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Association between dietary intakes and pregnancy complications: a two-sample Mendelian randomization analysis

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Abstract

Background Previous studies reported possible connections between dietary factors and pregnancy complications; however, confounders tend to confound the results. A two-sample Mendelian randomization (MR) study was carried out to explore the impact of dietary intakes on the risk of pregnancy complications.

Methods Exposure data in this study were derived from the IEU Open GWAS project, and the outcome data were from the FinnGen study. The inverse variance-weighted (IVW) method is the main analytical method used in this study. In addition, we verified the accuracy of the findings by performing sensitivity analyses using other methods.

Results After rigorous False Discovery Rate (FDR) correction, dried fruit intake can reduce the risk of ectopic pregnancy (OR [odds ratio]: 0.36, 95% CI [confidence interval]: 0.21–0.62). Fresh fruit intake was positively associated with pregnancy hypertension (OR: 2.26, 95% CI: 1.32–3.87), and cheese intake was negatively related to pregnancy hypertension (OR: 0.63, 95% CI: 0.47–0.85). In addition, cheese intake was negatively associated with pre-eclampsia (OR: 0.53, 95% CI: 0.38–0.72) and gestational diabetes (OR: 0.48, 95% CI: 0.36–0.64). There was no significant causality in this study for the analyses of other dietary intakes and pregnancy complications, and no heterogeneity or horizontal pleiotropy was found.

Conclusions Our two-sample MR study explores the causal association between dietary intakes and pregnancy complications, and our results contribute to the primary prevention of pregnancy complications. The mechanism by which dietary intakes affects pregnancy complications can be validated by further basic observational studies.

Keywords Dietary intakes, Pregnancy complications, Mendelian randomization

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Introduction

Complications of pregnancy are one of the common health problems of pregnant women, which are non-pregnant conditions that occur before or during pregnancy and may cause significant harm to maternal, fetal, and infant health, including ectopic pregnancy, pregnancy hypertension, pre-eclampsia, gestational diabetes, intrahepatic cholestasis in pregnancy, spontaneous abortion, and premature delivery [1]. Ectopic pregnancy occurs in 1–2% of pregnancies and is a leading cause of maternal mortality during the first trimester [2]. It is responsible for 75% of early pregnancy-related deaths and up to 8% of maternal deaths worldwide [3]. From 1990 to 2021, the global incidence of pregnancy hypertension rose from 31.33 million to 36.10 million cases, marking a 15.24% increase. Meanwhile, its prevalence skyrocketed from 6.15 million to 36.10 million cases, reflecting a dramatic 487% rise [4]. Pre-eclampsia alone causes approximately 46,000 maternal deaths and 500,000 fetal deaths worldwide each year [5]. Additionally, a report indicates that 12.8% of pregnant women globally are affected by gestational diabetes [6]. Intrahepatic cholestasis of pregnancy, a common liver disorder, affects between 0.5% and 1.5% of pregnancies in Europe [7]. Spontaneous abortion occurs in an estimated 12–24% of clinically recognized pregnancies [8]. The estimated global prevalence of premature delivery in 2020 was approximately 9.9%, while the rate in Central Asia was slightly lower, at about 7.9% [9].

The health of the pregnant woman herself can be significantly affected by her behavior during pregnancy. Inadequate care during this period can result in adverse consequences and potential negative effects [10]. For instance, maternal diet is associated with the incidence of gestational diabetes, in addition to fruit being an independent protective factor against pre-eclampsia [11, 12].

Studies have conducted comprehensive GWAS on food preferences in over 150,000 individuals, providing strong evidence that food preferences are influenced not only by culture and familiarity but also by significant biological factors [13]. Pre-pregnancy and pregnancy diets are also one of the key concerns identified by the World Health Organization (WHO). The majority of research on optimal pregnancy outcomes has centered on dietary intakes for pregnant women, such as nutrient consumption and the influence of diet on pregnancy [14]. Nutritional status during pregnancy can have an impact on maternal health. However, there is no conclusive evidence on which specific diets are beneficial during pregnancy [15]. Although some studies have investigated the influence of dietary risk factors on pregnancy complications, the majority of nutritional epidemiological studies have utilized food frequency questionnaires (FFQ) to assess intake, an approach that is prone to bias because of self-reported measurement error by subjects. Consequently, there is inadequate evidence to definitively establish a causal relationship between diet and pregnancy complications [16, 17].

The randomized controlled trial (RCT) is widely recognized as the most reliable method for establishing causality. However, RCTs are often difficult to implement due to a variety of factors such as technical limitations, research methodology, ethical considerations, and other objective factors. In light of these challenges, Mendelian randomization (MR) has been identified as a potential approach to tackle this problem [18, 19]. The advantage of MR over other studies is the use of genetic variants as an instrumental variable (IV) [20]. The principle of genetic variation in which parental genotypes are randomly assigned to offspring is followed in MR analyses, causal sequences are maintained, and common external confounders do not affect the association between exposure and outcome [21].

