

Bidirectional Associations Between Circulating Polyunsaturated Fatty Acids and Female Reproductive Endocrine-Related Diseases: A Mendelian Randomization Study

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Objective: Polyunsaturated fatty acids (PUFAs) are hypothesized to modulate female reproductive endocrine disorders, yet their causal relationships remain elusive. We employed Mendelian randomization (MR) to investigate bidirectional causality between circulating PUFAs (omega-3/6 subtypes, docosahexaenoic acid [DHA], linoleic acid) and endometriosis, infertility, polycystic ovary syndrome (PCOS), premenstrual syndrome, and premature ovarian insufficiency (POI).

Materials and Methods: In this two-sample MR study, exposure data from a GWAS of 115,006 Europeans were analyzed against outcome data (FinnGen and other large-scale GWAS). Forward MR assessed PUFA effects on disorders; reverse MR evaluated disorder-driven PUFA alterations. Sensitivity analyses (MR-Egger, MR-PRESSO, leave-one-out) ensured robustness.

Results: Elevated linoleic acid and total omega-6 levels increased endometriosis (OR=1.127, $P=0.039$; OR=1.123, $P=0.037$) and infertility risks (OR=1.155, $P=0.019$), while higher PUFA-to-total fatty acid ratios conferred protection (endometriosis: OR=0.857, $P=0.017$). PCOS genetically reduced DHA and total omega-3 levels while elevating omega-6/3 ratios ($P<0.05$). No reverse effects were observed for other disorders.

Conclusion: Our findings implicate linoleic acid and omega-6 PUFAs as potential risk factors for endometriosis and infertility, whereas balanced PUFA ratios may be protective. PCOS disrupts omega-3 homeostasis, suggesting bidirectional metabolic interplay. These results highlight PUFAs as modifiable targets for nutritional and therapeutic strategies in reproductive health, warranting further mechanistic and clinical validation.

Keywords: two-sample mendelian randomization, endometriosis, infertility, polycystic ovary syndrome, polyunsaturated fatty acids, omega-3 fatty acids

Introduction

Female reproductive endocrine disorders, including endometriosis, infertility, polycystic ovary syndrome (PCOS), premenstrual syndrome (PMS), and premature ovarian insufficiency (POI), are among the most prevalent and debilitating conditions affecting women of reproductive age worldwide.¹ Collectively, these disorders impact an estimated 10–20% of women globally, posing significant challenges to fertility, mental health, and overall quality of life.² Endometriosis alone is associated with an annual economic burden exceeding \$12,000 per patient in direct healthcare costs.³ Similarly, PCOS is associated with an increased risk of metabolic syndrome, type 2 diabetes, and cardiovascular disease, reflecting the broader systemic implications of these disorders.⁴ Despite advances in diagnostic and symptomatic management strategies, the underlying etiologies of these conditions remain incompletely

understood, involving complex interactions between genetic predisposition, endocrine dysregulation, immune dysfunction, and environmental factors.^{5–7} There is an urgent need to identify modifiable biomarkers that could pave the way for novel prevention and therapeutic strategies.

Polyunsaturated fatty acids (PUFAs), comprising omega-3 (eg., docosahexaenoic acid [DHA]) and omega-6 (eg., linoleic acid) subtypes, are emerging as key modulators in reproductive physiology and pathophysiology.⁸ Omega-3 PUFAs are known to exert anti-inflammatory effects by inhibiting cyclooxygenase-2 activity and reducing prostaglandin E2 synthesis, mechanisms that may limit the proliferation of ectopic endometrial tissue in endometriosis.^{9,10} Conversely, omega-6 PUFAs serve as precursors for pro-inflammatory eicosanoids such as leukotrienes and thromboxanes, which may exacerbate ovarian hyperandrogenism and insulin resistance in PCOS.¹¹ Observational studies have highlighted inverse associations between dietary omega-3 intake and endometriosis risk, with a pooled odds ratio (OR) of 0.78 (95% confidence interval [CI]: 0.65–0.94) in meta-analyses.¹² However, the evidence for omega-6 PUFAs remains inconclusive, with some studies suggesting null or even protective effects. These discrepancies underscore the need for robust methodologies that can disentangle causality from confounding. Although several clinical trials have demonstrated that supplementation of PUFAs (such as omega-3s) can alleviate PMS, the dose and durations of supplementation varied.^{13,14} In contrast, another study from Houghton et al suggested that individual PUFAs were not associated with risk of PMS.¹⁵ And to best of our knowledge, there was no study have investigated the relationship between PUFAs and POI.

Importantly, circulating PUFA levels should not be interpreted simply as direct surrogates of dietary intake. Although plasma and erythrocyte PUFA concentrations provide objective biomarkers of PUFA status and partially reflect habitual dietary intake, they are also influenced by endogenous metabolic processes, including intestinal absorption, hepatic lipid metabolism, fatty acid desaturation and elongation, β -oxidation, adipose tissue storage and mobilization.^{16–20} Meanwhile, body mass index (BMI) has been reported to determine the plasma long-chain PUFA response to dietary fat manipulation.²¹ Since the widely acknowledged association between BMI and metabolic dysfunction with female reproductive endocrine disorders,^{22,23} conventional observational studies are vulnerable to confounding by metabolic factors. In addition, reliance on self-reported dietary intake introduces recall bias and measurement error, while correlations between self-reported PUFA intake and circulating PUFA biomarkers are often only moderate, indicating substantial uncertainty in traditional nutritional epidemiology.^{24,25}

In addition, candidate-gene and polymorphism association studies, such as recent evidence on ADIPOQ variants in PCOS, suggest that sequence variations may contribute to PCOS-related phenotypes, although reported SNP–disease associations remain heterogeneous across populations and genetic loci.²⁶

To address these limitations, Mendelian randomization (MR) represents a robust epidemiological approach that employs genetic variants as instrumental variables (IVs) to proxy lifelong exposure levels.²⁷ By mimicking the principles of randomized controlled trials, MR reduces the influence of confounding and reverse causation, enabling robust causal inference.²⁸

The validity of MR findings hinges on three core assumptions: (1) the IVs are robustly associated with the exposure (F -statistic > 10); (2) the IVs are independent of confounders of the exposure-outcome relationship; and (3) the IVs influence the outcome exclusively through the exposure, with no horizontal pleiotropy.^{29,30} MR has been instrumental in elucidating causal links between lipid traits and cardiometabolic outcomes,³¹ yet its application to reproductive endocrine disorders is still in its infancy. To date, no MR study has comprehensively evaluated the bidirectional causal relationships between circulating PUFA subtypes and female reproductive disorders, leaving critical mechanistic gaps unaddressed. This study seeks to fill these gaps through a two-sample MR design, integrating data from large-scale genome-wide association studies (GWAS) on circulating PUFAs and female reproductive disorders. Specifically, we aim to provide novel insights into the role of PUFAs as mediators of reproductive pathophysiology, advancing our understanding of their potential as modifiable targets for intervention. By addressing key limitations in prior observational research and leveraging robust statistical frameworks, this work has the potential to inform precision nutrition and lifestyle interventions tailored to high-risk populations.

Materials and Methods

Study Design

This study employed a two-sample Mendelian randomization (MR) design to examine the causal effects of circulating polyunsaturated fatty acids (PUFAs) on female reproductive endocrine disorders (Figure 1).

By employing genetic variants as instrumental variables (IVs), the MR approach provides a robust method to infer causality, addressing limitations inherent in observational studies, such as residual confounding and reverse causation. The validity of MR relies on three key assumptions. First, the relevance assumption requires that the selected IVs are strongly associated with the exposure of interest, ensuring that genetic variants significantly predict circulating PUFA levels. Second, the independence assumption mandates that IVs are not associated with any confounders of the exposure-outcome relationship, which is generally supported by the random allocation of alleles during meiosis. Third, the exclusion restriction assumption specifies that IVs influence the outcome only through their effects on the exposure, with no alternative pathways such as horizontal pleiotropy. These assumptions were rigorously evaluated and validated to ensure reliable causal inference.

