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ORIGINAL RESEARCH

Causal Relationship Between 38 Dietary Factors, Including Sugar and Alcohol Intakes, and Polycystic Ovary Syndrome: A Two-Sample Mendelian Randomization Study

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Purpose: Emerging evidence suggests that diets high in sugar consumption may be implicated in the development of polycystic ovary syndrome (PCOS), but the causal nature of these associations remains unclear. This study aimed to explore the potential causal links between 38 specific dietary factors (including alcohol and added sugar), particularly sugar-sweetened beverage intake, and the risk of PCOS.

Patients and Methods: A two-sample Mendelian randomization (MR) approach was employed using genome-wide association study summary statistics. The inverse-variance weighted (IVW) method served as the primary analytical tool, with supplementary assessments conducted using the weighted median, weighted mode, and MR-Egger regression methods. Cochran's Q test evaluated heterogeneity, while MR-Egger regression and MR pleiotropy residual sum and outlier (MR-PRESSO) analysis were applied to detect horizontal pleiotropy. Robustness of findings was further assessed through leave-one-out analysis, along with visualization via forest and funnel plots.

Results: The IVW analysis indicated potential causal associations between PCOS and alcohol intake frequency (OR = 1.39, 95% CI: 1.03–1.88, P = 0.03) and sugar added to tea (OR = 0.43, 95% CI: 0.21–0.89, P = 0.022); these associations were only supported by the IVW method and not by the other MR methods. No significant associations were observed for the 36 other dietary factors. For all 38 dietary factors, the sensitivity analyses confirmed that the results were not driven by individual instrumental variables, no significant heterogeneity was observed using Cochran's Q test, and MR-Egger regression and MR-PRESSO detected no evidence of horizontal pleiotropy or outliers.

Conclusion: Genetically predicted alcohol intake frequency was causally associated with PCOS. Although the initial hypothesis considered added sugar as a potential risk factor, the observed protective association of "sugar in tea" could reflect a proxy effect of tea consumption itself rather than a direct benefit of sugar. Further population-based studies are warranted for validation.

Keywords: polycystic ovary syndrome, dietary factors, sugar intake, alcohol intake, tea, mendelian randomization, causal association, genome-wide association studies

Introduction

Polycystic ovary syndrome (PCOS) imposes health burdens on women of reproductive age, featuring hyperandrogenism, menstrual irregularities, and polycystic ovarian morphology.[1] The global prevalence of PCOS is estimated at 10% to 13% of women when using the Rotterdam criteria.[2] A PCOS prevalence of 5.6% to 8.6% was determined among Chinese women of 20–44 years of age.[3] Beyond reproductive impacts, women with PCOS exhibit an elevated risk of metabolic disturbances,[4] including insulin resistance, dyslipidemia, and obesity.[5] Furthermore, the psychological impact of PCOS, encompassing depression, anxiety, and diminished quality of life, underscores the profound psychosocial burden experienced by affected individuals.[6] The risk factors of PCOS comprise genetic predisposition,[7,8] excessive exposure

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of the female fetus to androgens, maternal obesity and smoking,[9] and exposure to environmental factors that may affect reproductive and metabolic functions.[10]

In addition to the recognized risk factors for PCOS, some evidence highlighted the possible role of sugar-sweetened beverages as a risk factor for PCOS.[11–14] Sugar-sweetened beverage intake represents a significant dietary concern globally due to its high sugar content and potential adverse health effects.[15,16] In 2019, China's annual production of sugar-sweetened beverages reached 177.6 million tons.[17] Consumption among children aged 8 to 14 also increased significantly, with daily volume doubling from 1998 to 2008.[17] The high glycemic load from frequent sugar-sweetened beverage consumption can lead to insulin resistance, a key component in the pathogenesis of several metabolic syndromes.[18] This insulin dysregulation can exacerbate the hormonal imbalances central to PCOS, promoting hyperandrogenism, which can worsen the clinical manifestations of the syndrome.[19] In addition, sugar-sweetened beverage intake contributes to adiposity due to their high caloric density and low satiety, potentially exacerbating conditions such as PCOS, where weight management is crucial for symptom management.[20] A population-based study from Brazil also indicated a positive correlation between the PCOS prevalence and sugar-sweetened beverage consumption.[13] Conversely, a longitudinal prospective cohort study found that lower sugar-sweetened beverage consumption was associated with higher odds of PCOS in Black women.[21] Furthermore, besides sugar-sweetened beverages, diets rich in carbohydrates and fat, low in fiber, and with a high glycemic index and glycemic load (ie., Western diets in general) are positively associated with PCOS risk.[22,23]

Alcohol can disrupt both endocrine regulation and metabolic homeostasis through multiple mechanisms along the hypothalamic-pituitary-ovarian (HPO) axis. Experimental and clinical data suggest that alcohol interferes with hypothalamic gonadotropin-releasing hormone (GnRH) pulsatility, leading to altered secretion of luteinizing hormone and follicle-stimulating hormone. This dysregulation can impair follicular development, ovulation, and luteal function, and has been linked to menstrual irregularities, subfertility, and changes in sex steroid concentrations. Chronic and heavy alcohol use may further exacerbate these disturbances through direct gonadal toxicity, oxidative stress, and modulation of neuroendocrine pathways involved in stress and energy balance.[24,25] In parallel, alcohol intake influences systemic metabolism, including glucose-lipid homeostasis and body composition. Ethanol provides energy but cannot be stored, and its preferential hepatic metabolism promotes triglyceride synthesis, steatosis, and dyslipidemia, while also affecting insulin sensitivity and gluconeogenesis. These metabolic effects contribute to central adiposity, insulin resistance, and an adverse cardiometabolic profile, even at moderate consumption in susceptible individuals. Because the HPO axis is highly sensitive to changes in energy availability, adiposity, and insulin signaling, alcohol-related metabolic perturbations may indirectly affect reproductive endocrine function, creating a bidirectional link between alcohol consumption, metabolic health, and ovarian function.[25–27]

