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Research article

A study on the relationship between cheese intake and caries occurrence based on Mendelian randomization method

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ABSTRACT

Objective: The study aims to investigate the causal relationship between cheese intake and caries occurrence by a two-sample Mendelian randomization method (TSMR).
Methods: Data from a genome-wide association study (GWAS) on cheese intake as an exposure factor were collected, and dental caries was the outcome variable, appropriate SNPs were selected as instrumental variables (IVs). The TSMR was analyzed by the inverse variance weighting (IVW) method, weighted median method, MR-Egger regression method, simple model and weighted model.
Results: We identified forty-four single-nucleotide polymorphisms (SNPs) in the gene encoding group-specific component (cheese) that were associated with cheese intake, and IVW was adopted. The IVW method supported a relationship between cheese intake and the risk of dental caries occurrence[OR,1.00(95 %CI,0.99–1.00), $P = 0.039 < 0.05$]. There was no horizontal pleiotropy between the IVs($b = -0.0037$, $P = 0.39$), and the sensitivity analysis using the "leave-one-out" method was robust to causal effects.
Conclusion: The results of the TSMR analysis supported that an appropriate intake of cheese could reduce the occurrence of dental caries.

1. Introduction

Dental caries is an intricate, persistent, and multifaceted disease with high prevalence in both developed and developing countries. Caries appear to be widespread among specific individual groups, and their causes remain unclear. Some studies have reported that individuals can resist caries even in the presence of a highly cariogenic diet. This implies that several genetic, physical, and environmental factors may determine the susceptibility or resistance to dental caries. Recent studies have indicated that genetics may be

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associated with caries incidence [1]. Studies examining the relationship between cheese intake and caries occurrence are relatively few and mainly observational in nature. Unmeasured confounding and reverse causation can impact the association between exposure and results in traditional epidemiological research, restricting the ability to infer causality [2].

The Mendelian randomization (MR) method is currently being extensively employed to investigate causality in genome-wide association study (GWAS) data. This method utilizes the random assortment and recombination of genetic variations during gamete development to randomly group populations. This approach theoretically mitigates the influence of factors that could distort the results and gives more importance to the genetic variation that is responsible for the exposure being studied [known as the instrumental variable (IV)]. This eliminates the issue of reverse causality, where the outcome affects the exposure instead of the other way around [3,4].

Two-sample MR (TSMR) is a statistical approach that utilizes genetic variation as an IV to evaluate whether the observed relationship between exposure factors and outcomes is indicative of a causal influence. This study employed a TSMR method to analyze the causal relationship between cheese intake and dental caries occurrence at the genetic level, using single-nucleotide polymorphism (SNP) as an IV and based on GWAS pooled data.

2. Information and methods

2.1. Data sources

The cheese intake-related data were acquired from the IEU open GWAS database (https://gwas.mrcieu.ac.uk/datasets/ukb-b-1489/). This dataset had a sample size of 451,486, and the SNP number was 9,851,867. The data related to dental caries were retrieved by accessing the IEU open GWAS database (https://gwas.mrcieu.ac.uk/datasets/ukb-b-4770/). The sample size of this database is 463,010, including 1997 caries patients and 461,013 control populations, and the number of SNPs is 9,851,867 (Table 1).

2.2. Screening for SNPs

First, Genomewide significant SNPs associated with cheese intake were selected and pooled ($P < 5 \times 10^{-8}$). We established a linkage disequilibrium (LD) threshold of $r2<0.05$ and a genetic distance of 10 MB. We next chose the SNPs with the lowest P value to ensure that the IVs were independent. Subsequently, data were obtained from both databases and combined to align the effect values for exposure and outcome with the same effect allele.

2.3. Three assumptions

The accuracy of causality analysis using MR depends on these three assumptions [5]: (1)Satisfying IV hypothesis 1- the IV is associated with exposure (cheese intake). This hypothesis could be supported by screening for genomewide significant SNPs related to cheese intake, $P < 5 \times 10\text{-}8$, and F-statistic values > 10. (2)Satisfying IV hypothesis 2- IV was independent of the combined effect of all confounding factors, such as bone and inherited genes. We examined the relationship between the LD of SNPs that were highly linked to exposure and SNPs that are potentially related to confounding factors. If the correlation coefficient is above a certain threshold ($r2 > 0.5$), the chosen SNPs will be excluded. (3) Satisfying IV hypothesis 3 considering exposure and confounding factors, IV is independent of the outcome (caries). Horizontal pleiotropy is that IV affects the outcome by means other than exposure, may violate this hypothesis and can be tested with MR-Egger regression and MR-PRESSO methods (Fig. 1).

Table 1
Source of data on cheese intake and incidence of dental caries.

