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Causal relationship between cheese intake and periodontal diseases

A two-sample Mendelian randomization study

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Abstract

Dietary habits have been confirmed to affect periodontal disease, but whether cheese intake is associated with periodontal disease remains unclear. This study aims to explore the causal relationship between cheese intake and periodontal disease by Mendelian randomization (MR) analysis. genome-wide association study data from the UK Biobank was utilized. In order to reveal the causal relationship between exposure (cheese intake) and outcome (periodontal disease), and to ensure the reliability of the conclusions, single nucleotide polymorphisms were rigorously selected as instrumental variables to replace the exposure. The following methods were applied for MR analysis: the inverse-variance weighted (IVW), MR-Egger, weighted median, simple mode and weighted mode methods. Sensitivity analyses included heterogeneity test, horizontal pleiotropy test and leave-one-out method. The IVW method indicated that the risk of periodontal diseases decreased as cheese intake increases (OR = 0.545, 95% CI = 0.364–0.816, P = .0032). Sensitivity analyses revealed no statistical evidence of heterogeneity or horizontal pleiotropy, confirming the robustness of the results. Increased cheese intake may reduce the risk of periodontal disease. This study provides genetic evidence supporting the inclusion of cheese in the diet for periodontal disease. Further research is needed to confirm these findings in different populations and to understand the underlying mechanisms.

Abbreviations: CI = confidence interval, GWAS = genome-wide association study, IBD = inflammatory bowel disease, IVs = instrumental variables, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, RANKL = receptor activator of nuclear factor kappa-B ligand, SNPs = single nucleotide polymorphisms, WM = weighted median.

Keywords: cheese, genome-wide association study (GWAS), Mendelian randomization analysis, periodontal diseases

1. Introduction

Periodontal disease is a chronic inflammatory disease triggered by microbial plaque, and clinically manifested as the progressive destruction of periodontal tissues and alveolar bone resorption, ultimately leading to tooth mobility and even loss.[1] According to the World Health Organization's Global Oral Health Status Report in 2022, approximately 19% of the global adult population suffers from severe periodontitis, equating to over 1 billion periodontitis patients worldwide.[2] Various systemic diseases, such as obesity, hypertension and diabetes, etc can influence the onset of periodontitis.[3] Lifestyle and dietary habits, such as smoking, alcohol consumption, and tea drinking, etc are also significant factors in the development of periodontal disease.[4,5]

The correlation between dairy intake and the risk of periodontal diseases has been a subject of considerable interest. An observational study indicated that individuals with periodontitis consumed less cheese compared to those with good periodontal health.[6] Al-Zahrani[7] study (2006) found a significant inverse relationship between dairy intake and the prevalence of periodontitis, although the study did not examine the relationship between different types of dairy products and periodontitis. However, Shimazaki[8] et al (2008) found no significant association between the intake of milk or cheese and periodontitis but reported that the consumption of yogurt or lactic acid drinks significantly reduced the incidence of periodontal disease. Similarly, Adegboye[9] study found a significant inverse relationship between the intake of milk or fermented foods and periodontal disease, but cheese intake had no effect on periodontal disease. Therefore, the current evidence regarding the impact of dairy products, especially cheese, on periodontal disease remains inconclusive.

Genetic polymorphisms and hereditary factors play a crucial role in the susceptibility to periodontal disease, significantly affecting the host's immune response to dental plaque and influencing the severity and clinical presentation of periodontal disease.[10] This study aims to further elucidate the relationship between

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The datasets generated during and/or analyzed during the current study are publicly available.

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cheese intake and periodontal disease using the Mendelian randomization (MR) method. MR is a statistical approach based on genetic principles, utilizing genetic variation as a natural randomized experiment to assess the causal effects of exposure factors on disease outcomes.[11] Compared to traditional observational studies, MR can effectively control confounding variables, avoid reverse causation, and minimize selection bias, thereby enhancing the credibility of causal inference.[12]

2. Materials and methods

2.1. Data sources

The genome-wide association study (GWAS) data utilized in this study were sourced from the UK Biobank (https://gwas.mrcieu.ac.uk/), consisting of European individuals of both sexes. The cheese intake dataset (ukb-b-1489) encompasses samples from 451,486 individuals, with 9851,867 single nucleotide polymorphisms (SNPs). The Periodontal disease dataset (finn-b-K11_GINGIVITIS_PERIODONTAL) includes 4120 cases and 195,395 controls, with 16,380,400 SNPs. Gender and age stratification were not available in the datasets, which is a limitation inherent to the UK Biobank.

