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ORIGINAL ARTICLE

Clinical and Translational Research

Different effects of 24 dietary intakes on gastroesophageal reflux disease: A mendelian randomization

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Abstract

BACKGROUND

In observational studies, dietary intakes are associated with gastroesophageal reflux disease (GERD).

AIM

To conduct a two-sample mendelian randomization (MR) analysis to determine whether those associations are causal.

METHODS

To explore the relationship between dietary intake and the risk of GERD, we extracted appropriate single nucleotide polymorphisms from genome-wide association study data on 24 dietary intakes. Three methods were adopted for data analysis: Inverse variance weighting, weighted median methods, and MR-Egger's method. The odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the causal association between dietary intake and GERD.

RESULTS

Our univariate Mendelian randomization (UVMR) results showed significant evidence that pork intake (OR, 2.83; 95%CI: 1.76-4.55; $P = 1.84 \times 10^{-5}$), beer intake (OR, 2.70, 95%CI: 2.00-3.64; $P = 6.54 \times 10^{-11}$), non-oily fish intake (OR, 2.41; 95%CI: 1.49-3.91; $P = 3.59 \times 10^{-4}$) have a protective effect on GERD. In addition, dried fruit intake (OR, 0.37; 95%CI: 0.27-0.50; 6.27×10^{-11}), red wine intake (OR, 0.34; 95%CI: 0.25-0.47; $P = 1.90 \times 10^{-11}$), cheese intake (OR, 0.46; 95%CI: 0.39-0.55; $P = 3.73 \times 10^{-19}$), bread intake (OR, 0.72; 95%CI: 0.56-0.92; $P = 0.0009$) and cereal intake (OR, 0.45;

95%CI: 0.36-0.57; $P = 2.07 \times 10^{-11}$) were negatively associated with the risk of GERD. There was a suggestive association for genetically predicted coffee intake (OR per one SD increase, 1.22, 95%CI: 1.03-1.44; $P = 0.019$). Multivariate Mendelian randomization further confirmed that dried fruit intake, red wine intake, cheese intake, and cereal intake directly affected GERD. In contrast, the impact of pork intake, beer intake, non-oily fish intake, and bread intake on GERD was partly driven by the common risk factors for GERD. However, after adjusting for all four elements, there was no longer a suggestive association between coffee intake and GERD.

CONCLUSION

This study provides MR evidence to support the causal relationship between a broad range of dietary intake and GERD, providing new insights for the treatment and prevention of GERD.

Key Words: Dietary; Gastroesophageal reflux disease; Mendelian randomization; Disease management; Randomized controlled trial

Core Tip: Through genetic prediction, this study demonstrated the protective effect of dried fruit, red wine, cheese, bread, and cereal intake against gastroesophageal reflux disease (GERD) and the detrimental effects of pig, beer, and non-oily fish intake. Furthermore, even after accounting for body mass index, major depressive disorder, smoking, and alcohol consumption, the effect of genetically predicted dried fruit, red wine, cheese, and cereal on GERD persisted. Additionally, this study discovered that the consumption of tea, milk, yogurt, oily fish, beef, lamb, bacon, processed meat, cooked and raw vegetables, fresh fruit, salted and unsalted nuts, salted and unsalted peanuts, and cooked and raw vegetables were not linked to GERD.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) refers to the flow of gastric contents back into the esophagus, causing discomfort and complications[1]. Meanwhile, GERD can progress to Barrett's esophagus and even increase the risk of esophageal adenocarcinoma[2]. It is estimated that about 20% of people in Western countries suffer from GERD[3]. The prevalence of GERD has gradually transitioned from the developed world to developing countries[4]. GERD patients in developing countries face a financial burden and discomfort due to deficient appropriate treatment[5]. As an easily accessible and modifiable factor, many researchers have begun to focus on the impact of diet on GERD. A cohort study has demonstrated that diet plays a vital role in gastroesophageal reflux disease in American women[6]. The NIH and the American College of Gastroenterology have also identified dietary modification as the first-line treatment for patients with GERD [7]. However, the evidence for most studies is incomplete and inconsistent[8-10]. In observational studies, causal inference of associations may be prevented by unobserved confounding, misclassification, reverse causation, and other biases [11]. Determining the causal relationship between these diets and GERD is critical to disease management.

Mendelian randomization (MR) is a powerful tool for epidemiological research; The central idea is to use genetic variation as an instrument to evaluate the causal relationship between exposure and outcomes[12]. The basic principle refers to Mendel's second law of inheritance: One of the alleles is randomly passed on to the next generation during meiosis, so the genetic information is fixed at the time of formation of the fertilized egg[11]. Similar to a traditional randomized controlled trials (RCT), subjects are randomly assigned to treatment or control groups based on MR rule[13]. In addition, the random distribution of genetic variation is not affected by external environmental factors, and the direction of causal relationships is determined, imitating the randomization process of RCT[14].

