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Association of dietary preferences with primary ovarian insufficiency (POI): a mendelian randomization-based analysis

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Abstract

Background Primary ovarian insufficiency (POI) is a critical cause of infertility and is increasingly recognized as a complex metabolic disorder. Dietary factors may influence the risk of POI, but causal relationships remain unclear.

Methods We conducted an MR study using genetic instrumental variables for 83 dietary preferences from the UK Biobank, with the Inverse Variance Weighted method as the primary analysis.

Results Consumption of butter and full-fat dairy products was strongly associated with an increased risk of primary ovarian insufficiency (POI). Women who consumed butter had nearly ten times the risk of developing POI (OR = 9.54, $p = 0.048$), while full-cream milk was associated with an even greater risk (OR = 29.22, $p = 0.018$). Interestingly, semi-skimmed milk, despite its lower fat content, also showed a significant positive association with POI (OR > 100, $p = 0.008$). In contrast, dietary patterns including oily fish and pork were protective against POI. Oily fish, rich in omega-3 fatty acids, was linked to a 82% reduced risk of POI (OR = 0.18, $p = 0.008$), and pork consumption also showed a protective effect (OR = 0.13, $p = 0.041$). Additionally, women who did not consume eggs had a significantly lower risk of POI (OR < 0.001, $p = 0.044$).

Conclusion This study demonstrates that high-fat dairy products may increase the risk of POI, while oily fish and pork consumption could offer protective effects. These findings providing a foundation for future clinical and public health strategies targeting reproductive health.

Keywords Primary ovarian insufficiency, Mendelian randomization, Dietary preferences, Food intake

Introduction

Primary ovarian insufficiency(POI), commonly referred to as primary ovarian failure (POF), is characterized by the cessation of ovarian function before the age of 40 and is a significant cause of infertility in women [1, 2]. The Study of Women's Health Across the Nation (SWAN) reports that primary ovarian insufficiency (POI) affects approximately 1.1% of women under the age of 40. However, a recent comprehensive meta-analysis estimated the global prevalence of POI to be 3.7% [3, 4]. A subsequent meta-analysis revealed that, according to subgroup analysis, the prevalence of primary ovarian insufficiency

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(POI) was highest among women with iatrogenic causes (11.2%), followed by those with autoimmune etiologies (10.5%). Regionally, North America exhibited the highest prevalence at 11.3%, while South America had a lower prevalence of 5.4%. In terms of economic development, the prevalence of POI was 5.3% in developing countries, compared to 3.1% in developed nations. Although the prevalence of POI has increased over the past two decades, this trend did not reach statistical significance ($p>0.05$) [5].

POI is influenced by various factors, including genetic predisposition, autoimmune diseases, and environmental exposures. Among these, dietary habits have emerged as a significant modifiable factor affecting ovarian function [6]. Specifically, high-fat and high-sugar (HFHS) diets have been linked to the accelerated decline of ovarian function, potentially increasing the risk of POI through multiple mechanisms [7]. These include oxidative stress, chronic low-grade inflammation, and metabolic disturbances. HFHS diets induce oxidative stress in ovarian cells by increasing reactive oxygen species (ROS) production, leading to cellular damage and dysfunction. Additionally, such diets may provoke an inflammatory response, with elevated levels of cytokines such as IL-6 and TNF-α, which can contribute to ovarian cell apoptosis and hinder follicular development. Metabolic disorders associated with HFHS diets, such as insulin resistance and dyslipidemia, further disrupt hormonal balance and impair ovarian function [8–10]. The latest research findings have underscored the significance of nutrition in influencing reproductive and metabolic health. Specific dietary patterns, such as those rich in antioxidants, omega-3 fatty acids, and phytoestrogens, have been associated with enhanced ovarian function and a delayed onset of POI. Conversely, a high intake of processed foods, refined sugars, and trans fats has been linked to accelerated ovarian aging [11–13]. In addition to reproductive dysfunction, POI is increasingly recognized as a complex metabolic disorder. Women with POI often exhibit metabolic disturbances, including altered lipid profiles, insulin resistance, and an elevated risk of cardiovascular diseases [14, 15]. These metabolic abnormalities suggest that POI may be closely linked to lifestyle factors, such as dietary preferences, hormone levels, and circadian rhythms, further complicating its pathophysiology [15, 16].