It is widely acknowledged that understanding the influence of dietary intakes on the risk of experiencing pregnancy complications can improve the knowledge of pregnant women regarding the link between diet and pregnancy complications and can also provide them with valuable dietary recommendations. Therefore, the exposures in our study were studied using a genome-wide association study sourced from the IEU Open GWAS program. The dataset encompassed a range of exposure variables, such as tea intake, alcohol intake frequency, coffee intake, cereal intake, bread intake, fresh fruit intake, dried fruit intake, milk intake, cheese intake, and oily fish intake. The outcome data were obtained through the FinnGen study. This study investigated the association between dietary intakes and pregnancy complications, offering credible evidence for the primary prevention of pregnancy complications.

Methods

Data sources

The exposures and outcomes in this study were from European-descent individuals. Exposures are genome-wide association study (GWAS) summary statistics related to dietary intake that will be obtained from the UK Biobank through the IEU Open Project (https://gwas.mrcieu.ac.uk/). GWAS summary statistics on pregnancy complications were obtained from version R9 of the Finnish Genetic Research Project (https://www.finngen.fi/en), released on May 11, 2023, integrating data from the Finnish Biobank and the Finnish Health Registry. This integration provides a unique entry point for studying disease-associated genetic variants in different populations [22]. Further details regarding the exposure and outcome datasets can be found in Tables 1 and 2, and Additional file 1: Table S1.

Table 1 Information on the dietary intakes datasets

IEU GWAS ID	Exposures	Number of IVs	Sample size
ukb-b-6066	Tea intake	41	447,485
ukb-b-5779	Alcohol intake frequency	91	462,346
ukb-b-5237	Coffee intake	76	428,860
ukb-b-15,926	Cereal intake	38	441,640
ukb-b-11,348	Bread intake	30	452,236
ukb-b-3881	Fresh fruit intake	50	446,462
ukb-b-16,576	Dried fruit intake	39	421,764
ukb-b-2966	Milk intake	5	64,943
ukb-b-1489	Cheese intake	59	451,486
ukb-b-2209	Oily fish intake	59	460,443

Abbreviation: IEU, Integrative Epidemiology Unit. GWAS, Genome-Wide Association Studies. IV: Instrumental Variable

Selection of IVs

The rationale for the MR analysis and the three hypotheses for the IVs are as follows [23]: (1) IVs are not associated with any confounders; (2) IVs are associated with exposure factors; (3) IVs were not associated with the outcome and could only be associated with the outcome through exposure. The three assumptions above are shown in Fig. 1 (A). We will use a Two-sample MR analysis with exposure and outcome data from different GWAS summary statistics for causal effect analysis, and the flow of the study is shown in Fig. 1 (B).

SNPs significantly associated with dietary intakes need to be selected as IVs in MR analyses, with the following criteria: (1) Selection of SNPs smaller than the genome-wide threshold of significance level ($P < 5 \times 10^{-8}$); (2) To prevent chaining imbalances between the included IVs, it is necessary to set the clumping window > 10,000 kb and the linkage disequilibrium ($R^2 < 0.01$); (3) In order to reduce the potential for weak instrumental variable bias and to establish a robust relationship between the IV and the exposure, it is necessary for the F-statistic to exceed 10 [24].

Statistical analysis

To investigate causality, we employed five MR approaches: inverse variance weighting (IVW), MR-Egger regression, weighted median, weighted model, and simple mode. In MR analysis, IVW is considered to be the most robust method for determining causality and is the main method used to estimate causality [25]. The IVW method integrates exposure and outcome in a regression analysis for each genetic variant through correlation, assuming no horizontal pleiotropy, ensuring that the results obtained from IVW are unbiased [26, 27]. The MR-Egger method is not required to satisfy the exclusion-restricted assumption but simply needs to fulfill the Instrument Strength Independent of Direct Effect (InSIDE) assumption that the direct effects of the IVs on the outcome are independent of the associated effect of the IVs on the exposure. Despite potential issues of low power and precision in MR-Egger, the results are considered reliable even in the presence of biases such as multidirectional effects [28, 29]. Since the weighted median method pools data from all genetic variants, it only requires the majority of the variants to be valid in comparison to the IVW analysis. The weighted median method tends to have higher finite-sample Type I error rates, making it a valuable complement to the IVW and MR-Egger regression methods [30, 31]. If the InSIDE assumption is not met, the weighted median method demonstrates greater efficacy in identifying causal effects, with a smaller bias compared to MR-Egger regression.

