted median analysis and MR-Egger analysis and the Maximum Likelihood method.

In MVMR, after adjusting for periodontitis, DMFS was significantly associated with an increased risk of postmenopausal osteoporosis with pathological fracture (OR = 1.422, [95% CI 1.027 to 1.969], $P = 0.034$, moderate evidence), suggesting that one standard deviation increase in DMFS is associated with a 42.2% higher risk of postmenopausal osteoporosis with pathological fracture.

Evaluation of assumptions and sensitivity analyses

DMFS and PD had no directional horizontal pleiotropy on osteoporosis, BMD or fractures, according to the results of the MR-Egger regression, in which the intercept term has a statistical difference with zero. The scatter plots for each outcome were shown in Supplementary Figure S1 and S2. There was no heterogeneity between the individual SNP according to the heterogeneity test (Table 2 and Supplementary Table 2).

Leave-one-out analysis indicated that the causal estimates of DMFS and PD were not driven by any single SNP. The leave-one-out analysis plots were shown in Supplementary Figure S3 and S4.

As shown in Supplementary Table 3 and 4, the MR-RAPS and Debiased IVW methods yielded similar results, supporting consistent causal effects of DMFS on osteoporosis (OR = 1.171, [95% CI 1.051 to 1.304], $P = 0.004$, strong evidence) and postmenopausal