For women with a family history of POI or those exposed to known risk factors (such as autoimmune conditions or chromosomal abnormalities), dietary modifications may represent a promising strategy for mitigating the risk of disease onset and progression [17]. Nevertheless, the precise relationship between dietary preferences and POI remains challenging due to the inherent limitations of observational studies, including reverse causality and confounding by other lifestyle factors. It is therefore imperative that robust, causal evidence be obtained to determine whether specific dietary interventions can effectively reduce the risk of POI in at-risk populations. Currently, treatment options for POI are limited. Hormone replacement therapy (HRT) is often the primary treatment to alleviate symptoms associated with estrogen deficiency, including vasomotor symptoms and bone loss [18]. However, HRT does not restore fertility and is associated with long-term risks, such as thromboembolism and breast cancer [19]. Additionally, there are no established treatments that can effectively delay or prevent the progression of POI [20]. Given these therapeutic challenges, identifying modifiable risk factors, such as diet, may offer new avenues for prevention and management.

Mendelian randomization (MR) offers a powerful approach to assess the causal impact of dietary factors on POI risk. By using genetic variants as instrumental variables (IVs), MR minimizes confounding and reverse causality, providing more reliable causal estimates than traditional observational studies [21]. This study leverages MR and large-scale genome-wide association studies (GWAS) to clarify the role of specific dietary choices in POI risk, offering insights for potential prevention strategies in genetically predisposed individuals.

Materials and methods

Mendelian randomization study design

Mendelian Randomization (MR) employs genetic variants as instrumental proxies to assess causal relationships between exposures and outcomes. This method relies on three foundational assumptions: Instrument Relevance; Instrument Independence and Exclusion-Restriction Criterion [22]. Using these principles, our study implemented a Mendelian Randomization framework to explore the direct causal effects of dietary preferences on the risk of primary ovarian insufficiency(POI), as depicted in Fig. 1. This approach allows us to navigate the complex interplay of genetics and environmental factors, providing a clearer understanding of how specific dietary behaviors may influence the development of POI, thereby offering insights that could guide future interventions and policy decisions.

Data source

For the investigation of dietary habits, genetic instrumental variables (IVs) were derived from published data based on the UK Biobank. Using a stringent threshold of $p<5\times10^{-6}$, a total of 83 distinct dietary preferences were included in the final analysis [23]. In parallel, POI was examined using the dataset designated as finn-b-E4_OVARFAIL, sourced from the Finnish FinnGen database (https://r8.risteys.finngen.fi/phenocode/E4_OVARFAIL), which includes data up to 2021 [24]. This dataset focuses