Data Sources

Exposure Data

Genetic associations for circulating PUFA levels were sourced from a large-scale genome-wide association study (GWAS) of 115,006 individuals of European ancestry. This GWAS dataset provided comprehensive coverage of PUFA-related traits, including docosahexaenoic acid (DHA), linoleic acid, total omega-3 fatty acids, total omega-6 fatty acids, the ratio of omega-6 to omega-3 fatty acids, total PUFAs, and the ratio of PUFAs to total fatty acids. These data were sourced from the European Bioinformatics Institute (EBI) database, with relevant summary statistics published under GWAS Catalog IDs ranging from ebi-a-GCST90092816 to ebi-a-GCST90092941. The high-quality data from this large cohort provided a robust foundation for exploring the genetic determinants of PUFA levels and their subsequent effects on health outcomes.

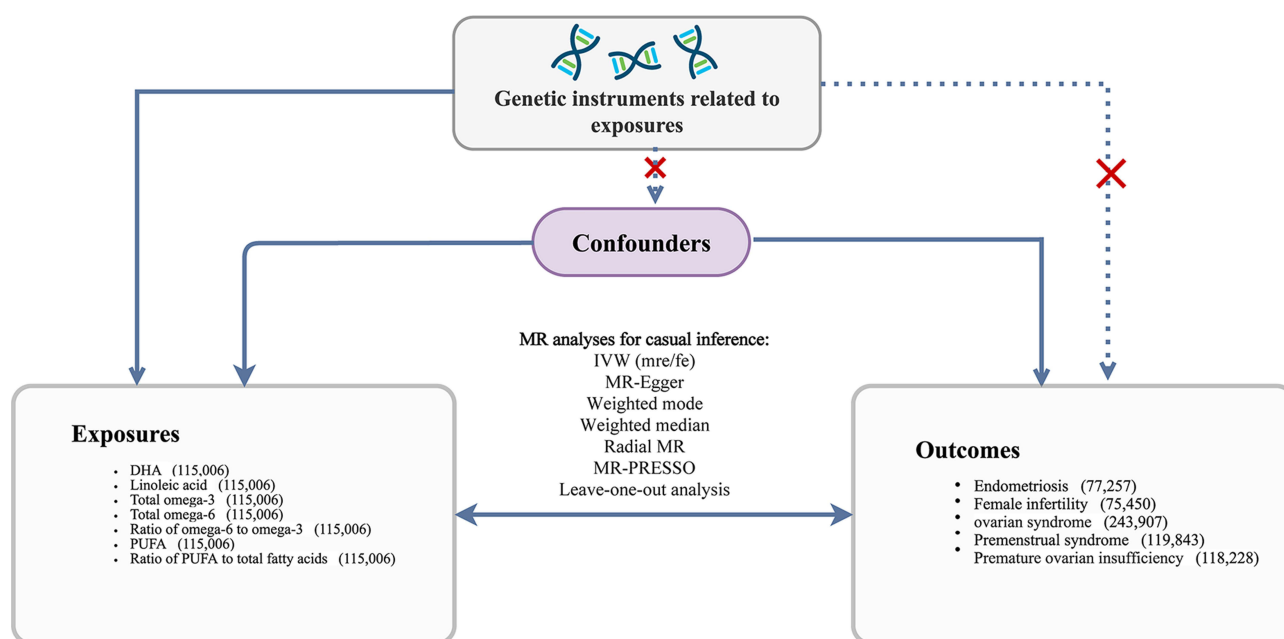


Figure 1 Directed acyclic graph illustrating the bidirectional Mendelian randomization framework between circulating polyunsaturated fatty acid-related traits and female reproductive endocrine disorders. Solid arrows indicate assumed causal pathways, and the double-headed arrow indicates the bidirectional MR design. Red cross symbols indicate that genetic instruments should not be associated with confounders or directly affect outcomes except through exposures. Bold text denotes the main analytical components.

Abbreviations: IVW, inverse-variance weighted; MR, Mendelian randomization; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid.

Outcome Data

The outcome data were derived from GWAS datasets representing European ancestry populations from the FinnGen biobank analysis round 5. Specifically, endometriosis was examined in 77,257 participants (of whom 8,288 were cases),³² female infertility in 75,450 participants, polycystic ovarian syndrome in 220,609 individuals, premenstrual syndrome in 111,878 participants, and premature ovarian insufficiency in 118,228 participants. These datasets were selected for their large sample sizes, comprehensive genomic coverage, and rigorous phenotypic characterization, which together maximize statistical power and enhance the reliability of causal estimates. All data are publicly available at <https://gwas.mrcieu.ac.uk/>.

Selection of Instrumental Variables (IVs)

Instrumental variables were selected from the PUFA GWAS based on genome-wide significance thresholds ($P < 5 \times 10^{-8}$) to ensure strong associations with PUFA levels, satisfying the relevance assumption. To maintain independence between selected variants, clumping procedures were applied to remove linkage disequilibrium (LD) using an r^2 threshold of 0.001 within a 10,000 kilobase window. Palindromic single nucleotide polymorphisms (SNPs) with intermediate allele frequencies were excluded to minimize strand ambiguity and ensure consistency in allele alignment across datasets. These rigorous criteria ensured that the selected SNPs were robustly associated with circulating PUFA levels while minimizing potential bias introduced by LD or technical errors.

Horizontal Pleiotropy Assessment

The potential influence of horizontal pleiotropy, where IVs affect outcomes through pathways independent of the exposure, was assessed using multiple approaches. MR-Egger regression was employed to detect directional pleiotropy, with the intercept term providing a quantitative measure of deviation from the exclusion restriction assumption. A significant intercept term ($P < 0.05$) indicated the presence of pleiotropy. To address this, sensitivity analyses were conducted using methods robust to pleiotropy, including the weighted mode and weighted median approaches, which provide valid estimates even when a portion of the IVs are invalid. Additionally, MR-PRESSO (Pleiotropy Residual Sum and Outlier) was used to detect and correct for outliers that might bias causal estimates. Harmonization of SNPs across exposure and outcome datasets ensured consistent alignment of alleles, further reducing the risk of pleiotropic bias.

Strength of Instruments

The strength of the selected IVs was evaluated using the F -statistic and the proportion of variance in the exposure explained by the IVs (R^2).³³ The F -statistic was calculated using the formula:

$$F = \frac{R^2(n - 1 - k)}{(1 - R^2)k} \quad (1)$$

where n is the sample size, k is the number of IVs, and R^2 represents the proportion of exposure variance explained by the IVs.³⁴ An F -statistic exceeding 10 was used to define strong instruments, minimizing the risk of weak instrument bias and ensuring robust causal inference.

Causal Effect Estimation

Causal effects were estimated using the inverse variance-weighted (IVW) method, the primary approach for two-sample MR analyses. Both multiplicative random-effects and fixed-effects models were applied, with random-effects results prioritized in the presence of heterogeneity. Sensitivity analyses complemented the primary IVW approach, including the weighted median method, which provides robust estimates when up to 50% of IVs are invalid, and the MR-Egger regression, which accounts for pleiotropy under the Instrument Strength Independent of Direct Effect (InSIDE) assumption. MR-PRESSO was used to identify and correct for outlier SNPs, while Radial MR was implemented to detect influential SNPs and assess small-sample bias. To further evaluate the robustness of causal estimates, a leave-one-out analysis was conducted by systematically excluding individual SNPs from the analysis.

