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ORIGINAL ARTICLE

The causal effect of life course adiposity on periodontitis: A Mendelian randomization study

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Abstract

Background: To establish whether life course adiposity, including birth weight (BW), childhood and adulthood body mass index (BMI), waist–hip ratio (WHR), and body fat percentage (BF%), has a causal influence on periodontitis.

Methods: We used single-nucleotide polymorphisms with significant associations with life course adiposity as instrumental variables. We examined their association with periodontitis risk in a genome-wide association study involving periodontitis cases (n = 17,353) and healthy controls (n = 28,210) using a two-sample Mendelian randomization (MR) strategy. The association of life course adiposity with periodontitis risk was estimated with inverse-variance weighting with random effects. We performed sensitivity analyses using MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO), weighted median, and MR-Egger methods. We calculated the odds ratios (ORs) for one standard deviation (SD) increase per risk factor to estimate the effect on the risk of periodontitis.

Results: After correction for multiple testing, there was an association between each SD increase in gene-predicted adulthood BMI with a higher periodontitis risk (OR = 1.15, 95% confidence interval [CI]: 1.06–1.23, $p = 3.1 \times 10^{-4}$), with a similar influence for BF% on periodontitis risk (OR = 1.29, 95% CI: 1.12–1.49, $p = 3.3 \times 10^{-4}$). No causal association was detected for gene-predicted BW, childhood BMI, or WHR with periodontitis risk.

Conclusion: We present new proof supporting a causal function of greater adiposity, especially high BMI and BF%, being associated with higher periodontitis risk. We recommend that future studies focus on periodontitis from a life course perspective.

KEYWORDS
adiposity, Mendelian randomization, periodontitis

Wenjing Li and Ying He contributed equally to this work.

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1 | INTRODUCTION

Periodontitis is a protracted inflammatory disease caused by bacteria; it has an effect on the tooth-supporting and surrounding structures.[1] It is one of the most widespread and consequential oral diseases, imposes severe economic and health burdens, and dramatically diminishes life quality.[2] Although periodontitis does not directly lead to death, most of the top 10 global leading causes of death, such as heart disease, diabetes, and preterm birth, are closely associated with periodontitis.[3,4] To date, observational studies have established that obesity is associated with periodontitis.[5] However, observational studies tend toward bias, confounding, and reverse causality, and the causal influence obesity has on periodontitis is unclear. Clarifying this causal association is vital, as adiposity has arisen as a worldwide health issue.[6]

Mendelian randomization (MR) has become an extensively applied genetic epidemiology method in recent years. It exploits genetic variants termed instrumental variables (IVs) or proxy indicators to determine if the putative risk factor and the disease have a causal association.[7–9] The advantage of MR is that it can overcome the issues of bias, confounding, and reverse causality in standard observational studies. A previous study that utilized the MR methodology failed to find evidence of a causal relationship between body mass index (BMI) and periodontitis.[10] However, the genetic instrument used in the study included few genetic markers, whereas a stronger genetic instrument based on a larger number of markers will yield better power and avoid weak-instrument bias. Since the most updated genome-wide association study (GWAS) data for BMI have been released,[11] with a much larger number of markers, it enables us to conduct a new analysis with the advantages of sufficient power and updated methods.

Furthermore, adiposity changes throughout a person's life course. Many studies have examined its relationship with disease from a life course perspective.[12] As a chronic inflammatory disease, periodontitis is more likely to be affected by adiposity throughout life. In addition to adiposity in adulthood,[5] childhood and adolescent obesity have also been associated with periodontitis risk,[13] suggesting that adiposity in early life might play a critical role in the pathogenesis of periodontitis. However, there was no sufficient evidence for the association of early-life adiposity with periodontitis risk. Apart from that, adiposity is a complex trait. Although BMI is widely used as a marker of obesity, it ignores crucial health determinants such as muscle mass and distribution of adiposity and, therefore, could not give us a complete picture of a person's health risk. Other anthropometric indices of adiposity, such as body fat percentage (BF%) and waist–hip ratio (WHR), which represent the level of total fat and abdominal visceral adipose tissues, should also be evaluated for their relationship with periodontitis.

