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Association between adjustable dietary factors and periodontitis: NHANES 2009–2014 and Mendelian randomization

Li Chen[1], Rui Zhao[2,3*] and Yarong Zhang[1,2*]

Abstract

Background Periodontitis is the major cause of tooth loss in adults and one of the most common non-communicable diseases. Clinically, periodontitis impairs oral health and associated with various systemic diseases. Maintaining a healthy diet is considered risk reduction of periodontitis. To explore the causal effect between dietary data and periodontitis by Mendelian randomization (MR) analyses.

Methods A total of 11,704 participants and 21 dietary variables from the NHANES were in random forest to rank the importance in predicting periodontitis. Data were from the genome wide association studies (GWASs) database to estimate causal relationships between diet data and periodontitis. Two-sample MR analyses were conducted by using the inverse-variance weighted (IVW) method.

Results The MR showed alcohol consumption and sugars intake increased the risk of chronic periodontitis with odds ratio (OR) 2.768 (95% CI: 1.03e + 00–7.42e + 00) and 2.123 (95% CI: 1.06e + 00–4.26e + 00) respectively. Vitamins and minerals, including folic acid and folate, magnesium, vitamin A, vitamin E, vitamin C, calcium, vitamin D and zinc, were not causally associated with chronic periodontitis. Alcohol consumption greater than 2.5 drinks per day and sugar intake more than 4.88 g increased the risk of periodontitis, with a calculated relative risk of 1.33 and 1.61, respectively.

Conclusion It is suggested to drink alcohol less than 2.5 drinks/day and consume sugar less than 4.88 g/day to avoid alcohol and sugar consumption promoting the development of periodontitis. Establishing a dietary pattern conducive to periodontal health may be the focus of further clinical research.

Keywords Periodontitis, Alcohol, Sugar, Diet, Mendelian randomization, NHANES

*Correspondence:
Rui Zhao
zhaorui0122@126.com
Yarong Zhang
zyr_0928@sina.com
[1]State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & West China Hospital of Stomatology, Sichuan University, Chengdu 610041, Sichuan, China
[2]Department of Anesthesiology, Laboratory of Mitochondria Metabolism, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China
[3]Division of Gastrointestinal Surgery, West China Hospital of Sichuan University, Chengdu 610041, China

Introduction

Periodontitis is a chronic inflammation of periodontal supporting tissues, leading to the loss of connective tissue and bone support. In severe cases, periodontitis can make loosening or even loss of teeth and lead to poor oral health-related quality of life [1]. Besides impaired oral health, periodontitis is also considered to have a cause-and-effect relationship with various systemic diseases [2–5]. Periodontitis can negatively affect glucose control [6, 7] and increase the risk of cardiovascular diseases [8, 9]. Periodontitis is one of the most common non-communicable diseases (NCDs). The average global prevalence of severe periodontitis is estimated to be 11.2% [10]. The global burden of periodontitis epidemic poses a serious clinical and public health challenge, making reduction of risk factors for the development of periodontitis extremely important.

According to the common risk factor approach to NCDs and the adjustability of daily diets, maintaining a healthy diet is recognized as an important means of preventing a range of NCDs [11–13]. In addition to preventing periodontitis through oral procedures, dietary modifications are also noteworthy risk reduction measures. There is evidence that high consumption of added sugars is associated with periodontal disease [14, 15] and may link periodontitis to systemic disease [16, 17]. Similarly, high alcohol consumption is associated with an increased incidence of periodontitis [11, 18–20]. A meta-analysis found that each 1 g/day increment in alcohol consumption is with 0.4% higher risk of periodontitis [18]. And with increasing alcohol consumption, the clinical parameters of pocket depth (PD) and attachment loss (AL) also increase, worsening periodontal status [19]. Micronutrients also affect periodontitis. Antioxidant vitamins such as vitamin A, vitamin C, and vitamin E can overcome periodontal tissue inflammation [21–25] and vitamin D deficiency is associated with a higher prevalence of periodontitis [26]. However, the causal relationships between alcohol, sugars consumption and periodontitis have not been clearly established.

Most of the above findings were obtained by observational studies. Traditional observational research may be disturbed by differences in the study populations, reverse causation, and confounding factors. Therefore, to investigate the causal relationships between sugar, alcohol and periodontitis, more definitive conclusions can be obtained by improving the research methodology. Mendelian randomization (MR) is one of the research methods that can be adopted. MR is a data analysis technique used to assess etiology inference in epidemiological studies, which uses genetic variation strongly correlated with exposure factors as instrumental variables (IVs) to assess causal relationships between exposure factors and outcomes [27–29]. Compared to traditional observational research, MR is unlikely to be affected by confounding factors and causal inversion. Also, compared to randomized controlled trials, MR analysis is an economical method. In the present study, MR enables analysis of multiple dietary factors associated with periodontitis and avoids the unethical issues of factors expected to have adverse effects.