Emerging evidence suggests that certain types of tea may have beneficial adjunctive effects in women with PCOS, particularly through metabolic and hormonal pathways. Green tea and green tea extracts, which are rich in catechins and other antioxidants, have been reported in small clinical trials and systematic reviews to promote modest weight loss, improve fasting glucose and insulin levels, and reduce markers of insulin resistance in women with PCOS, changes that could secondarily improve ovulatory function and hyperandrogenism. Some studies also indicate potential reductions in free testosterone and improvements in reproductive hormone profiles and ovulatory parameters, although findings are not entirely consistent and sample sizes are often limited.[28,29] Despite these findings, observational studies can be susceptible to confounders and biases, thus restricting the capacity to conclusively ascertain the direct impact of sugar-sweetened beverages on PCOS. Besides, the causal effects of PCOS on sugar-sweetened beverage intake have been largely unknown, which hinders the management of sugar-sweetened beverage intake.

Mendelian randomization (MR) offers a robust approach for assessing causal relationships in epidemiology by using genetic variants as instrumental variables (IVs), thereby reducing confounding and reverse causation.[30] This method relies on the random allocation of alleles during meiosis, analogous to the randomization process in traditional randomized controlled trials (RCTs).

In this study, a two-sample MR framework was employed to explore the potential causal link between sugar-sweetened beverage consumption and the PCOS risk. By elucidating this potential causal pathway, the study could

contribute to the understanding of PCOS etiology and offer insights into potential preventive strategies targeting modifiable dietary behaviors to prevent or manage PCOS.

Materials and Methods

Study Design

A two-sample MR analysis was conducted to examine the potential causal relationship between PCOS and dietary factors. The study utilized publicly available summary-level data from previously published genome-wide association studies (GWAS), which involved de-identified participants. The ethics committee of Obstetrics & Gynecology Hospital of Fudan University confirmed that ethical approval was not required for this study because it was based solely on publicly available, de-identified summary data from previously published genome-wide association studies (GWAS). According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (Article 32, February 18, 2023, China), such research is exempt from ethics committee review.

Genetic variants associated with PCOS were initially selected as IVs to assess their effect on sugar-sweetened beverage intake and related dietary traits. In a reverse analysis, variants linked to sugar-sweetened beverage intake were also used as IVs to explore their potential influence on PCOS risk. Instrument selection followed the key assumptions of MR:[31] (1) the single nucleotide polymorphisms (SNPs) are strongly associated with the exposure, (2) they are independent of confounding variables, and (3) they influence the outcome solely through the exposure of interest. The study design is illustrated in Figure 1.

Data Sources

PCOS summary statistics were obtained from a large-scale population-based case-control GWAS within the FinnGen cohort,[32] which combines genomic data with nationwide electronic health records in Finland.[33] The dataset (GWAS ID FINNGEN_R12_E4_PCOS) included 2214 diagnosed cases of PCOS (ICD-10 code E28.2) and 267,780 controls of European ancestry. FinnGen participants were recruited from Finnish biobanks via samples collected over decades, spanning legacy collections from the late 1980s through prospective sampling up to spring 2023. Genetic data on sugar-sweetened beverage intake, including sugar-sweetened coffee and tea, and dietary factors were sourced from the UK Biobank by self-reported questionnaire. The UK Biobank is a large-scale prospective cohort study that enhances comprehension of the genetic and environmental factors influencing various health conditions, encompassing over 500,000 participants aged 40 to 69 years enrolled between 2006 and 2010.[34] The datasets are presented in Table S1. To minimize population stratification bias, all SNPs and summary statistics were obtained exclusively from studies involving individuals of European descent.

Selection of IVs

IVs were selected under strict quality control to satisfy the core assumptions of MR. SNPs significantly associated with sugar-sweetened beverage intake and PCOS were initially screened using a genome-wide significance threshold of $P < 5\times10^{-8}$. For dietary traits with limited associated SNPs, such as sugar added to coffee or tea, bran cereal, and oat cereal, the threshold was relaxed to $P < 5\times10^{-6}$ to retain sufficient instruments. Variants with a minor allele frequency (MAF) ≤ 0.01 were excluded. To control for linkage disequilibrium (LD), SNPs within 10,000 kb and $R^2 \geq 0.001$ were removed.[35] When outcome data lacked specific SNPs, proxy variants in strong LD ($R^2 > 0.8$) were substituted to maintain instrument strength. Palindromic SNPs were discarded to avoid strand ambiguity, and harmonization aligned effect alleles with the reference human genome (build 37), excluding duplicates and ambiguous variants.[33] Instrument strength was evaluated using the F-statistic, with values above 10 indicating sufficient strength and low susceptibility to weak instrument bias.[36]