Heterogeneity Testing

Heterogeneity among SNP-specific causal estimates was assessed using Cochran's Q statistic, which quantifies the deviation of individual SNP effects from the overall IVW estimate. Significant heterogeneity, indicated by $P < 0.05$, prompted the use of random-effects models, which account for between-SNP variability. The presence of heterogeneity was considered when interpreting results, as it may reflect biological differences in SNP effects or potential violations of MR assumptions.

Reverse Causality Testing

To examine the potential for reverse causation, the MR-Steiger test was conducted, evaluating whether the genetic variants explained more variance in the exposure than in the outcome. This approach ensured the validity of causal directionality, distinguishing exposure-driven effects from outcome-driven genetic associations.

Sensitivity Analyses and Statistical Significance

Sensitivity analyses included the consistency of results across multiple MR methods, such as IVW, MR-Egger, weighted median, and weighted mode. Results were considered robust if causal estimates were consistent in direction and magnitude across methods. Statistical significance was defined at a two-sided $\alpha = 0.05$, with findings contextualized within biological plausibility and prior literature. All analyses were conducted using the TwoSampleMR R package and related statistical tools, ensuring transparency and reproducibility in the analytical process.

Results

Overview of Data and Outcomes

An additional file summarizes the GWAS data sources for the PUFA-related traits and the five female reproductive endocrine disorders investigated ([Table S1](#)). The exposures, including circulating levels of DHA, linoleic acid, total omega-3, total omega-6, the omega-6/omega-3 ratio, PUFA, and the PUFA to total fatty acids ratio, originate from a European population GWAS ($N=115,006$). The outcomes of interest were endometriosis, female infertility, PCOS, premenstrual syndrome, and POI, each obtained from distinct large-scale GWAS consortia or FinnGen releases. This dataset provides a comprehensive foundation for forward Mendelian randomization (MR) analyses to test the causal roles of circulating PUFA phenotypes, as well as for reverse MR to explore the potential impact of these disorders on PUFA levels.

Instrument Selection

In the forward MR, each exposure was instrumented by SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$). An additional file details the number of original, LD-pruned, and palindromic-removed SNPs, along with the resultant F-statistics and proportion of variance explained (R^2) ([Table S2](#)). For instance, 34–43 SNPs were retained for DHA, each set explaining roughly 4.09% to 4.14% of the phenotypic variance, with F-values above 100 in most cases, suggesting robust instruments. Similarly, 41–46 instruments were identified for linoleic acid (R^2 , 5.12%–5.65%) and 49–57 instruments for total omega-6 (R^2 , 5.64%–6.20%). This table also indicates if any outlier SNPs were detected by MR-PRESSO or Radial MR, such as rs115478735 for linoleic acid, total omega-6, and PUFA in the endometriosis analysis. No substantial issues with weak instrument bias were observed, as all F-statistics exceeded the conventional threshold of 10.

Horizontal Pleiotropy, Heterogeneity, and Directionality Testing

Before estimating causal effects, we checked for potential pleiotropy and heterogeneity among the genetic instruments. [Table 1](#) reports the MR-Egger intercept for each exposure–outcome pair (to detect horizontal pleiotropy), the MR-Steiger direction test, and Cochran's Q statistics for both MR-Egger and IVW models (to evaluate between-SNP heterogeneity). In nearly all comparisons, the MR-Egger intercept did not reach statistical significance, implying that unbalanced horizontal pleiotropy was not a major issue. The MR-Steiger tests consistently confirmed the hypothesized direction of causality (exposure $\rightarrow$ outcome). However, Cochran's Q test revealed notable heterogeneity among the instrumental variables (IVs) for DHA, Total omega-3, Total omega-6, the ratio of omega-6 to omega-3, and PUFA with respect to

Table 1 The Pleiotropic and Heterogeneity Test

Outcome and Exposure	Horizontal Pleiotropic Test		Casual Direction Test		Heterogeneity Test			
	Egger Intercept	P	MR Steiger	P	MR Egger Q	P	IVW Q	P
Endometriosis								
DHA	−0.008	0.109	TRUE	<0.001	42.725	0.397	45.516	0.328
Linoleic acid	0.009	0.242	TRUE	<0.001	48.659	0.291	50.215	0.274
Total omega-3	0.002	0.693	TRUE	<0.001	53.551	0.237	53.730	0.264
Total omega-6	0.002	0.701	TRUE	<0.001	61.800	0.246	61.967	0.272
Ratio of omega-6 to omega-3	0.002	0.818	TRUE	<0.001	38.085	0.097	38.159	0.119
PUFA	−0.001	0.894	TRUE	<0.001	61.555	0.197	61.576	0.223
Ratio of PUFA to total fatty acids	−0.013	0.076	TRUE	<0.001	54.238	0.117	58.398	0.072
Female infertility								
DHA	0.005	0.444	TRUE	<0.001	50.918	0.138	51.661	0.146
Linoleic acid	0.015	0.055	TRUE	<0.001	28.611	0.965	32.500	0.918
Total omega-3	0.007	0.262	TRUE	<0.001	63.047	0.059	64.775	0.054
Total omega-6	0.004	0.522	TRUE	<0.001	50.494	0.647	50.909	0.667
Ratio of omega-6 to omega-3	0.000	0.956	TRUE	<0.001	20.312	0.853	20.315	0.883
PUFA	0.002	0.773	TRUE	<0.001	53.845	0.442	53.931	0.477
Ratio of PUFA to total fatty acids	−0.011	0.149	TRUE	<0.001	51.921	0.165	54.522	0.133
Polycystic ovarian syndrome								
DHA	0.007	0.615	TRUE	<0.001	48.593	0.030	48.985	0.036
Linoleic acid	0.016	0.319	TRUE	<0.001	52.688	0.071	54.067	0.068
Total omega-3	0.010	0.399	TRUE	<0.001	68.569	0.004	69.785	0.005
Total omega-6	0.000	0.996	TRUE	<0.001	71.065	0.013	71.065	0.017
Ratio of omega-6 to omega-3	−0.021	0.127	TRUE	<0.001	38.056	0.046	41.847	0.025
PUFA	−0.004	0.806	TRUE	<0.001	71.518	0.009	71.613	0.012
Ratio of PUFA to total fatty acids	−0.013	0.379	TRUE	<0.001	52.044	0.051	53.160	0.052
Premenstrual syndrome								
DHA	0.020	0.405	TRUE	<0.001	25.607	0.781	26.318	0.789
Linoleic acid	0.056	0.079	TRUE	<0.001	39.048	0.468	42.311	0.372
Total omega-3	0.029	0.179	TRUE	<0.001	39.065	0.557	40.931	0.518
Total omega-6	0.070	0.014	TRUE	<0.001	38.704	0.800	45.249	0.586
Ratio of omega-6 to omega-3	0.004	0.878	TRUE	<0.001	13.940	0.963	13.965	0.973
PUFA	0.048	0.094	TRUE	<0.001	50.093	0.314	53.270	0.246
Ratio of PUFA to total fatty acids	0.012	0.655	TRUE	<0.001	29.976	0.787	30.178	0.813
Premature ovarian insufficiency								
DHA	0.001	0.971	TRUE	<0.001	27.037	0.954	27.038	0.964
Linoleic acid	0.025	0.494	TRUE	<0.001	45.547	0.408	46.039	0.429
Total omega-3	−0.003	0.912	TRUE	<0.001	28.370	0.986	28.383	0.989
Total omega-6	−0.004	0.900	TRUE	<0.001	45.908	0.804	45.924	0.829
Ratio of omega-6 to omega-3	0.013	0.655	TRUE	<0.001	18.478	0.913	18.682	0.929
PUFA	−0.023	0.440	TRUE	<0.001	41.719	0.868	42.324	0.875
Ratio of PUFA to total fatty acids	0.000	0.990	TRUE	<0.001	51.432	0.177	51.432	0.206

Note: Bold text indicates outcome disease categories.