No MR studies are exploring the causal effect of multiple diets on GERD. We conducted a two sample MR study to examine the correlation between 24 dietary intake and GERD risk.

MATERIALS AND METHODS

Study design

We evaluated the causal effects of 24 dietary incomes on GERD using two-sample Mendelian randomization. Then, we used multivariable MR (MVMR) to adjust for risk factors that could affect GERD occurrence. Our MR study is based on three hypotheses: Genetic variants are closely associated with the exposure of interest, not causally related to the outcome

but only through the exposure, and not confounded by other variables[15]. An overview of the principles, design, and procedures of our MR study is shown in Figure 1.

Data source

Genetic variations of 24 dietary intakes were collected from participants of the UK Biobank cohort. Related exposure included coffee, tea, milk, yogurt, cheese, cereal, bread, oily fish, non-oily fish, beef, lamb, pork, bacon, processed meat, cooked vegetables, raw vegetables, fresh fruit, dried fruit, salted nuts, unsalted nuts, salted peanuts, unsalted peanuts, red wine, and beer. Genetic data for gastroesophageal reflux disease was also obtained from the genome-wide association study (GWAS) catalog database with single nucleotide polymorphisms (SNP) volumes of 2320781[16]. Furthermore, we identified variables commonly associated with esophageal disorders: body mass index (BMI)[17], major depressive disorder (MDD)[18], smoking, and alcohol consumption[19]. The specific GWAS data information is shown in Table 1 and Supplementary Table 1.

Instrument variable selection

First, SNPs with significant association with dietary intake ($P < 5.0 \times 10^{-8}$) were selected. A parameter R^2 threshold of 0.001 and a kilobase pair (kb) of 10000 were set to exclude interference from linkage disequilibrium (LD)[20]. Then, The SNPs were obtained and isolated from the outcome data, and the SNPs significantly associated with the outcomes ($P < 1\times10^{-5}$) were excluded[21]. If any SNPs were not found in the outcome datasets, proxies with LD $R^2 > 0.8$ were used[22]. However, if the proxy SNP is also not found, remove this SNP from the tool variable. Finally, to ensure that the effect allele is consistent in the exposure and outcome data, we harmonize the exposure and outcome data of the unification. Alleles that were either allele incompatible (*e.g.*, A/C paired with A/G) or being palindromic with intermediate allele frequency were also excluded, yielding the final SNP data[23]. Additionally, we calculated the F value to exclude the presence of weak instrumental variable bias. This is the formula to calculate F: $F = [(N-k-1)/k] \times [R^2/(1-R^2)]$. Here, N refers to the number of samples, k is the total number of SNPs selected for MR analysis, and R2 is the total proportion of phenotypic variation that is explained by all SNPs in the MR analysis[24]. $R^2 = \Sigma [2 \times (1\text{-MAF}) \times \text{MAF} \times (\beta/\text{SD})^2$ where SD and β are the standard deviations and β coefficients of the effect sizes and MAF is the minor allele frequency for each SNP[25]. When F values > 10, there was no weak instrumental variable bias[26].

Statistical analysis

Three methods were used for MR analysis: inverse variance weighted analysis (IVW), MR egger, and weighted median. The IVW approach integrates the Wald ratio estimated for each SNP through meta-analysis[27]. IVW method was used as the primary statistical method, which is divided into two models: fixed effect (exposure constructed by ≥ 3 SNPs) and random effect (exposure constructed by < 3 SNPs)[27]. We prioritize using random effect-IVW, which assumes that MR estimates obtained for different SNPs conform to a normal distribution. This assumption is more reasonable and is somewhat tolerant of heterogeneity[28]. Assuming that > 50% of the weights come from effective SNPs, the weighted median (WM) method can provide consistent estimates. It has lower statistical efficacy than the IVW method[29]. The MR-Egger method is the most tolerant of horizontal pleiotropy, allowing all SNPs to fail to satisfy the three MR hypotheses[30]. It is the least statistically effective. In addition, MR Egger intercept can be used to test significant level pleiotropy[30]. Genetically predicted, the *P* value of the IVW method is substantial, and other methods are in the consistent direction as IVW. Then, the results are significant. To investigate whether the genetic predisposition of dietary intake is independently associated with GERD risk after adjusting for BMI, MDD, smoking, and alcohol consumption, we conducted a multivariate MR analysis using genetic predictive risk factors. We utilized the Steiger filtering method to determine correct inference directions and mitigate reverse association. The Steiger filtering directionality test was implemented through the TwoSampleMR R package.