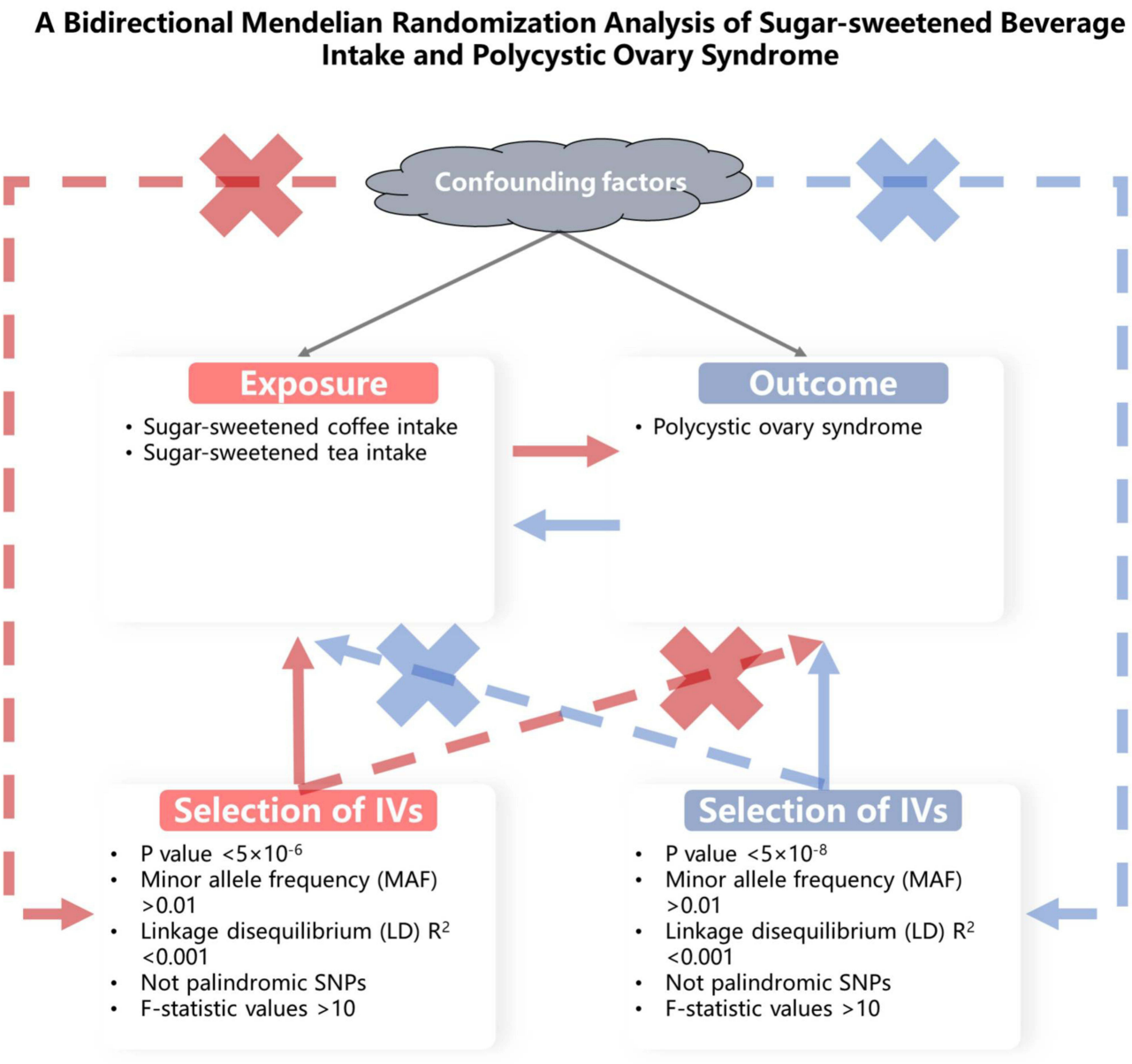

Figure 1 Flowchart of the study design. A bidirectional Mendelian randomization analysis of sugar-sweetened beverage intake and polycystic ovary syndrome.

MR Analysis

The inverse variance weighted (IVW) method served as the primary approach to estimate causal effects between dietary exposures and PCOS. IVW calculates a weighted average of SNP-specific estimates, using the inverse of their variance as weights.[37] To validate findings and account for pleiotropy, additional analyses were conducted using MR-Egger regression, weighted median, and weighted mode methods. MR-Egger accommodates directional pleiotropy through an intercept term.[37] The weighted median approach yields consistent estimates if at least half the instruments are valid.[38] The weighted mode method identifies the most frequent causal estimate across all IVs, incorporating a weight distribution based on SNP precision.[39] All MR analyses were performed using the "TwoSampleMR" R package (version 0.4.26), and results were visualized through scatter plots and diagnostic graphics.

Sensitivity Analysis

Heterogeneity across SNP estimates was tested using Cochran's Q statistic, with significance defined as $P < 0.05$. To assess robustness, leave-one-out analysis iteratively removed individual SNPs to evaluate their influence on the overall causal estimate. Funnel plots were used to visualize asymmetry, which may indicate heterogeneity or outliers. MR-Egger regression further tested for horizontal pleiotropy, where a non-significant intercept suggests minimal directional bias.[40] The MR pleiotropy residual sum and outlier (MR-PRESSO) method was applied to detect and remove outlier variants,[41] and causal estimates were recalculated after exclusion to correct for pleiotropic distortion.

Results

Selection of IVs

The detailed SNP information is listed in Table S2. The IV numbers for each exposure and the F-values are listed in Table S3. All F-values were >10, indicating the absence of weak instrumental bias. The unmatching and palindromic SNPs are shown in Table S3. Those SNPs could not be used in the MR analysis and were replaced, when possible, by the SNPs indicated in Table S3.

Causal Associations of Dietary Factors on PCOS

The IVW analysis identified potential causal associations between PCOS and two dietary exposures: alcohol intake frequency (OR = 1.39, 95% CI: 1.03–1.88, P = 0.03) and sugar added to tea (OR = 0.43, 95% CI: 0.21–0.89, P = 0.022) (Table 1). However, these associations were not corroborated by the MR-Egger regression, weighted median, and weighted mode methods, as none yielded statistically significant results (all P > 0.05; Table S4), indicating that the

Table 1 Causal Relationships Between Dietary Factors and PCOS in the MR Analysis (Due to the Extensive Results, Only the IVW Results are Displayed Here. The Complete Results Can Be Found in Table S3)