Abbreviations: DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; MR, Mendelian randomization; IVW, inverse-variance weighted.

Polycystic Ovarian Syndrome. This finding prompted the use of a multiplicative random-effects IVW model rather than a fixed-effects model.

Subsequently, we focused on outlier SNP detection as detailed in Table 2. In the MR-PRESSO and Radial MR tests, several outlier SNPs (eg., rs115478735) were identified. Where necessary, these outlier SNPs were removed to correct for potential horizontal pleiotropy. Importantly, the corrected analyses generally did not drastically alter the magnitude or

Table 2 The MR-PRESSO and Radial Test in Forward MR

Variables	MR-PRESSO		MR-PRESSO (Outlier Corrected)		Radial MR		Radial MR (Outlier Corrected)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Endometriosis								
DHA	0.857 (0.741–0.991)	0.043			0.997 (0.907–1.096)	0.951		
Linoleic acid	1.127 (1.000–1.270)	0.057			1.127 (1.000–1.270)	0.051	1.097 (0.993–1.213)	0.069
Total omega-3	1.123 (1.001–1.259)	0.052			1.056 (0.975–1.143)	0.182		
Total omega-6	0.997 (0.907–1.096)	0.951			1.123 (1.001–1.259)	0.047	1.096 (0.992–1.210)	0.071
Ratio of omega-6 to omega-3	1.056 (0.975–1.143)	0.188			1.089 (0.980–1.210)	0.111		
PUFA	1.089 (0.980–1.210)	0.117			0.960 (0.879–1.048)	0.362	1.070 (0.977–1.171)	0.144
Ratio of PUFA to total fatty acids	0.960 (0.879–1.048)	0.370			0.857 (0.741–0.991)	0.037		
Female infertility								
DHA	0.972 (0.873–1.082)	0.606			0.972 (0.873–1.082)	0.603		
Linoleic acid	1.059 (0.953–1.176)	0.293			1.155 (1.042–1.281)	0.006		
Total omega-3	0.998 (0.909–1.096)	0.967			0.998 (0.909–1.096)	0.967		
Total omega-6	1.109 (0.992–1.239)	0.073			1.109 (0.992–1.239)	0.068		
Ratio of omega-6 to omega-3	0.870 (0.749–1.011)	0.077			1.059 (0.953–1.176)	0.288		
PUFA	1.155 (1.042–1.281)	0.009			1.039 (0.970–1.113)	0.276		
Ratio of PUFA to total fatty acids	1.039 (0.970–1.113)	0.285			0.870 (0.749–1.011)	0.070		
Polycystic ovarian syndrome								
DHA	0.765 (0.560–1.047)	0.102			0.957 (0.773–1.184)	0.684		
Linoleic acid	1.214 (0.940–1.567)	0.146			1.214 (0.940–1.567)	0.138		
Total omega-3	1.121 (0.867–1.450)	0.389			1.016 (0.841–1.226)	0.872		
Total omega-6	1.071 (0.843–1.360)	0.578			1.121 (0.867–1.450)	0.384		
Ratio of omega-6 to omega-3	0.995 (0.825–1.200)	0.958			1.071 (0.843–1.360)	0.575		
PUFA	1.016 (0.841–1.226)	0.873			0.995 (0.825–1.200)	0.958		
Ratio of PUFA to total fatty acids	0.957 (0.773–1.184)	0.687			0.765 (0.560–1.047)	0.094		
Premenstrual syndrome								
DHA	0.779 (0.460–1.322)	0.361			1.243 (0.876–1.763)	0.223		
Linoleic acid	0.937 (0.564–1.556)	0.802			0.937 (0.564–1.556)	0.801		
Total omega-3	1.376 (0.869–2.179)	0.18			1.294 (0.937–1.786)	0.118		
Total omega-6	1.302 (0.820–2.068)	0.269			1.376 (0.869–2.179)	0.173		
Ratio of omega-6 to omega-3	0.833 (0.654–1.061)	0.15			1.302 (0.820–2.067)	0.263		
PUFA	1.294 (0.937–1.786)	0.125			0.833 (0.654–1.061)	0.138		
Ratio of PUFA to total fatty acids	1.243 (0.876–1.763)	0.232			0.779 (0.459–1.322)	0.355		

(Continued)

Table 2 (Continued).

Variables	MR-PRESSO		MR-PRESSO (Outlier Corrected)		Radial MR		Radial MR (Outlier Corrected)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Premature ovarian insufficiency								
DHA	0.728 (0.364–1.458)	0.375			0.765 (0.529–1.108)	0.156		
Linoleic acid	0.765 (0.529–1.108)	0.163			1.458 (0.815–2.609)	0.204		
Total omega-3	0.855 (0.637–1.148)	0.302			0.855 (0.637–1.148)	0.297		
Total omega-6	1.458 (0.815–2.609)	0.211			1.534 (0.930–2.528)	0.094		
Ratio of omega-6 to omega-3	1.533 (0.930–2.528)	0.099			1.040 (0.668–1.620)	0.862		
PUFA	1.040 (0.668–1.620)	0.863			1.279 (0.934–1.752)	0.125		
Ratio of PUFA to total fatty acids	1.279 (0.934–1.752)	0.136			0.728 (0.364–1.458)	0.370		

Note: Bold text indicates outcome disease categories.

Abbreviations: DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

direction of the causal estimates. For example, the causal relationships between Linoleic acid, Total omega-6, and PUFA with Endometriosis remained statistically insignificant even after the exclusion of the outlier SNPs (as shown in Table 1 and Table 2), thereby supporting the robustness of the main finding.

MR Results

The primary MR analyses, based on IVW estimates (both fixed-effects and multiplicative random-effects), evaluated the relationships between PUFA-related exposures on various female endocrine disorders (Table 3). The visualization of Mendelian randomization showed stable results, further confirming the reliability of our study findings. Graphical representations, including forest plots (Figure 2) and scatter plots (Figure 3), were used to illustrate these associations.