The MRPRESSO method is a useful tool to evaluate horizontal pleiotropy. It consists of three components: Firstly, the MR-PRESSO global test is used to detect the presence of horizontal pleiotropy. Secondly, the MR-PRESSO outlier test is utilized to remove any abnormal SNPs (outliers) and estimate the corrected outcome, which eliminates horizontal pleiotropy. Lastly, the MR-PRESSO distortion test is conducted to compare pre- and post-correction results[31]. Cochran's Q test assessed the heterogeneity of the IVW. Cochran's *Q*-test $P < 0.05$ indicated heterogeneity, which can be tolerated using the random effect-IVW[27]. Additionally, the "Leave-one-out" approach removes each SNP in turn. Then, the remaining SNPs serve as instrumental variables in a two-sample MR analysis to determine the impact of a single SNP on the causal association effect[12].

The study used the 95% confidence interval (CI) of the odds ratio (OR) to evaluate the impact of dietary intakes on GERD. $P < 0.05$ was considered suggestive; Significant associations required $P < 0.002$ (= 0.05/24) by Bonferroni correction[32]. Bonferroni correction was not applied to MVMR analysis due to its mutual adjustment nature[33].

RESULTS

Supplementary Tables 2-17 show SNPs associated with 24 dietary intake and GERD. The total F-value of the intake of cooked vegetables, salad/raw vegetables, and fresh fruits is less than 10, indicating a weak instrumental bias among these three variables. Therefore, it is believed that there is no causal relationship between them and GERD. The F statistics for the rest of the phenotypes was > 10, indicating a small probability of weak instrument variable bias. Furthermore, we applied Steiger filtering to determine the accurate direction of inference.

Table 1 Univariate Mendelian randomization analysis for genetically causal associations of 24 dietary intake with gastroesophageal reflux disease risk

Dietary intake	R^2	F-statistic	SNPs	IVW		WM		MR-egger	
				OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Pork intake	0.0004	20.499	9	2.83 (1.76, 4.55)	1.84E-05	3.60 (2.14, 6.07)	1.52E-06	49.55 (1.55, 1579.54)	0.063
Bacon intake	NA	NA	0	NA	NA	NA	NA	NA	NA
Processed meat intake	0.0014	40.506	12	0.96 (0.69, 1.33)	0.794	1.12 (0.78, 1.59)	0.544	0.19 (0.01, 3.67)	0.296
Cooked vegetable intake	0.0003	10.983	9	1.87 (1.28, 2.75)	0.001	1.56 (0.95, 2.55)	0.081	0.71 (0.01, 64.25)	0.885
Salad/raw vegetable intake	0.0003	18.628	10	0.84 (0.60, 1.18)	0.309	0.90 (0.57, 1.42)	0.639	2.39 (0.42, 13.44)	0.352
Fresh fruit intake	0.0008	18.132	37	0.79 (0.56, 1.11)	0.178	0.87 (0.60, 1.27)	0.472	1.65 (0.46, 5.88)	0.443
Dried fruit intake	0.0009	12.062	26	0.37 (0.27, 0.50)	6.27E-11	0.44 (0.30, 0.61)	9.00E-07	0.13 (0.02, 0.86)	0.045
Salted nuts intake	NA	NA	1	NA	NA	NA	NA	NA	NA
Unsalted nuts intake	NA	NA	0	NA	NA	NA	NA	NA	NA
Salted peanuts intake	NA	NA	0	NA	NA	NA	NA	NA	NA
Unsalted peanuts intake	NA	NA	1	NA	NA	NA	NA	NA	NA
Average weekly red wine intake	0.0007	15.584	12	0.34 (0.25, 0.47)	1.90E-11	0.33 (0.24, 0.47)	7.03E-10	0.35 (0.04, 3.37)	0.388
Average weekly beer plus cider intake	0.0005	11.283	11	2.70 (2.00, 3.64)	6.54E-11	2.59 (1.75, 3.83)	1.82E-06	5.19 (0.73, 36.97)	0.134
Coffee intake	0.0017	23.483	26	1.22 (1.03, 1.44)	0.019	1.28 (1.06, 1.56)	0.010	1.43 (1.05, 1.94)	0.034
Tea intake	0.0025	33.827	28	1.12 (0.97, 1.29)	0.119	1.23 (1.04, 1.45)	0.014	1.32 (0.97, 1.80)	0.086
Milk intake	NA	NA	2	NA	NA	NA	NA	NA	NA
Yogurt intake	NA	NA	1	NA	NA	NA	NA	NA	NA
Cheese intake	0.0020	21.543	38	0.46 (0.39, 0.55)	3.73E-19	0.57 (0.47, 0.69)	8.65E-09	0.83 (0.33, 2.13)	0.704
Cereal intake	0.0012	16.373	27	0.45 (0.36, 0.57)	2.07E-11	0.49 (0.38, 0.63)	4.36E-08	0.58 (0.20, 1.64)	0.314
Non-oily fish intake	0.0002	13.416	5	2.41 (1.49, 3.91)	< 0.001	1.96 (1.06, 3.62)	0.033	13.70 (0.11, 1761.13)	0.368
Oily fish intake	0.0020	19.800	37	0.88 (0.76, 1.03)	0.122	0.89 (0.74, 1.08)	0.244	0.64 (0.32, 1.30)	0.227
Lamb intake	NA	NA	0	NA	NA	NA	NA	NA	NA
Beef intake	0.0004	15.600	19	0.72 (0.56, 0.92)	0.001	0.80 (0.61, 1.05)	0.108	0.69 (0.25, 1.86)	0.470
Bread intake	0.0010	20.202	7	0.77 (0.49, 1.22)	0.271	0.57 (0.36, 0.91)	0.018	0.03 (0.00, 0.25)	0.022

SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted; OR: Odds ratio; CI: Confidence interval; WM: Weighted median; GERD: Gastroesophageal reflux disease; NA: Not available.

UVMR analysis

Higher genetically predicted pork intake, beer intake, and non-oily fish intake were associated with an increased risk of GERD. The OR of GERD was 2.83 (95% confidence interval (CI), 1.76, 4.55; $P = 1.84 \times 10^{-5}$) for one standard deviation (SD) increase in pork intake, 2.70 (95%CI: 2.00-3.64; $P = 6.54 \times 10^{-11}$) for a one-unit increase in log-transformed OR of beer intake, and 2.41 (95%CI: 1.49-3.91; $P = 3.59 \times 10^{-4}$) for one SD increase in non-oily fish intake. In addition, dried fruit intake (OR 0.37; 95%CI: 0.27-0.50; 6.27×10^{-11}), red wine intake (OR 0.34; 95%CI: 0.25-0.47; $P = 1.90 \times 10^{-11}$), cheese intake

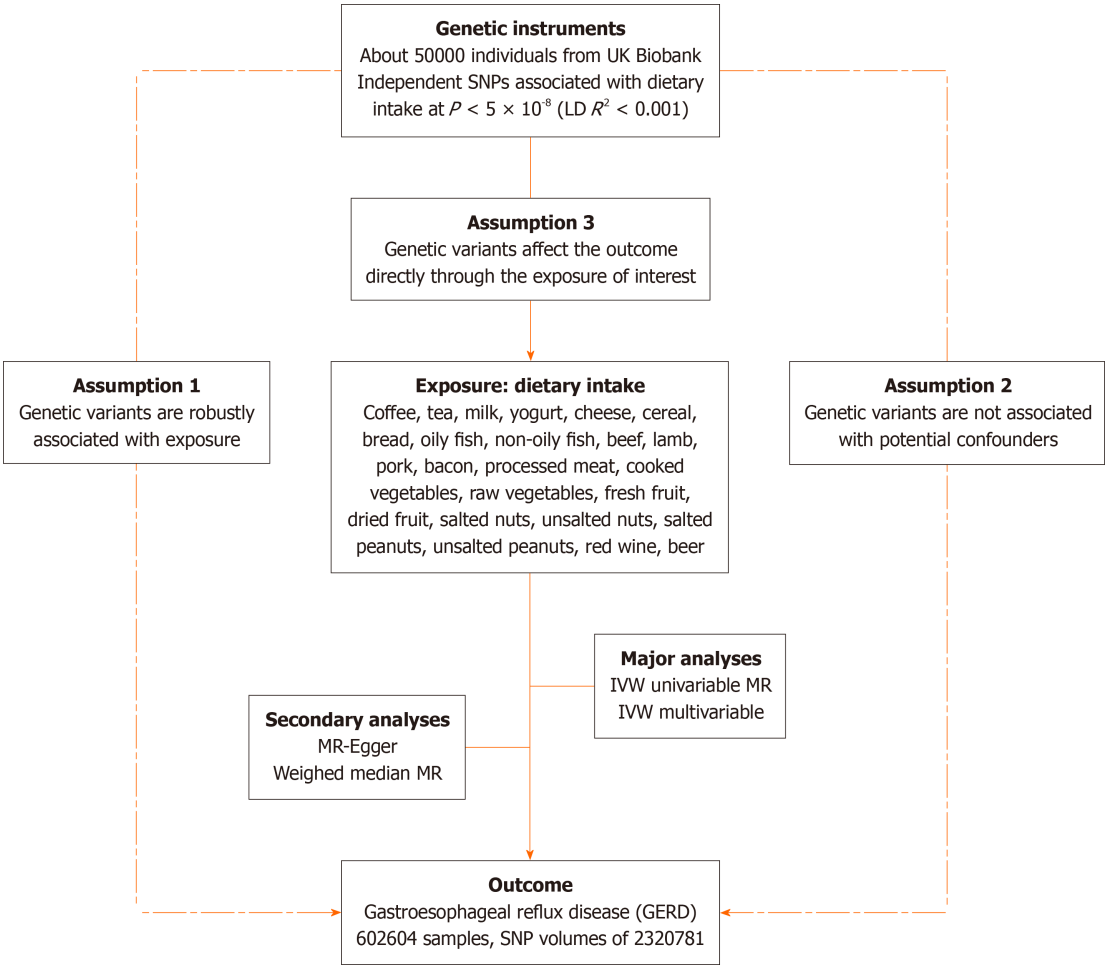

Figure 1 Overview of mendelian randomization rationale, design, and procedures. UVMR: Univariate mendelian randomization; MVMR: Multivariate Mendelian randomization; SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted; LD: Linkage disequilibrium; UK: United Kingdom.

(OR 0.46; 95%CI: 0.39-0.55; $P = 3.73 \times 10^{-19}$), bread intake (OR, 0.72; 95%CI: 0.56-0.92; $P = 0.0009$), and cereal intake (OR 0.45; 95%CI: 0.36-0.57; $P = 2.07 \times 10^{-11}$) were negatively associated with the risk of GERD. There was a suggestive association for genetically predicted coffee intake (OR per one SD increase, 1.22, 95%CI,:1.03-1.44; $P = 0.019$) (Figure 2). This study also found that tea intake, milk intake, yogurt intake, oily fish intake, beef intake, lamb intake, bacon intake, processed meat intake, cooked vegetable intake, raw vegetable intake, fresh fruit intake, salted nuts intake, unsalted nuts intake, salted peanuts intake, unsalted peanuts intake was not associated with GERD (Figure 2). Table 1 displays the outcomes of three Mendelian methods. The scatter plots of dietary intake on GERD are shown in Supplementary Figures R1-16.