2.2. Instrument selection

For conducting MR analysis, SNPs which affected the outcomes only through exposures were selected as valid instrumental variables (IVs), and the following conditions must be met: relevance, independence, and exclusivity.[13]

To satisfy the relevance assumption, the SNPs strongly associated with cheese intake ($P < 5 \times 10^{-8}$) to ensure a strong genetic association with exposure. To meet the independence assumption, SNPs related to potential confounders were excluded. SNPs with r^2<0.01 were chosen, and it was ensured that the physical distance between any 2 SNPs exceeded 10,000 kb to prevent linkage disequilibrium caused by proximity. For the exclusivity assumption, ensuring that SNPs affect periodontal disease solely through cheese intake rather than other biological pathways, the intercept of the MR-Egger regression was assessed. A significantly nonzero intercept indicates potential horizontal pleiotropy, and such SNPs will be excluded. The final included SNPs were required to have sufficient instrument strength ($F > 10$),[14] enabling the MR analysis to investigate the potential causal relationship between cheese intake and periodontal disease.

2.3. Statistical analysis

Statistical analyses were conducted using R software (version 4.2.3) and the TwoSampleMR package (version 0.5.11). The TwoSampleMR package is available on https://mrcieu.github.io/TwoSampleMR/, and the MR analysis code can be accessed on https://mrcieu.github.io/TwoSampleMR/articles/perform_mr.html. Causal effects described by odds ratios (OR) were was estimated by the inverse-variance weighted (IVW) method, weighted median (WM) method, MR-Egger method, weighted mode, and simple mode.

Firstly, the IVW method used as the primary 2-sample MR analysis was employed to explore the effects of all IV.[15] To account for potential pleiotropy, the WM method, MR-Egger regression, weighted mode, and simple mode were also applied to obtain more robust causal effect estimates. Cochran *Q* test was used to assess heterogeneity, and the intercept of the MR-Egger regression was used to evaluate horizontal pleiotropy.[16] Leave-one-out analysis was conducted to assess the impact of individual SNPs on the overall causal effect.[17] Unless otherwise specified, the significance level for all statistical tests was set at $\alpha = 0.05$.

3. Results

3.1. Instrumental variable results

After excluding IVs with linkage disequilibrium, 64 SNPs were identified as associated with cheese intake in the ukb-b-1489 GWAS dataset, and 63 SNPs were identified as associated with periodontal disease in the finn-b-K11_GINGIVITIS_PERIODONTAL GWAS dataset. During the harmonization of SNP-exposure and SNP-outcome data, 1 palindromic SNP with intermediate allele frequency (rs1024853) was excluded.[18] For periodontal disease, rs11130540 was used as a proxy SNP for rs4681981. Ultimately, 62 SNPs were included in the analysis.

3.2. Causal effect analysis

The causal relationship between cheese intake and periodontal diseases was assessed using MR methods, and the results are presented in Table 1, Figures 1 and 2. The IVW method revealed a significant protective effect of cheese intake on periodontal diseases (OR = 0.545, 95% CI = 0.364–0.816, $P = .0032$). Figure 1, a scatter plot comparing 5 MR methods, demonstrates consistent effect directions across all methods, as IVW provides the most reliable estimate owing to its robust statistical framework. Figure 2, a forest plot, shows the individual causal effects of each SNP, where the majority of estimates are positioned to the left of the null line (OR = 1). The aggregated result from the IVW method is also displayed in the plot, clearly indicating a significant negative association between cheese intake and the risk of periodontal diseases. These findings highlight the robustness of the IVW method, supported by the consistent results from alternative MR methods and individual SNP effects, reinforcing the protective role of cheese intake in reducing periodontal disease risk.

3.3. Sensitivity analysis

Sensitivity analyses were conducted to assess heterogeneity and pleiotropy in the results. Cochran *Q* test was used to evaluate heterogeneity among the IVs. The results of Cochran *Q* test for IVW (Q = 48.85, df = 61, $P = .87$) indicated no significant heterogeneity among the SNPs when considering cheese intake as the exposure and the risk of periodontal disease as the outcome,

Table 1

Estimates of the causal relationship between cheese intake and periodontal diseases using different MR methods.