Therefore, we aimed to examine whether adiposity development at different stages of life has a causal influence on periodontitis risk and to determine the degree to which different measures of obesity affect the risk of periodontitis in an MR framework.

2 | MATERIAL AND METHODS

2.1 | Selection of genetic instruments and data sources

We identified the genetic variants used as IVs from the largest GWASs available to date or from recent meta-analyses. The analyses were restricted to single-nucleotide polymorphisms (SNPs) with genome-wide significance ($p < 5 \times 10^{-8}$) in individuals of European ancestry to fulfill the first MR assumption (Figure 1). We excluded the correlating SNPs based on linkage disequilibrium measures ($r^2 < 0.01$). Birth weight (BW) instruments were identified from the meta-GWAS, which involved 321,223 individuals (~92.8% of European ancestry), using UK Biobank and Early Growth Genetics (EGG) consortium data.[14] Instruments for childhood BMI were identified from the EGG consortium, which involved 20 studies in the discovery stage (n = 35,668 children) and 13 studies in the replication stage (n = 11,873 children).[15] The instruments for WHR adjusted for BMI and for BMI were developed from GWAS meta-analyses, combined UK Biobank and Genetic Investigation of Anthropometric Traits (GIANT) consortium data, and involved an estimated 700,000 European ancestry participants.[11,16] The BF% instruments were obtained from GWAS data from UK Biobank, which involved 454,633 European descent participants.[17,18] Additionally, to ensure comparable outcome data (periodontitis) and the exposure data (life course adiposity), the effect of the SNPs was harmonized to the same effect allele in both datasets. We checked and corrected palindromic SNPs via the frequency of the effect allele. If the minor allele frequency of an SNP was >0.42, it would be replaced by the non-palindromic proxy SNP ($r^2 = 1$) to prevent strand direction ambiguity.[19]

For periodontitis, we used GWAS summary statistics from the consortium of Gene-Lifestyle Interactions in Dental Endpoints (GLIDE), which involved clinically confirmed periodontitis cases (n = 17,353) and controls (n = 28,210) of European ancestry.[20] For each life course adiposity-associated SNP, we obtained the summary-level data for either the same or a proxy SNP in elevated linkage disequilibrium ($r^2 > 0.8$) from the datasets.

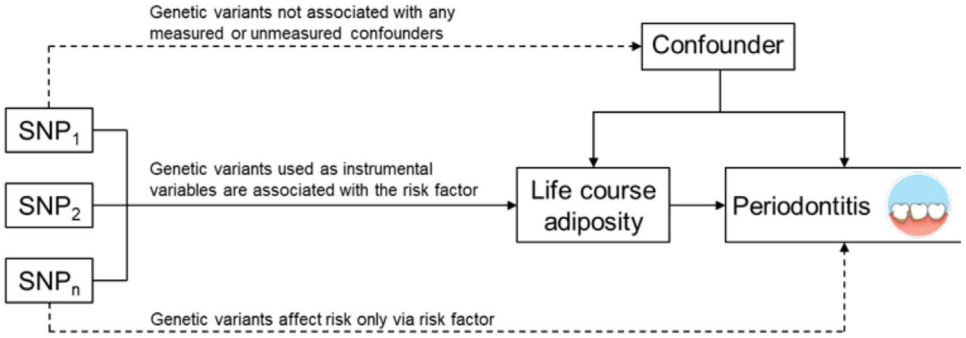

FIGURE 1 Principles of Mendelian randomization and assumptions that need to be satisfied to derive unbiased causal effect estimates. SNP, single-nucleotide polymorphism