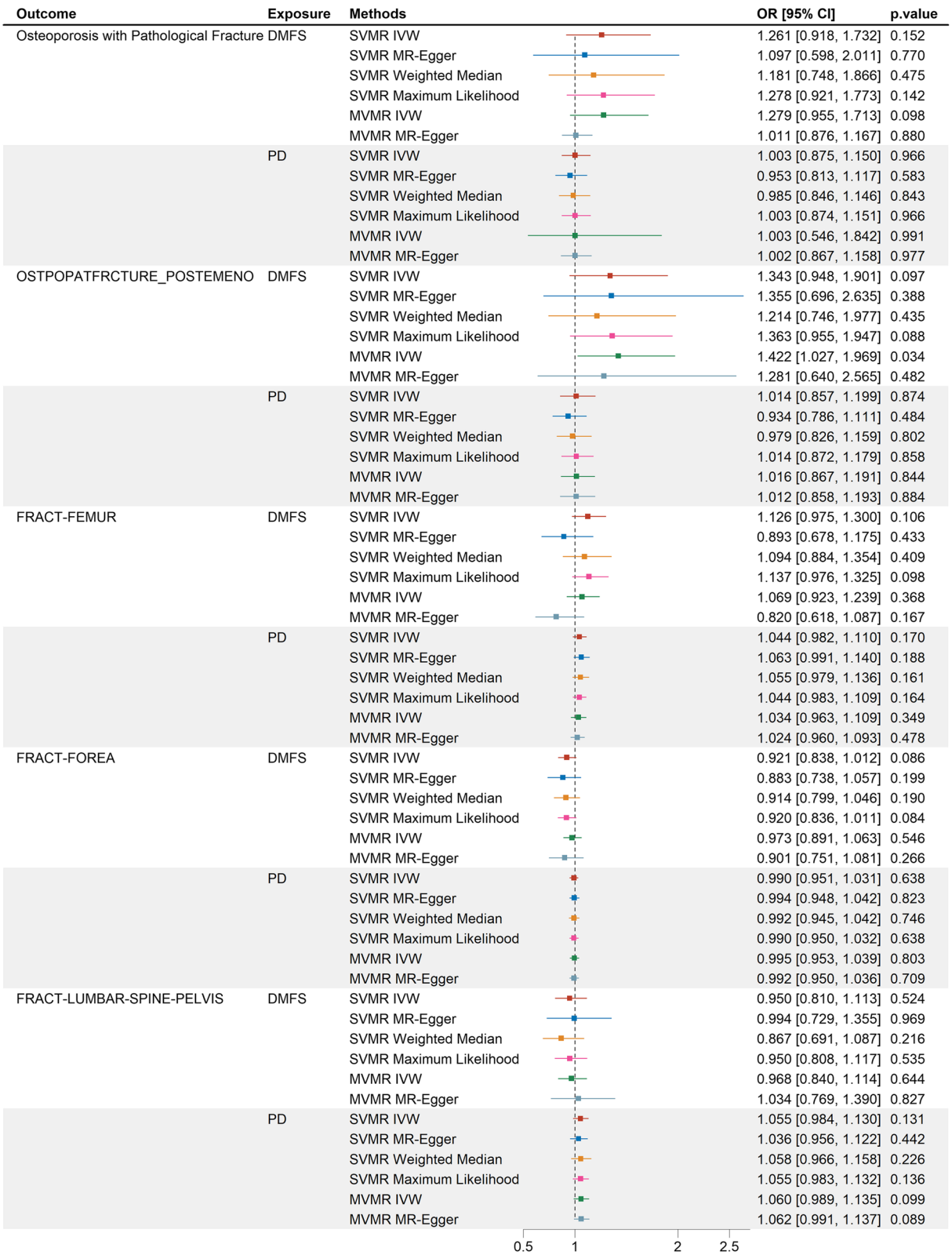

Fig. 4 Different methods for MR analyses of the causal effect of DMFS and periodontitis on fractures. SVMR, single-variable Mendelian randomization; MVMR, multivariable Mendelian randomization; IVW, inverse variance weighted; OR, odds ratio; PD, periodontitis; DMFS, the sum of decayed, missing, and filled tooth surfaces; OSTPOPATFRCTURE_POSTEMENO, postmenopausal osteoporosis with pathological fracture; FRACT-FEMUR, fracture of femur; FRACT-FOREA, fracture of forearm; FRACT-LUMBA, fracture of lumbar spine

Table 2 Sensitivity analysis of the causal association between oral diseases and osteoporosis and related fractures in MVMR analysis

Exposure	Outcome	Cochran's Q test		MR-Egger		MR-PRESSO Global Test
		Q value	*P* value	Intercept	*P* value	*P* value
DMFS and PD in MVMR analysis	Osteoporosis	14.639	0.745	−0.011	0.259	0.929
	FN-BMD	7.286	0.980	0.007	0.172	0.911
	LS-BMD	12.787	0.750	0.014	0.034	0.693