	Cheese intake	dental caries
Datasets	ukb-b-1489	ukb-b-4770
Year	2018	2018
Category	Categorical Ordered	Binary
Subcategory	NA	NA
Population	European	European
Sex	Males and Females	Males and Females
Sample size	451486	463010
Number of SNPs	9851867	9851867
Unit	SD	SD
Priority	1	1
Author	Ben Elsworth	Ben Elsworth
Consortium	MRC-IEU	MRC-IEU
Ontology	NA	NA
Build	HG19/GRCh37	HG19/GRCh37
Note	1408: Output from GWAS pipeline utilizing Phesant-derived variables from UKBiobank	41202#K029: Output from GWAS pipeline employing Phesant-derived variables from UKBiobank

2.4. Confounders removal for IVs

The secondary phenotypes of each SNP were found on Phenoscanner(http://www.phenoscanner.medschl.cam.ac.uk/), removing SNPs with exposure and outcome-related confounding factors, rs1024853 was found to be strongly associated with confounding factors in this study and was therefore excluded.

2.5. IV sensitivity analysis

The MR-PRESSO method was utilized for detecting outliers and reanalyzing them after removing them. After excluding one SNP at a time, a "leave-one-out" sensitivity analysis was conducted on the remaining SNPS to determine the influence of individual SNPS on the results. In addition, the intercept term of MR-Egger regression was also employed to test for the presence of horizontal pleiotropy of SNPs, while utilizing Cochran Q to test for IV heterogeneity.

2.6. Statistical analysis

This study mainly employed inverse variance weighted analysis (IVW) to examine the cheese intake and dental caries relationship; IVW result is the main index of this study. This study used the heterogeneity function in the MR package to check the heterogeneity and found $p < 0.05$. This study shows a strong heterogeneity, and the random-effects model is utilized. Additional analyses were conducted through MR-Egger, weighted median method and MR-PRESSO to further validate the IVW results reliability, where MR-Egger regression analysis is often used as a sensitivity analysis to other statistical results. Statistical analyses were carried out using R 4. 1. 0. and the TSMR software package[6–8].

3. Results

3.1. Basic information of SNPs

Our study included 45 SNPs, and the rs number, effect allele, and non-effect allele of each SNP locus were extracted, which are detailed in Table 2 and Fig. 2. Multiple statistical methods were applied to the included SNPs to infer the causal correlation between cheese intake and dental caries.

3.2. Sensitivity analysis of MR

The pleiotropy_test function in the MR Package was employed to assess pleiotropy. The primary assessment is determining if there is horizontal pleiotropy among several IVs, with the intercept term of the MR-Egger method frequently employed to indicate this. The outcome is a p-value of 0.3997821, suggesting no horizontal pleiotropy.

The heterogeneity function is mainly used. Significant differences between IVs suggest a high heterogeneity level among these IVs throughout testing. Our results showed $P < 0.05$, so the random effect model was used, and the IVW test result was $b = -0.003664317$, p-val = 0.03885259. It can be considered that there is no heterogeneity among IVs, and the causal correlation is unlikely to be affected by the differences between IVs.

The regression results of the five methods are shown in Table 3. The IVW method supported a relationship between cheese intake and dental caries occurrence risk [OR,1.00(95 %CI,0.99–1.00), $P = 0.039 < 0.05$].

3.3. Visual analysis of MR results

2.3.1 The scatter Fig. 3 depicts MR analysis results between the exposure and outcome factors. Each point represents the line on

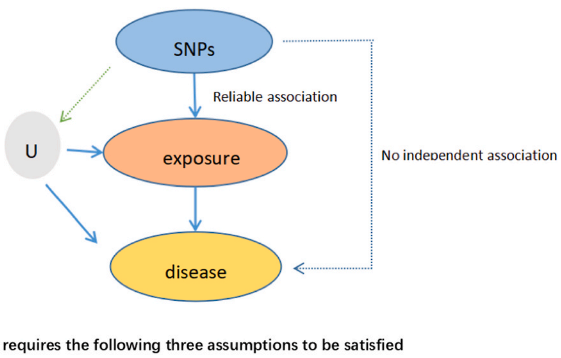

Fig. 1. MR requires the following three assumptions to be satisfied.

Table 2
Basic information on instrumental variables related to cheese intake and dental caries occurrence.