In addition, we conducted a sensitivity analysis to evaluate the robustness of the association. If the instrumental variables exhibit horizontal pleiotropy, it violates the independence and exclusivity assumptions, two of the three core assumptions. This means that the instruments may affect the outcome through pathways unrelated to the exposure, which could lead to biased IVW estimates. This can be mitigated by incorporating a "non-zero" intercept in the regression of the outcome on the exposure, which accounts for directional horizontal pleiotropy. In MR-Egger, the intercept estimate reflects the average pleiotropic effect across all variants, while the slope provides the causal effect after adjusting for pleiotropy [32]. We use the MR-Egger intercept test to evaluate the average pleiotropic effect and apply the MR-PRESSO method to identify and correct horizontal pleiotropy outliers, thus addressing the bias in MR estimates caused by horizontal pleiotropy. MR-PRESSO provides a comprehensive test to calculate the *p*-value for overall horizontal

Table 2 Information on the pregnancy complications datasets

FinnGen ID	Outcomes	Cases	Controls	Sample size	Consortium
O15_PREG_ECTOP	Ectopic pregnancy	5,648	149,622	155,270	FinnGen
O15_HYPTENSPREG	Pregnancy hypertension	14,727	196,143	210,870	FinnGen
O15_PREECLAMPS	Pre-eclampsia	6,663	194,266	200,929	FinnGen
GEST_DIABETES	Gestational diabetes	13,039	197,831	210,870	FinnGen
O15_ICP_WIDE	Intrahepatic Cholestasis of Pregnancy	2,503	130,682	133,185	FinnGen
O15_ABORT_SPONTAN	Spontaneous abortion	16,906	149,622	166,528	FinnGen
O15_PRETERM	Premature delivery	8,507	162,777	171,284	FinnGen

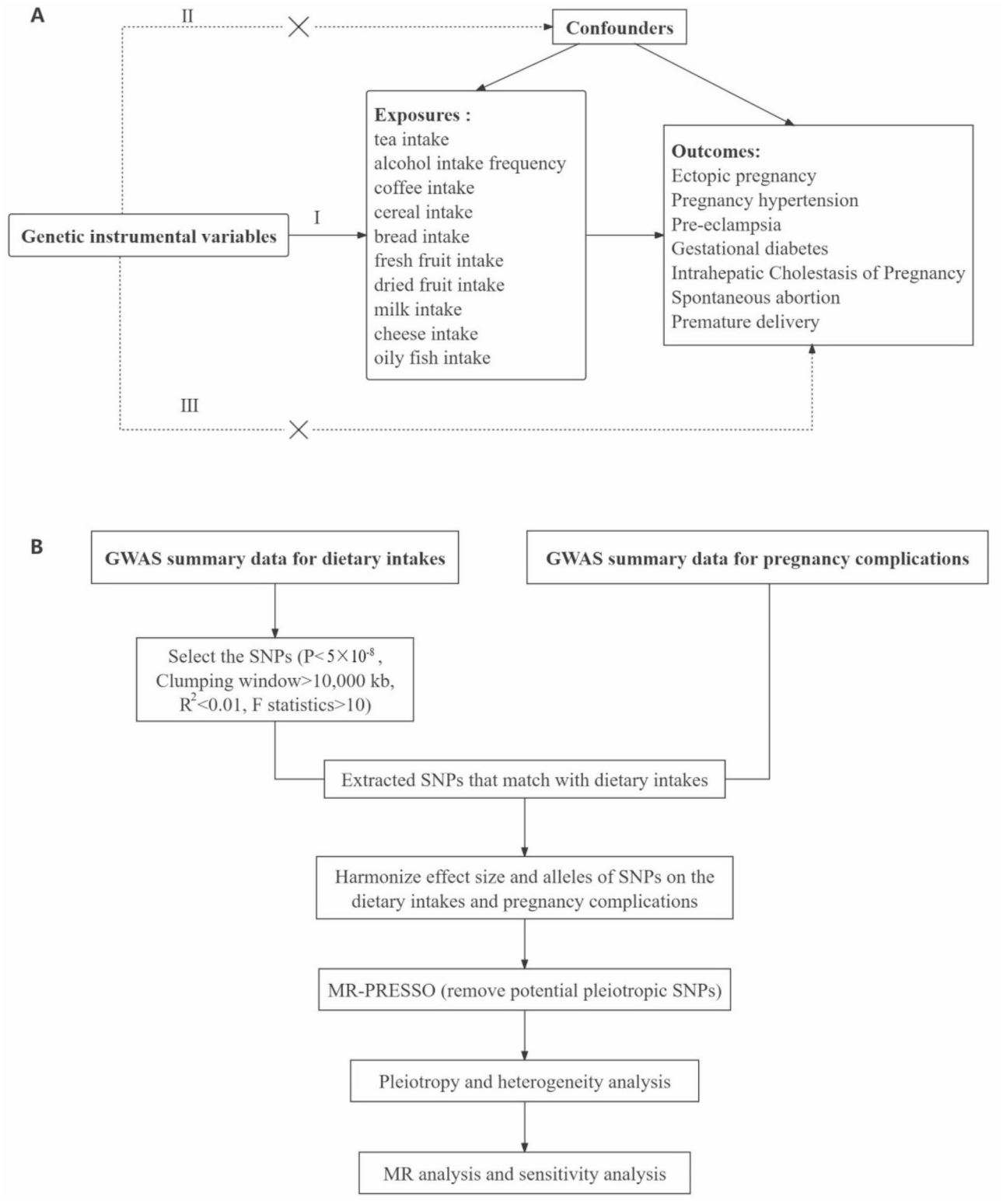


Fig. 1 (**A**) Study Design Chart. (**B**) Study Flowchart

pleiotropy. When abnormal *p*-values are detected for specific SNPs, these variants are systematically removed one by one until the *p*-value exceeds 0.05. This iterative process ensures the validity of subsequent MR analyses [29]. If heterogeneity is present in the study, it would violate the exclusivity assumption, one of the three core assumptions of MR. Heterogeneity was assessed using the *p*-value from Cochran's Q-statistic test, which measures whether differences in effect sizes among the selected genetic variants are due to genuine variations between SNPs rather than sampling error. A *p*-value less than 0.05 suggests the presence of heterogeneity [33]. Additionally, the leave-one-out analysis tactic was carried out to ascertain whether the causal associations were influenced by any single SNP.