Table 3 The MR Results of Exposures and Outcomes

Variables	nSNPs	Fixed Effects		Multiplicative Random Effects	
		OR (95% CI)	P	OR (95% CI)	P
Endometriosis					
DHA	43	0.997 (0.911–1.092)	0.949	0.997 (0.907–1.096)	0.951
Linoleic acid	46	1.127 (1.006–1.262)	0.039	1.127 (1.000–1.270)	0.051
Total omega-3	49	1.056 (0.979–1.138)	0.158	1.056 (0.975–1.143)	0.182
Total omega-6	57	1.123 (1.007–1.252)	0.037	1.123 (1.001–1.259)	0.047
Ratio of omega-6 to omega-3	30	0.960 (0.889–1.037)	0.296	0.960 (0.879–1.048)	0.362
PUFA	55	1.089 (0.987–1.202)	0.089	1.089 (0.980–1.210)	0.111
Ratio of PUFA to total fatty acids	45	0.857 (0.755–0.972)	0.017	0.857 (0.741–0.991)	0.037
Female infertility					
DHA	43	0.972 (0.882–1.071)	0.564	0.972 (0.873–1.082)	0.603
Linoleic acid	46	1.155 (1.024–1.304)	0.019	1.155 (1.042–1.281)	0.006
Total omega-3	49	0.998 (0.921–1.081)	0.962	0.998 (0.909–1.096)	0.967
Total omega-6	57	1.109 (0.987–1.246)	0.082	1.109 (0.992–1.239)	0.068
Ratio of omega-6 to omega-3	30	1.039 (0.957–1.128)	0.362	1.039 (0.970–1.113)	0.276
PUFA	55	1.059 (0.953–1.176)	0.289	1.059 (0.953–1.176)	0.288
Ratio of PUFA to total fatty acids	45	0.870 (0.760–0.996)	0.044	0.870 (0.749–1.011)	0.070
Polycystic ovarian syndrome					
DHA	34	0.957 (0.803–1.140)	0.620	0.957 (0.773–1.184)	0.684
Linoleic acid	41	1.214 (0.974–1.512)	0.085	1.214 (0.940–1.567)	0.138
Total omega-3	43	1.016 (0.878–1.175)	0.836	1.016 (0.841–1.226)	0.872
Total omega-6	49	1.121 (0.907–1.385)	0.290	1.121 (0.867–1.450)	0.384
Ratio of omega-6 to omega-3	27	0.995 (0.858–1.153)	0.947	0.995 (0.825–1.200)	0.958
PUFA	48	1.071 (0.882–1.300)	0.489	1.071 (0.843–1.360)	0.575
Ratio of PUFA to total fatty acids	45	0.765 (0.587–0.997)	0.048	0.765 (0.560–1.047)	0.094
Premenstrual syndrome					
DHA	34	1.243 (0.840–1.838)	0.277	1.243 (0.876–1.763)	0.223
Linoleic acid	41	0.937 (0.572–1.534)	0.795	0.937 (0.564–1.556)	0.801
Total omega-3	43	1.294 (0.933–1.794)	0.123	1.294 (0.937–1.786)	0.118
Total omega-6	49	1.376 (0.857–2.209)	0.186	1.376 (0.869–2.179)	0.173
Ratio of omega-6 to omega-3	27	0.833 (0.598–1.158)	0.277	0.833 (0.654–1.061)	0.138
PUFA	48	1.302 (0.843–2.010)	0.234	1.302 (0.820–2.068)	0.263
Ratio of PUFA to total fatty acids	39	0.779 (0.431–1.410)	0.410	0.779 (0.460–1.322)	0.355
Premature ovarian insufficiency					
DHA	43	0.765 (0.482–1.213)	0.255	0.765 (0.529–1.108)	0.156
Linoleic acid	46	1.458 (0.820–2.592)	0.199	1.458 (0.815–2.609)	0.204
Total omega-3	49	0.855 (0.583–1.254)	0.422	0.855 (0.637–1.148)	0.297

(Continued)

Table 3 (Continued).

Variables	nSNPs	Fixed Effects		Multiplicative Random Effects	
		OR (95% CI)	P	OR (95% CI)	P
Total omega-6	57	1.533 (0.883–2.663)	0.129	1.533 (0.930–2.528)	0.094
Ratio of omega-6 to omega-3	30	1.279 (0.864–1.893)	0.219	1.279 (0.934–1.752)	0.125
PUFA	55	1.040 (0.631–1.716)	0.878	1.040 (0.668–1.620)	0.862
Ratio of PUFA to total fatty acids	45	0.728 (0.383–1.384)	0.333	0.728 (0.364–1.458)	0.370

Notes: Bold text in the Variables column indicates outcome disease categories, and bold OR and P values indicate statistically significant associations with $P < 0.05$.

Abbreviations: DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

A notably consistent finding was the positive association of genetically predicted linoleic acid levels with both endometriosis and female infertility. In the fixed-effects IVW analysis, linoleic acid exhibited an odds ratio (OR) of approximately 1.127 for endometriosis and 1.155 for female infertility (Figure 2); the random-effects models yielded similar or slightly stronger estimates. These results suggest that elevated circulating linoleic acid may increase susceptibility to these gynecological conditions (Figures 3B and C).

Total omega-6 also demonstrated a significant positive causal association with endometriosis, with an OR near 1.123 in the fixed-effects IVW analysis (Figure 2). The random-effects analysis was marginally significant as well, indicating that higher total omega-6 levels might contribute to an increased risk of endometriosis (Figure 3A).

In contrast, an intriguing inverse association was observed for the ratio of PUFA to total fatty acids (TFAs). This ratio appeared protective against endometriosis, female infertility, and polycystic ovarian syndrome. Specifically, for endometriosis, the fixed-effects IVW analysis showed an OR of roughly 0.857 (Figure 2), with similar trends observed under random-effects modeling. For female infertility and PCOS, protective effects were apparent under fixed-effects, although these associations were less robust in the random-effects models (Figure 3D–F) (visually depict how higher values of this ratio align with lower disease risk).

Additionally, leave-one-out analysis validated the stability of the results, with no single SNP significantly altering the causal estimates (see Figure S1–S6). These sensitivity analyses collectively affirm the robustness of our MR results.

Furthermore, no definitive causal relationships were consistently identified for DHA, total omega-3, the ratio of omega-6 to omega-3, or total PUFA with respect to most outcomes (including premenstrual syndrome and premature ovarian insufficiency). Although some secondary or sensitivity analyses (eg., MR-PRESSO results for DHA and endometriosis) suggested minor trends, these findings were not supported by the primary IVW analyses.

Overall, the IVW results indicate that increased circulating levels of linoleic acid and total omega-6 may elevate the risk of endometriosis and, in the case of linoleic acid, female infertility, whereas a higher ratio of PUFA to total fatty acids may confer a protective effect against endometriosis, female infertility, and polycystic ovarian syndrome. Additional analyses using weighted median and weighted mode methods are provided in supplementary materials (Table S3).

Reverse MR Analyses

We additionally tested whether reproductive endocrine disorders—endometriosis, female infertility, PCOS, premenstrual syndrome, and POI—causally affect circulating PUFA traits. In these reverse models, the MR Egger intercept tests generally indicated minimal horizontal pleiotropy and the Cochran’s Q tests suggested little heterogeneity. However, for PCOS, evidence of horizontal pleiotropy was detected by the MR-Egger intercept test for SNPs associated with circulating PUFA, the ratio of PUFA to total fatty acids, total omega-6, and linoleic acid, whereas Cochran’s Q test continued to show no significant heterogeneity (Table S4).

Among all reverse analyses, polycystic ovarian syndrome showed the strongest potential to influence certain PUFA measures. Specifically, genetic liability to PCOS was associated with decreased levels of the ratio of PUFA to total fatty acids, total omega-3, and DHA, and a potential increase in the ratio of omega-6 to omega-3. Although the effect sizes