	FA-BMD	11.715	0.817	0.001	0.930	0.604
	Osteoporosis with Pathological Fracture	19.397	0.432	0.018	0.372	0.669
	OSTPOPATFRCTURE_POSTEMENO	19.692	0.413	0.008	0.737	0.723
	FRACT-FEMUR	21.138	0.329	0.020	0.035	0.292
	FRACT-FOREA	21.404	0.314	0.006	0.348	0.528
	FRACT-LUMBAR-SPINE-PELVIS	11.587	0.903	−0.005	0.616	0.939

MVMR multivariable Mendelian randomization, *PD* Periodontitis, *DMFS* the sum of Decayed, Missing, and Filled tooth Surfaces, *FN-BMD* femoral neck bone mineral density, *LS-BMD* lumbar spine bone mineral density, *FA-BMD* forearm bone mineral density, *OSTPOPATFRCTURE_POSTEMENO* Postmenopausal osteoporosis with pathological fracture, *FRACT-FEMUR* fracture of femur, *FRACT-FOREA* fracture of forearm, *FRACT-LUMBAR-SPINE-PELVIS* fracture of lumbar spine and pelvis

Significance level at $P < 0.05$

osteoporosis with pathological fracture (OR = 1.401, [95% CI 1.040 to 1.887], $P = 0.027$, moderate evidence).