Outcome	Exposure	Methods	OR	95% CI	*P*
Gingivitis and periodontal diseases	Cheese intake	IVW	0.545	0.364 to 0.816	.003
		MR-Egger	0.785	0.142 to 4.339	.782
		Weighted median	0.572	0.314 to 1.041	.067
		Simple mode	0.496	0.142 to 1.737	.277
		Weighted mode	0.531	0.166 to 1.702	.291

CI = confidence interval, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio.

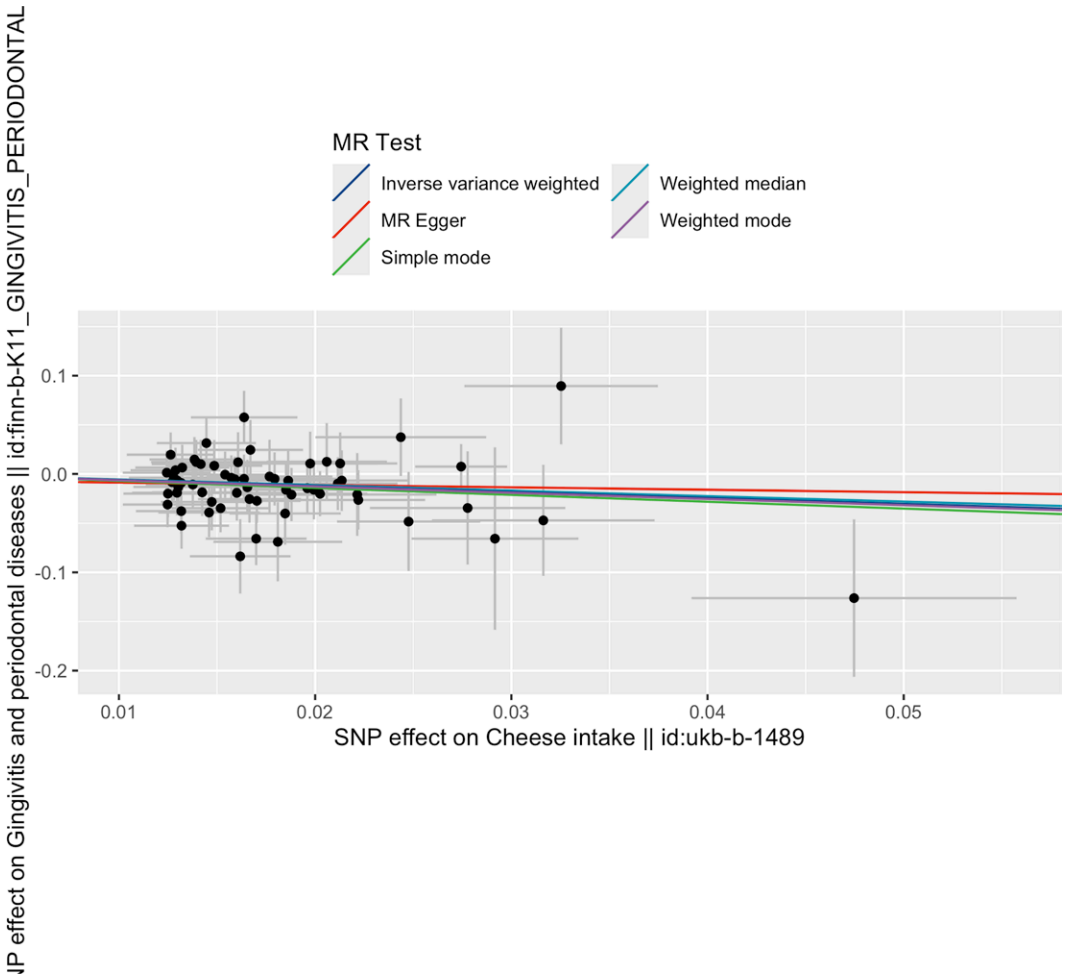

Figure 1. Scatter plot of the causal relationship for cheese Intake on periodontal disease using different MR methods. MR = Mendelian randomization.

and MR-Egger regression (Q = 48.67, df = 60, P = .85) showing nonsignificant heterogeneity. The funnel plot displayed a symmetrical distribution of causal effect estimates when using individual SNPs as IVs, suggesting a low likelihood of bias influencing the causal relationship (Fig. 3). To detect and correct for horizontal pleiotropy, the intercept from the MR-Egger regression was analyzed, yielding an intercept of –0.0062 (se = 0.015, P = .67), which indicated no significant horizontal pleiotropy affecting the MR causal effect estimates. Additionally, a leave-one-out analysis was performed to ensure the robustness of the results, showing that no single SNP significantly influenced the causal estimate of periodontal disease (Fig. 4). Conclusively, these sensitivity analyses confirmed the stability and reliability of the causal relationship between cheese intake and the risk of periodontal disease.