The estimates from other MR methods, including WM and MR-Egger, consistently supported the causal inferences. Furthermore, there is no causal relationship between other dietary intake and GERD. In sensitivity analyses, the MR-PRESSO Distortion Test found outliers in the 16 dietary intakes (Supplementary Table 2-17). After excluding outliers, the nominal association between dietary intakes and GERD remained consistent. An analysis of the relationship between beef intake and GERD showed evidence of horizontal pleiotropy (P for MR-Egger intercept < 0.05) (Table 2). Leave-one-out analysis further supported that any single SNP did not drive the causalities (Supplementary Figures H1-16). Additionally, the funnel plot results indicated a symmetrical distribution of causal association effects when using SNPs individually as instrumental variables, and no potential bias was detected (Supplementary Figures S1-16). The forest plot also demonstrated the causal effect of each SNP on the risk of GERD (Supplementary Figures T1-16).

MVMR analysis

To determine whether the nine dietary intake directly or through common GERD risk factors affect GERD risk, we conducted MVMR analysis. MVMR analysis was performed to adjust for BMI, MDD, smoking, and alcohol drinking in the analysis of GERD. The effect of genetically predicted dried fruit intake, red wine intake, cheese intake, and cereal intake on GERD remained after adjusting for BMI, MDD, smoking, and alcohol drinking. However, the association between genetic predisposition toward Pork intake and GERD was attenuated with adjustment of alcohol drinking. Genetically predicted beer intake was not associated with GERD in the MVMR analysis adjusting for MDD and smoking, respectively. In addition, non-oily fish intake was unrelated to GERD after adjusting to BMI and alcohol drinking separately. The association of bread intake on GERD didn't remain statistically significant after multivariable adjustment for BMI. Notably, after adjustment for BMI, coffee income showed an inverse association with GERD. However, after adjusting for

Table 2 Heterogeneity and pleiotropy evaluations for genetically causal associations of 24 dietary intake with gastroesophageal reflux disease risk