This study aims to analyze daily diet data through random forest (RF) to explore their importance when predicting periodontitis. In conjunction with the two-sample MR analysis, the causal relationship between periodontitis and possible risk factors in daily diet will be determined. This study has clinical implications in managing dietary risk factors for periodontitis.

Methods

Study design

The present study was conducted in three stages, as shown in Fig. 1. In stage 1, the RF was performed to rank the importance of dietary variables using data from the National Health and Nutrition Examination Survey (NHANES 2009–2014). The workflow was trained with 70% random samples, validated by the remaining 30% samples. The important variables were selected by Mean Decrease in Accuracy (MDA). In stage 2 and 3, we assessed the causal effect of genetically determined nutrients intake on periodontitis by MR analysis of summary statistics data from the genome-wide association study (GWAS) and obtain relevant dietary thresholds. There are three key assumptions of MR analyses: (1) genetic variants must be associated with exposures, (2) genetic variants must not be associated with confounders, and (3) genetic variants must affect outcomes only through exposures, not through other pathways.

NHANES data and study population

The data were from NHANES, a cross-sectional survey conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). The CDC-NCHS institutional review board approved the original survey protocol, and all survey participants provided written informed consent. The dietary data collected through two 24-h recalls is derived from NHANES dietary questionnaire and 21 dietary variables were included in RF analysis. There were 30,468 participants participated in the NHANES examination from 2009 to 2014. Among these participants, according to the CDC/AAP definitions, 14,071 participants were older than 30 years of age to complete periodontal examinations, and 2,367 participants who did not complete all periodontal examinations were excluded. A total of 11,704 participants were finally included in periodontitis assessment. And the missing values were filled by k-Nearest Neighbors algorithm.