Exposure	Outcome	n SNP	Method	OR (95% CI)	P
Alcoholic drinks per week	Polycystic ovarian syndrome	34	Inverse variance weighted	1.24 (0.48–3.17)	0.657
Bread intake	Polycystic ovarian syndrome	30	Inverse variance weighted	1.18 (0.33–4.21)	0.799
Bread intake	Polycystic ovarian syndrome	28	Inverse variance weighted	0.59 (0.21–1.64)	0.313
Lamb or mutton intake	Polycystic ovarian syndrome	31	Inverse variance weighted	1.42 (0.40–5.02)	0.59
Hot drink temperature	Polycystic ovarian syndrome	68	Inverse variance weighted	0.85 (0.33–2.21)	0.744
Cheese intake	Polycystic ovarian syndrome	64	Inverse variance weighted	0.55 (0.29–1.04)	0.066
Water intake	Polycystic ovarian syndrome	39	Inverse variance weighted	1.57 (0.67–3.68)	0.304
Cereal intake	Polycystic ovarian syndrome	39	Inverse variance weighted	1.08 (0.43–2.73)	0.873
Dark chocolate intake	Polycystic ovarian syndrome	14	Inverse variance weighted	1.45 (0.32–6.61)	0.635
Dried fruit intake	Polycystic ovarian syndrome	40	Inverse variance weighted	1.16 (0.46–2.90)	0.752
Alcohol usually taken with meals	Polycystic ovarian syndrome	33	Inverse variance weighted	0.88 (0.24–3.20)	0.844
Average weekly spirits intake	Polycystic ovarian syndrome	4	Inverse variance weighted	0.73 (0.05–9.85)	0.814
Non-oily fish intake	Polycystic ovarian syndrome	11	Inverse variance weighted	1.81 (0.19–17.29)	0.606
Salad or raw vegetable intake	Polycystic ovarian syndrome	19	Inverse variance weighted	1.90 (0.31–11.88)	0.49
Oily fish intake	Polycystic ovarian syndrome	61	Inverse variance weighted	1.30 (0.67–2.54)	0.443
Intake of sugar added to coffee	Polycystic ovarian syndrome	14	Inverse variance weighted	0.93 (0.41–2.10)	0.854
Beef intake	Polycystic ovarian syndrome	15	Inverse variance weighted	0.39 (0.09–1.63)	0.196
Fresh fruit intake	Polycystic ovarian syndrome	53	Inverse variance weighted	3.20 (0.92–11.16)	0.068
Fresh fruit intake (after outlier removal)	Polycystic ovarian syndrome	51	Inverse variance weighted	2.91 (0.94–8.98)	0.063
Average weekly beer plus cider intake	Polycystic ovarian syndrome	19	Inverse variance weighted	0.82 (0.18–3.83)	0.803
Coffee intake	Polycystic ovarian syndrome	39	Inverse variance weighted	1.64 (0.70–3.81)	0.254
Coffee intake (after outlier removal)	Polycystic ovarian syndrome	39	Inverse variance weighted	1.91 (0.86–4.25)	0.112
Average weekly red wine intake	Polycystic ovarian syndrome	18	Inverse variance weighted	0.90 (0.25–3.22)	0.865
Pork intake	Polycystic ovarian syndrome	13	Inverse variance weighted	1.26 (0.14–11.76)	0.838
Average weekly champagne plus white wine intake	Polycystic ovarian syndrome	4	Inverse variance weighted	0.60 (0.04–7.98)	0.698
Alcohol intake frequency	Polycystic ovarian syndrome	96	Inverse variance weighted	1.39 (1.03–1.88)	0.03

(*Continued*)

Table 1 (Continued).

Exposure	Outcome	n SNP	Method	OR (95% CI)	P
Tea intake	Polycystic ovarian syndrome	39	Inverse variance weighted	1.00 (0.48–2.07)	0.991
Tea intake (after outlier removal)	Polycystic ovarian syndrome	38	Inverse variance weighted	0.86 (0.44–1.66)	0.649
Processed meat intake	Polycystic ovarian syndrome	23	Inverse variance weighted	0.51 (0.15–1.72)	0.275
Poultry intake	Polycystic ovarian syndrome	7	Inverse variance weighted	1.12 (0.10–12.40)	0.928
Cooked vegetable intake	Polycystic ovarian syndrome	17	Inverse variance weighted	1.64 (0.22–12.13)	0.629
Salt added to food	Polycystic ovarian syndrome	101	Inverse variance weighted	0.83 (0.50–1.37)	0.465
Intake of sugar added to tea	Polycystic ovarian syndrome	18	Inverse variance weighted	0.43 (0.21–0.89)	0.022
Bran cereal (e.g., All Bran, Branflakes)	Polycystic ovarian syndrome	12	Inverse variance weighted	0.06 (0.00–2.68)	0.149
Biscuit cereal (e.g., Weetabix)	Polycystic ovarian syndrome	2	Inverse variance weighted	0.98 (0.00–2842.31)	0.996
Oat cereal (e.g., Ready Brek, porridge)	Polycystic ovarian syndrome	20	Inverse variance weighted	1.89 (0.16–22.30)	0.612
Muesli	Polycystic ovarian syndrome	10	Inverse variance weighted	2.34 (0.05–106.04)	0.662
Other (e.g., Cornflakes, Frosties)	Polycystic ovarian syndrome	10	Inverse variance weighted	0.42 (0.01–19.78)	0.66

results should be interpreted with caution. Scatter plots and forest plots for these associations are presented in Figures 2A, B and 3A, B. The scatter plots represent the estimated causal effect of the exposure on the outcome. In the MR scatter plot, each point represents an SNP, with its association with exposure on the x-axis and with outcome (PCOS) on the y-axis; the slope of the fitted IVW line corresponds to the overall causal estimate of the exposure on PCOS. The forest plot indicates the association of each individual SNP from the exposure with PCOS.

Leave-one-out analyses are performed by sequentially excluding each SNP in turn and examining whether the exclusion of a single SNP influences the association. Leave-one-out analyses demonstrated that no single instrumental variable disproportionately influenced the results (Figures 2C and 3C). Approximately symmetrical funnel plots suggest the absence of directional pleiotropy, heterogeneity, and outliers. Here, the funnel plots suggested a lack of heterogeneity and outliers (Figures 2D and 3D).