4. Discussion

The relationship between dairy intake and the risk of periodontal disease remains controversial. Several studies have indicated that the intake of yogurt or probiotic-containing yogurt can reduce periodontal indices such as probing bleeding[19–21] and decrease tooth loss due to periodontal disease.[22] However, Al-Zahrani[7] et al found a significant inverse relationship between dairy intake and the prevalence of periodontal disease. Yoshihiro Shimazaki[8] et al reported there was no significant association between milk or cheese intake and periodontitis, but found that fermented dairy products such as yogurt and lactic acid drinks significantly reduced the incidence of periodontitis. Adegboye[9] et al also found fermented foods intakes could reduce risk of periodontitis, but cheese and other dairy foods intakes could not. By using the 2016 to 2018 data of the Korean National Health and Nutrition Examination Survey, it showed that men but not women with higher milk consumption were more likely to have a lower prevalence of severe periodontitis.[23,24] Another Korean research team also reported that frequent consumption of dairy food including milk may have a beneficial effect on periodontal disease in the Korean adult population.[23,24]

This study employed large-scale GWAS data and MR analysis to explore the causal relationship between cheese intake and the risk of periodontal disease. The findings demonstrate a significant protective effect, with higher cheese intake associated with a reduced risk of periodontal disease (IVW: OR = 0.545, 95% CI = 0.364–0.816, P = .0032). As shown in Figure 1, the scatter plot illustrates consistent effect directions across all MR methods, and Figure 2, the forest plot, highlights the individual causal effects of SNPs, with most estimates aligning with the overall protective effect from the IVW method. Together, these figures visually confirm the significant negative association and the robustness of the causal inference. The robustness of these findings is further supported by sensitivity analyses. As summarized in Table 1, no evidence of heterogeneity (Cochran Q test: P = .87) or horizontal pleiotropy (MR-Egger intercept: P = .67) was found. Additionally, Figure 3 provides a visual demonstration of the low likelihood of bias, as indicated by the symmetrical funnel plot, while Figure 4 shows that removing any single SNP does not disproportionately affect the overall causal estimate. These analyses visually underscore the stability and reliability of the observed causal relationship. In conclusion, these