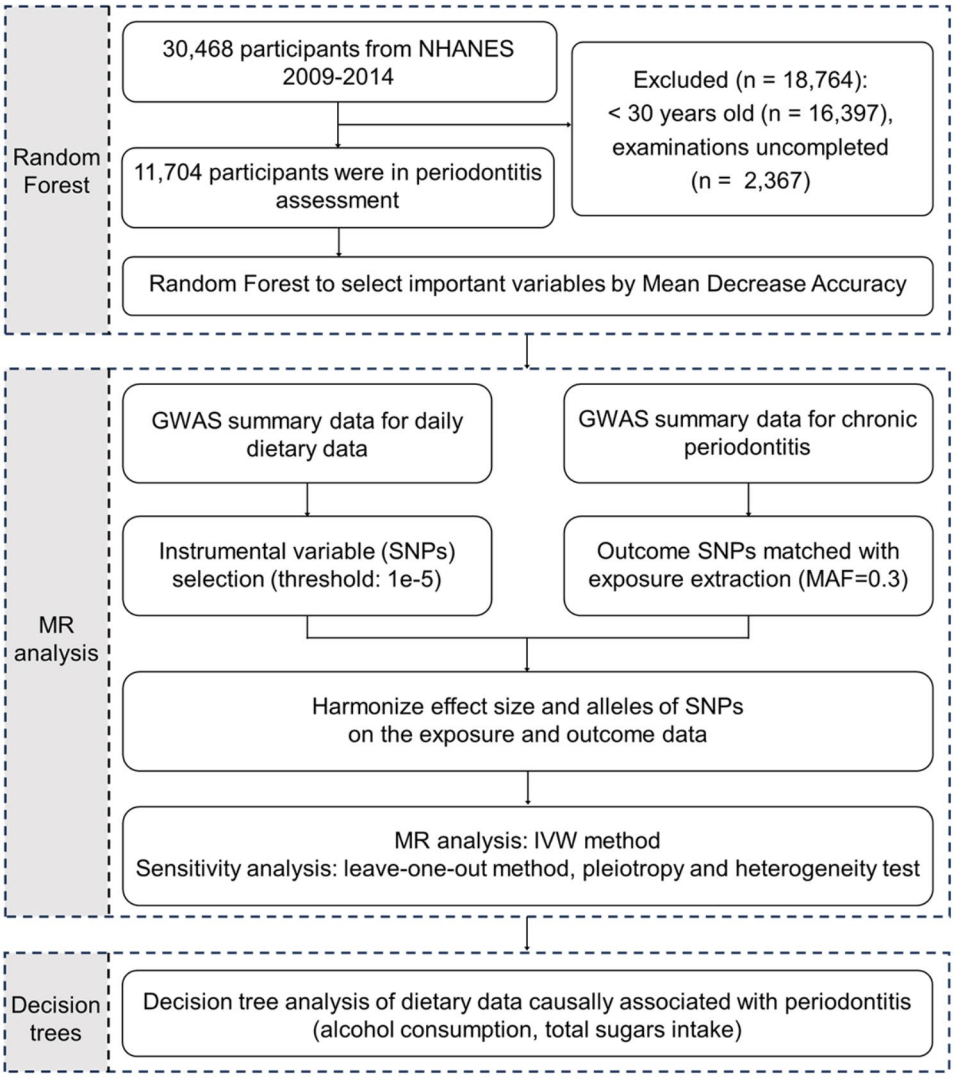

Fig. 1 Overview of study design and workflow. Abbreviations: SNPs, single-nucleotide polymorphisms; MAF, minor allele frequency; MR: Mendelian randomization

Periodontitis assessment

Periodontal information was measured at the medical examination. The case definition for periodontitis was carried out by using the 2012 CDC/AAP criteria [30, 31]. Participants were categorized into four groups: (1) mild periodontitis: ≥2 interproximal sites with clinical AL ≥ 3 mm and ≥ 2 interproximal sites with PD ≥ 4 mm, on different teeth, or one site with PD ≥ 5 mm; (2) moderate periodontitis: ≥2 interproximal sites with clinical AL ≥ 4 mm, on different teeth, or ≥ 2 interproximal sites with PD ≥ 5 mm, on different teeth; (3) severe periodontitis: ≥2 interproximal sites with clinical AL ≥ 6 mm, on different teeth, and ≥ 1 interproximal site with PD ≥ 5 mm; and (4) no periodontitis: does not meet any of the criteria for periodontitis.

Data sources

We selected variables for inclusion in MR analysis based on RF results and obtained aggregated numbers of exposure levels from GWAS. For two-sample MR on diet, the data of alcohol consumed (ukb-b-10923), sugars intake, calcium (ukb-a-495), folic acid or folate (ukb-b-3563), magnesium (ukb-b-5536), vitamin A (ukb-a-458), vitamin D (ukb-a-462), vitamin E, iron (ukb-b-14863) and zinc (ukb-b-13891) were extracted from IEU OpenGWAS project(https://gwas.mrcieu.ac.uk/) and GWAS catalog (https://www.ebi.ac.uk/gwas/). And the GWAS id of exposure is finn-b-K11_PERIODON_CHRON.

The data from all original studies available from published GWASs have obtained the ethical approval and informed consent. The details such as the list of covariates, recruitment criteria of population and quality

control of genetic data can be found in the original studies. Exposure data from UK Biobank and outcome data from the Finnish database are independent from each other.

Instrument selection

Firstly, we combined the genetic instruments from the relevant GWASs and the selection of IVs should meet MR's three key assumptions. The threshold for exposure data was 1×10^{-5} to satisfy the first assumption. Secondly, we clumped by linkage disequilibrium based on a pairwise $R^2 > 0.001$ to ensure that single-nucleotide polymorphisms (SNPs) were independent. R^2 was extracted from the original dataset to indicate the proportion of the phenotypic variance explained by the IVs. As required by the independence assumption, we removed confounders by using PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) to search for relationships between instrum ental variables and phenotypes. And then we calculated F statistics to evaluate weak instrument bias [32]. SNPs with F-statistics less than 10 were considered to be weak instruments and were therefore removed to ensure that the weak instrument bias was unlikely to influence the MR estimates.

Statistical analyses

SNP effects and corresponding standard errors were extracted from the diet composition GWAS summary statistics and harmonized with the outcome chronic periodontitis GWAS information. Palindromic SNPs with indeterminate allele frequencies [minor allele frequency (MAF) > 0.3]. Two-sample MR analyses were then conducted by using the inverse variance weighted (IVW) method [33] to estimate the association of general health status and daily diet with periodontitis risk. Furthermore, we carried out sensitivity analyses of the results, including genetic pleiotropy test (Cochran's Q statistic), heterogeneity test (MR-Egger intercept), and the "leave-one-out" method [34, 35]. Then we assessed statistical power using the mRnd power calculator, available at https://sb452.shinyapps.io/power/. Above MR analyses were used and interpreted in compliance with the STROBE-MR (Strengthening the Reporting of Observational Studies in Epidemiology - Mendelian Randomisation) checklist (Table S1). Finally, we performed a decision tree analysis of dietary data causally associated with periodontitis. We used the presence of periodontitis as a binary outcome variable and diet as exposure data to obtain relevant dietary thresholds.