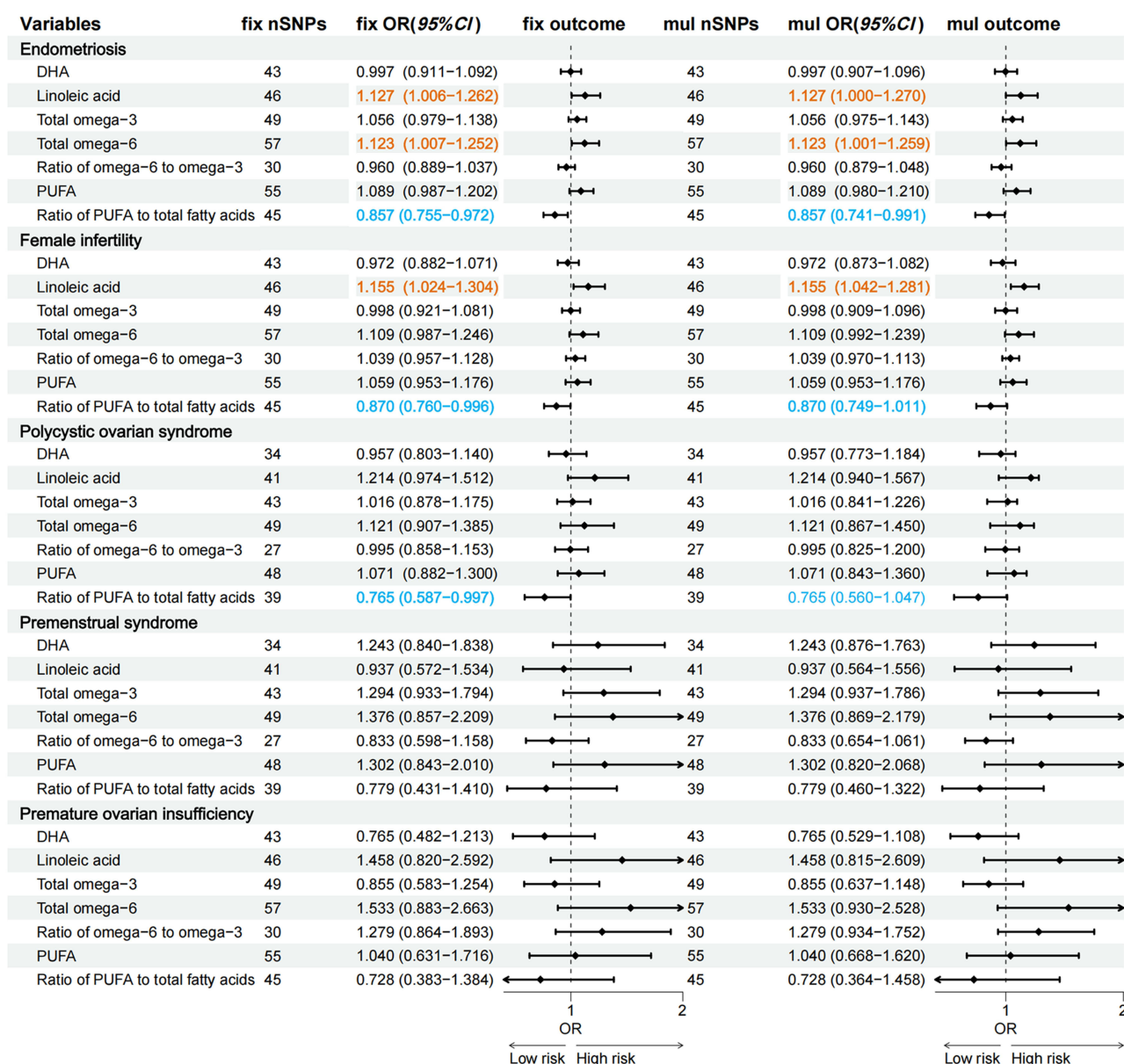


Figure 2 Forest plot of the forward Mendelian randomization analysis using fixed-effect IVW and multiplicative random-effect IVW models. The left and right panels show estimates from the fixed-effect IVW and multiplicative random-effect IVW models, respectively. Dots represent OR estimates, horizontal bars represent 95% CIs, and the vertical dashed line indicates OR = 1. Orange and blue text indicate statistically significant risk and protective effects, respectively, while black text indicates non-significant associations. Bold text indicates grouped PUFA-related exposure categories, and indented non-bold text indicates the corresponding outcome traits.

Abbreviations: IVW, inverse-variance weighted; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; SNP, single nucleotide polymorphism; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid.

were modest, the directions of these associations were consistent across both fixed-effects and multiplicative random-effects IVW models (Table 4) and Figure 4 visually depicts an inverse association for PCOS with the ratio of PUFA to total fatty acids, total omega-3, and DHA (all below unity), as well as a positive shift in the ratio of omega-6 to omega-3 in certain analyses.

In contrast, endometriosis, female infertility, premenstrual syndrome, and POI did not exhibit robust causal effects on the measured PUFA phenotypes. Across multiple tests, most estimates were centered around null values, providing no strong evidence that these conditions directly alter fatty acid profiles in circulation.

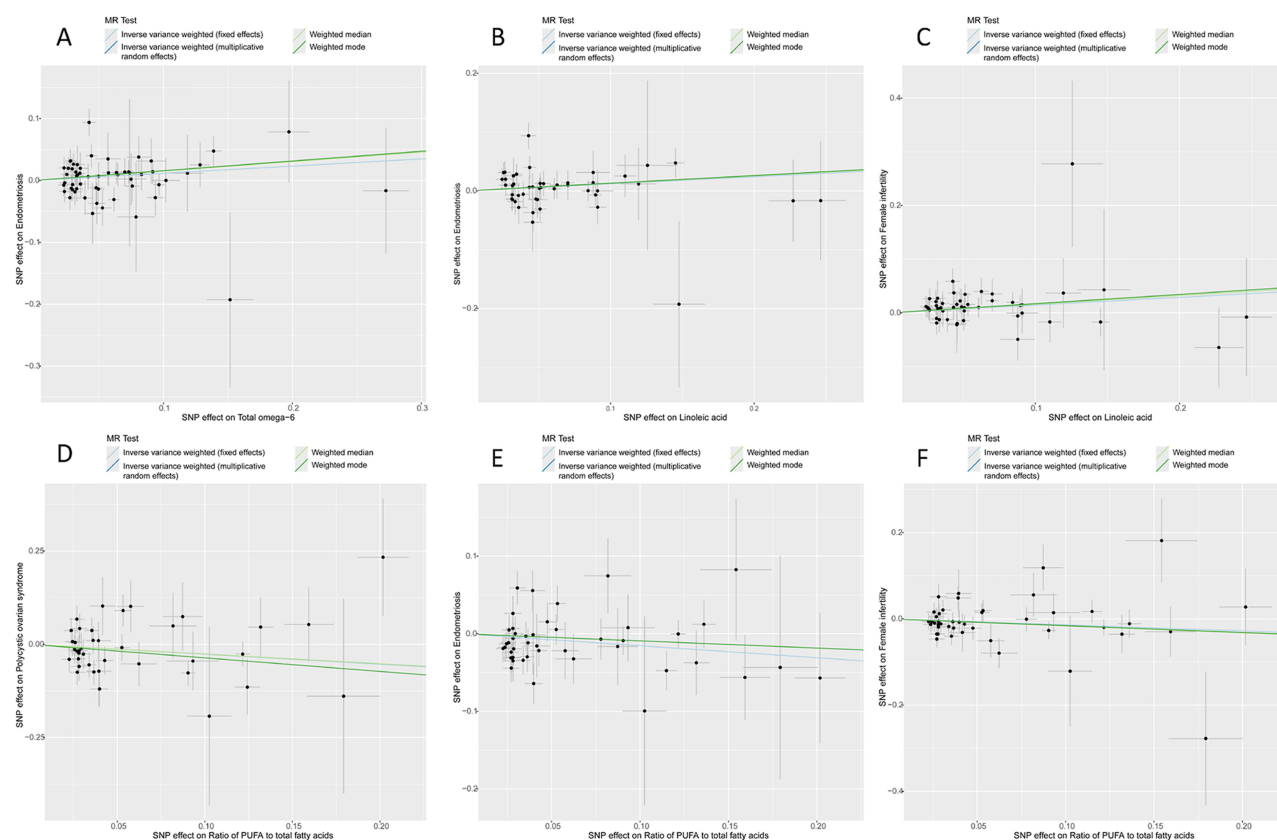


Figure 3 The scatter plots for different Mendelian randomization (MR) methods show consistent β values. (A) Total omega-6 to Endometriosis. (B) Linoleic acid to Endometriosis. (C) Linoleic acid to Female infertility. (D) Ratio of PUFA to total fatty acids to Polycystic ovarian syndrome. (E) Ratio of PUFA to total fatty acids to Endometriosis. (F) Ratio of PUFA to total fatty acids to Female infertility.