2.2 | Statistical analysis

We investigated the causal influence of life course adiposity on periodontitis risk via several MR approaches. We performed the principal analyses utilizing inverse-variance weighted (IVW) meta-analysis under a random-effects model, which combined the estimated IV ratios across the exposure-associated SNPs.[21] The IVW method yields a consistently robust causal effect and evaluates when each genetic variant satisfies the assumptions of an IV. We also used three additional MR models as sensitivity analyses to assess the degree to which directional pleiotropy could prejudice the MR causal estimates. In the first sensitivity analysis, we applied the MR-Egger method, which depends on the Instrument Strength Independent of Direct Effect (InSIDE) supposition. Using the MR-Egger method, the SNP's effect on the adipose-related trait is plotted against its impact on periodontitis; an intercept dissimilar from the origin yields proof of pleiotropic results. The method produces equitable estimates even if all selected SNPs are invalid.[22] The second sensitivity analysis involved the median-based process, which yields a valid estimate if valid IVs constitute at least half of the genetic variants.[23] The simple and weighted median estimates are identical when all the weights are equivalent. In the last sensitivity analysis, the potential outlier SNPs ($p < 0.05$) were excluded from the IVs, and the effect estimate for the relevant risk factor of concern was reassessed with the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method.[24] Furthermore, to evaluate whether the MR estimate was propelled by one SNP, we conducted a leave-one-out analysis, where one SNP at a time was sequentially omitted to detect heterogeneous outcomes.

In addition, to separate the independent effects of childhood and adult adiposity on periodontitis risk, a multivariable MR analysis was employed. Multivariable MR is an extension of univariable MR that uses multiple genetic variants associated with multiple exposures to estimate the direct causal effect of each risk factor on an outcome.[25] Multivariable MR using the IVW method was conducted to fit BW, childhood BMI, and adult BMI as simultaneous risk factors for periodontitis. This enabled the estimation of the "direct" effect of early-life adiposity on periodontitis after accounting for adult BMI or vice versa.

The results are reported as odds ratios (ORs) and their 95% confidence intervals (CIs), which yielded a relative risk estimate of periodontitis produced by each standard deviation (SD) rise in each adiposity-associated trait presented in this study. A Bonferroni-corrected threshold of $p < 0.01$ ($p = 0.05/5$, reflecting the testing of five adiposity measures) was used to explain multiple comparisons. Associations with p-values between 0.01 and 0.05 were considered indicative proof of association. All statistical analyses were performed using R v4.0.0 and the TwoSampleMR package.[26] We estimated statistical power according to the method proposed by Brion et al.[27] and present it in Table S1 in the Supporting Information (see Table S1 in the online *Journal of Periodontology*).

3 | RESULTS

Table 1 details the mean and SD of each potential risk factor, the share of variance clarified by the IVs (BW, BF%, childhood and adulthood BMI, WHR), and the SNP numbers constituting the IVs per exposure. In total, the following number of independent SNPs were associated with life course adiposity measures: 134 for BW, 14 for childhood BMI, 653 for adult BMI, 316 for WHR, and 387 for BF%. Table S2 in the Supporting Information presents the summary statistics data for the SNP–life course adiposity and SNP–periodontitis associations (see Table S2 in the online *Journal of Periodontology*).

Here, we used the IVW method as the main method of testing the causal effect. We found an association between a predicted 1-SD increase in BF% with higher periodontitis risk (OR = 1.29, 95% CI: 1.12–1.49, $p = 3.3 \times 10^{-4}$; Figure 2) at the Bonferroni-corrected significance level ($p < 0.01$).

TABLE 1 Description of SNPs employed as instrumental variables for life course adiposity measurements

Exposure	Mean (SD)	Units	*n* SNP	Variance (%)
Birth weight	3396 (470)	g	134	7
Childhood BMI	16.9 (2.6)	kg/m^2	14	2
BMI (UK Biobank)	27.2 (4.7)	kg/m^2	653	6
WHR (UK Biobank)	1.0 (0.1)	cm/cm	316	3.9
Body fat percentage	31.8 (6.6)	%	387	3.5

Abbreviations: BMI, body mass index; SD, standard deviation; SNP, single-nucleotide polymorphism; WHR, waist–hip ratio.