SNP	CHIR	EA	OA	Cheese intake			dental caries		
				β	SE	P	β	SE	P
rs6873324	5	C	A	−0.01	2.27 × 10^{-3}	<0. 001	1. 96 × 10^{-4}	1. 39 × 10^{-4}	0.160
rs2960578	18	G	T	0.02	2.24 × 10^{-3}	<0. 001	−2.12 × 10^{-4}	1. 36 × 10^{-4}	0.120
rs1291145	20	C	T	−0.02	2.41 × 10^{-3}	<0. 001	6.05 × 10^{-5}	1. 47 × 10^{-4}	0.680
rs524468	12	G	A	−0.01	2.55 × 10^{-3}	<0. 001	3.78 × 10^{-4}	1. 56 × 10^{-4}	0.015
rs13257887	8	C	T	0.02	2.56 × 10^{-3}	<0. 001	−4.46 × 10^{-5}	1. 56 × 10^{-4}	0.780
rs7386207	8	T	C	−0.01	2.27 × 10^{-3}	<0. 001	−2.69 × 10^{-4}	1. 38 × 10^{-4}	0.052
rs10938397	4	G	A	−0.01	2.26 × 10^{-3}	<0. 001	3 −1. 82 × 10^{-4} 89	1. 38 × 10^{-4}	0.190
rs2352974	3	T	C	−0.01	2.24 × 10^{-3}	<0. 001	4.23 × 10^{-4}	1. 37 × 10^{-4}	0.002
rs4776970	15	T	A	0.02	2.33 × 10^{-3}	<0. 001	−1. 32 × 10^{-4}	1. 42 × 10^{-4}	0.350
rs35270670	15	G	A	0.02	2.71 × 10^{-3}	<0. 001	−6.56 × 10^{-5}	1. 65 × 10^{-4}	0.690
rs9649582	7	T	A	−0.01	2.41 × 10^{-3}	<0. 001	5.66 × 10^{-5}	1. 47 × 10^{-4}	0.700
rs4503172	9	T	C	0.01	2.30 × 10^{-3}	<0. 001	−9.70 × 10^{-5}	1. 40 × 10^{-4}	0.490
rs7012814	8	A	G	−0.02	2.25 × 10^{-3}	<0. 001	−1.49 × 10^{-4}	1. 37 × 10^{-4}	0.280
rs1931805	6	C	T	0.01	2.24 × 10^{-3}	<0. 001	1.10 × 10^{-6}	1. 36 × 10^{-4}	0.990
rs10896050	11	T	G	−0.02	2.83 × 10^{-3}	<0. 001	3.68 × 10^{-5}	1. 73 × 10^{-4}	0.830
rs12786959	11	T	A	−0.02	2.82 × 10^{-3}	<0. 001	1.53 × 10^{-5}	1. 72 × 10^{-4}	0.930
rs26579	5	C	G	−0.01	2.30 × 10^{-3}	<0. 001	−3.15 × 10^{-4}	1. 40 × 10^{-4}	0.024
rs4692708	4	C	A	0.01	2.59 × 10^{-3}	<0. 001	1.11 × 10^{-4}	1. 58 × 10^{-4}	0.480
rs975303	6	G	A	0.02	2.90 × 10^{-3}	<0. 001	−2.13 × 10^{-4}	1. 77 × 10^{-4}	0.230
rs34198643	7	T	C	−0.01	2.68 × 10^{-3}	<0. 001	−6.14 × 10^{-5}	1. 63 × 10^{-4}	0.710
rs12672200	7	A	G	−0.01	2.40 × 10^{-3}	<0. 001	4.99 × 10^{-5}	1. 46 × 10^{-4}	0.730
rs62034322	16	A	G	−0.01	2.30 × 10^{-3}	<0. 001	−2.58 × 10^{-5}	1. 40 × 10^{-4}	0.850
rs531358	1	T	C	0.01	2.34 × 10^{-3}	<0. 001	−1.63 × 10^{-4}	1. 43 × 10^{-4}	0.250
rs61953351	12	T	G	0.01	2.58 × 10^{-3}	<0. 001	−1.32 × 10^{-4}	1. 57 × 10^{-4}	0.400
rs1514755	2	G	A	0.01	2.62 × 10^{-3}	<0. 001	−9.37 × 10^{-6}	1. 60 × 10^{-4}	0.950
rs4296548	3	G	T	0.01	2.29 × 10^{-3}	<0. 001	−5.96 × 10^{-5}	1. 40 × 10^{-4}	0.670
rs113367286	7	T	C	0.01	2.50 × 10^{-3}	<0. 001	1.06 × 10^{-4}	1. 53 × 10^{-4}	0.490
rs4681981	3	A	C	−0.01	2.24 × 10^{-3}	<0. 001	−2.57 × 10^{-4}	1. 37 × 10^{-4}	0.060
rs12475594	2	G	A	0.02	2.93 × 10^{-3}	<0. 001	−1.06 × 10^{-4}	1. 78 × 10^{-4}	0.550
rs1434511	18	T	C	0.01	2.26 × 10^{-3}	<0. 001	7.70 × 10^{-5}	1. 38 × 10^{-4}	0.580
rs61734410	16	T	C	0.02	2.62 × 10^{-3}	<0. 001	−4.07 × 10^{-4}	1. 60 × 10^{-4}	0.011
rs6126641	20	A	G	0.01	2.40 × 10^{-3}	<0. 001	1.29 × 10^{-4}	1. 46 × 10^{-4}	0.380
rs11649653	16	G	C	0.01	2.29 × 10^{-3}	<0. 001	−1.61 × 10^{-4}	1. 40 × 10^{-4}	0.250
rs6685323	1	T	C	−0.01	2.42 × 10^{-3}	<0. 001	−1.32 × 10^{-5}	1. 47 × 10^{-4}	0.930
rs9504123	6	C	A	0.01	2.50 × 10^{-3}	<0. 001	1.30 × 10^{-4}	1. 53 × 10^{-4}	0.390
rs2339928	2	A	G	0.01	2.44 × 10^{-3}	<0. 001	1.05 × 10^{-4}	1. 49 × 10^{-4}	0.480
rs504675	2	T	C	0.03	2.34 × 10^{-3}	<0. 001	−3.91 × 10^{-5}	1. 43 × 10^{-4}	0.780
rs7936836	11	A	C	0.02	2.27 × 10^{-3}	<0. 001	−3.31 × 10^{-4}	1. 39 × 10^{-4}	0.017
rs7298331	12	C	A	−0.01	2.31 × 10^{-3}	<0. 001	2.37 × 10^{-4}	1. 41 × 10^{-4}	0.092
rs17115145	14	T	C	−0.01	2.29 × 10^{-3}	<0. 001	1.69 × 10^{-4}	1. 40 × 10^{-4}	0.230
rs2854175	17	A	C	0.02	2.57 × 10^{-3}	<0. 001	−2.48 × 10^{-4}	1. 57 × 10^{-4}	0.110
rs67238148	11	T	G	0.02	2.71 × 10^{-3}	<0. 001	−2.76 × 10^{-4}	1. 66 × 10^{-4}	0.096
rs71386942	16	A	C	0.01	2.52 × 10^{-3}	<0. 001	1.66 × 10^{-4}	1. 54 × 10^{-4}	0.280
rs1073242	13	A	G	0.02	2.29 × 10^{-3}	<0. 001	−1.73 × 10^{-4}	1. 40 × 10^{-4}	0.210