Heterogeneity reflects inconsistency between SNP-specific causal estimates beyond that expected by chance, which can indicate pleiotropy or violation of the instrumental variable assumptions. Cochran's Q test revealed significant heterogeneity in several exposures, including alcohol consumption, bread, cereal, cheese, coffee, vegetables, fruits, processed meat, and tea (P-values < 0.05; Table 2). Horizontal pleiotropy occurs when genetic instruments affect the outcome via pathways independent of the exposure, potentially biasing MR estimates if not appropriately accounted for. MR-Egger intercepts showed no evidence of horizontal pleiotropy across the analyses (all P > 0.05; Table 2). MR-PRESSO identified outlier SNPs for coffee, bread, fresh fruit, and tea intake (Table 3), but exclusion of these variants and re-estimation via IVW yielded consistent findings (Table 1, "after exclusion" rows).

Discussion

This two-sample MR study examined the potential causal links between dietary exposures, including sugar-sweetened beverage intake, and PCOS. The findings indicated that genetically predicted alcohol intake frequency was positively associated with PCOS risk, whereas the intake of sugar added to tea showed a potential protective effect. These results warrant further investigation to confirm their validity and explore the underlying mechanism.

The association between alcohol intake and PCOS observed in the IVW analysis aligned with previous epidemiological evidence. Alcohol consumption may disrupt endocrine function in women by altering estrogen levels, impairing menstrual regularity, and exacerbating insulin resistance.[42–44] In addition, alcohol intake has been linked to metabolic disturbances—including obesity, insulin resistance, and hypertension[45,46]—which commonly co-occur in individuals with PCOS.[47] Alcohol consumption can disrupt lipid metabolism, leading to increased triglyceride levels, reduced HDL cholesterol, and potentially contributing to steatosis.[48,49] Alcohol can interfere with glucose metabolism, leading to insulin resistance and potentially contributing to type 2 diabetes.[50,51] Alcohol is calorie-dense, and excessive consumption can contribute to weight gain and obesity.[48] In addition, alcohol can damage the intestinal barrier, leading to increased gut permeability and the release of toxins into the bloodstream, which can contribute to liver inflammation and

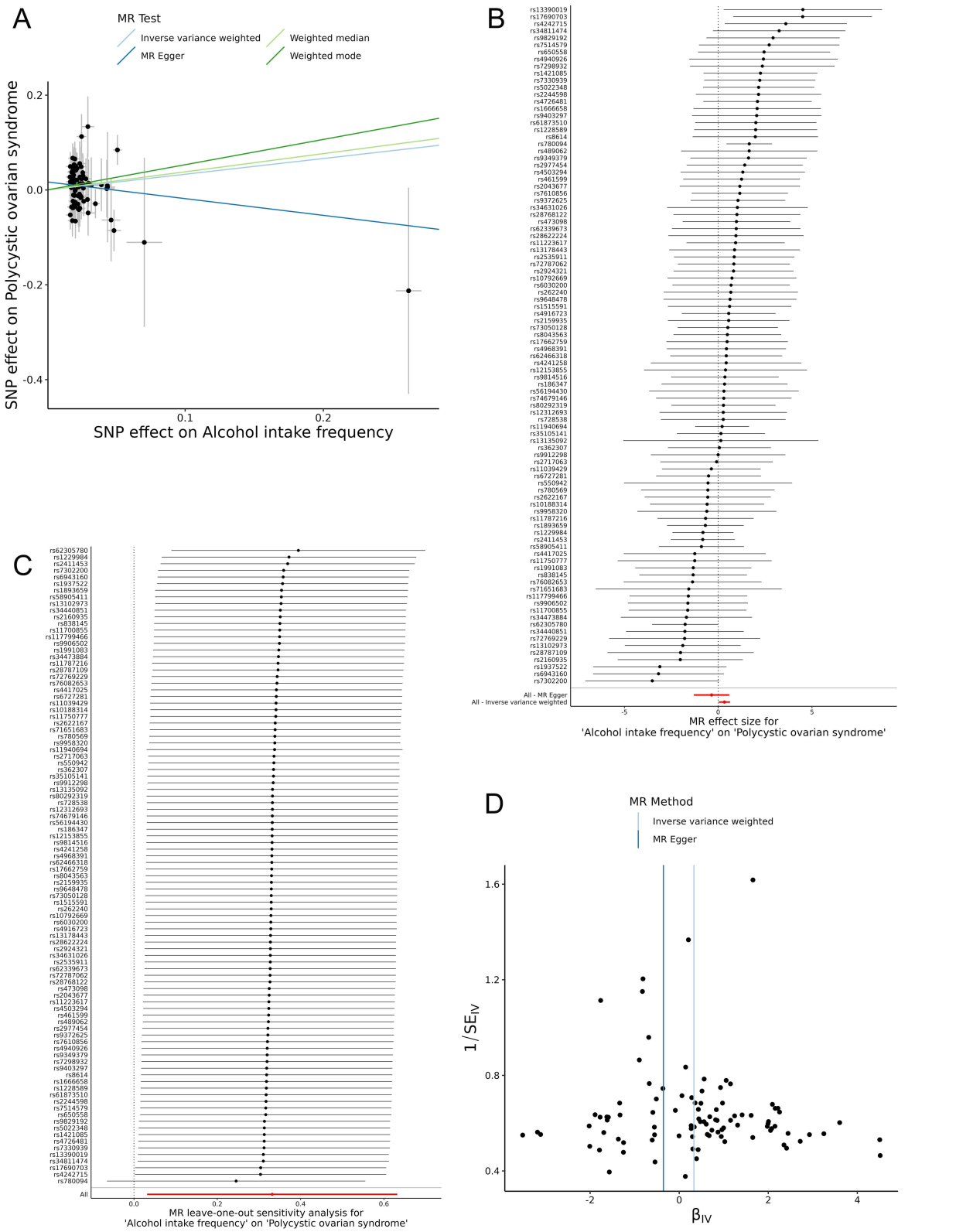

Figure 2 The causal relationships between alcohol intake frequency and PCOS using Mendelian randomization. (**A**) Scatter plot. (**B**) Forest plot. (**C**) Leave-one-out forest plot. (**D**) Funnel plot.