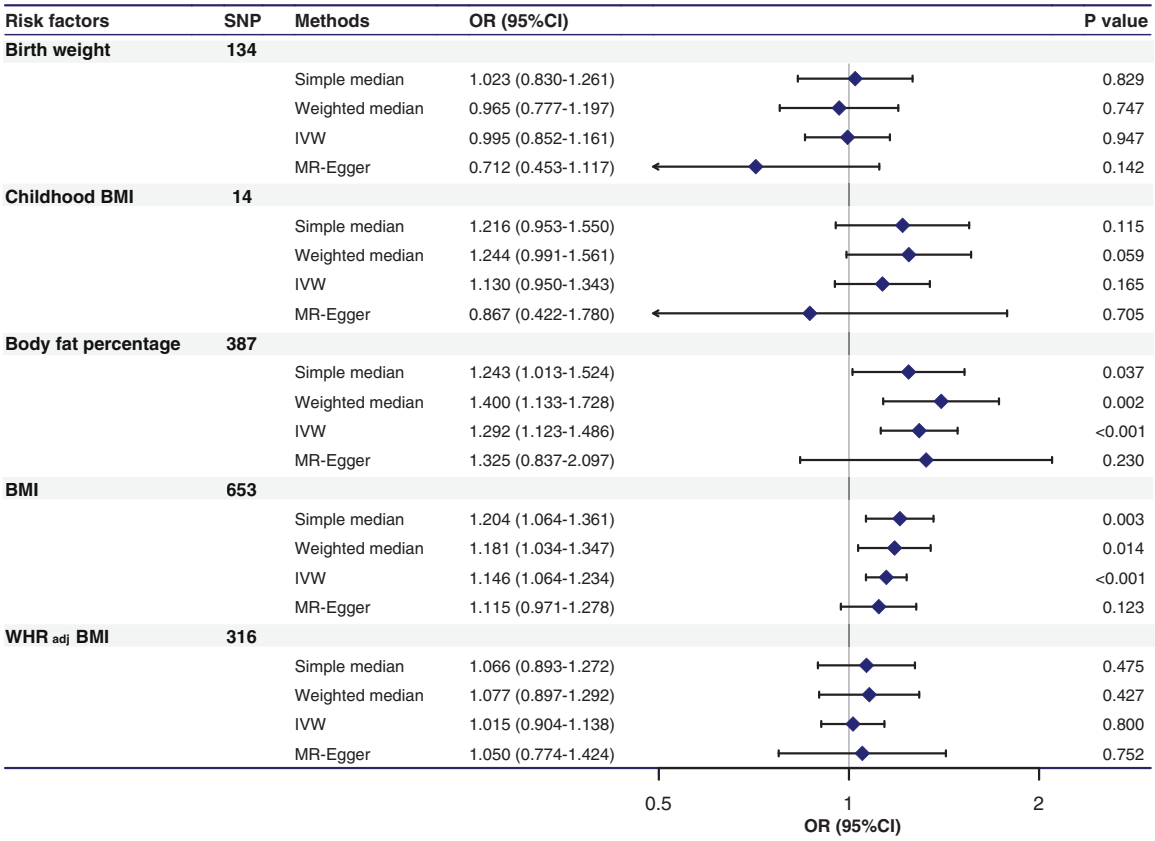

FIGURE 2 Forest plot depicting odds ratio (OR) estimates of periodontitis for the instrumental variables defined by genetic markers of obesity-related risk factors. BMI, body mass index; IVW, inverse-variance weight; MR, Mendelian randomization; SNP, single-nucleotide polymorphism; WHR, waist–hip ratio

We obtained a similar finding when testing the association between adulthood BMI and periodontitis. For periodontitis risk, the OR per gene-predicted 1-SD rise in BMI was 1.15 (95% CI: 1.06–1.23, $p = 3.1 \times 10^{-4}$; Figure 2). However, no causal role was detected for gene-predicted BW (OR = 0.99, 95% CI: 0.85–1.16, $p = 0.947$), childhood BMI (OR = 1.13, 95% CI: 0.95–1.34, $p = 0.165$), or WHR (OR = 1.02, 95% CI: 0.90–1.14, $p = 0.800$) on periodontitis risk. Additionly, we obtained similar results from the simple complementary median-based and weighted median-based MR methods but with lower precision.