Analyses were performed using R version 4.3.1 (R Foundation) with a $p\ value < 0.05$ indicating significance. The RF was done through R package 'randomForest' (version 4.7–1.1). The R package 'TwoSampleMR' (version 0.5.7) was used for MR [36]. And the CART was generated by the R package 'caret' version 6.0–94), 'rpart' (version 4.1.19) and 'rpart.plot' (version 3.1.1).

Table 1 Importance of variables ranked based on the MDA derived from RF

Variable	Mean Decrease Accuracy
Vitamin A	29.661
Vitamin E	29.060
Calcium	26.151
Zinc	24.949
Total alcohol consumption	24.404
Magnesium	23.301
Vitamin D	22.548
Vitamin C	22.460
Total dietary folate	22.348
Total dietary sugars	22.338
Iron	22.231
Beta-carotene	22.012
Moisture	20.494
Energy	20.468
Selenium	20.221
Vitamin.B6	20.066
Caffeine	19.195
Vitamin.B12	18.813
Total dietary fat	18.716
Protein	17.156
Theobromine	14.651

A higher MDA corresponds to higher importance

Results

Dietary factors were important for periodontitis

The specific values of MDA outputted by the RF algorithm are listed in Table 1. Of note, the MDA values only suggest how important the variables are in predicting periodontitis but not indicating the positive or negative relationship between them. Figure 2 displays the top 10 variables ranked by MDA, including alcohol and sugars. Among these variables, the most important factor was vitamin A (MDA = 29.661), followed by vitamin E (MDA = 29.060). The remaining variables in the top ten were calcium (MDA = 26.151), zinc (MDA = 24.949), total alcohol consumption (MDA = 24.404), magnesium (MDA = 23.301), vitamin D (MDA = 22.548), vitamin C (MDA = 22.460), total dietary folate (MDA = 22.348) and total dietary sugars (MDA = 22.338). The predictive model derived from the RF is with an AUC of 0.568 [95% confidence interval (CI) 0.538–0.599] (Fig. S1).

Dietary sugars intake and alcohol consumption were causally associated with periodontitis

We selected the dietary factors to be analyzed by MR based on the top ten result of RF algorithm. After clumping and harmonization, different number of SNPs of different variables were selected (Table 2). The average F statistics of the IVs for alcohol consumption, sugar

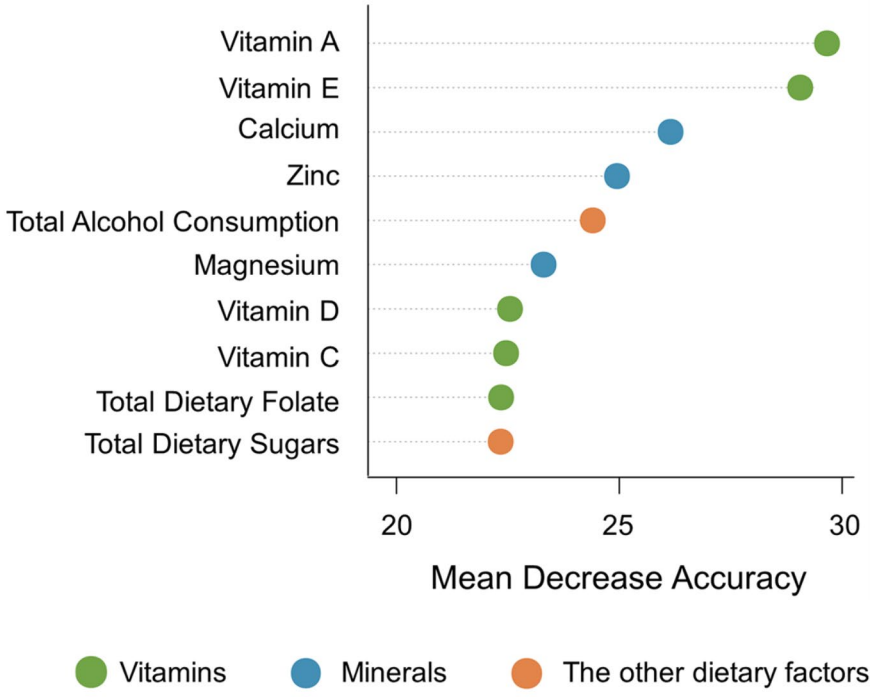

Fig. 2 The importance plot of periodontitis potential prediction dietary factors from RF models. This reveals the importance ranking of variables according to their MDA values. Different types of dietary variable were distinguished by three colors. Green: vitamin, blue: mineral, orange: other type