In the case of multiple testing, we calculated the false discovery rate (FDR) for each of the main analyses and adjusted the *P*values. This study uses FDR correction, which is a relatively mild correction method, rather than simply dividing the threshold α of a single test by the number of tests n. The most common approach is to adjust each *p*-value and convert it into a q-value. The formula is q = p * n / rank, where rank refers to the position of the *p*-value in the sorted order from smallest to largest [34]. This algorithm is also known as the Benjamini-Hochberg (BH) procedure. The correlation is considered significant only when $P_{\_FDR}$<0.05, while *P*values below 0.05, uncorrected for FDR, may suggest a potential causal association but are not deemed statistically significant [34]. The FDR correction in this study was performed for different pregnancy complications, which could better control the false positive rate and maintain the statistical detection ability.

The study was adhered to the STROBE-MR guide-lines (Additional File 3: STROBE-MR) [35]. All statistical analyses were performed using R (version 4.3.1). MR analyses were performed using the TwoSampleMR package (version 0.5.6) [36].

Results

Our study explores genetically predicted causal associations between 10 different dietary intakes and 7 pregnancy complications from a genetic perspective. A set of 450 SNPs was employed as IVs for the 10 dietary intakes exposures according to the IVs screening criteria (all *F* statistic > 10). Our MR test showed no heterogeneity or horizontal pleiotropy. No other anomalous SNPs were found in subsequent sensitivity analyses. The resultant IVs were analyzed by MR, and the results of the MR analysis are shown in Table S2-8.

Ectopic pregnancy

Among the factors of dietary intake that were studied, it was found that dried fruit intake was negatively correlated with ectopic pregnancy and reduced the risk of disease (OR: 0.36, 95% CI: 0.21–0.62, $P < 0.001$, FDR < 0.001, IVW). No significant results were found between the other exposures in this study and ectopic pregnancy. (Fig. 2)

Pregnancy hypertension

By MR analysis, this study found that fresh fruit intake and cheese intake were associated with pregnancy hypertension. Fresh fruit intake showed a positive causal association (OR: 2.26, 95% CI:1.32–3.87, *P*: 0.003, FDR: 0.018, IVW), and cheese intake showed a negative causal association (OR: 0.63, 95% CI: 0.47–0.85, *P*: 0.003, FDR: 0.018, IVW). Furthermore, a causal relationship was not identified between the remaining dietary intakes and pregnancy hypertension. (Fig. 3)

Outcome	No.SNPs	Heterogeneity test		Pleiotropy test		MR. Presso		OR(95%CI)	*p*-Value	FDR
		Cochran.s.Q statistic	*p*-Value	MR.Egger intercept	*p*-Value	Global.Tes	*p*-Value			
Ectopic pregnancy										
tea	40	33.999	0.655	0.005	0.530	36.501	0.707	0.90(0.62 - 1.29)	0.565	0.706
alcohol intake frequency	91	99.539	0.188	0.003	0.663	103.545	0.275	1.07(0.88 - 1.30)	0.520	0.706
coffee	38	30.199	0.740	0.003	0.735	37.315	0.648	0.93(0.60 - 1.46)	0.759	0.759
cereal	38	35.207	0.364	-0.016	0.342	41.962	0.360	0.89(0.53 - 1.50)	0.660	0.733
bread	25	21.013	0.580	0.029	0.173	30.353	0.440	0.77(0.43 - 1.39)	0.383	0.706
fresh fruit	51	49.998	0.434	0.009	0.373	53.245	0.435	0.74(0.39 - 1.41)	0.367	0.706
dried fruit	39	41.484	0.281	-0.005	0.765	46.149	0.310	0.36(0.21 - 0.62)	<0.010	0.002
milk	5	2.005	0.571	0.224	0.388	4.371	0.606	1.03(0.97 - 1.10)	0.304	0.706
cheese	59	50.488	0.716	-0.017	0.199	62.142	0.491	0.88(0.61 - 1.25)	0.465	0.706
oily fish	58	57.773	0.410	0.024	0.065	64.013	0.373	0.83(0.56 - 1.24)	0.363	0.706

p<0.05 was considered statistically significant

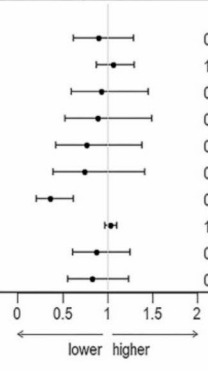


Fig. 2 The results of the MR analysis of the association between dietary intakes and ectopic pregnancy ($P < 5 \times 10^{-8}$)