Dietary intake	No. SNPs	Heterogeneity		Pleiotropy					
		Q-MR Egger	Q-IVW	P-MR Egger	P-IVW	Intercept	SE	*P* value	MRPRESSO global test *P*
Pork intake	9	10.80	14.92	0.148	0.061	-0.028	0.018	0.146	0.091
Bacon intake	0	NA	NA	NA	NA	NA	NA	NA	NA
Processed meat intake	12	22.74	25.39	0.012	0.008	0.023	0.022	0.306	0.01
Cooked vegetable intake	9	9.61	9.86	0.212	0.275	0.036	0.032	0.242	0.314
Salad / raw vegetable intake	10	7.800	9.26	0.453	0.414	-0.011	0.009	0.262	0.39
Fresh fruit intake	37	119.23	124.00	4.05E-11	1.35E-11	-0.007	0.006	0.245	< 0.001
Dried fruit intake	26	66.08	69.47	8.43E-06	4.61E-06	0.012	0.011	0.278	< 0.001
Salted nuts intake	1	NA	NA	NA	NA	NA	NA	NA	NA
Unsalted nuts intake	0	NA	NA	NA	NA	NA	NA	NA	NA
Salted peanuts intake	0	NA	NA	NA	NA	NA	NA	NA	NA
Unsalted peanuts intake	1	NA	NA	NA	NA	NA	NA	NA	NA
Average weekly red wine intake	12	24.28	24.28	0.007	0.012	-0.001	0.016	0.974	0.043
Average weekly beer plus cider intake	11	12.74	13.36	0.175	0.204	-0.008	0.012	0.525	0.32
Coffee intake	26	43.08	45.59	0.010	0.007	-0.003	0.003	0.249	0.008
Tea intake	28	52.56	55.47	0.002	0.001	-0.004	0.003	0.241	0.002
Milk intake	2	NA	NA	NA	NA	NA	NA	NA	NA
Yogurt intake	1	NA	NA	NA	NA	NA	NA	NA	NA
Cheese intake	38	80.85	84.39	2.70E-05	1.45E-05	-0.009	0.007	0.217	< 0.001
Cereal intake	27	60.22	60.77	9.74E-05	1.32E-04	-0.004	0.007	0.638	0.003
Non-oily fish intake	5	4.17	4.86	0.244	0.302	-0.018	0.026	0.531	0.376
Oily fish intake	37	56.19	57.51	0.013	0.013	0.004	0.005	0.369	0.015
Lamb intake	0	NA	NA	NA	NA	NA	NA	NA	NA
Beef intake	19	4.43	11.58	0.619	0.115	0.031	0.012	0.037	0.138
Bread intake	7	42.02	42.04	0.001	0.001	0.001	0.007	0.928	0.002

SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted; SE: Standard error.

all four factors, there was no longer a suggestive association between coffee intake and GERD. The results of MVMR are presented in Figure 3. The complementary MVMR analysis results of the causal effects of dietary intake on GERD are shown in Supplementary Table 18.

DISCUSSION

This MR study found that higher genetically predicted pork intake, beer intake, and non-oily fish intake were associated with an increased risk of GERD. Moreover, we found that dried fruit, red wine, cheese, bread, and cereal have a protective effect against gastroesophageal reflux. Higher genetically forecasted coffee intake was suggestively associated with GERD. In addition, after adjusting for BMI, MDD, smoking, and alcohol consumption, the effects of dried fruits, red wine, cheese, and cereal on GERD still exist.

For dried fruit and GERD, a retrospective study from Maekita T found that daily intake of dried Japanese apricots helped improve GERD symptoms[34]. However, an animal model study found that consuming dried fruits had no effect on the cellular antioxidant status in rats with reflux-induced esophagitis[35]. Our study found a significant protective effect of dried fruits against GERD after adjusting for BMI, MDD, smoking, and alcohol drinking. This strongly indicates that this protective effect is at least unrelated to the common risk factors of GERD. Dried fruits contain a variety of

Dietary intake	No. SNPs	Method	Odds ratio (95%CI)	*P* value
Pork intake	9	IVW	2.83 (1.76,4.55)	< 0.001
Processed meat intake	12	IVW	0.96 (0.69,1.33)	0.794
Cooked vegetable intake	9	IVW	1.87 (1.28,2.75)	0.001
Salad/raw vegetable intake	10	IVW	0.84 (0.60,1.18)	0.309
Fresh fruit intake	37	IVW	0.79 (0.56,1.11)	0.178
Dried fruit intake	26	IVW	0.37 (0.27,0.50)	< 0.001
Average weekly red wine intake	12	IVW	0.34 (0.25,0.47)	< 0.001
Average weekly beer plus cider intake	11	IVW	2.70 (2.00,3.64)	< 0.001
Coffee intake	26	IVW	1.22 (1.03,1.44)	0.019
Tea intake	28	IVW	1.12 (0.97,1.29)	0.119
Cheese intake	38	IVW	0.46 (0.39,0.55)	< 0.001
Cereal intake	27	IVW	0.45 (0.36,0.57)	< 0.001
Non-oily fish intake	5	IVW	2.41 (1.49,3.91)	< 0.001
Oily fish intake	37	IVW	0.88 (0.76,1.03)	0.122
Beef intake	19	IVW	0.72 (0.56,0.92)	0.001
Bread intake	7	IVW	0.77(0.49,1.22)	0.271

Figure 2 Univariate mendelian randomization analysis for genetically causal associations of dietary intakes with gastroesophageal reflux disease risk. SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted.