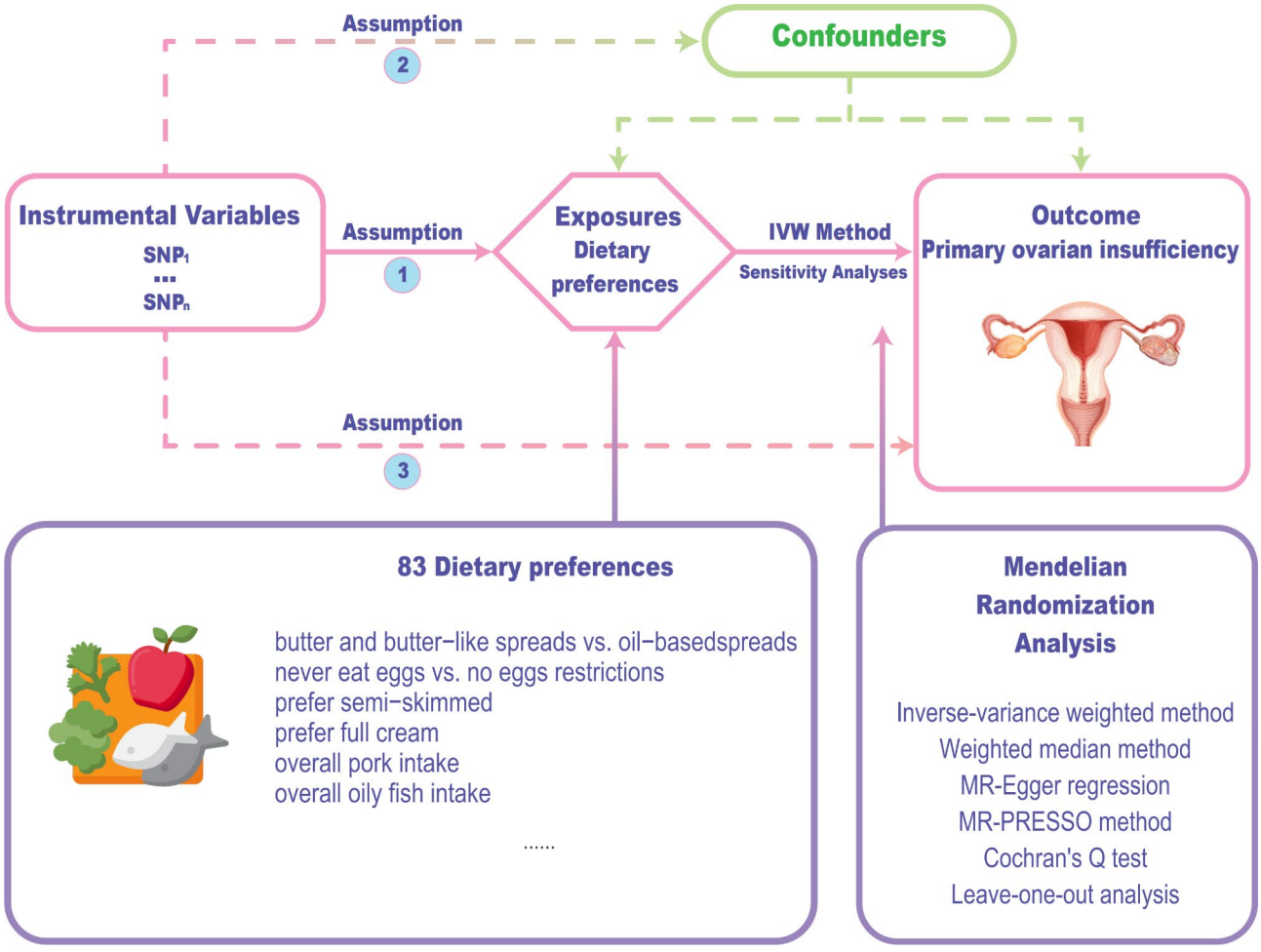

Fig. 1 This section describes the study design for the MR analysis. The analysis is based on three core hypotheses: (1) a strong association between instrumental variables and exposure factors; (2) no association between instrumental variables and confounders; (3) instrumental variables can only affect the outcome through exposure factors and not through other means. In this study, we deemed a genome-wide level of statistical significance to have been reached when $p < 5 \times 10^{-6}$. We removed linkage disequilibrium based on the criteria of r2 > 0.001 and kb = 10,000. Furthermore, we investigated the relationship between exposure and outcome using five methods, including IVW, and conducted sensitivity analyses

specifically on a European female population, allowing for a high degree of demographic specificity in our analysis. The use of this dataset ensures that our investigation into POI is tailored to the population most affected by the condition, thus improving the relevance and generalizability of the results. By integrating detailed dietary data from the UK Biobank with the comprehensive POI data from the Finnish cohort, this dual-faceted strategy establishes a robust foundation for our Mendelian randomization study. This approach strengthens the causal inference drawn from the genetic IVs, reducing the risk of confounding and enhancing the accuracy of our findings regarding the relationship between dietary preferences and the risk of POI. The circular heatmap in Fig. 2 summarises the effect of 83 dietary preferences on the occurrence of POIs.

Genetic instruments

In our preliminary analysis, we initially applied a stringent significance threshold of $p < 5 \times 10^{-8}$ for SNP selection. However, for exposures where SNP discovery proved more challenging, this threshold did not yield a sufficient number of SNPs for downstream analyses [25]. To address this limitation, we adopted a more relaxed threshold of $p < 5 \times 10^{-6}$ to ensure an adequate number of SNPs for robust analysis. All other parameters, including $r^2 \geq 0.001$ and an LD distance of ≤ 10,000 kb, were kept as default and remained unchanged [26].

We also took precautionary steps by removing palindromic SNPs and proxy SNPs, which could otherwise compromise the accuracy of our Mendelian Randomization (MR) analysis. To further guard against the influence of weak instruments, we set an F-statistic threshold greater than 10. This ensures the strength of the instrumental variables, as a higher F-statistic reduces the risk