Table 2 MR results for the relationship between diet and periodontitis

Inverse variance weighted	Number of SNPs	Se	OR [a] (95%CI)	*P* value
Alcohol total consumption	**13**	**0.503**	**2.768 (1.03e + 00, 7.42e + 00)**	**0.043**
Total dietary sugars	**21**	**0.355**	**2.123 (1.06e + 00, 4.26e + 00)**	**0.034**
Folic acid and Folate	7	6.549	4.274 (1.14e-05, 1.60e + 06)	0.824
Magnesium	7	3.044	3.443 (8.82e-03, 1.34e + 03)	0.685
Vitamin A	18	4.567	1.855 (2.41e-04, 1.43e + 04)	0.892
Vitamin E	28	0.023	0.994 (9.50e-01, 1.04e + 00)	0.775
Vitamin C	28	0.146	0.984 (7.40e-01, 1.31e + 00)	0.913
Calcium	5	2.058	0.412 (7.30e-03, 2.32e + 01)	0.666
Vitamin D	14	3. 065	0.170 (4.18e-04, 6.92e + 01)	0.563
Zinc	24	3.173	0.143 (2.84e-04, 7.16e + 01)	0.540

[a] Indicates the odds for chronic periodontitis per one-s.d. increase in mean of each dietary variable. All statistical tests were two-sided. Results with *p value* < *0.05* were considered significant and are all bolded. The results of other variables were arranged by OR value size. Abbreviations: SNPs, single-nucleotide polymorphisms; Se, standard error; CI, confidence interval; OR, odds ratio

intake, folic acid and folate, magnesium, vitamin A, vitamin E, vitamin C, calcium, vitamin D and zinc were 224, 206, 2182, 1411, 2430, 13, 87, 676, 1130 and 1577, indicating that our analyses were unlikely to be biased by weak instruments. And the "leave-one-out" method confirmed that single SNPs of alcohol consumption and sugar intake did not influence the main causal results (Fig. S2, Fig. S3). All funnel plots were symmetrical (Fig. S4, Fig. S5), indicating that the estimates were not violated. The *p values* from Cochran's Q statistic and MR-Egger intercept were greater than 0.05, signifying the absence of heterogeneity and pleiotropy (Table S2). And the statistical power of the MR analysis yielded results of 0.99 of the results of total dietary sugars and alcohol total consumption (Table S2).

The two-sample MR showed that alcohol consumption, total dietary sugars might promote chronic periodontitis. A one-s.d. increment in genetically predicted alcohol consumption was associated with a 2.768 (95% CI: 1.03e + 00–7.42e + 00, $p = 0.039$) fold higher risk of chronic periodontitis. And each s.d. increase in genetically predicted sugar intake was associated with a 2.123 (95% CI: 1.06e + 00–4.26e + 00, $p = 0.034$) fold higher odds of chronic periodontitis. For other vitamins and minerals, we found no evidence of causal relationships between

them and chronic periodontitis across all MR methods (*p value* > *0.05*).

We focused on the variables with causally association. The scatter plots (Fig. 3a and c) of alcohol consumption/sugars intake and periodontitis risk association for the instruments indicated significantly positively causal relationships. MR estimates for the effects of the SNPs associated with alcohol consumption/sugar intake on periodontitis risk are presented in forest plots (Fig. 3b and d), with all inverse variance weighed > 0. And analysis of clinical public database, quantitative RT-PCR and cell counting kit-8 analysis initially validated the above results. We found that inflammation decreased the expression of genes related to glucose metabolism and alcohol metabolism, while high glucose and high alcohol up-regulated the expression of inflammatory factor genes and inhibited the proliferation of human periodontal ligament fibroblasts (Fig. S6-7).