Summary of the Experimental Results

Graphical representations of the forward MR results (Figure 2) illustrate that the slope of the fitted lines—whether estimated via IVW or MR-Egger—remains consistent with the statistical findings. Our analysis indicates that elevated levels of linoleic acid or total omega-6 are implicated in an increased risk of several reproductive disorders. Conversely, a higher PUFA-to-TFA ratio is linked to a protective effect against these conditions. In contrast, Figure 4, which presents the reverse MR scenario through forest plots, confirms that PCOS is consistently linked with lower levels of beneficial PUFA fractions, including DHA, total omega-3, and the ratio of PUFA to total fatty acids, while also showing an increased ratio of omega-6 to omega-3.

Collectively, these analyses indicate that elevated circulating linoleic acid and total omega-6 may raise the risk of endometriosis—and, in the case of linoleic acid, female infertility—while a higher ratio of PUFAs to TFAs may protect against endometriosis, female infertility, and PCOS. Conversely, reverse MR analyses suggest that genetic liability to PCOS may reduce beneficial PUFA-related measures and shift the balance towards a more pro-inflammatory state by increasing the ratio of omega-6 to omega-3. These findings underscore the importance of monitoring specific fatty acid subtypes in women's health and suggest that interventions targeting the balance between omega-6 and omega-3 could potentially mitigate the burden of endometriosis, infertility, and other reproductive conditions in susceptible populations.

Discussion

This study applied a two-sample Mendelian randomization (MR) framework to examine the causal relationships between circulating PUFA traits and female reproductive endocrine disorders—including endometriosis, female infertility, PCOS, PMS and POI.

Table 4 The Reverse MR Results of Exposures and Outcomes

Variables	nSNPs	Fixed Effects		Multiplicative Random Effects	
		OR (95% CI)	P	OR (95% CI)	P
PUFA					
Endometriosis	11	1.011 (0.993–1.031)	0.233	1.011 (0.993–1.030)	0.213
Polycystic ovarian syndrome	196	0.998 (0.995–1.001)	0.121	0.998 (0.996–1.000)	0.051
Ratio of PUFA to total fatty acids					
Endometriosis	11	0.987 (0.969–1.005)	0.166	0.987 (0.963–1.012)	0.303
Polycystic ovarian syndrome	196	0.990 (0.988–0.993)	0.000	0.990 (0.988–0.993)	0.000
Total omega-3					
Endometriosis	11	1.009 (0.991–1.028)	0.318	1.009 (0.988–1.032)	0.398
Polycystic ovarian syndrome	196	0.997 (0.994–1.000)	0.032	0.997 (0.995–0.999)	0.006
DHA					
Endometriosis	11	1.004 (0.985–1.022)	0.692	1.004 (0.980–1.028)	0.765
Polycystic ovarian syndrome	196	0.989 (0.987–0.992)	0.000	0.989 (0.987–0.991)	0.000
Total omega-6					
Endometriosis	11	1.010 (0.991–1.029)	0.290	1.010 (0.991–1.030)	0.300
Polycystic ovarian syndrome	196	0.999 (0.996–1.001)	0.319	0.999 (0.996–1.001)	0.225
Linoleic acid					
Endometriosis	11	1.010 (0.991–1.029)	0.307	1.010 (0.988–1.033)	0.387
Polycystic ovarian syndrome	196	1.000 (0.997–1.002)	0.788	1.000 (0.998–1.002)	0.707
Ratio of omega-6 to omega-3					
Endometriosis	11	0.995 (0.976–1.013)	0.567	0.995 (0.971–1.019)	0.664
Polycystic ovarian syndrome	196	1.003 (1.001–1.006)	0.015	1.003 (1.001–1.006)	0.001

Notes: Bold text in the Variables column indicates grouped PUFA-related traits, and bold OR and P values indicate statistically significant associations with $P < 0.05$.

Abbreviations: DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

By leveraging both forward and reverse MR analyses, our study addresses the inherent limitations of traditional observational studies, such as unmeasured confounding and reverse causation, thereby strengthening the evidence for causal conclusions.

In the forward MR analyses, elevated levels of linoleic acid and total omega-6 were positively associated with endometriosis and female infertility, with linoleic acid showing the strongest and most consistent effects. It could be explained by the role of omega-6-related lipid metabolism in reproductive tract inflammation.³⁵ Linoleic acid is the parent omega-6 PUFA and can be metabolically connected to downstream omega-6 pathways, including arachidonic acid-derived eicosanoid production.³⁶ Arachidonic acid serves as a precursor for prostaglandins and leukotrienes, which are central mediators of inflammatory signaling.³⁶ On the other hand, prostaglandins and leukotrienes could be directly involved in reproductive physiology and pathology. In endometriosis, endometriotic lesions show increased COX-2 expression and COX-2-derived PGE2 biosynthesis compared with normal endometrium.³⁷ COX-2/PGE2 axis promotes inflammatory activation, lesion survival, angiogenesis, pain sensitization, and local estrogen production, thereby supporting the inflammatory microenvironment required for lesion persistence.³⁷ Leukotrienes, generated through the 5-lipoxygenase pathway, may further amplify inflammatory cell recruitment, vascular permeability, and peritoneal inflammatory responses.³⁶ For female infertility, PUFA-derived prostaglandin signaling may also influence reproductive physiology by regulating prostaglandin synthesis, steroid metabolism, ovulation, endometrial receptivity, and implantation.³⁵ Conversely, a higher ratio of PUFAs to TFAs appeared to be protective against endometriosis, female infertility, and PCOS. This protective effect likely reflects the anti-inflammatory role of omega-3 PUFAs, which counteract omega-6-mediated inflammation by producing mediators such as resolvins and protectins.³⁸ Notably, the ratio of omega-6 to omega-3, an established marker of inflammatory balance³⁹ did not show significant causal associations, suggesting that overall PUFA balance may be more critical than their relative proportions.