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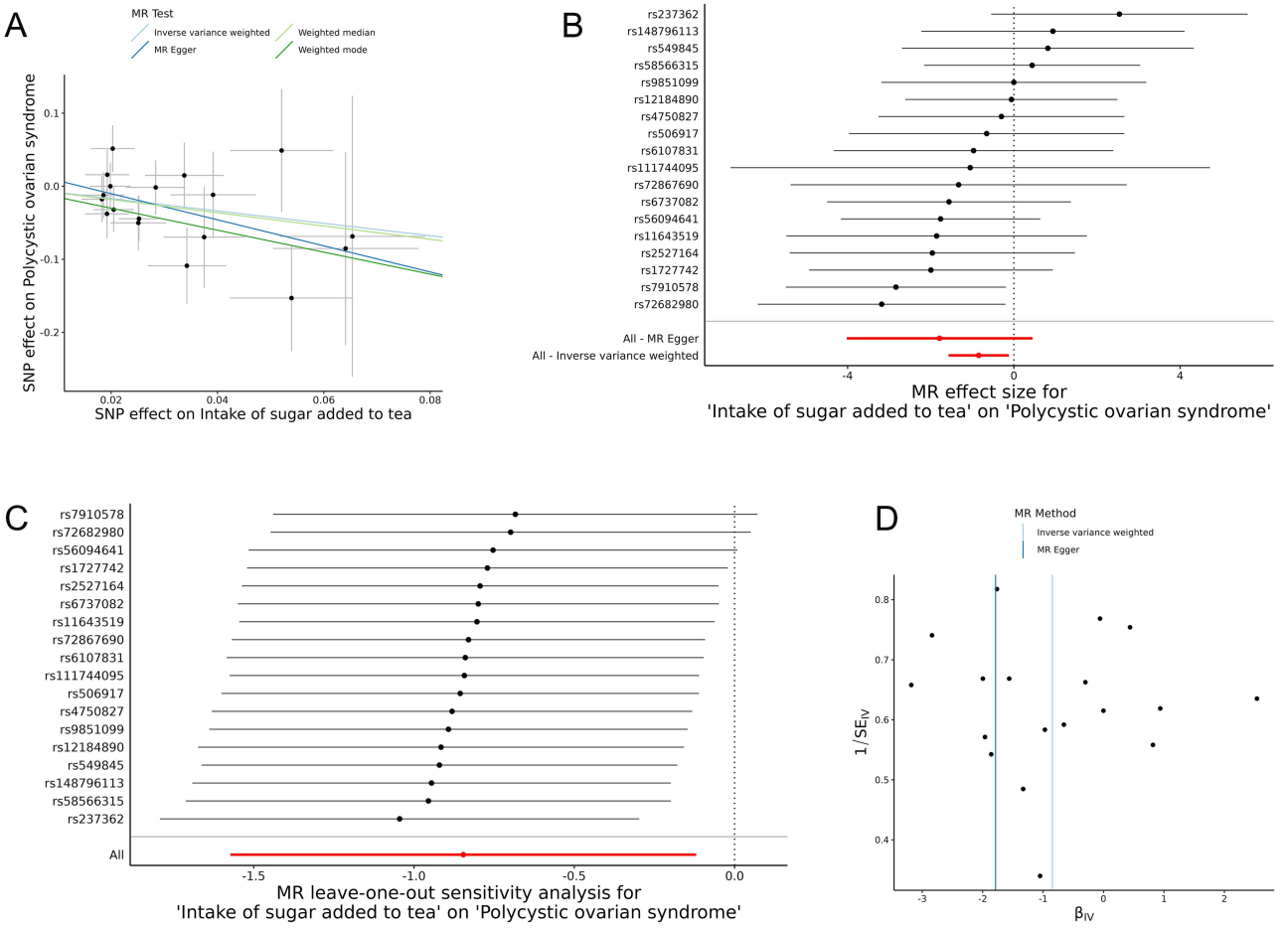

Figure 3 The causal relationships between intake of sugar in tea and PCOS using Mendelian randomization. (**A**) Scatter plot. (**B**) Forest plot. (**C**) Leave-one-out forest plot. (**D**) Funnel plot.

metabolic dysfunction.[52] Clinically, patients with PCOS or at risk of PCOS should be recommended to limit their alcohol intake.

This study identified a potential protective causal association between the intake of sugar added to tea and the PCOS risk, a finding that contrasts with prior observational research. For instance, a positive relationship was noted between

Table 2 Heterogeneity and Horizontal Pleiotropy Between Sugar-Sweetened Beverage Intake and PCOS

Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q Statistic (IVW)	*P* value	MR-Egger Intercept	*P* value
Alcohol intake frequency	Polycystic ovarian syndrome	88.43105	0.669792	0.017084	0.136782
Alcohol usually taken with meals		21.87155	0.910783	0.015386	0.702427
Alcoholic drinks per week		53.2659	0.014194	0.001536	0.936442
Average weekly beer plus cider intake		26.31965	0.092671	0.03672	0.402048
Average weekly champagne plus white wine intake		1.172461	0.759617	−0.02505	0.961088
Average weekly red wine intake		21.84438	0.190778	−0.05992	0.192583
Average weekly spirits intake		3.710296	0.294494	0.145762	0.231352
Beef intake		8.302671	0.872969	−0.01275	0.817122