Outcome	No.SNPs	Heterogeneity test		Pleiotropy test		MR. Presso		OR(95%CI)	p-Value	FDR
		Cochran.s.Q statistic	p-Value	MR.Egger intercept	p-Value	Global.Tes	p-Value			
Pregnancy Hypertension										
tea	20	14.904	0.669	-0.006	0.439	16.981	0.699	1.22(0.88 - 1.70)	0.234	0.390
alcohol intake frequency	49	52.946	0.255	0.003	0.663	55.086	0.317	1.19(1.00 - 1.42)	0.047	0.123
coffee	20	16.984	0.524	-0.010	0.163	22.980	0.412	1.13(0.76 - 1.68)	0.539	0.674
cereal	22	22.289	0.325	0.021	0.187	26.838	0.297	1.07(0.69 - 1.64)	0.770	0.770
bread	12	12.451	0.256	0.014	0.470	16.85	0.321	0.60(0.36 - 1.00)	0.049	0.123
fresh fruit	27	30.709	0.199	-0.003	0.790	33.025	0.259	2.26(1.32 - 3.87)	0.003	0.015
dried fruit	20	26.434	0.090	-0.006	0.760	29.059	0.141	0.76(0.46 - 1.26)	0.293	0.419
milk	4	3.045	0.218	-0.176	0.523	6.861	0.368	1.01(0.96 - 1.05)	0.755	0.770
cheese	32	34.694	0.254	0.002	0.836	37.059	0.298	0.63(0.47 - 0.85)	0.003	0.015
oily fish	23	26.980	0.172	0.006	0.707	29.967	0.189	0.70(0.46 - 1.07)	0.100	0.200

p<0.05 was considered statistically significant

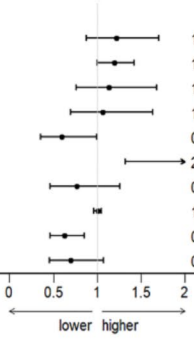


Fig. 3 The results of the MR analysis of the association between dietary intakes and pregnancy hypertension ($P < 5 \times 10^{-8}$)

Outcome	No.SNPs	Heterogeneity test		Pleiotropy test		MR. Presso		OR(95%CI)	p-Value	FDR
		Cochran.s.Q statistic	p-Value	MR.Egger intercept	p-Value	Global.Tes	p-Value			
Pre-eclampsia										
tea	36	28.934	0.755	-0.005	0.470	31.562	0.781	1.06(0.76 - 1.47)	0.734	0.893
alcohol intake frequency	84	76.802	0.641	0.009	0.329	79.470	0.640	1.23(1.02 - 1.49)	0.033	0.297
coffee	33	27.554	0.644	0.002	0.737	30.179	0.669	1.22(0.80 - 1.84)	0.353	0.893
cereal	36	27.324	0.784	-0.017	0.269	30.165	0.781	1.18(0.74 - 1.87)	0.487	0.893
bread	21	13.225	0.827	0.018	0.350	15.652	0.831	1.10(0.62 - 1.93)	0.751	0.893
fresh fruit	51	64.479	0.068	0.003	0.751	68.288	0.082	1.03(0.59 - 1.82)	0.912	0.912
dried fruit	39	34.005	0.419	-0.002	0.893	36.133	0.465	0.67(0.40 - 1.13)	0.13	0.585
milk	5	4.713	0.194	-0.247	0.389	9.466	0.225	1.01(0.95 - 1.07)	0.794	0.893
cheese	59	65.515	0.205	0.013	0.307	70.217	0.245	0.53(0.38 - 0.72)	<0.01	<0.01
oily fish	52	41.56	0.796	0.018	0.118	45.613	0.758	1.10(0.76 - 1.60)	0.606	0.893

p<0.05 was considered statistically significant

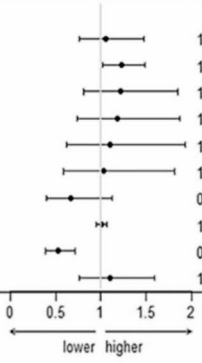


Fig. 4 The results of the MR analysis of the association between dietary intakes and pre-eclampsia ($P < 5 \times 10^{-8}$)

Pre-eclampsia

The study analyzed the relationship between exposure and pre-eclampsia and found only one statistically significant result, that is, cheese intake as a protective factor showed a negative association with pre-eclampsia (OR: 0.53, 95% CI: 0.38–0.72, $P < 0.001$, FDR < 0.001, IVW). (Fig. 4)