Excessive sugars intake and alcohol consumption increased the risk of periodontitis

Based on the results of RF and Mendelian randomization, other dietary factors that did not have a statistically significant causal relationship with periodontitis (*p value* > *0.05*) were not further analyzed. And we finally screened two dietary variables with a causal relationship with chronic periodontitis, i.e. sugar intake and alcohol consumption, to calculate their cut-off values (Fig. 4). The risk of periodontitis was increased when the alcohol consumption was greater than 2.5 drinks/day, with

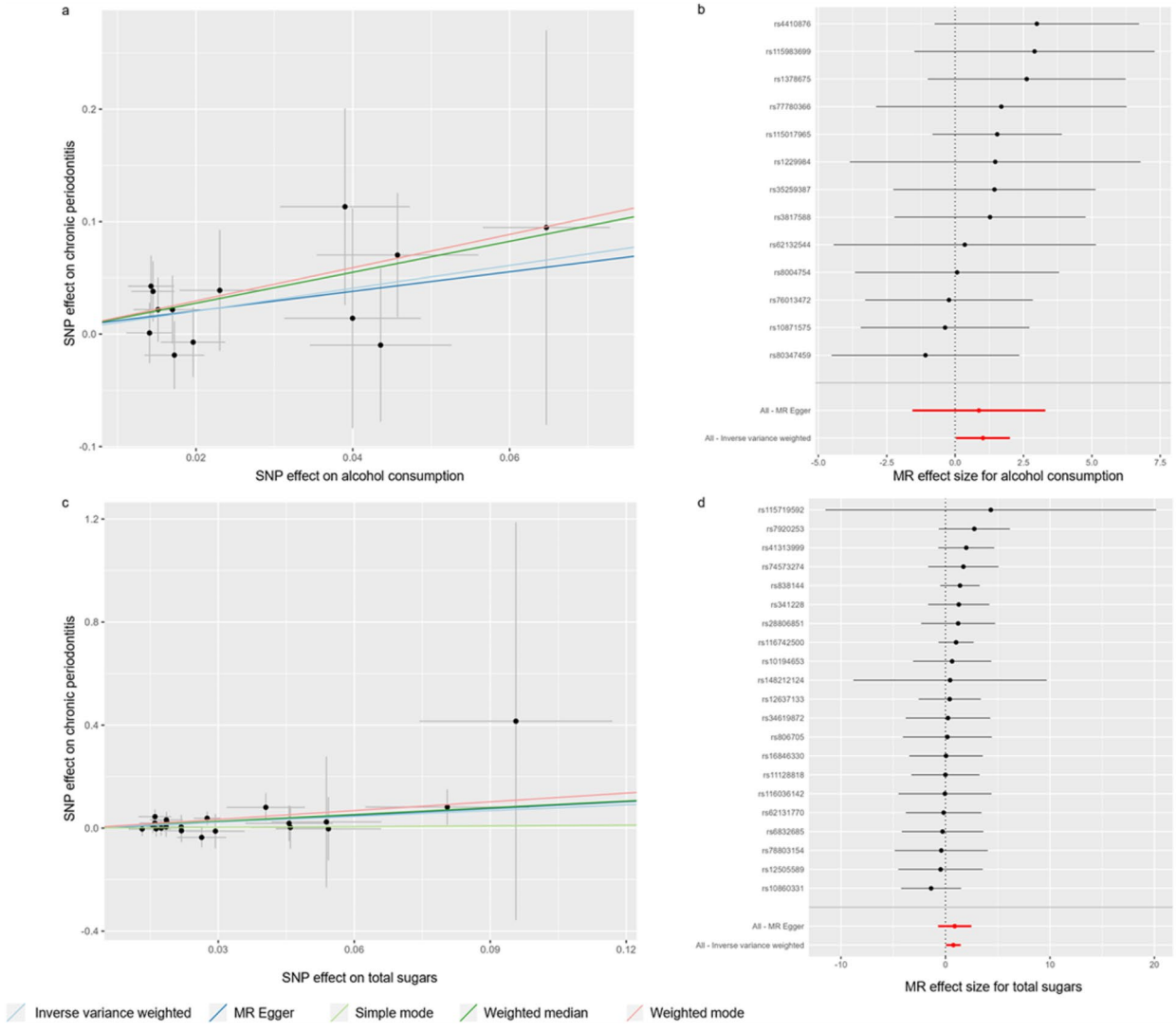

Fig. 3 MR plots for the relationship of dietary variables with chronic periodontitis. Forest plot of individual and combined SNP MR-estimated effect sizes. Scatter plot of SNP effects on alcohol consumption (**a**) and sugar (**c**) versus periodontitis, with the slope of each line corresponding to the estimated MR effect per method. The data are expressed as raw β values with 95% CIs. The effect estimates represent the log odds for periodontitis per one-s.d. increase in mean alcohol consumption (**b**) and sugar (**d**), and the error bars represent 95% CIs