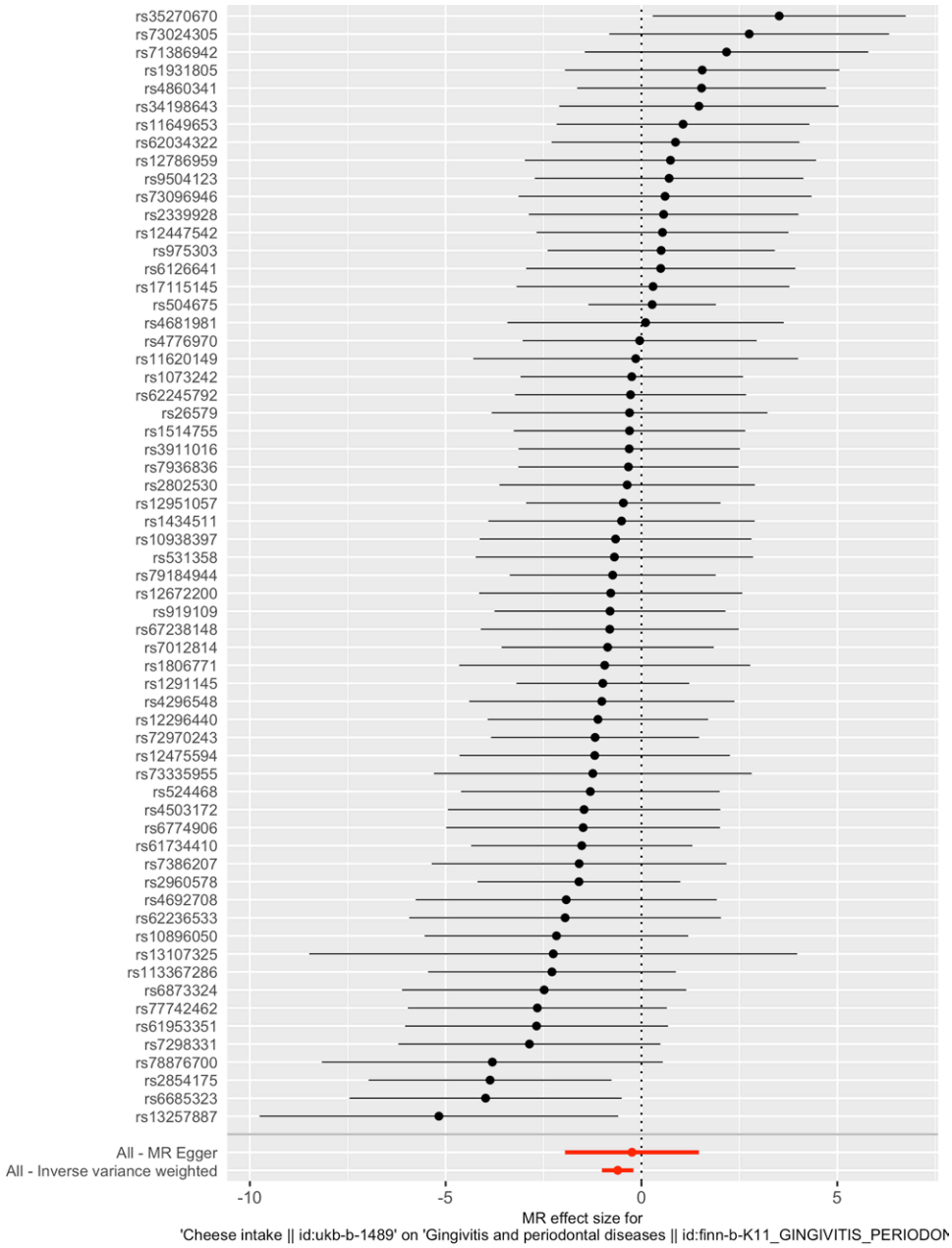

Figure 2. Forest plot of MR analysis for the causal effect of cheese Intake on periodontal disease. MR = Mendelian randomization.

findings provide robust evidence supporting the protective role of cheese intake in reducing periodontal disease risk. By integrating comprehensive statistical analyses and sensitivity tests, this study offers valuable insights into potential dietary recommendations aimed at mitigating the risk of periodontal diseases.

Cheese, a fermented dairy product, contains abundant probiotics such as *Lactobacilli* and *Bifidobacteria*, and primarily derives from the milk of cows, sheep and other mammals etc. Based on previous research, the mechanisms for that cheese intake reduces the risk of periodontal disease may involve the following aspects: Inhibits periodontal pathogens: The fermented probiotics in cheese, such as *Lactobacilli* and *Bifidobacteria*, could reduce the adhesion of *Porphyromonas gingivalis* and inhibit the growth of Gram-negative bacteria by producing metabolites such as lactic acid.[25] Suppression of pro-inflammatory factors in periodontal tissues: Cheese intake may exert periodontal protective effects by inhibiting the expression of pro-inflammatory factors in periodontal tissues. An in vivo study by Lorena Vasconcelos Vieira and colleagues demonstrated that the intake of fermented dairy products containing *Lactobacilli*[26] significantly reduced alveolar bone resorption in periodontitis and decreased the expression of inflammatory factors such as IL-6, TNF-α, and IL-1β in periodontal ligaments. Importantly, it has been proven that IL-1, IL-6, and TNF-α play key roles in alveolar bone resorption in periodontitis by inducing the expression of RANKL (receptor activator of nuclear factor kappa-B ligand).[27] Regulation of gut microbiota and reduction of intestinal inflammation: Epidemiological surveys and cross-sectional studies had shown that inflammatory bowel disease (IBD) patients had a higher prevalence of periodontal disease due to the increase of probing bleeding and attachment loss. Dysbiosis and bacterial metabolites as well as inflammatory factors in IBD may promote the development of periodontal disease through systemic circulation. Studies also had indicated alteration in microbial diversity and species in the periodontal tissues of IBD patients. Moreover, IL-6 and TNF-α