Gestational diabetes

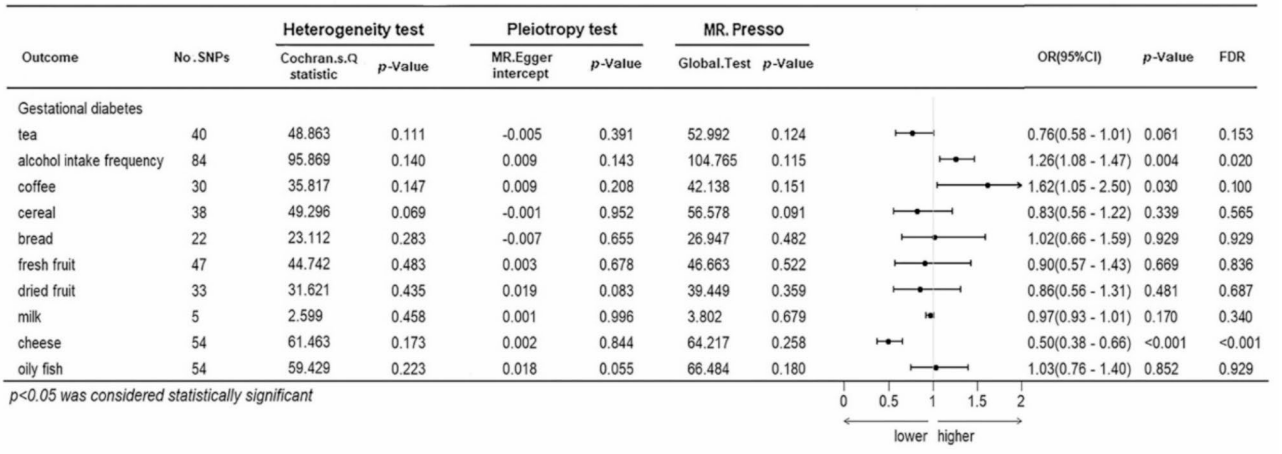
The results showed a negative causal association between the development of gestational diabetes and cheese intake (OR: 0.48, 95% CI: 0.36–0.64, $P < 0.001$, FDR < 0.001, IVW). Alcohol intake frequency and coffee intake were judged to be nonsignificant results due to the inconsistent direction of the results of the sensitivity analysis. (Additional file 1: Table S5) The results don't show any other associations. (Fig. 5)

Potential causal relationship

Some statistically significant results, after correction for FDR, we did not find a genetic correlation between dietary factors and these pregnancy complications ($P < 0.05$, FDR > 0.05), suggesting that there may be some suggestive causal relationship. For example, coffee intake and intrahepatic cholestasis of pregnancy; dried fruit intake and spontaneous abortion, premature delivery, etc.

Sensitivity analyses

To strengthen the robustness and reliability of our causal inferences, we conducted various sensitivity analyses. Firstly, we evaluated heterogeneity and pleiotropy using multiple methods, including Cochran's Q statistic, Egger-intercept, and MR-PRESSO, and chose the most suitable primary analysis approach depending on the specific circumstances. Secondly, to validate the robustness of the primary findings, we utilized four supplementary MR methods: MR-Egger regression, weighted mode, simple mode, and weighted median method. These methods



Outcome	No.SNPs	Heterogeneity test		Pleiotropy test		MR. Presso		OR(95%CI)	p-Value	FDR
		Cochran.s.Q statistic	p-Value	MR.Egger intercept	p-Value	Global.Test	p-Value			
Gestational diabetes										
tea	40	48.863	0.111	-0.005	0.391	52.992	0.124	0.76(0.58 - 1.01)	0.061	0.153
alcohol intake frequency	84	95.869	0.140	0.009	0.143	104.765	0.115	1.26(1.08 - 1.47)	0.004	0.020
coffee	30	35.817	0.147	0.009	0.208	42.138	0.151	1.62(1.05 - 2.50)	0.030	0.100
cereal	38	49.296	0.069	-0.001	0.952	56.578	0.091	0.83(0.56 - 1.22)	0.339	0.565
bread	22	23.112	0.283	-0.007	0.655	26.947	0.482	1.02(0.66 - 1.59)	0.929	0.929
fresh fruit	47	44.742	0.483	0.003	0.678	46.663	0.522	0.90(0.57 - 1.43)	0.669	0.836
dried fruit	33	31.621	0.435	0.019	0.083	39.449	0.359	0.86(0.56 - 1.31)	0.481	0.687
milk	5	2.599	0.458	0.001	0.996	3.802	0.679	0.97(0.93 - 1.01)	0.170	0.340
cheese	54	61.463	0.173	0.002	0.844	64.217	0.258	0.50(0.38 - 0.66)	<0.001	<0.001
oily fish	54	59.429	0.223	0.018	0.055	66.484	0.180	1.03(0.76 - 1.40)	0.852	0.929

p<0.05 was considered statistically significant

Fig. 5 The results of the MR analysis of the association between dietary intakes and gestational diabetes ($P < 5 \times 10^{-8}$)

yielded consistent causal estimates in both magnitude and direction (Figs. 2, 3, 4 and 5, Additional File 1: Table S2-8). Thirdly, Cochran's Q test did not detect heterogeneity, and no pleiotropic effect was observed using the MR-Egger regression, MR-PRESSO test, or MR-Egger intercept test, which also revealed no directional pleiotropic effects (Figs. 2, 3, 4 and 5, Additional File 1: Tables S2-8). Fourthly, the leave-one-out analysis yielded consistent results, indicating that the causal effects were not influenced by any individual SNP (Additional file 2: Figure S9-13). In addition, the scatter plot provided visual displays of the causality of dietary intakes on pregnancy complications risk (Additional file 2: Figure S2-8).