Except for BW, there was little evidence of SNP heterogeneity for each life course adiposity instrument (see Table S3 in the online *Journal of Periodontology*). In addition, the MR-Egger regression estimated intercept centered on zero and did not present strong proof for uneven horizontal pleiotropy ($P_{\text{MR-Egger intercept}} > 0.124$). However, MR-PRESSO yielded proof of pleiotropy (global test *p*-value = 0.009) of BW, but no outlier SNPs were identified. The life course adiposity instrument funnel plot suggested a proportional distribution of effect estimates; the leave-one-out histogram did not show that any individual SNP drove the overall association with the risk of periodontitis. Multivariable MR is an approach to determine whether adiposity at different stages throughout the life course influences periodontitis along the same causal pathway or

whether they have independent effects. Using multivariable MR, similar findings were identified, as adulthood BMI directly increased risk of periodontitis (OR = 1.12, 95% CI: 1.01–1.25, $p = 0.034$), while little evidence was found of a direct effect between periodontitis and genetically predicted BW (OR = 1.00, 95% CI: 0.86–1.16, $p = 0.997$) and childhood BMI (OR = 1.02, 95% CI: 0.92–1.12, $p = 0.766$).

4 | DISCUSSION

The present MR analysis confirms the function of higher adulthood BMI in periodontitis etiology and presents new proof for a function of BF%. In contrast, we found little proof for the function of the other life course adiposity risk factors examined in causing periodontitis, that is, BW, childhood BMI, and WHR, adjusted for BMI.

As far as we know, this is the first time that the causal effect of adiposity on periodontitis has been evaluated from a life course perspective. Exploring the impact of such growth trajectories may help guide routine growth monitoring to achieve better dental health benefits. In our study, we determined a positive causal correlation between gene-predicted adulthood BMI and periodontitis. Previous observational studies strongly support our findings.[28,29] The potential mechanisms by which obesity increases periodontitis risk include inflammation, immunodeficiency, the oral microbiota, and hyperglycemia/diabetes.[5] However, a previous MR study using a 3-SNP genetic score (FTO, MC4R, TMEM18) could not provide evidence for a causal link between BMI and periodontitis (OR = 1.01, 95% CI: 0.99–1.03).[30] In contrast, our study used a 653-SNP instrument for adult BMI and reported an OR of 1.15 (95% CI: 1.06–1.23), which suggested a causal effect of BMI on prevalent periodontitis. The genetic instrument used in the previous study included few genetic markers, and owing to this, it is possible that some aspects of BMI that are not captured by the three SNPs might bear stronger relationships with periodontitis. In the current study, we utilized the findings from the latest GWAS,[11] which captured various aspects of the etiology of BMI, and resulted in a higher overall statistical power than the previous smaller MR study. Similarly, a recent MR study using 65 SNPs as IVs demonstrated a weak association between BMI and periodontitis (OR = 1.143, 95% CI: 0.975–1.340, $p = 0.099$), and a positive association between BMI and a combined trait comprising periodontitis and loose teeth (OR = 1.115, 95% CI: 1.064–1.169, $p < 0.001$).[31]

Contrary to expectations, we found no causal relationship between gene-predicted BW and childhood BMI with periodontitis risk. Although observational studies have demonstrated that having a high BMI in early life is associated with an increased risk of periodontitis in later life,[13] our findings imply that previously observed associations are likely a result of a higher BMI persisting into adulthood. This suggests that adiposity in early life does not begin to exert its effect on periodontitis. We speculate that the reason is adulthood obesity might cause systemic inflammatory accumulation, insulin resistance, and metabolic disorders,[5,32] thereby increasing periodontitis risk, while the cumulative effect of BW and childhood obesity is insufficient to influence periodontitis. Therefore, the implication of our findings is that avoiding overnutrition during the critical period of adulthood might attenuate the accelerated development of periodontitis, leading to a lower risk of dental problems in later life.