each point of an IV SNP, which actually reflects the 95 % confidence interval. The abscordinate and vertical axes are the effect of SNP on the exposure (cheese intake) and outcome factors (dental caries), respectively. The ratio of the two effects, the impact of exposure on the outcome, can be determined by the slope of the colored line depicted in the figure above. The lines with different colors represent different algorithms, and the results show that the lines with different algorithms are generally tilted downward, which means that the risk of dental caries decreases with the increase in cheese intake.

2.3.2 The results of MR Analysis of the IV, which is the forest Fig. 4 of SNPS. The solid line is positioned entirely to the left of 0, indicating that this SNP is associated with an elevated cheese intake and a decreased incidence of dental caries. Results beyond 0 exhibit a non-obvious effect. The single SNP results are not robust because cheese intake is affected by multiple SNPS here, so we need to look at the results together. The bottom red line, bottom red line shows that an increase in cheese intake can reduce the risk of dental caries.

2.3.3 After MR Results analysis, sensitivity analysis should be conducted to evaluate the results' reliability and stability, one of which is leave-one-out. Leave-one-out refers to the stepwise elimination of each SNP, computing the meta impact of the other SNPs, and assessing if the results are altered by excluding each SNP. A significantly changed result after removing a specific SNP indicates the substantial influence of this particular SNP on the results. Additionally, there may be outliers that should be eliminated (Fig. 5). The overall error line remains very stable, with all error lines positioned to the left of 0, demonstrating the results' reliability.

2.3.4 If there are particular outlier points indicating that there are outliers, MR Analysis can be performed again after removal.

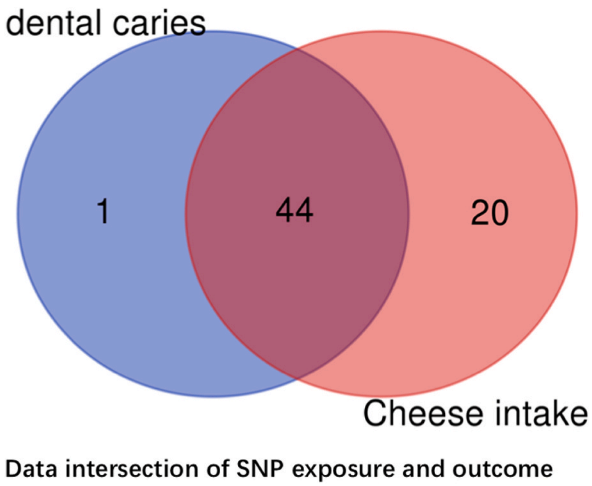

Fig. 2. Data intersection of SNP exposure and outcome.

Table 3
Cheese ingestion with the occurrence of dental caries Two-sample Mendelian randomization analysis.

method	SNPs	b	SE	OR(95%CI)	P
MR-Egger	44	−0.01	0.01	0.99 (0.97 , 1.01)	0.232
Weighted median	44	−0.003	0.00	1.00 (0.99 , 1.00)	0.193
Inverse variance weighted	44	−0.004	0.00	1.00 (0.99 , 1.00)	0.039
Simple mode	44	−0.004	0.01	1.00 (0.99 , 1.01)	0.454
Weighted mode	44	−0.003	0.00	1.00 (0.99 , 1.01)	0.483

After heterogeneity analysis of MR results, funnel Fig. 6 shows the heterogeneity of SNPS. We noticed that the points on either side of the IVW line had a roughly symmetrical pattern, indicating reliable results.