Discussion

Our study used two-sample MR to explore genetic causal associations between 10 dietary intakes and 7 pregnancy complications. By using large-scale GWAS summary statistics, our study draws several conclusions: (1) dried fruit intake is negatively associated with ectopic pregnancy, (2) fresh fruit intake is positively associated with pregnancy hypertension, (3) cheese intake is negatively associated with pregnancy hypertension, pre-eclampsia, and gestational diabetes.

A study presented the results of a GWAS on food preferences conducted in 161,625 participants from the UK Biobank. When compared to corresponding food consumption traits, a high genetic correlation was observed, with preferences exhibiting twice the heritability [13]. The GWAS analysis identified 1,401 significant associations with food preferences, which showed consistent effect directions across 11 independent cohorts [37]. Studies have also suggested that since dietary factors influence epigenetic variations, using dietary compounds to target epigenetic modifications could be valuable in preventing and treating diseases such as cancer [38]. Another twin study found that food preferences have a moderate genetic basis during late puberty. This suggests that common environmental factors influencing food preferences in childhood may not have a lasting impact into adulthood [39].

Our findings suggest that dried fruits have a negative causal association with ectopic pregnancy, which is characterized by the implantation of a fertilized ovum outside the uterine cavity, affecting 5-10% of pregnancies [40]. Ectopic pregnancy has a substantial influence on maternal morbidity and mortality worldwide. Its characteristic symptoms include abdominal pain and vaginal bleeding, with inflammation or infection of the fallopian tubes being the most prevalent cause of ectopic pregnancy [41]. Some countries recommend that pregnant women adhere to a "prudent" dietary pattern that incorporates dried fruits [42, 43]. Dried fruits have high nutritional value and serve as a rich source of micronutrients, including vitamin A, folate, and iron [44]. which are rich in a variety of phytochemicals and bioactive components (i.e. polyphenols, flavonoids) that can influence the development of disease by affecting metabolic pathways and cellular responses. In a study of trends in the global burden of ectopic pregnancy, it was shown that iron deficiency may contribute to the development of ectopic pregnancy [45]. Neisseria gonorrhoeae is a cause of tubal injury, and the pathogen-specific regulator, MpeR, increases the expression of the siderophore receptor FetA in conditions of iron deficiency [46]. Vitamin A deficiency will tend to the keratinization of the endothelium in the fallopian tubes, reducing the likelihood of successful implantation of a fertilized ovum in the uterus [47]. Additionally, animal studies have demonstrated that retinoic acid enhances the developmental capacity of bovine oocytes [48]. Our findings align with prior research indicating that dietary intakes may be modifiable factors contributing to ectopic pregnancy.

This study suggests that a higher intake of fresh fruit may be associated with an increased incidence of pregnancy hypertension. The risk of developing gestational hypertension and pre-eclampsia showed a negative causal association with genetically predicted cheese intake. High blood pressure that develops after the 20th week of pregnancy is called gestational hypertension [49], which usually increases the probability of maternal cardiovascular disease [50]. Elevated blood pressure during pregnancy with proteinuria (≥ 300 mg/d) was defined as pre-eclampsia. These two complications are among the most common complications of pregnancy, affecting approximately 15% of all pregnancies worldwide [51, 52]. It is well known that consuming high-GI fruits can lead to increased blood glucose levels in the body, and a longitudinal study has demonstrated that elevated glucose serves as an independent risk factor for the development of hypertension [53]. The possible mechanisms are as follows: (1) Alteration of the Renin-Angiotensin System: Elevated blood glucose may alter the renin-angiotensin system, which can result in changes to blood pressure levels [54]; (2) PKC-Mediated Vascular Smooth Muscle Contraction: Elevated glucose levels trigger PKCα/PKCβ-mediated suppression of Kv electrical currents in vascular smooth muscle, leading to an increased contractile response, which can raise blood pressure [55]; (3) Oxidative Stress and Vascular Damage: Oxidative stress caused by high blood glucose contributes to vascular remodeling and inflammation, which ultimately causes vascular damage and exacerbates hypertension [56]. The present study demonstrated a negative causal relationship between cheese intake and the development of gestational hypertension and preeclampsia, consistent with previous findings [57, 58]. This can be explained by the following mechanism: Firstly, Calcium and Fatty Acids Interaction: Cheese is rich in calcium, which interacts with fatty acids in the gastrointestinal tract to form insoluble soaps. This interaction negatively correlates with total cholesterol and LDL levels, ultimately inhibiting the absorption of fatty acids [59]. Secondly, Anti-inflammatory Protein Components: Cheese contains proteins such as casein, α-lactalbumin, and β-lactoglobulin, which are dairy proteins that have beneficial effects on inflammation [60].