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q Statistic (IVW)	*P* value	MR-Egger Intercept	*P* value
Biscuit cereal (e.g., Weetabix)		0.014875	0.902929		
Bran cereal (e.g., All Bran, Branflakes)		4.717236	0.944084	0.017494	0.570092
Bread intake		63.54115	0.00022	0.005414	0.904656
Bread intake (after outlier removal)		35.22298	0.133307	0.027233	0.439566
Cereal intake		53.44004	0.049469	0.00311	0.916153
Cheese intake		88.13894	0.019994	−0.02072	0.372432
Coffee intake		55.26841	0.034717	−0.00791	0.582521
Coffee intake (after outlier removal)		47.06881	0.12415	−0.00433	0.749729
Cooked vegetable intake		27.77658	0.033618	0.003671	0.97565
Dark chocolate intake		13.21669	0.431217	0.059464	0.060159
Dried fruit intake		44.74017	0.243453	0.001475	0.95533
Fresh fruit intake		81.08681	0.006051	−0.00055	0.978574
Fresh fruit intake (after outlier removal)		60.80756	0.14073	0.010844	0.550029
Hot drink temperature		70.28883	0.368061	0.013676	0.475642
Intake of sugar added to coffee		13.73561	0.392724	0.007718	0.823558
Intake of sugar added to tea		15.12005	0.586835	0.025537	0.396142
Lambormutton intake		33.69057	0.293372	0.015995	0.599827
Muesli		13.56421	0.138694	0.013843	0.884709
Non-oily fish intake		17.65105	0.061143	0.03909	0.585558
Oat cereal (e.g., Ready Brek, porridge)		16.37192	0.632337	0.002882	0.912081
Oily fish intake		70.60485	0.164445	0.003324	0.875391
Other (e.g., Cornflakes, Frosties)		13.6318	0.136039	−0.08156	0.401548
Pork intake		18.16402	0.1108	0.030339	0.69599
Poultry intake		6.773096	0.342342	−0.63785	0.149784
Processed meat intake		35.4738	0.034547	0.055988	0.242396
Salad or raw vegetable intake		21.7132	0.244967	0.023123	0.637409
Salt added to food		110.0563	0.231066	0.008001	0.526944
Tea intake		59.14253	0.015579	−0.01018	0.528133
Tea intake (after outlier removal)		45.74621	0.15332	−0.01293	0.36821
Water intake		47.28716	0.143609	0.015696	0.399457

Notes: Cochran's Q statistic is used for detecting heterogeneity about the IVW estimate.

Table 3 Detection and Correction of Horizontal Pleiotropy Using MR-PRESSO Method

Exposure	Outcome	Raw		Outlier Corrected		Global P	Number of Outliers	Distortion P
		OR (CI%)	*P*	OR (CI%)	*P*			
Hot drink temperature	Polycystic ovarian syndrome	0.85 (0.33–2.21)	0.75	NA (NA - NA)	NA	0.365		
Oily fish intake		1.30 (0.67–2.54)	0.45	NA (NA - NA)	NA	0.182		
Salt added to food		0.83 (0.50–1.37)	0.47	1.91 (0.86–4.25)	0.12	0.206		
Coffee intake		1.64 (0.70–3.81)	0.26	NA (NA - NA)	NA	0.043	rs780093	0.765
Coffee intake (after outlier removal)		1.91 (0.86–4.25)	0.12	NA (NA - NA)	NA	0.131		
Alcohol intake frequency		1.39 (1.04–1.86)	0.03	NA (NA - NA)	NA	0.649		
Cheese intake		0.55 (0.29–1.04)	0.07	NA (NA - NA)	NA	0.026	NA	
Water intake		1.57 (0.67–3.68)	0.31	0.59 (0.21–1.64)	0.32	0.117		
Bread intake		1.18 (0.33–4.21)	0.8	NA (NA - NA)	NA	<0.001	rs4665972,rs6580721	0.324

(*Continued*)

Table 3 (Continued).

Exposure	Outcome	Raw		Outlier Corrected		Global P	Number of Outliers	Distortion P
		OR (CI%)	P	OR (CI%)	P			
Bread intake (after outlier removal)		0.59 (0.21–1.64)	0.32	NA (NA - NA)	NA	0.149		
Beef intake		0.39 (0.13–1.17)	0.12	NA (NA - NA)	NA	0.862		
Dried fruit intake		1.16 (0.46–2.90)	0.75	NA (NA - NA)	NA	0.228		
Cereal intake		1.08 (0.43–2.73)	0.87	2.91 (0.94–8.98)	0.07	0.045	NA	
Fresh fruit intake		3.20 (0.92–11.16)	0.07	NA (NA - NA)	NA	0.007	rs28479795,rs586346	0.858
Fresh fruit intake (after outlier removal)		2.91 (0.94–8.98)	0.07	NA (NA - NA)	NA	0.133		
Alcoholic drinks per week		1.24 (0.48–3.17)	0.66	NA (NA - NA)	NA	0.011	NA	
Cooked vegetable intake		1.64 (0.22–12.13)	0.64	NA (NA - NA)	NA	0.036	NA	
Bran cereal (e.g., All Bran, Branflakes)		0.06 (0.01–0.74)	0.05	NA (NA - NA)	NA	0.939		
Dark chocolate intake		1.45 (0.32–6.61)	0.64	NA (NA - NA)	NA	0.451		
Processed meat intake		0.51 (0.15–1.72)	0.29	NA (NA - NA)	NA	0.027	NA	
Poultry intake		1.12 (0.10–12.40)	0.93	NA (NA - NA)	NA	0.377		
Salad or raw vegetable intake		1.90 (0.31–11.88)	0.5	0.86 (0.44–1.66)	0.65	0.249		
Tea intake		1.00 (0.48–2.07)	0.99	NA (NA - NA)	NA	0.019	rs72797284	0.847
Tea intake (after outlier removal)		0.86 (0.44–1.66)	0.65	NA (NA - NA)	NA	0.148		
Alcohol usually taken with meals		0.88 (0.30–2.56)	0.81	NA (NA - NA)	NA	0.889		
Average weekly red wine intake		0.90 (0.25–3.22)	0.87	NA (NA - NA)	NA	0.181		
Average weekly beer plus cider intake		0.82 (0.18–3.83)	0.81	NA (NA - NA)	NA	0.1		
Pork intake		1.26 (0.14–11.76)	0.84	NA (NA - NA)	NA	0.118		
Muesli		2.34 (0.05–106.04)	0.67	NA (NA - NA)	NA	0.154		
Oat cereal (e.g., Ready Brek, porridge)		1.89 (0.19–18.68)	0.59	NA (NA - NA)	NA	0.636		
Lambormutton intake		1.42 (0.40–5.02)	0.59	NA (NA - NA)	NA	0.307		
Intake of sugar added to tea		0.43 (0.22–0.85)	0.03	NA (NA - NA)	NA	0.579		
Other (e.g., Cornflakes, Frosties)		0.42 (0.01–19.78)	0.67	NA (NA - NA)	NA	0.168		
Non-oily fish intake		1.81 (0.19–17.29)	0.62	NA (NA - NA)	NA	0.053		
Intake of sugar added to coffee		0.93 (0.41–2.10)	0.86	NA (NA - NA)	NA	0.402		
Average weekly champagne plus white wine intake		0.60 (0.12–3.02)	0.58	NA (NA - NA)	NA	0.774		
Average weekly spirits intake		0.73 (0.05–9.85)	0.83	NA (NA - NA)	NA	0.339		