4. Discussion

As a common oral disease of preschool children, tooth decay is mainly caused by the invasion of bacteria into the teeth, resulting in the enzymatic decomposition of the organic matter of the teeth, which leads to the destruction of the dental tissue [9]. Dental caries has been regarded as one of the key prevention and control diseases by the World Health Organization, which not only causes pain but also easily develops into serious oral diseases such as pulpitis and periapical inflammation if not treated in time. The healthy development of children is seriously hindered [10]. With the continuous development of society, people's dietary structure and diet are also changing. More and more foods with high sugar content appear in the public view and draw the attention of parents of children, and the lack of oral knowledge makes the incidence of dental caries gradually increase [11].

The correlation between nutrition and dental wellness is a well-discussed subject. The investigation of cheese's cavity resistance has been a recent prominent subject of study. The majority of research has indicated that consuming cheese as the final item in a meal can aid in the prevention of dental caries. Mechanisms related to the possible reduction of enamel demineralization by cheese have been proposed. Wang et al. showed that consuming a large amount of yogurt and a little amount of cheese was linked to a lower risk of developing dental caries among U.S. children and adolescents [12]. These outcomes can be used to update and complement public health policy regarding milk and dairy products and evidence for caries prevention [13]. The Lempert SM study validated that consuming a substantial amount of dairy products was linked to a reduced risk of experiencing caries in the future [14]. Tanaka K's study demonstrated a potential correlation between increased yogurt intake and reduced occurrence of dental caries in young children [15]. The results of the study by Lorenzini EC showed that consuming cheese after dinner offers essential micronutrients such as calcium, vitamins, and certain amino acids. This alters the oral pH close to the basic conditions, resulting in a slight alteration of the oral microbiota, thus reducing the total number of acidophilic bacteria. It provides a better protective environment to reduce the formation and development of caries [16].

MR analysis utilizes genetic variants to evaluate the causal effects of phenotypes influenced by these genetic variants on health outcomes. This represents a new and innovative method for conducting epidemiological studies, which involves using genetic variation to determine the cause-and-effect relationship between exposure factors and outcome variables. Our findings indicate that the results obtained using both the IVW and MR-Egger regression methods were in agreement. The TSMR results confirmed the causal relationship between cheese and the risk of dental caries. Consuming cheese has a positive impact in reducing the occurrence of dental caries. MR analysis offers a method to investigate relationships without the inherent biases in standard epidemiological studies, such as