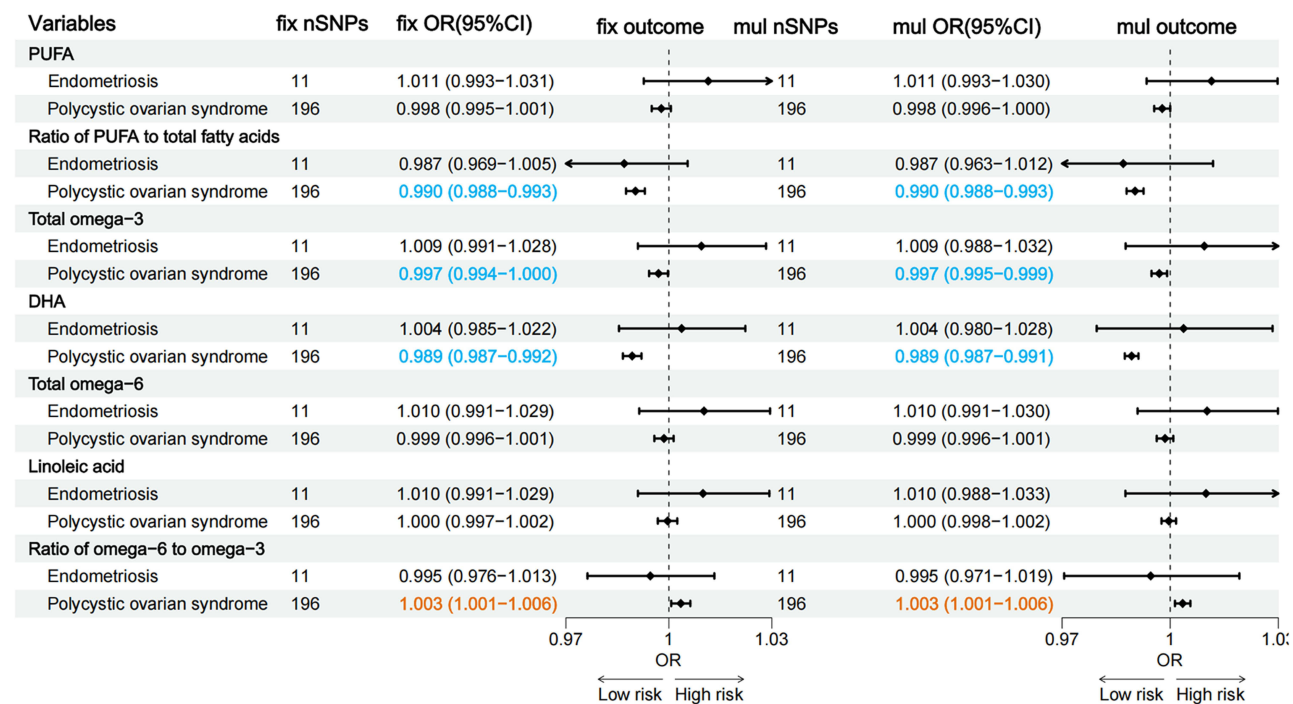


Figure 4 Forest plot of the reverse Mendelian randomization analysis using fixed-effect IVW and multiplicative random-effect IVW models. The left and right panels show estimates from the fixed-effect IVW and multiplicative random-effect IVW models, respectively. Dots represent OR estimates, horizontal bars represent 95% CIs, and the vertical dashed line indicates OR = 1. Orange and blue text indicate statistically significant positive and negative associations, respectively, while black text indicates non-significant associations. Bold text indicates grouped reproductive disorder categories, and indented non-bold text indicates the corresponding PUFA-related traits. **Abbreviations:** IVW, inverse-variance weighted; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; SNP, single nucleotide polymorphism; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid.

Reverse MR analyses further revealed that genetic liability to PCOS might lead to systemic changes in lipid profiles, specifically by reducing total omega-3 and DHA levels and increasing the ratio of omega-6 to omega-3. Although the effect sizes were modest, these findings suggest that PCOS may shift the PUFA profile toward a more pro-inflammatory state, potentially exacerbating the condition. One possible explanation involves the FADS1–FADS2 desaturase pathway. The FADS gene cluster has been associated with PCOS susceptibility, and FADS2 encodes $\Delta 6$ desaturase, a key enzyme involved in the endogenous conversion of essential fatty acid precursors, including α -linolenic acid and linoleic acid, into their long-chain PUFA metabolites.^{40,41} Because omega-3 and omega-6 precursors share desaturase and elongase enzymes, reduced FADS2 expression or activity could create a metabolic bottleneck that limits the conversion of α -linolenic acid toward long-chain omega-3 species, including DHA, while favoring a higher omega-6 to omega-3 balance under conditions of abundant omega-6 substrate availability.^{42,43}

In addition to the FADS1–FADS2 pathway, hormonal imbalance may also partly explain the reverse associations between PCOS and altered PUFA profiles. Female reproductive endocrine disorders are characterized by distinct endocrine disturbances, including hyperandrogenism and ovulatory dysfunction in PCOS, estrogen-dependent inflammatory activity in endometriosis, impaired follicular development in female infertility, cyclic ovarian steroid fluctuations in PMS, and estrogen–gonadotropin dysregulation in POI.^{44–46} These hormonal abnormalities may influence lipid metabolism, inflammatory mediator production, and circulating PUFA levels. Moreover, PCOS and other inflammatory reproductive disorders are closely linked to immune-inflammatory dysregulation, including altered interleukin and cytokine signaling, which may further connect endocrine disturbance with PUFA-related inflammatory metabolism.^{47–49}

This study has several notable strengths. First, the use of both forward and reverse MR analyses minimizes biases from confounding and reverse causation, offering robust causal inferences. Second, the utilization of large-scale GWAS datasets provided comprehensive genetic coverage and statistical power, particularly for European populations. Third,

extensive sensitivity analyses—including MR-Egger, weighted median, and MR-PRESSO—bolstered the credibility of our findings by addressing potential horizontal pleiotropy and weak instrument bias.

However, certain limitations should be acknowledged. The absence of individual-level data restricted our ability to perform more detailed analyses on the causal relationships between specific circulating PUFA traits and reproductive disorders. Because this study was based on publicly available GWAS summary-level data, we could not directly control the original inclusion and exclusion criteria of the recruited participants, such as disease severity, age distribution, or other cohort-specific clinical characteristics. Also, similar studies in non-European and multi-ethnic populations are warranted for the validation. Meanwhile, as this study was based on summary-level genetic data, the exploration of specific biological mechanisms underlying the observed associations could be interesting in the future. Finally, because our study was based on genetic data from individuals of European descent, the findings may not be generalizable to other ethnic groups, which could have differing genetic architectures and dietary patterns.

Overall, our findings have important implications for public health and clinical practice. The identification of elevated linoleic acid and total omega-6 levels as potential risk factors for endometriosis and infertility suggests that dietary interventions aimed at reducing omega-6 intake and promoting omega-3 consumption could be beneficial. Additionally, the protective association observed with a higher ratio of PUFAs to TFAs highlights the potential of maintaining a balanced PUFA profile to improve reproductive health. Future research should aim to validate these findings in more diverse populations and explore gene-diet interactions that may further influence these associations, as well as elucidate the underlying biological mechanisms through experimental studies.

Conclusion

In summary, our two-sample Mendelian randomization study provides genetic evidence supporting a potential causal association between circulating polyunsaturated fatty acid profiles and female reproductive endocrine disorders. Genetically predicted higher circulating linoleic acid and total omega-6 levels were associated with increased risks of endometriosis and female infertility, whereas a higher genetically predicted ratio of PUFAs to total fatty acids was associated with lower risks of these conditions and PCOS. Reverse MR analyses further suggested that PCOS may influence circulating lipid profiles, which may partly reflect altered endogenous lipid metabolism and inflammatory regulation. Therefore, our findings suggest that PUFA-related metabolic pathways may contribute to the pathophysiology of female reproductive endocrine disorders, while the potential benefits of dietary or therapeutic modulation of PUFA profiles require further validation in mechanistic studies, randomized trials, and diverse populations.

Abbreviations

CI, Confidence interval; DHA, Docosahexaenoic acid; GWAS, Genome-wide association study; IV, Instrumental variables; IVW, Inverse variance weighting; LD, Linkage disequilibrium; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization-pleiotropy residual sum and outlier; OR, Odds ratio; PCOS, Polycystic ovary syndrome; POI, Premature ovarian insufficiency; PUFA, Polyunsaturated fatty acid; SNP, Single nucleotide polymorphism; TFA, Total fatty acids; WM, Weighted mean.

Data Sharing Statement

All data are available within the article and its supplementary materials.

Ethics Approval and Consent to Participate

Since this study exclusively utilized de-identified, publicly available summary-level data from GWAS database, and no individual-level data were involved, additional ethical approval was not required. The original studies have obtained approval from their respective ethics committees. This study is exempt from ethical review by the Institutional Review Board of the International Peace Maternity & Child Health Hospital based on national legislation guidelines, such as Article 32 of the Measures for Ethical Review of Research Involving Human Biological Sciences and Medical Research, China. This study was performed according to the principles expressed in the Declaration of Helsinki.

Consent for Publication

The FinnGen was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS/990/2017). Written informed consent was obtained from all participants before their participation in the survey.

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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 report no conflicts of interest in this work.

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