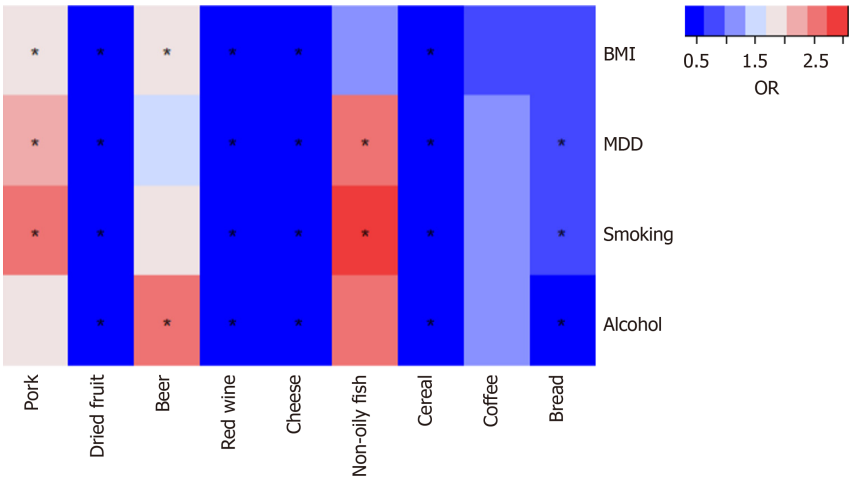

Figure 3 Associations between nine dietary intakes and gastroesophageal reflux disease after adjusting for each of the four risk factors. Asterisk represents a significant correlation. OR: Odds ratio; BMI: Body mass index; MDD: Major depressive disorder.

macronutrients, micronutrients, and health-promoting bioactive. These compounds exhibit antioxidant and free radical scavenging activities, which help improve digestive tract disorders[36]. A meta-analysis suggests that dried fruits have preventive value against certain cancers, particularly cancers of the digestive system[37]. Further research is needed on how dried fruits can reduce the increased risk of GERD.

Between alcohol consumption and GERD, the MR study by Yuan *et al*[38] found that genetic prediction of alcohol consumption was not causally associated with the incidence of GERD. The finding may be due to inadequate statistical power or a possible association between heavy alcohol consumption or abuse and GERD. Nevertheless, another observational study suggested red wine does not reduce lower Esophageal sphincter pressure and Retards Gastric Motility[39]. Our MR study found that red wine intake helps reduce the risk of GERD development. This may be related to the lower ethanol content in red wine. Several observational studies have shown that beer causes GERD, consistent with our findings[40,41]. It is worth noting that in multivariate MR, the association between beer intake and GERD became insignificant, which may be explained by the synergistic effect between alcohol and smoking or MDD.

Fermented dairy products are known to be nutritious, high in probiotics, and rich in calcium-quality proteins, bioactive molecules, vitamins, and other ingredients[42]. Their availability can be increased due to the fermentation process[43]. A retrospective study suggests high consumption of milk products and dietary fat is associated with severe GERD symptoms[44]. However, another RCT showed that dairy products do not affect GERD, heartburn, or acid reflux symptoms [45]. The contradictory findings may be due to inherent heterogeneity between studies and residual confounding in ob-

servational studies. Our study found that the MR method is highly effective in mitigating the impact of residual confounding. And our findings indicated a significant correlation between consumption of cheese and heightened susceptibility to GERD. The probiotics found in cheese provide numerous health benefits to the body, including reducing pathological changes, stimulating mucosal immunity, interacting with inflammatory mediators, and strengthening the immune system[46].