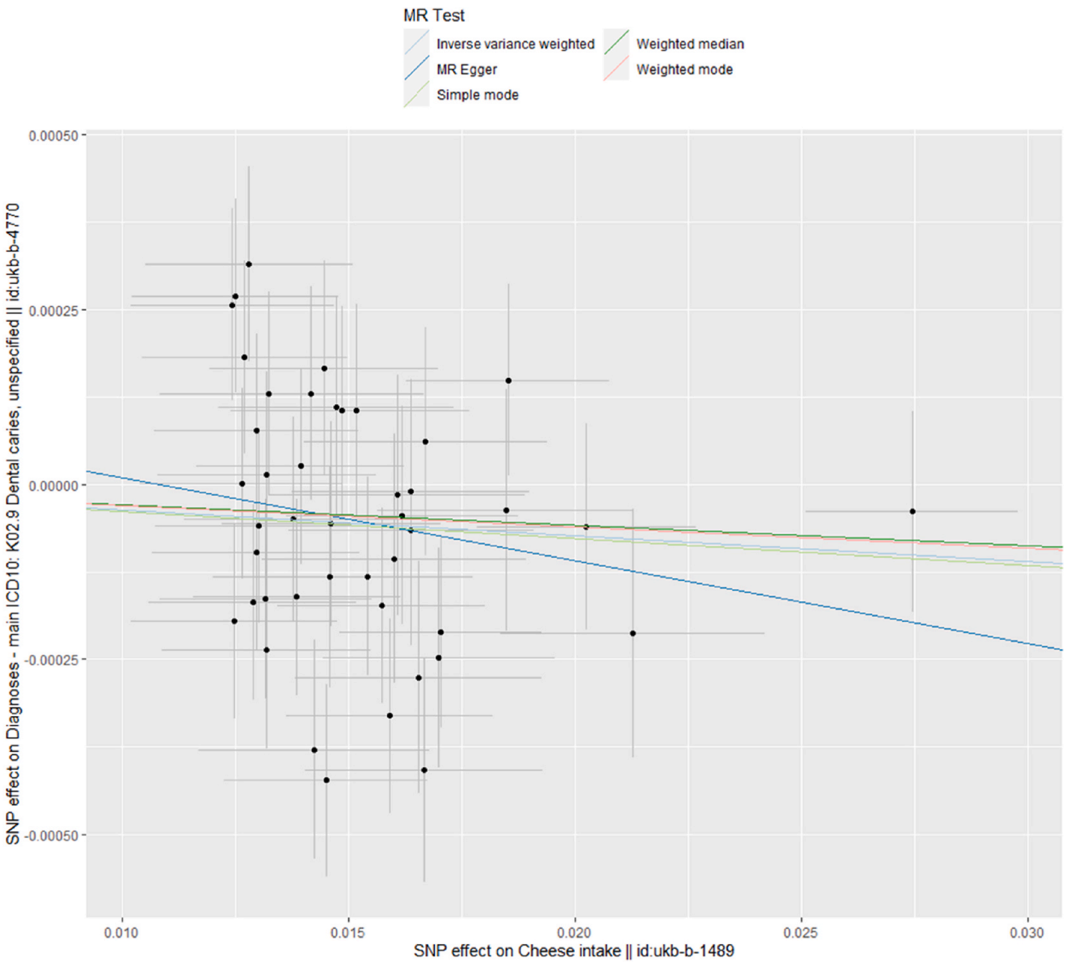

Fig. 3. The X- and Y-axis represent the effect of the SNP on exposure and outcome, respectively, and the slope <0 represents cheese intake as a favorable factor for dental caries.

reverse causal links and potential confounding factors [17].

4.1. Limitation

This study validated the applicability of the MR method for assessing the risk of chronic diseases in a European population. To explore the differences in caries-related genetic loci between Chinese and European populations and to find the key risk factors of caries that can be prevented at the microscopic level according to the characteristics of Chinese populations, it is also meaningful to prevent caries early in China. Nevertheless, GWAS data available for Asian and Chinese populations are limited. Additionally, acquiring and organizing data from other databases poses a challenge. Therefore, validating our findings in Chinese populations in conjunction with clinical and randomized controlled trials is imperative.

5. Conclusion

This study shows that cheese exhibited a causal relationship with dental caries risk: the intake of cheese is beneficial in reducing dental caries occurrence.

Availability of data and materials

The datasets generated and analyzed throughout our study are available in the [IEU open GWAS] repository, https://gwas.mrcieu.ac.uk/datasets/ukb-b-1489/https://gwas.mrcieu.ac.uk/datasets/ukb-b-4770/

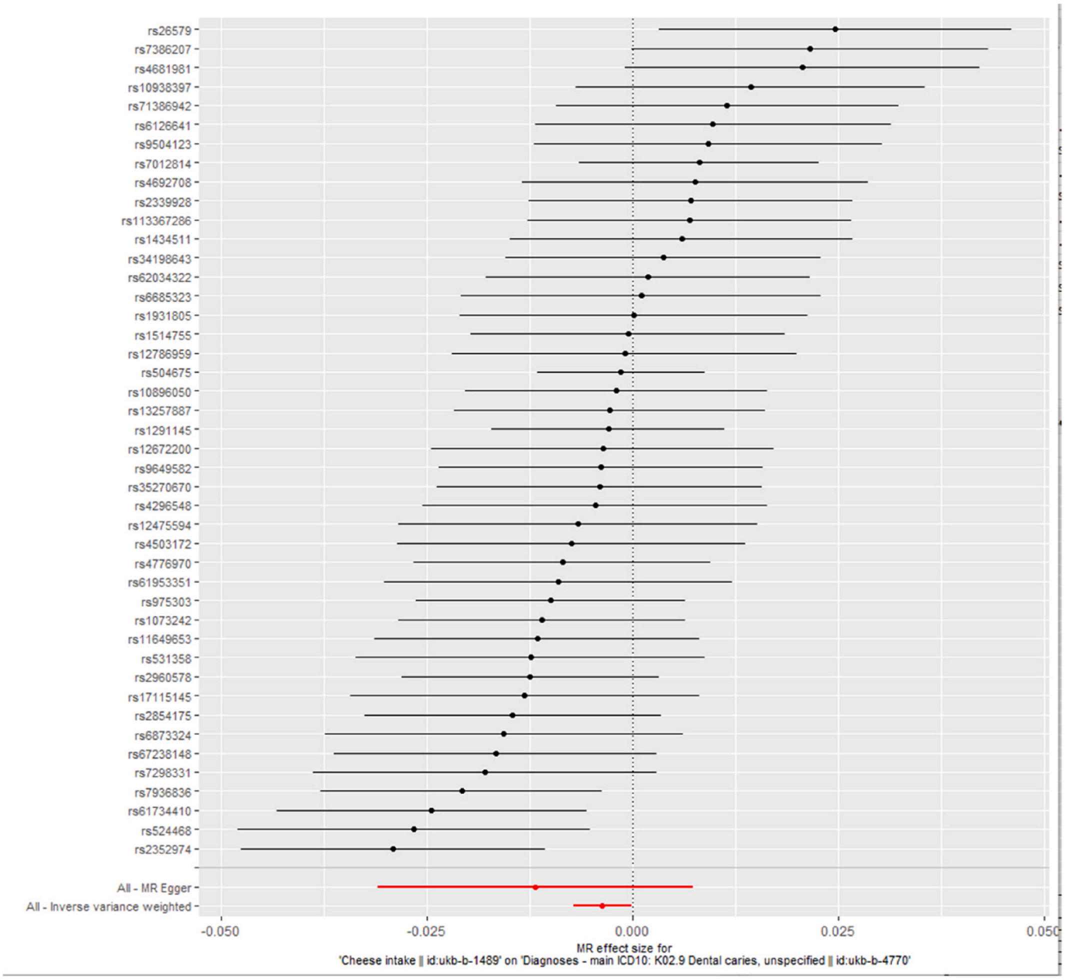

Fig. 4. Each horizontal solid line represents a single SNP estimated by the Wald ratio method.