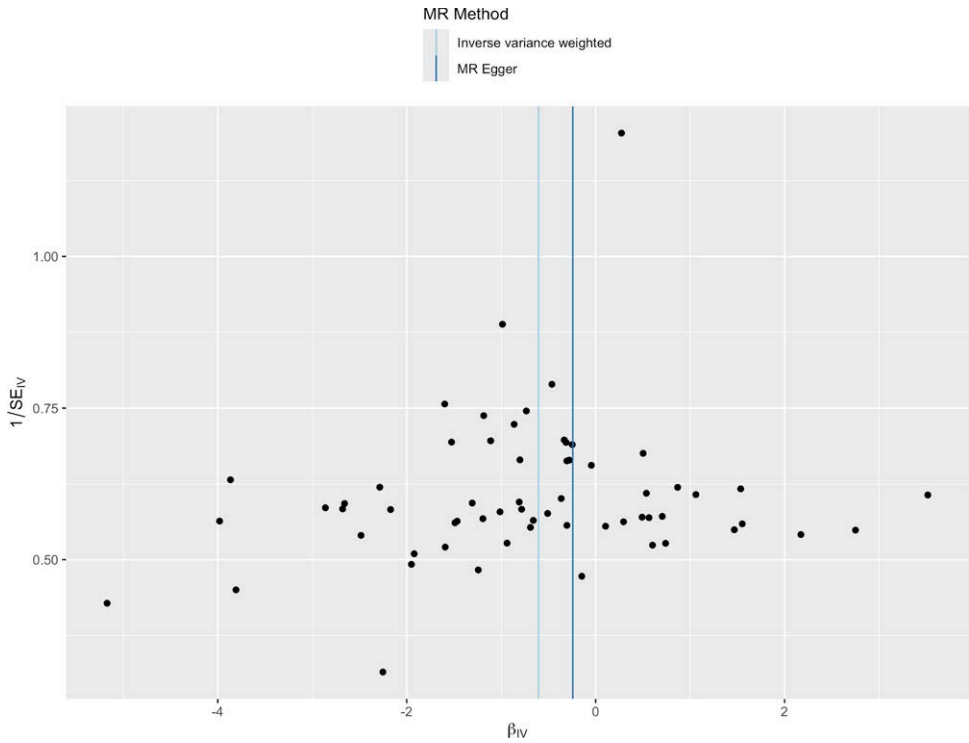

Figure 3. Funnel plot of SNP for MR analysis of cheese intake on periodontal disease. MR = Mendelian randomization, SNPs = single nucleotide polymorphisms.

expression was upregulated and alveolar bone resorption happened in these patients.[2,5,28,29] Additionally, rat models showed that cheese consumption significantly reduced intestinal inflammation and dysbiosis caused by *Salmonella* compared with the control group. Moreover, cheese containing *Lactobacillus rhamnosus* was more effective in relieving gut inflammation.[30] This suggests that cheese exerting protective effects on periodontal disease through improvement of intestinal inflammation.

In conclusion, this study provides genetic evidence for the causal effect of cheese intake on periodontal disease, and offers a scientific basis for including cheese and other dairy products in daily dietary habits to prevent periodontal disease. However, this study has certain limitations. Firstly, this study's findings are based on data predominantly from European populations, limiting their applicability to other ethnic groups. Additionally, the dataset lacked stratifications by gender or age, which may influence the observed causal relationship. Future studies should include diverse populations and stratified data. Secondly, the dataset used reflects overall cheese consumption without differentiating cheese types (e.g., soft, hard, goat cheese), restricting the analysis of type-specific effects. Future research should classify cheese types for a more detailed investigation. Lastly, while MR analysis suggests a causal link, the underlying mechanisms through which cheese impacts periodontal disease remain unclear and warrant further exploration.

5. Conclusion

This study found that moderate cheese intake may reduce the risk of periodontitis in the population. However, before promoting it as a daily dietary habit, these findings should be validated through long-term randomized controlled trials.