Our MR results further show that periodontitis risk was associated with genetically predicted BF%. This is consistent with observational study results.[29,33] The causal relationship might be explained by the fact that excessive fat accumulation may increase periodontitis risk through systemic immune inflammation.[5] BF% is considered a better anthropometric index of excess body fatness than BMI. Since they are strongly phenotypically correlated, it is difficult to quantify the true independent effects of different measures of adiposity in observational studies alone. Owing to the benefits of MR to minimize bias from traditional sources, we could explore the causal effects of different measures of adiposity on periodontitis. However, considering the high genetic correlation between BMI and BF%,[34] it is difficult to examine the direct effects of BMI and BF% on periodontitis in the framework of multivariable MR analysis. Further studies are needed to detangle the underlying mechanism and potential mediating pathways. The WHR, which measures visceral fat and central obesity, might be a superior means of measuring obesity to other anthropometric measures, especially in people with atypical body habitus.[35] Observational studies have shown a strong association between WHR and periodontitis risk.[29,33] However, we did not detect a causal role of gene-predicted WHR in periodontitis. Considering the limitations of weak IV bias[36] in the MR study, the association between gene-predicted WHR and periodontitis should be explored with further research.

The strengths of our study include the MR design, following the Mendelian law of "parental allele randomly assigned to offspring," and a natural randomized controlled trial. The most important advantage of MR is that genetic variation can be measured directly and accurately; it is not affected by the external environment, social behavior, and other factors, and it is a long-term and stable exposure factor. In addition, we innovatively explored the effect of adiposity on periodontitis from a life course perspective. The result that gene-predicted adulthood obesity, and not BW or childhood BMI, was causally associated with periodontitis suggests that more attention should be

paid to adult obesity to prevent the occurrence of periodontitis. Furthermore, apart from BMI, we also explored the causal effect of gene-predicted BF% and WHR on periodontitis, which previous MR studies have not examined. The finding on the causality effect of gene-predicted BF% on periodontitis hints that targeted control of BF% might reduce periodontitis risk. Finally, the findings suggest that a beneficial diet is advised as the basis for preventing periodontitis, and energy intake should be confined to that required for maintaining or achieving a healthy weight (i.e., a BMI of 20–25 kg/m^2 and BF% $\leq$ 20% for men and 25% for women).

This study also has its limitations. First, the exposure factors in an MR study are predicted based on genetic IVs; it may not be possible to avoid weak IV bias. In addition, due to the potential association between SNPs and confounders, the association between heredity and exposure might have been overestimated, affecting the causal association between adiposity and periodontitis risk. Third, numerous genetic variants defined every trait in the present study, but it is tremendously challenging to rule out pleiotropy or an alternative direct causal pathway entirely.

5 | CONCLUSION

Our results present new proof supporting a causal effect of increased adiposity, especially high BMI and BF%, on higher periodontitis risk. It yields new recommendations for the precise prevention of periodontitis, where overweight and obese people can aim to lower their periodontitis risk by reducing adulthood BMI and BF%.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design of the study. Wenjing Li and Ying He have been involved in data analysis, data interpretation, drafting the manuscript, and revising it critically. Xuliang Deng and Qiwen Zheng have been involved in revising the manuscript critically and gave final approval of the version to be published.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest concerning the authorship and publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at http://egg-consortium.org/index.html (birth weight and childhood BMI), https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files (BMI and WHR), https://www.ukbiobank.ac.uk/ (BF%), and https://data.bris.ac.uk/data/dataset/2j2rqgzedxlq02oqbb4vmycnc2 (periodontitis).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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