Discussion

This was the first study to examine whether genetically predicted oral diseases are causally associated with osteoporosis, BMD or fractures at different skeletal sites by applying a MR approach. We found the casual effect between DMFS and increased risk of osteoporosis, as well as postmenopausal osteoporosis with pathological fracture. No causal association was seen between periodontitis and other outcomes.

Over the past 30 years, the global distribution and burden of untreated dental caries in both primary and permanent teeth have remained relatively stable, remaining the most common health condition globally [2]. Thus, more attention should be focused on the potential impacts of oral diseases on bone loss. Recent studies have revealed oral health was associated with bone mineral density disorders (osteoporosis and decreased bone mineral density) [12]. Ito et al. also detected poor oral health status is a risk factor for the incidence of fractures in community-dwelling older Japanese individuals [38]. Recent animal model studies have demonstrated biologically plausible mechanisms whereby oral diseases may increase susceptibility to bone loss [17, 39]. One possible reason was that oral diseases can expand an osteoclast precursors (OCPs) population in the bone marrow by inducing systemic IL-6 [40]. Then the OCPs can traffic to bone for site-specific resorption by boosting osteoclastogenesis in response to locally produced RANKL [41]. Another possible reason may be that bacteria and their products (for example, lipopolysaccharide (LPS) or gingivalis) can elevated hematopoietic tissue activity and trained immunity in the bone marrow [42]. The recruitment of trained/hyper-reactive myeloid cells to bone can lead to inflammatory bone loss [43].

As two of the most prevalent and consequential oral diseases globally, periodontitis and its association with osteoporosis have been more extensively studied than dental caries [44]. In one cross-sectional study involving 125,324 participants, periodontitis was found to be significant associated with osteoporosis in a multiple logistic regression analysis (OR: 2.16, 95% CI: 2.01–2.31, $P < 0.001$). While the OR of periodontitis for fracture was 1.54 (95% CI 1.46–1.62; $P < 0.001$) [45]. Additionally, periodontitis who underwent regular dental care was associated with lower risk of osteoporosis than that without regular check-ups [46]. However, we found no causal effects of periodontitis on OP related outcomes in MR analysis. One possible explanation for this discrepancy is that observational studies may conflate reverse causation (e.g., osteoporosis amplifying the alveolar bone loss and periodontitis) and residual confounding (e.g., smoking, Vitamin D deficiency) [15]. Additionally, the biological pathways linking periodontal disease and osteoporosis may be more complex or indirect, such as enhanced cytokine production and elevated inflammatory response [15]. These factors complicate experimental research and may obscure any direct causal relationship. Moreover, there was also insufficient evidence to suggest whether dental caries influence osteoporosis, fractures, and decreased bone mineral density. Our study was the first to focus on the causal relationship between dental caries and bone loss. A potential

mechanism underlying this association could be the oral dysbiosis. Dysbiotic microbiota in gut can lead to bone loss by increased migration of TNF-expressing Th17 cells from the gut to the bone marrow [47]. Similar to the gut, the oral cavity, as the foremost segment of the digestive tract, harbored a complex microbial ecosystem that can influence the pathogenesis of various systemic diseases [17]. Dental caries caused by dysbiosis can also cause the expansion of resident memory T helper 17 (TH17) cells [48]. The further migration of TH17 cells might be one of the causes of osteoporosis.

Although some studies have indicated an association between the number of missing natural teeth and an increased risk of hip fractures as well as reduced bone mineral density, it was important to note that both dental caries and periodontitis can lead to tooth loss [3]. These two chronic and complex oral diseases shared common risk factors and social determinants, which may explain their frequent co-occurrence in the same individual [49]. Previous observational studies have predominantly focused on periodontitis, potentially overlooking maybe the true underlying factor contributing to osteoporosis, BMD and fractures: dental caries. Our study, by employing a multivariable Mendelian Randomization (MR) approach, provided deeper insights into the respective effects of dental caries and periodontitis on BMD disorders. Notably, the findings revealed that, compared to periodontitis, dental caries causally increased the risk of osteoporosis, and are more likely to be the true cause of this condition. This suggested that oral health assessments could serve as an effective early screening tool for identifying individuals at risk of osteoporosis, particularly in older adults.