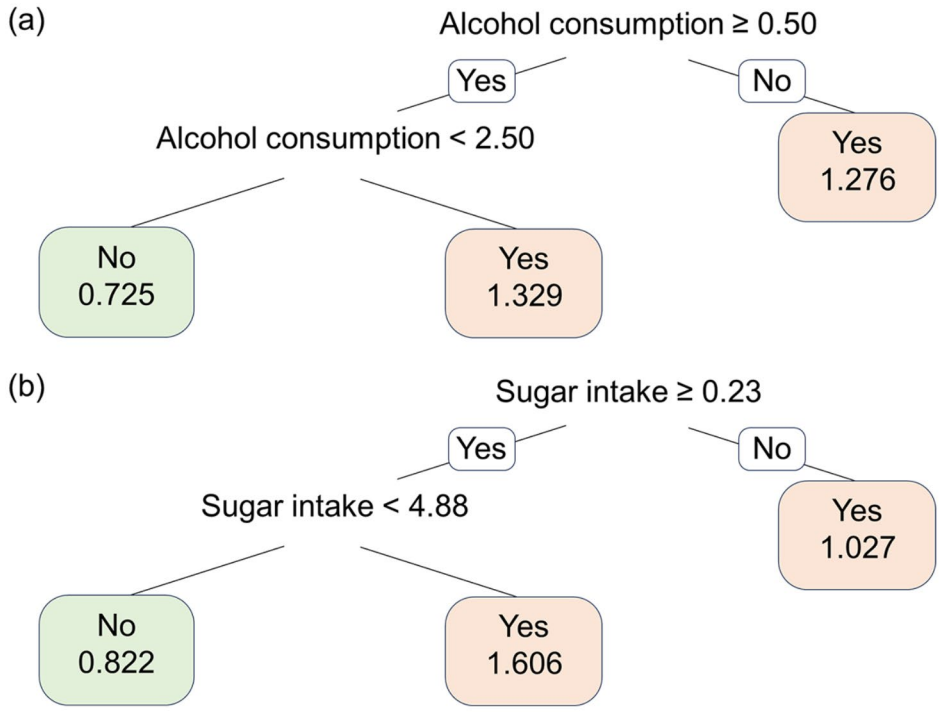

Fig. 4 Decision tree for alcohol consumption and sugar intake. The unit of alcohol consumption (**a**) is drink per day. The unit of sugar intake (**b**) is gram per day. The branch of each node is yes on the left and no on the right. In each box, the first row predicts the outcome, and the second row is the relative risk. The orange boxes show the prediction of with periodontitis, the green boxes show the prediction of without periodontitis

a calculated relative risk (RR) of 1.33. Similarly, consuming sugar more than 4.88 g/day increases the risk of periodontitis by 1.61 times. And the acceptable range of sugar intake is between 0.23 and 4.88 g/day. Moderate total sugars intake reduces the risk of periodontitis by 17.80%.

Discussion

The present study found that vitamins, minerals, alcohol and sugars intake were important in predicting periodontitis. The MR analysis showed that genetically predicted sugars intake and alcohol consumption were causally associated with chronic periodontitis. Specifically, high sugar intake and excessive alcohol consumption increasing the risk of periodontitis. But no significant causal relationships between vitamins/minerals intake and periodontitis were observed.

Our study suggests that chronic high sugars intake is harmful for periodontal conditions. The possible mechanism is that chronic high intake of sugar may cause hyperglycemia [37]. Hyperglycemia may lead to the M1 macrophage polarization and induce the overproduction of inflammatory cytokines, such as tumor necrosis factor (TNF) -α and interleukin (IL) -6 [39]. These changes may lead to alveolar bone loss and promote periodontitis. Hyperglycemia also can induce macrophage pyroptosis by inducing activation of gasdermin D (GSDMD) [38, 39] and macrophage senescence by reducing SET Domain Bifurcated Histone Lysine Methyltransferase 1 (SETDB1) [40, 41]. Both macrophage pyroptosis and senescence have key roles in promoting periodontitis [42–44]. And from a clinical perspective, our findings are consistent with the WHO guidelines of reducing free sugars intake to less than 25 g/day [45], but provide new insights into specific values. Our results indicate that sugar intake between 0.23 and 4.88 g/day could reduce the risk of periodontitis by 17.80%. Differences between the values may be because the WHO takes into account a number of health indicators and dietary factors. It is also likely to indicate that periodontal tissues are more sensitive to sugar intake than systemic health.