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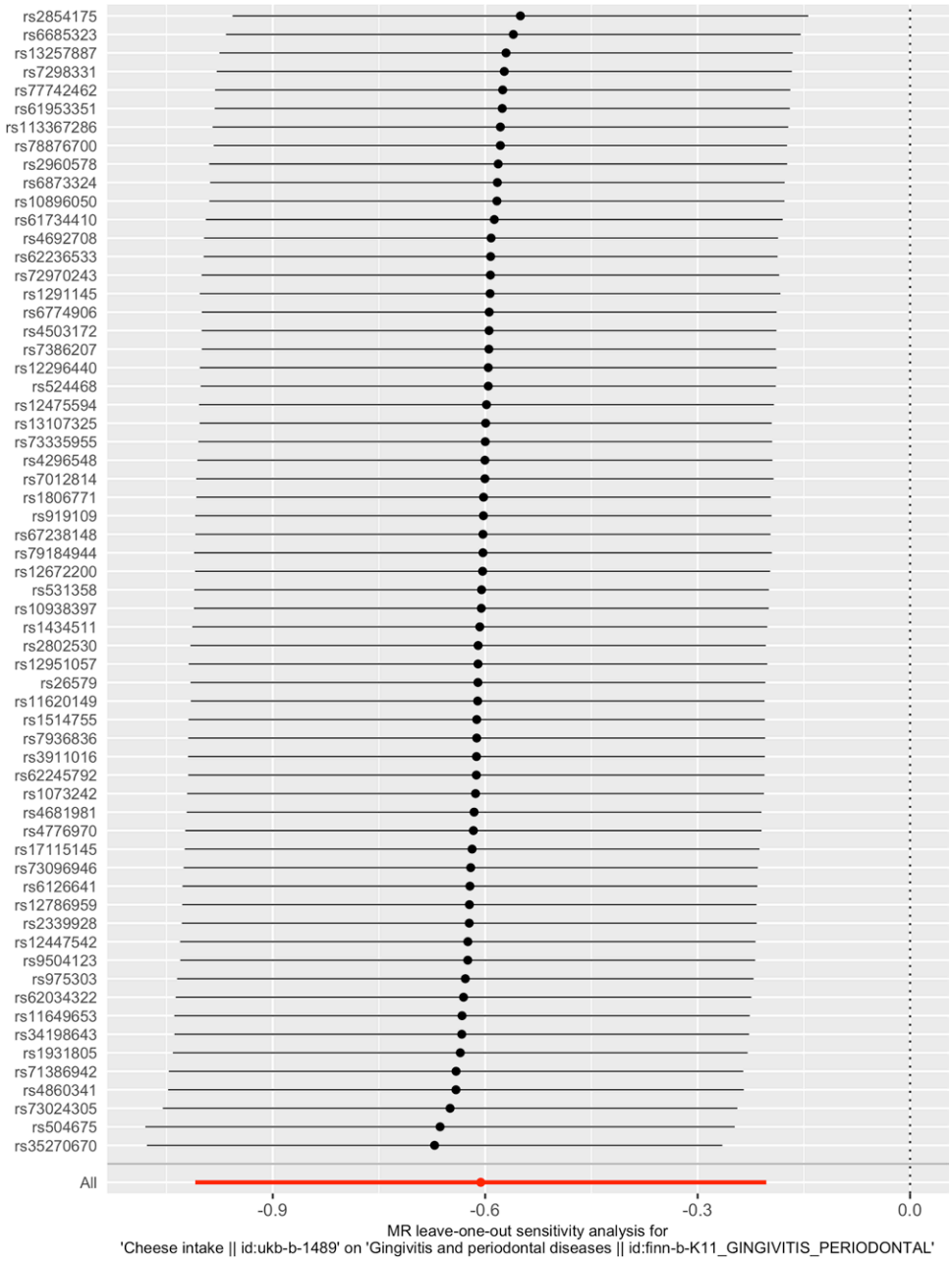

Figure 4. Leave-one-out plot for the sensitivity analysis of cheese intake on periodontal disease.

References

[1] Usui M, Onizuka S, Sato T, Kokabu S, Ariyoshi W, Nakashima K. Mechanism of alveolar bone destruction in periodontitis – periodontal bacteria and inflammation. Jpn Dent Sci Rev. 2021;57:201–8.

[2] Pattamatta M, Chapple I, Listl S. The value-for money of preventing and managing periodontitis: opportunities and challenges [published online ahead of print May 24, 2024]. Periodontol 2000. doi: 10.1111/prd.12569.

[3] Isola G, Santonocito S, Lupi SM, et al. Periodontal health and disease in the context of systemic diseases. Mediators Inflamm. 2023;2023:9720947.

[4] Bartold PM. Lifestyle and periodontitis: the emergence of personalized periodontics. Periodontol 2000. 2018;78:7–11.

[5] Santonocito S, Giudice A, Polizzi A, et al. A cross-talk between diet and the oral microbiome: balance of nutrition on inflammation and immune system's response during periodontitis. Nutrients. 2022;14:2426.