Dietary fiber, particularly from cereal sources, has been found to be linked to a lower risk of adenocarcinoma in the esophagus and gastric cardia[47]. A case-control study from M Nilsson showed that the risk of reflux was significantly reduced as the amount of dietary fiber increased[48]. This is highly consistent with our findings. In addition, cereal intake played an independent and significant role after excluding the effects of risk factors. The biological mechanism underlying this discovery remains a matter of speculation. Dietary fibers scavenge nitrites in the stomach, reducing availability for non-enzymatic nitric oxide synthesis. This may potentially lower the concentration of nitric oxide in the gastro-esophageal junction, thereby helping to prevent reflux[49]. The protective effect of bread against GERD demonstrated in our study should be similar to the mechanism of cereal intake. Notably, a cross-sectional data on the dietary fiber content of the main types of bread consumed showed a dose-dependent reduction in the risk of reflux symptoms with increasing fiber content[50]. Besides, MVMR analysis further revealed that the protective effect of bread intake on GERD might be driven by BMI. MR study from Yuan *et al*[38] suggests that a higher genetically predicted BMI is associated with an increased risk of GERD. So, we hypothesized that bread intake reduces GERD risk by controlling obesity.

Our study found pork intake increased GERD risk. This is consistent with the results of several observational studies [51,52]. Further MVMR analysis indicated that the harmful effect of pork intake on GERD might be driven by alcohol assumption. Red meat is rich in hemoglobin and iron, which can catalytically oxidize and cause oxidative stress damage to the body[53]. Then, this can cause wear on the esophageal sphincter and exacerbate reflux. Similar to pork intake, our study found that non-oily fish intake enhances the risk of GERD development. A cross-sectional study in China found that the prevalence of GERD was increased by excessive non-oily fish intake[54]. Additionally, BMI and alcoholic drinking drive the harmful effects of non-oily fish intake on GERD.

There are several observational studies on the effects of coffee on GERD, and their evidence results are inconsistent[55-57]. Hence, there is a lack of high-level evidence to confirm the association. Our MR study suggested that coffee intake has a suggestive association with GERD before adjusting for four risk factors. However, after adjusting for all four elements, there was no longer a suggestive association between coffee intake and GERD. A cross-sectional study found that the effects of coffee exposure were significantly different when analyzed univariately and multivariate, primarily because of positive confounding by smoking[58]. Another MR study from Yuan *et al*[38] found that coffee consumption was associated with an increased risk of GERD symptoms. The confounding factors of GERD may lead to this situation without adjustment. It is worth noting that after adjusting for BMI, coffee intake has a protective effect against GERD. The effect of BMI on the association between coffee intake and GERD deserves further investigation.

One of the advantages of this study is that it comprehensively characterizes the relationship between dietary intakes and GERD through MR analysis. Second, our analysis is superior to previous studies as we used pooled data from GWAS with larger sample sizes and more SNPs, avoiding biases such as unobserved confounding, misclassification, and reverse causation. Third, we also adjusted for the effect of some risk factors for GERD, further validating the second hypothesis of MR.

This study has some noticeable drawbacks. Firstly, horizontal pleiotropy is a major limitation in MR design, where SNPs affect outcomes through alternative pathways rather than exposure[31]. We used the MR-Egger intercept and MRPRESSO global test to detect pleiotropy. After excluding outliers, there was still horizontal pleiotropy for several phenotypes in the MRPRESSO global test. However, we found no evidence of horizontal pleiotropy in the MR-Egger analysis, which is consistent with the results of several sensitivity analyses. Secondly, this study only covered European populations, which may limit its applicability to other ethnic groups. Finally, we found different causal effect estimates for the MR-Egger and other MR methods. Due to its calculation of horizontal pleiotropy, it has weaker statistical efficacy than other MR methods. Our primary approach is to rely on the findings from the IVW method.

To our knowledge, there have been numerous MR studies investigating the risk factors and protective factors of GERD [59-61]. However, there are few studies on the intake of meat, staple foods, fruits, vegetables, and beverages. GERD has a severe impact on the quality of life of patients and lacks an effective treatment. Our conclusions can help clinicians to educate patients about their health and to develop suitable recipes for patients with GERD. For GERD patients, dietary changes can be made to alleviate reflux symptoms and reduce financial burdens.

CONCLUSION

This study revealed the protective effects of dry fruit intake, red wine intake, cheese intake, bread intake, and grain intake on GERD through genetic prediction, as well as the harmful effects of pork intake, beer intake, and non-oily fish intake on GERD. Furthermore, the effect of genetically predicted dried fruit, red wine, cheese, and cereal on GERD remained after adjusting for BMI, MDD, smoking, and alcohol drinking. Higher genetically forecasted coffee intake was suggestively associated with GERD. However, after adjusting for all four factors, there was no longer a suggestive association between coffee intake and GERD. This study also found that tea intake, milk intake, yogurt intake, oily fish intake, beef intake, lamb intake, bacon intake, processed meat intake, cooked vegetable intake, raw vegetable intake, fresh fruit intake, salted nuts intake, unsalted nuts intake, salted peanuts intake, unsalted peanuts intake were not associated with GERD.

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FOOTNOTES

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