sugar-sweetened beverage consumption and PCOS prevalence among reproductive-age women.[13] Conversely, a hospital-based case-control study suggested an inverse association between coffee intake and PCOS risk.[53] Another study found no significant relationship between the intake of caffeinated or sugary beverages and antral follicle count, an indicator of ovarian reserve.[54] Possible explanations include that unmeasured confounding factors not accounted for in our analysis could influence the observed associations. The non-linear and multifactorial nature of PCOS, influenced by genetic, environmental, and lifestyle factors, may also contribute to the observed findings.[55]

There is also a possibility that that particular variable has a confounder effect because sugar intake in teas involves tea consumption. Although the a priori hypothesis considered added sugar as a potential risk factor, an apparently protective association was observed for sugar in tea. This finding is difficult to reconcile with the broader literature, which consistently links high intakes of added sugars and sugar-sweetened beverages with insulin resistance, adverse metabolic profiles, and features that overlap with PCOS pathophysiology.[13,56] Experimental and epidemiologic data indicate that diets rich in added sugars promote hyperinsulinemia, visceral adiposity, and impaired glucose tolerance, all of which are established contributors to reproductive and metabolic disturbances in women of reproductive age. Therefore, a genuine protective effect of sugar itself on PCOS risk appears biologically implausible. A more plausible explanation is that sugar in tea behaves as a behavioral proxy for tea consumption rather than reflecting a direct benefit of sugar. Indeed, a meta-analysis showed that tea consumption by women with PCOS improved insulin resistance parameters and body weight.[57] Green tea extracts also have beneficial effects in women with PCOS,[29] and green tea promotes weight loss in women with PCOS.[58] On the other hand, Tea intake, before or after outlier removal, was not causally associated with PCOS in the present study. Those results warrant further investigation. The lack of significance for "tea intake" itself, contrasted with the significant protective effect of "sugar in tea," might be attributed to differences in the statistical power of the

genetic instruments or the possibility that "sugar in tea" acts as a more specific behavioral marker for long-term, high-volume tea consumption patterns in this particular cohort. It is therefore conceivable that individuals who typically add sugar to tea differ from non-users in overall tea intake patterns or correlated lifestyle characteristics, and that any apparent protective signal is driven by tea itself or residual confounding rather than the sugar added to it. Consequently, this result should be interpreted cautiously, and we do not infer a causal protective role of sugar from this association.

Except for the two dietary factors described above, no causal associations have been identified despite the fact that observational studies associated the Western diet with PCOS.[22,23] Diseases are often the result of the interactions of several genetic and environmental factors.[59,60] These inconsistencies may reflect the influence of environmental modifiers or residual confounding that MR analyses cannot fully account for. Negative or counterintuitive MR findings do not necessarily exclude a causal relationship; they may result from weak genetic instruments or insufficient variance explained by the selected SNPs. Such limitations are well recognized in MR studies, especially when genetic proxies exert minimal effects on the exposure of interest. To address these complexities, future research should consider multivariable MR approaches that account for potential confounders and explore gene–environment interactions.

The present analysis offered several strengths. First, it is the first MR study to investigate the causal effects of specific dietary factors on PCOS, offering novel insights into the potential role of modifiable lifestyle factors in disease prevention.[61] Second, the use of multiple complementary MR methods further strengthens the reliability of the findings. The results from the sensitivity analyses further corroborated the validity of the associations or their lack thereof. However, the analysis still has limitations. First, generalizability remains limited, as the analysis was based exclusively on individuals of European ancestry. Caution is therefore warranted when extending these results to other populations, such as those of Asian descent. Second, the FinnGen database contained only a small number of participants with PCOS. Third, while MR analysis can help mitigate confounding by measured and unmeasured factors, residual confounding may still exist due to unaccounted environmental or genetic factors, potentially influencing the observed causal estimates.

Conclusion

This study supports, through genetic evidence, that frequent alcohol consumption is a potential causal risk factor for PCOS, and that added sugar to tea shows an unexpected negative correlation (but it may be influenced by the benefits of tea itself). Analyses have not found a direct genetic causal association between 36 other dietary factors, including sugary coffee and most soft drinks, and PCOS. This underscores the importance of limiting alcohol intake in the management of PCOS. External validation of the results remains necessary.

Data Sharing Statement

All data generated or analyzed during this study are included in this article and supplementary information files.

Ethics Approval and Informed Consent

The ethics committee of Obstetrics & Gynecology Hospital of Fudan University confirmed that ethical approval was not required for this study because it was based solely on publicly available, de-identified summary data from previously published genome-wide association studies (GWAS). According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (Article 32, February 18, 2023, China), such research is exempt from ethics committee review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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