[6] Ertaş Öztürk Y, Şahin T, Özmeriç Kurtuluş N. Comparison of dietary intakes and fermented food consumption in patients with and without periodontal disease. comparison of dietary intakes and fermented food consumption in patients with and without periodontal disease. Black Sea J Health Sci. 2023;6:617–24.

[7] Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. J Periodontol. 2006;77:289–94.

[8] Shimazaki Y, Shirota T, Uchida K, et al. Intake of dairy products and periodontal disease: the Hisayama study. J Periodontol. 2008;79:131–7.

[9] Adegboye AR, Christensen LB, Holm-Pedersen P, Avlund K, Boucher BJ, Heitmann BL. Intake of dairy products in relation to periodontitis in older Danish adults. Nutrients. 2012;4:1219–29.

[10] Zhang J, Sun X, Xiao L, Xie C, Xuan D, Luo G. Gene polymorphisms and periodontitis. Periodontol 2000. 2011;56:102–24.

[11] Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. JAMA. 2017;318:1925–6.

[12] Burgess S, Scott RA, Timpson NJ, Smith G D, Thompson SG. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol. 2015;30:543–52.

[13] Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol. 2016;27:3253–65.

[14] Burgess S, Thompson SG; CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011;40:755–64.
[15] Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32:377–89.
[16] Haycock PC, Burgess S, Wade KH, Bowden J, Relton C, Davey Smith G. Best (but oft-forgotten) practices: the design, analysis, and interpretation of Mendelian randomization studies. Am J Clin Nutr. 2016;103:965–78.
[17] Hemani G, Zheng J, Elsworth B, et al. The MR-base platform supports systematic causal inference across the human phenome. Elife. 2018;7:e34408.
[18] Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations: update for summer 2023. Wellcome Open Res. 2019;4:186.
[19] Kuru BE, Laleman I, Yalnızoğlu T, Kuru L, Teughels W. The influence of a bifidobacterium animalis probiotic on gingival health: a randomized controlled clinical trial. J Periodontol. 2017;88:1115–23.
[20] Özener H, Kuru L, Kadir T, Kuru B. Bifidobacterium animalis subsp. lactis as adjunct to non-surgical periodontal treatment in periodontitis: a randomized controlled clinical trial. Clin Oral Investig. 2023;27:1965–72.
[21] Yuki O, Furutani C, Mizota Y, et al. Effect of bovine milk fermented with Lactobacillus rhamnosus L8020 on periodontal disease in individuals with intellectual disability: a randomized clinical trial. J Appl Oral Sci. 2019;27:e20180564.
[22] Ma J, Furuta M, Uchida K, et al. Yogurt product intake and reduction of tooth loss risk in a Japanese community. J Clin Periodontol. 2022;49:345–52.
[23] Lee K, Kim J. Dairy food consumption is inversely associated with the prevalence of periodontal disease in Korean adults. Nutrients. 2019;11:1035.
[24] Min EJ, Jeong S, Park JB. Evaluation of the association between amount and type of milk consumption and periodontitis: data from the Korea National Health and Nutrition Examination Survey (2016-2018). Nutrients. 2023;15:914.
[25] Zhou T, Xu W, Wang Q, et al. The effect of the "Oral-Gut" axis on periodontitis in inflammatory bowel disease: a review of microbe and immune mechanism associations. Front Cell Infect Microbiol. 2023;13:1132420.
[26] Vieira LV, de Sousa LM, Maia TAC, et al. Milk Kefir therapy reduces inflammation and alveolar bone loss on periodontitis in rats. Biomed Pharmacother. 2021;139:111677.
[27] Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol. 2008;79(8 Suppl):1585–91.
[28] Lira-Junior R, Figueredo CM. Periodontal and inflammatory bowel diseases: is there evidence of complex pathogenic interactions? World J Gastroenterol. 2016;22:7963–72.
[29] Vavricka SR, Manser CN, Hediger S, et al. Periodontitis and gingivitis in inflammatory bowel disease: a case-control study. Inflamm Bowel Dis. 2013;19:2768–77.
[30] Rolim FRL, Oliveira CJB, de Freitas Neto OC, et al. Microbiological, immunological, and histological changes in the gut of Salmonella Enteritidis-challenged rats fed goat cheese containing Lactobacillus rhamnosus EM1107. J Dairy Sci. 2021;104:179–97.