The study has several strengths. The peak prevalence of dental caries was observed in younger age groups, while osteoporosis was more prevalent in older individuals [2]. Hence, establishing a real-world cohort to clarify the causal relationship between these two diseases has been challenging. Mendelian randomization (MR) offers a reliable method for assessing the causality of modifiable exposures on the trait of interest, in contrast to traditional observational studies. Additionally, sensitivity analyses and outlier assessments considering different pleiotropy patterns strengthen the robustness of analytical results, thereby improving the scientific validity and reliability of our conclusions.

There are also several limitations in our study. First, the periodontitis GWAS data were derived from 7 studies using difference diagnostic criteria, which may introduce pleiotropy and weak instrument bias. The relatively small sample size of the periodontitis GWAS data limits statistical power and may result in false negatives. Second, there may be overlap in participants between the exposure and outcome studies, but it is difficult to estimate the degree of sample overlap in this study. To avoid this, GWAS data from different Consortiums and powerful instruments (e.g., F statistic much greater than 10) were used in this study to minimize potential bias [50]. Nonetheless, weak instrument bias due to unmeasured confounders remains a possibility, and the proportion of variance explained by the genetic instruments for periodontitis was relatively small (0.298%). So, we further implemented bias correction methods including Debiased IVW and MR-RAPS, most of which produced concordant results. Dental caries (DMFS) even demonstrated a more robust causal effect on the increased risk of osteoporosis. Third, the result indicated possible genetic correlations and causal associations between DMFS and increased LS-BMD at the genetic level. However, further mechanistic studies are needed to further confirm whether these associations reflect underlying biological mechanisms. Forth, using a relaxed selection threshold ($P < 5 \times 10^{-6}$) to retain more instrumental variables inherently elevates risks of weak instrument bias and horizontal pleiotropy. Finally, dental caries and osteoporosis are influenced by shared factors and exhibit overlapping pathophysiological pathways. To clarify the mechanistic roles of these shared factors—whether they act as mediators or confounders-targeted mediation analyses using Mendelian randomization are essential. However, the use of multiple methods based on different assumptions may increase the possibility of getting inconsistent or contrary results and make the conclusion become obscured. It is warranted that longitudinal follow-up cohort studies and clinical trials with a larger sample size should be carried out to complement the outcomes of the MR study and to examine sex-specific and age-related genetic interactions.

Conclusions

In conclusion, dental caries causally increases the risk of OP and postmenopausal OP with pathological fracture, suggesting the existence of teeth-bone axis. Proactive osteoporosis screening in patients with severe dental caries may be warranted for clinical consideration.

Abbreviations

SVMR	Single-variable Mendelian randomization
MVMR	Multivariable Mendelian randomization
IVW	Inverse variance weighted
SNP	Single-nucleotide polymorphism
PD	Periodontitis
DMFS	The sum of Decayed, Missing, and Filled tooth Surfaces
OP	Osteoporosis
BMD	Bone mineral density

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-025-05735-7.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Acknowledgements
The authors acknowledge the GLIDE Consortium for sharing the GWAS and thank the investigators of sharing the GWAS meta-analysis data. We also would like to acknowledge the participants and investigators of the FinnGen study.

Authors' contributions
Writing the first draft of the manuscript: G.Z. and Y.Z.; Statistical analysis, data curation: G.Z. and J.Z.; Writing review and editing: M.Z. and J.Z.; Investigation, statistical analysis, and editing: Y.L., Y.G. and W.W.; Critically reviewing, editing, and partial funding: L.Z. and M.X.; Conceptualization, designed the study, supervised, editing, and reviewed, revised the manuscript, and funding: L.H. All authors reviewed the manuscript.