I. ethical approval and participation consent

IEU open GWAS is a public database. The patients included in the database have received ethical approval. Users have the ability to freely download pertinent data for research purposes and publish related articles. The foundation of our analysis relies on publicly available data, eliminating any ethical concerns or potential conflicts of interest.

ii. Consent to publication

Not applicable.

ii. Data availability statement

The datasets generated and analyzed throughout our study are available in the IEU open GWAS repository.

The data related to cheese intake were retrieved by accessing the IEU open GWAS database (https://gwas.mrcieu.ac.uk/datasets/ukb-b-1489/). The sample size of this dataset was 451,486, and the SNP number was 9,851,867. The data related to dental caries were retrieved by accessing the IEU open GWAS database (https://gwas.mrcieu.ac.uk/datasets/ukb-b-4770/). The sample size of this database is 463,010, including 1997 caries patients and 461,013 control populations, and the number of SNPs is 9,851,867.

Conflict of interest：

None of the authors have any relevant financial relationship(s) with a commercial interest.

Fig. 5. The effect of each SNP on the Mendelian randomization analysis results were judged, and if there were outliers that needed to be removed and reanalyzed.

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Health Commission of Jiangxi Province, lncRNASNHG18 regulates miR-211-5p targeting ACSL4 to promote iron death in oral squamous cell cancer cells (SKJP220226210);

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CRediT authorship contribution statement

Ruoyan Zhang: Writing – review & editing, Visualization, Investigation. **Huaxiang Jiang:** Writing – original draft, Data curation. **Zishun Qin:** Supervision, Resources, Writing – review & editing, Funding acquisition, Conceptualization, Visualization, Investigation, Data curation, Software, Methodology, Formal analysis. **Jun Wang:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Xi Hu:** Writing – original draft, Software, Methodology, Investigation, Formal analysis.