Also, our analysis extends the observational findings [18–20, 46] by showing the causal role of high alcohol consumption on the risk of periodontitis. The mechanism may be that alcohol affects the levels of microorganisms and further influence the development of periodontitis [47, 48]. Specific impact pathways include direct cytotoxic effects on bacteria [49], alterations in microenvironmental pH [50], and provision of ethanol as a substrate for bacterial metabolism [51]. Also, chronic alcohol diet can exacerbate the inflammatory response and osteoclastogenesis [52] by IL-6 expression and TNF-α in vivo [53, 54], which stimulates osteoclast differentiation and leads to bone resorption. As for the clinical point of view, a

recent Lancet study [55] found that drinking 0.114–1.87 drinks/day (a standard drink contains about 10 g of alcohol) may be beneficial for people over the age of 40. This suggests that controlling alcohol consumption to a level good for systemic health is also beneficial for periodontal health. However, the role of alcohol in the onset and progression of periodontitis is complex. Therefore, further more in-depth studies on underlying molecular basis are needed.

In this study machine learning and MR were combined for data analysis. Several methods were used to infer robust causal estimates of MR. Robust IV with F statistics over 10 were selected. The LD cutoff was set to $R^2 < 0.001$ to guarantee the independence of the data. The genome-wide significance threshold was $p\ value = 1 \times 10^{-5}$. A sensitivity analysis, including heterogeneity, pleiotropy and the leave-one-out method was performed to ensure the reliability of the results. Furthermore, Phenoscanner was used to ensure that no potential risk variables contradicting our findings. The above methodology allowed us to eliminate as many interferences as possible and increase the credibility. And compared to previous MR studies, using data from the NHANES to assess the significance of different variables and their cut-off values makes the results more clinically meaningful. Our findings will have implications for managing dietary risk factors for periodontitis, in addition to daily teeth brushing and regularly scaling, diet also deserves attention. High sugar and alcohol diet that tend to cause irritation to periodontal tissues should be avoided.

However, there are some limitations that need discussion. First, the fact that different food intakes can exert synergistic or antagonistic effects on one another is not considered in this study. Further study of the mutual influence of multiple food such as multivariate MR is needed. And a comprehensive analysis could be further conducted to provide more clear guidance. Second, hormonal changes and age-related alterations in immune function may influence periodontitis. And genetic variation cannot be considered an exact proxy for exposure. Also, the recruited individuals were from USA and European. Therefore, clinical research to clarify whether reducing sugar and alcohol intake is helpful in the treatment of periodontitis is needed. And future stratified analyses by age and sex and multicenter clinical trials could be conducted before generalizing the results to other populations of different ethnicities and regions.

To better apply our findings to clinical practice, the periodontics team is recommended to perform a nutritional assessment with basic treatment. In particular, evaluation scales that encompass inquiries about dietary behaviors can be formulated in collaboration with community periodontal index. This scale can be employed as a risk assessment tool to identify individual risks and to guide patient follow-up once validated.

Conclusions

In exploring risk factors for the development of periodontitis, vitamins, minerals, sugar and alcohol intake are important. The MR investigations provide evidence that alcohol consumption and sugars intake are possibly causally related to development of chronic periodontitis. As for adjustable dietary variables, high sugars intake and alcohol consumption will increase the risk of periodontitis. To prevent excessive alcohol and sugar consumption that could be risk factors for the development of periodontitis, drinking alcohol less than 2.5 drinks/day and consuming sugar less than 4.88 g/day is recommended.

Abbreviations

AL	Attachment loss
CDC	Centers for Disease Control and Prevention's
CI	Confidence interval
GSDMD	Gasdermin D
GWAS	Genome-wide association studies
IVW	Inverse-variance weighted
LINE-1	Long interspersed element 1
MAF	Minor allele frequency
MDA	Mean Decrease Accuracy
MR	Mendelian randomization
NCDs	Non-communicable diseases
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NLRC4	NLR Family CARD Domain Containing 4
OR	Odds ratio
PD	Pocket depth
RF	Random forest
RR	Relative risk
SETDB1	SET Domain Bifurcated Histone Lysine Methyltransferase 1
SNPs	Single-nucleotide polymorphisms

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-024-05972-4.

Supplementary Material 1

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Author contributions

All authors contributed to the design of this study. Data preparation and data collection were performed by L. C. and R. Z. L. C. performed the analyses. L. C., R. Z. and Y. Z. wrote the manuscript. Y. Z. and R.Z. revised the paper.

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Data availability

The data sets used in this study are freely available for download from sources in the public domain: NHANES (https://www.cdc.gov/nchs/nhanes/index.ht

m), MR-Base (https://www.mrbase.org/) and GWAS Catalog (https://www.ebi.ac.uk/gwas/home).

Declarations

Ethics approval and consent to participate
This study used summary-level statistics from published studies and publicly available GWASs. No ethical approval was required for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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