Our study took a genetic approach to establish causality using MR studies and showed a negative causal association with gestational diabetes. The idea that increasing cheese intake during pregnancy reduces the risk of gestational diabetes has been demonstrated in previous studies [61, 62]. Gestational diabetes refers to the initial onset of diabetes or abnormal glucose tolerance during pregnancy [63], and affects 15-20% of the world's pregnancies. Gestational diabetes increases the risk of other complications in pregnant women, leading to possible epigenetic changes in the new generation and increasing the chances of obesity and type 2 diabetes [64]. Our findings can be explained by two aspects. On the one hand, uncontrolled insulin secretion during pregnancy leads to the production of lipid peroxidation factors and the body is in a state of oxidative stress, which can be reduced by the higher amount of nutrients in cheese (proteins, calcium, zinc, vitamins, probiotics, etc.) [65]. On the other hand, cheese intake not only counteracts the negative effects of its high saturated fatty acids, but the lactobacilli in cheese also maintain the balance of the intestinal flora, which is beneficial in gestational diabetes [66, 67]. Although the use of MR analysis can be effective in addressing biases caused by confounding variables, it should be noted that MR analysis should be viewed as an important complement to, and not a substitute for randomized controlled trials and descriptive studies. Consequently, it is advisable to interpret the findings of this study with caution [68].

The results of this study suggest that dietary interventions can strengthen maternal health education and improve nutritional management during pregnancy, thereby reducing the occurrence of pregnancy complications and enhancing the quality of life and well-being of pregnant women. However, in clinical practice, dietary interventions should consider factors such as individual genetic background, cultural differences, and lifestyle. Pregnancy complications are influenced by multiple factors. Therefore, it is recommended that the findings of this study be used as supplementary evidence, rather than the sole basis for clinical decision-making. Future research should further validate these associations and assess the effectiveness of dietary recommendations in more diverse populations to ensure their feasibility and accuracy in clinical practice. Additionally, it is suggested that systematic screening be conducted early in pregnancy to identify women at risk for diet-related complications and provide early intervention. Current research on the impact of dietary intake on pregnancy complications is still incomplete, and the underlying mechanisms need to be further explored in future animal experiments and observational studies.

Our study possesses several notable advantages. First, the study explores the causal relationship between dietary intake and pregnancy complications through MR analysis, which effectively eliminates confounding factors that may influence this relationship. The use of a reasonable time sequence in causal inference ensures the reliability of our conclusions. Second, the F-statistics for each exposure exceed 10, which helps avoid weak instrument bias. Third, our study participants were exclusively of European descent, which mitigates the potential for population stratification bias. Finally, we conducted Cochran's Q statistic and comprehensive pleiotropy tests to assess heterogeneity and pleiotropic effects. Outliers were detected

and removed using the MR-PRESSO method, further ensuring the robustness of our findings.

Moreover, this study has certain limitations. First, we used data at the summary level and the individual-level data were not available, for example, we could not know the type of fresh fruit intake (e.g., high-GI fruits such as mango and pineapple honey or low-GI fruits such as grapefruit and oranges), family history of pregnancy hypertension in pregnant women, and relevant medical history of the study participants at baseline, and we were therefore unable to examine the presence of nonlinear causality between dietary intakes and the risk of pregnancy complications. Second, the analysis was primarily conducted on individuals of European ancestry, which may limit the generalizability of the findings to other populations. Genetic structure and environmental factors may vary significantly across different populations, potentially leading to differences in health outcomes. Third, we endeavored to identify multiple dietary intakes patterns, yet we encountered challenges in discerning specific effects under various dietary combinations. Further research is therefore necessary to explore these issues.

Conclusions

This study revealed a negative association between dried fruit intake and ectopic pregnancy. Fresh fruit intake is positively associated with pregnancy hypertension. Cheese intake is negatively related to pregnancy hypertension, pre-eclampsia, and gestational diabetes. In summary, future studies on the association between pregnancy complications and diet should utilize multiple genomic platforms to explore genetic effects in combination with environmental synthesis. Our findings are informative for the primary prevention of pregnancy complications, but further research is needed to explore these relationships before dietary intakes recommendations can be made.

Abbreviations

FDR	False Discovery Rate
FFQ	Food Frequency Questionnaires
GWAS	Genome-Wide Association Studies
IEU	Integrative Epidemiology Unit
IV	Instrumental Variable
IVW	Inverse Variance-Weighted
MR	Mendelian Randomization
RCT	Randomized Controlled Trial
SNP	Single-nucleotide Polymorphism
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Data collection, data curation, Methodology, Formal analysis, Software, and Visualization were performed by ZZ, TC, XL, XZ, JC, YZ, and XL. Writing original draft: ZZ, YZ. Funding acquisition: ML. Writing review and editing: YZ, XL, and ML. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

This study uses publicly available datasets, which can be found in the IEU Open Project (https://gwas.mrcieu.ac.uk/), and the FinnGen study (https://www.finngen.fi/en).

Declarations

Ethics approval and consent to participate

Data for this study were obtained from published databases, and informed consent and ethical review approval were obtained in the original study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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