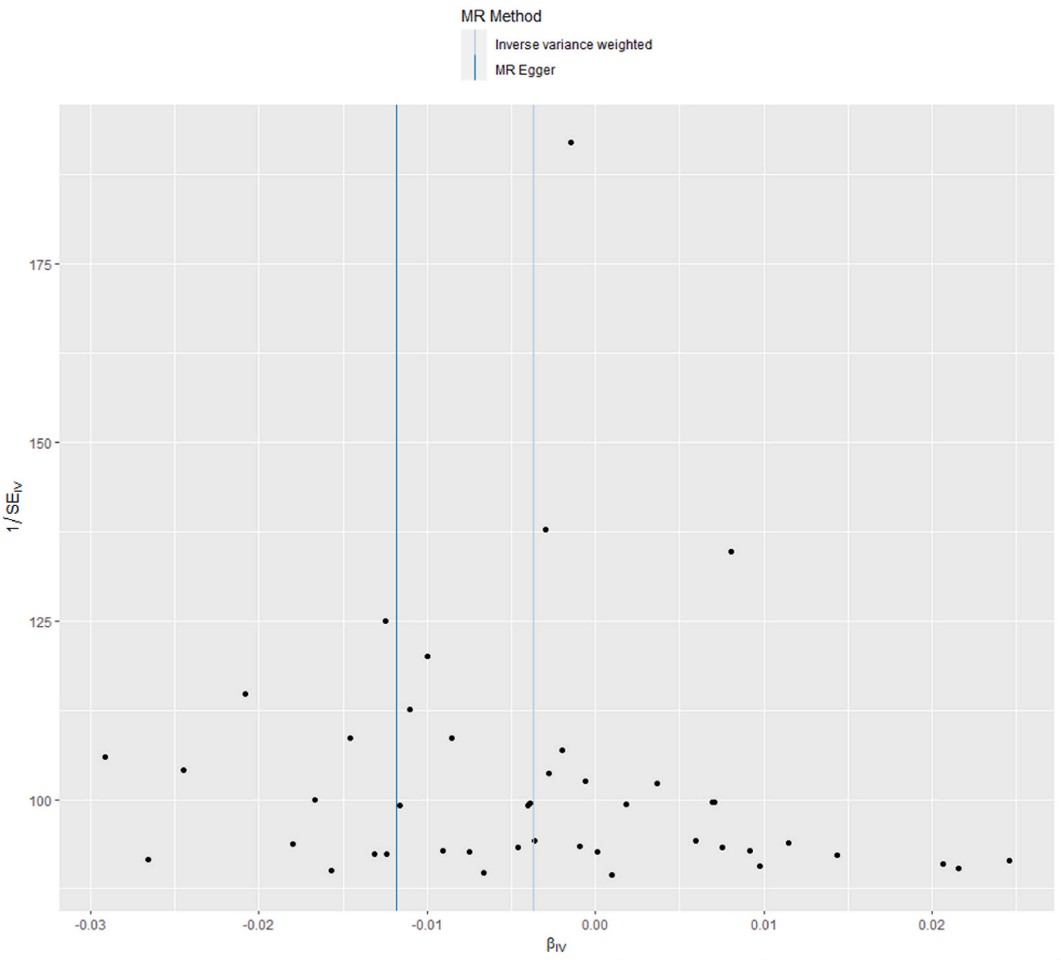

Fig. 6. A roughly symmetrical pattern of the points on either side of the IVW line.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] S. Opal, S. Garg, J. Jain, I. Walia, Genetic factors affecting dental caries risk, Aust. Dent. J. 60 (2015) 2–11.
[2] F.P. Hartwig, M.C. Borges, B.L. Horta, J. Bowden, G. Davey Smith, Inflammatory Biomarkers and risk of Schizophrenia: a 2-sample Mendelian randomization study, JAMA Psychiatr. 74 (2017) 1226–1233.
[3] D.M. Evans, G. Davey Smith, Mendelian randomization: new Applications in the coming Age of hypothesis-Free causality, Annu Rev Genomics Hum Genet. 16 (2015) 327–350.
[4] S.C. Bae, Y.H. Lee, Coffee consumption and the risk of rheumatoid arthritis and systemic lupus erythematosus: a Mendelian randomization study, Clin. Rheumatol. 37 (2018) 2875–2879.
[5] S. Burgess, A. Butterworth, S.G. Thompson, Mendelian randomization analysis with multiple genetic variants using summarized data, Genet. Epidemiol. 37 (2013) 658–665.
[6] S.C. Bae, Y.H. Lee, Vitamin D level and risk of systemic lupus erythematosus and rheumatoid arthritis: a Mendelian randomization, Clin. Rheumatol. 37 (2018) 2415–2421.

[7] J. Bowden, G. Davey Smith, P.C. Haycock, S. Burgess, Consistent estimation in Mendelian randomization with Some Invalid Instruments using a weighted median estimator, Genet. Epidemiol. 40 (2016) 304–314.
[8] S. Burgess, S.G. Thompson, Interpreting findings from Mendelian randomization using the MR-Egger method, Eur. J. Epidemiol. 32 (2017) 377–389.
[9] V. Machiulskiene, G. Campus, J.C. Carvalho, I. Dige, K.R. Ekstrand, A. Jablonski-Momeni, M. Maltz, D.J. Manton, S. Martignon, E.A. Martinez-Mier, N.B. Pitts, A.G. Schulte, C.H. Splieth, L.M.A. Tenuta, A. Ferreira Zandona, B. Nyvad, Terminology of dental caries and dental caries management: Consensus Report of a workshop organized by ORCA and cariology research group of IADR, Caries Res. 54 (2020) 7–14.
[10] N.P. Innes, J.E. Clarkson, G.V.A. Douglas, et al., Child caries management: a randomized controlled trial in dental practice, Dent Res 99 (2020) 36–43.
[11] M.M. Almoudi, A.S. Hussein, M.I. Abu Hassan, et al., Dental caries and vitamin D status in children in Asia, Pediatr. Int. 61 (2019) 327–338.
[12] E.L. Herod, The effect of cheese on dental caries: a review of the literature, Aust. Dent. J. 36 (1991) 120–125.
[13] J. Wang, G. Jin, K. Gu, J. Sun, R. Zhang, X. Jiang, Association between milk and dairy product intake and the risk of dental caries in children and adolescents: nhanes 2011-2016, Asia Pac. J. Clin. Nutr. 30 (2021) 283–290.
[14] S.M. Lempert, L.B. Christensen, K. Froberg, K. Raymond, B.L. Heitmann, Association between dairy intake and caries among children and adolescents. results from the Danish EYHS follow-up study, Caries Res. 49 (2015) 251–258.
[15] K. Tanaka, Y. Miyake, S. Sasaki, Intake of dairy products and the prevalence of dental caries in young children, J. Dent. 38 (2010) 579–583.
[16] E.C. Lorenzini, B. Lazzari, G.M. Tartaglia, G. Farronato, V. Lanteri, S. Botti, F. Biscarini, P. Cozzi, A. Stella, Oral ecological environment modifications by hard-cheese: from pH to microbiome: a prospective cohort study based on 16S rRNA metabarcoding approach, J. Transl. Med. 20 (2022) 312.
[17] H.Y. Guo, W. Wang, H. Peng, H. Yuan, Bidirectional two-sample Mendelian randomization study of causality between rheumatoid arthritis and myocardial infarction, Front. Immunol. 2022 (13) (2022) 1017444.