Funding
This study was supported by the National Key Research and Development Program of China (No. 2022YFB4703500).

Data availability
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Rehabilitation, Chinese PLA General Hospital, No.28 Fuxing Road, Haidian District, Beijing 100853, People's Republic of China. [2]School of Sport Medicine and Rehabilitation, Beijing Sport University, Beijing, China. [3]Department of Orthopedics, Chinese PLA General Hospital, No.28 Fuxing Road, Haidian District, Beijing 100853, People's Republic of China. [4]Department of Graduate School, Tianjin Medical University, Tianjin, China.

Received: 12 December 2024 Accepted: 28 February 2025
Published online: 05 March 2025

References

1. Richards D. Review finds that severe periodontitis affects 11% of the world population. Evid Based Dent. 2014;15:70–1. https://doi.org/10.1038/sj.ebd.6401037.
2. Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, Vos T, Murray CJL, Marcenes W. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990–2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. J Dent Res. 2017;96:380–7. https://doi.org/10.1177/0022034517693566.
3. Peres MA, Macpherson LMD, Weyant RJ, et al. Oral diseases: a global public health challenge. Lancet. 2019;394:249–60. https://doi.org/10.1016/s0140-6736(19)31146-8.
4. Botelho J, Mascarenhas P, Viana J, Proença L, Orlandi M, Leira Y, Chambrone L, Mendes JJ, Machado V. An umbrella review of the evidence linking oral health and systemic noncommunicable diseases. Nat Commun. 2022;13:7614. https://doi.org/10.1038/s41467-022-35337-8.
5. Nakamura T, Zou K, Shibuya Y, Michikawa M. Oral dysfunctions and cognitive impairment/dementia. J Neurosci Res. 2021;99:518–28. https://doi.org/10.1002/jnr.24745.
6. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015;15:30–44. https://doi.org/10.1038/nri3785.
7. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone. 2008;42:467–75. https://doi.org/10.1016/j.bone.2007.11.001.
8. Curtis EM, van der Velde R, Moon RJ, van den Bergh JP, Geusens P, de Vries F, van Staa TP, Cooper C, Harvey NC. Epidemiology of fractures in the United Kingdom 1988–2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone. 2016;87:19–26. https://doi.org/10.1016/j.bone.2016.03.006.
9. Reddy MS. Morgan SL (2013) Decreased bone mineral density and periodontal management. Periodontol. 2000;61:195–218. https://doi.org/10.1111/j.1600-0757.2011.00400.x.
10. Brennan-Calanan RM, Genco RJ, Wilding GE, Hovey KM, Trevisan M, Wactawski-Wende J. Osteoporosis and oral infection: independent risk factors for oral bone loss. J Dent Res. 2008;87:323–7. https://doi.org/10.1177/154405910808700403.
11. Geurs NC, Lewis CE, Jeffcoat MK. Osteoporosis and periodontal disease progression. Periodontol. 2003;2000(32):105–10. https://doi.org/10.1046/j.0906-6713.2003.03208.x.
12. Dibello V, Lobbezoo F, Solfrizzi V, et al. Oral health indicators and bone mineral density disorders in older age: A systematic review. Ageing Res Rev. 2024;100: 102412. https://doi.org/10.1016/j.arr.2024.102412.
13. Zhou YS, Song JK, Zheng ZJ, Li SY, Liu JG, Peng JX. Heel bone mineral density and various oral diseases: a bidirectional Mendelian randomization. J Bone Miner Metab. 2023;41:673–81. https://doi.org/10.1007/s00774-023-01443-w.
14. Zhang ZY, Xie MR, Liu Y, Li YX, Wu K, Ding YM. Effect of Periodontal Pathogens on Total Bone Volume Fraction: A Phenotypic Study. Curr Med Sci. 2020;40:753–60. https://doi.org/10.1007/s11596-020-2243-8.
15. Yu B. Wang CY (2022) Osteoporosis and periodontal diseases - An update on their association and mechanistic links. Periodontol. 2000;89:99–113. https://doi.org/10.1111/prd.12422.
16. Yuan Y, Yang J, Zhuge A, Li L, Ni S. Gut microbiota modulates osteoclast glutathione synthesis and mitochondrial biogenesis in mice subjected to ovariectomy. Cell Prolif. 2022;55: e13194. https://doi.org/10.1111/cpr.13194.
17. Wang N, Zheng L, Qian J, Wang M, Li L, Huang Y, Zhang Q, Li Y, Yan F. Salivary microbiota of periodontitis aggravates bone loss in ovariectomized rats. Front Cell Infect Microbiol. 2022;12: 983608. https://doi.org/10.3389/fcimb.2022.983608.
18. Albandar JM, Susin C, Hughes FJ. Manifestations of systemic diseases and conditions that affect the periodontal attachment apparatus: Case definitions and diagnostic considerations. J Clin Periodontol. 2018;45(Suppl 20):S171-s189. https://doi.org/10.1111/jcpe.12947.
19. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. Wellcome Open Res. 2019;4:186. https://doi.org/10.12688/wellcomeopenres.15555.2.
20. Richmond RC, Davey Smith G. Mendelian Randomization: Concepts and Scope. Cold Spring Harb Perspect Med. 2022;12. https://doi.org/10.1101/cshperspect.a040501.
21. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA. 2021;326:1614–21. https://doi.org/10.1001/jama.2021.18236.
22. Shungin D, Haworth S, Divaris K, et al. Genome-wide analysis of dental caries and periodontitis combining clinical and self-reported data. Nat Commun. 2019;10:2773. https://doi.org/10.1038/s41467-019-10630-1.

23. Page RC, Eke PI. Case Definitions for Use in Population-Based Surveillance of Periodontitis. J Periodontol. 2007;78:1387–99. https://doi.org/10.1902/jop.2007.060264.
24. Finucane HK, Bulik-Sullivan B, Gusev A, et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. Nat Genet. 2015;47:1228–35. https://doi.org/10.1038/ng.3404.
25. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613:508–18. https://doi.org/10.1038/s41586-022-05473-8.
26. Morris JA, Kemp JP, Youlten SE, et al. An atlas of genetic influences on osteoporosis in humans and mice. Nat Genet. 2019;51:258–66. https://doi.org/10.1038/s41588-018-0302-x.
27. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002;359:1761–7. https://doi.org/10.1016/s0140-6736(02)08657-9.
28. Genomes Project C, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. A map of human genome variation from population-scale sequencing. Nature. 2010;467:1061–73. https://doi.org/10.1038/nature09534.
29. Burgess S, Thompson SG, Collaboration CCG. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011;40:755–64. https://doi.org/10.1093/ije/dyr036.
30. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011;40:755–64. https://doi.org/10.1093/ije/dyr036.
31. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37:658–65. https://doi.org/10.1002/gepi.21758.
32. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44:512–25. https://doi.org/10.1093/ije/dyv080.
33. Muff S, Nilsen EB, O'Hara RB, Nater CR. Rewriting results sections in the language of evidence. Trends Ecol Evol. 2022;37:203–10. https://doi.org/10.1016/j.tree.2021.10.009.
34. Boehm FJ, Zhou X. Statistical methods for Mendelian randomization in genome-wide association studies: A review. Comput Struct Biotechnol J. 2022;20:2338–51. https://doi.org/10.1016/j.csbj.2022.05.015.
35. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. Stat Med. 2017;36:1783–802. https://doi.org/10.1002/sim.7221.
36. Bowden J, Del Greco MF, Minelli C, Zhao Q, Lawlor DA, Sheehan NA, Thompson J, Davey Smith G. Improving the accuracy of two-sample summary-data Mendelian randomization: moving beyond the NOME assumption. Int J Epidemiol. 2019;48:728–42. https://doi.org/10.1093/ije/dyy258.
37. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum Mol Genet. 2018;27:R195–208. https://doi.org/10.1093/hmg/ddy163.
38. Ito W, Komiyama T, Ohi T, Hiratsuka T, Matsuyama S, Sone T, Tsuji I, Watanabe M, Hattori Y. Relationship Between Oral Health and Fractures in Community-Dwelling Older Japanese Adults. J Am Med Dir Assoc. 2021;22:1184-1189.e1181. https://doi.org/10.1016/j.jamda.2021.01.058.
39. Anbinder AL, Moraes RM, Lima GMG, Oliveira FE, Campos DRC, Rossoni RD, Oliveira LD, Junqueira JC, Ma Y, Elefteriou F. Periodontal disease exacerbates systemic ovariectomy-induced bone loss in mice. Bone. 2016;83:241–7. https://doi.org/10.1016/j.bone.2015.11.014.
40. Zhao Y, Li Z, Su L, Ballesteros-Tato A, Katz J, Michalek SM, Feng X, Zhang P. Frontline Science: Characterization and regulation of osteoclast precursors following chronic Porphyromonas gingivalis infection. J Leukoc Biol. 2020;108:1037–50. https://doi.org/10.1002/jlb.1hi0620-230r.
41. Herrera BS, Bastos AS, Coimbra LS, Teixeira SA, Rossa C Jr, Van Dyke TE, Muscara MN, Spolidorio LC. Peripheral blood mononuclear phagocytes from patients with chronic periodontitis are primed for osteoclast formation. J Periodontol. 2014;85:e72-81. https://doi.org/10.1902/jop.2013.130280.
42. Ling MR, Chapple IL, Matthews JB. Peripheral blood neutrophil cytokine hyper-reactivity in chronic periodontitis. Innate Immun. 2015;21:714–25. https://doi.org/10.1177/1753425915589387.
43. Jacome-Galarza CE, Percin GI, Muller JT. Developmental origin, functional maintenance and genetic rescue of osteoclasts. Nature. 2019;568(7753):541–5.
44. Wang CJ, McCauley LK. Osteoporosis and Periodontitis. Curr Osteoporos Rep. 2016;14:284–91. https://doi.org/10.1007/s11914-016-0330-3.
45. Hong SJ, Yang BE, Yoo DM, Kim SJ, Choi HG, Byun SH. Analysis of the relationship between periodontitis and osteoporosis/fractures: a cross-sectional study. BMC Oral Health. 2021;21:125. https://doi.org/10.1186/s12903-021-01496-1.
46. Huang Y-F, Chang C-T, Liu S-P, Muo C-H, Tsai C-H, Hong H-H, Shen Y-F, Wu C-Z. The Impact of Oral Hygiene Maintenance on the Association Between Periodontitis and Osteoporosis. Medicine. 2016;95. https://doi.org/10.1097/md.0000000000002348.
47. Lorenzo J. From the gut to bone: connecting the gut microbiota with Th17 T lymphocytes and postmenopausal osteoporosis. J Clin Invest. 2021;131. https://doi.org/10.1172/jci146619.
48. Dutzan N, Kajikawa T, Abusleme L, et al. A dysbiotic microbiome triggers T(H)17 cells to mediate oral mucosal immunopathology in mice and humans. Sci Transl Med. 2018;10. https://doi.org/10.1126/scitranslmed.aat0797.
49. Jepsen S, Blanco J, Buchalla W, et al. Prevention and control of dental caries and periodontal diseases at individual and population level: consensus report of group 3 of joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. J Clin Periodontol. 2017;44(Suppl 18):S85-s93. https://doi.org/10.1111/jcpe.12687.
50. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol. 2013;178:1177–84. https://doi.org/10.1093/aje/kwt084.

Publisher's Note