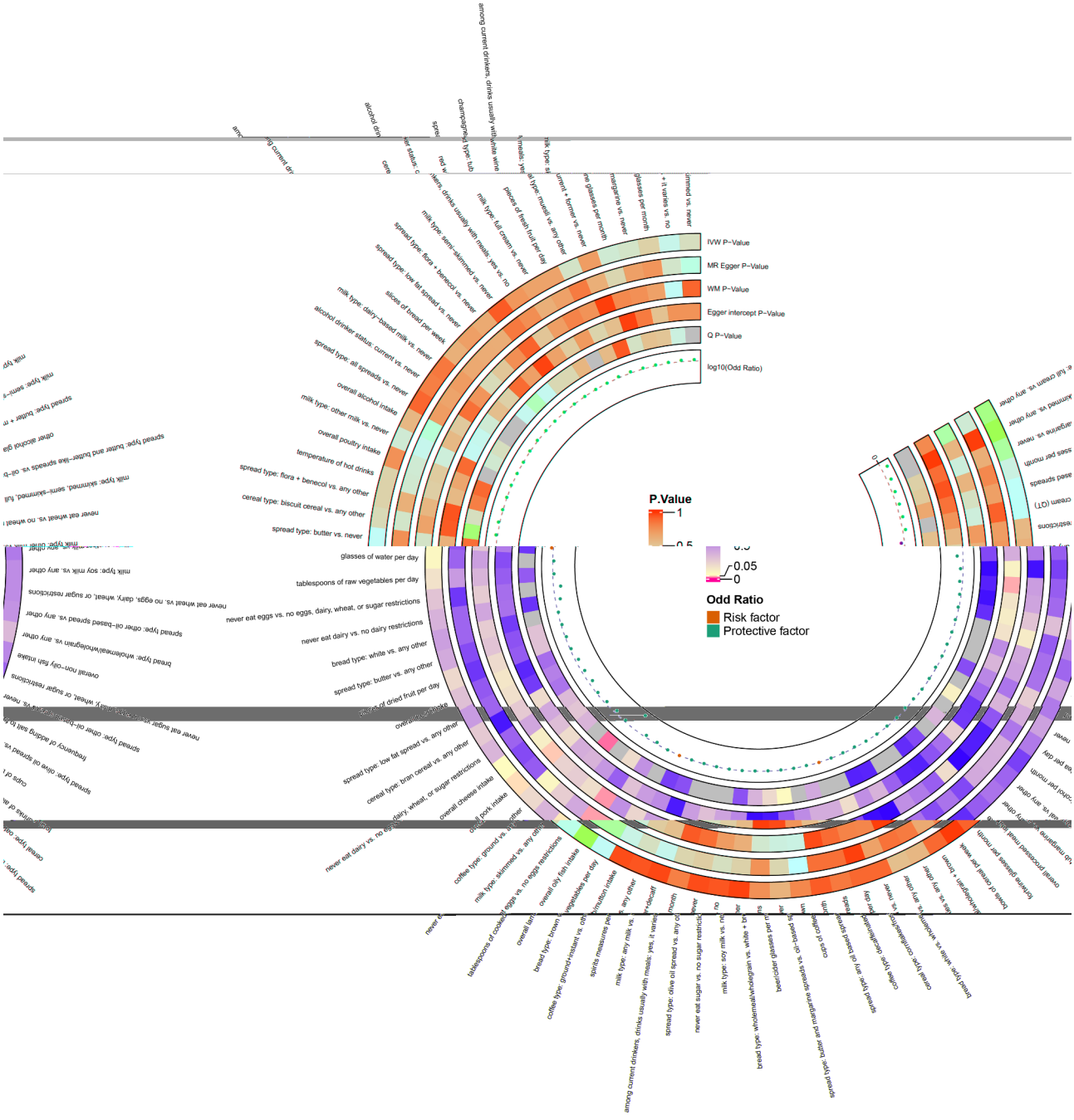

Fig. 2 Associations between 83 Dietary Preferences and Primary Ovarian Insufficiency (POI) Analyzed Using Mendelian Randomization (MR) Models. The figure illustrates odds ratios (OR) and 95% confidence intervals (CI) for 83 dietary exposures in relation to POI, analyzed using three MR methods: Inverse Variance Weighted (IVW), Weighted Median (WM), and MR Egger regression. Each point represents the log-transformed OR for a specific dietary variable, including types and frequencies of consumption. The y-axis lists individual dietary items or patterns, while the x-axis presents the log-transformed OR with 95% CI, distinguishing risk factors (values > 1) and protective factors (values < 1). The color-coded markers correspond to the statistical significance of p-values derived from the IVW, WM, and MR Egger methods, with specific markers denoting p-values below the 0.05 threshold. Significance in p-values across methods indicates robust associations, while discrepancies highlight potential pleiotropy or methodological sensitivity. Additional annotations include p-values for MR Egger intercepts, which assess directional pleiotropy, and Cochran's Q statistic for heterogeneity

of bias from weak instruments. The F-statistic was calculated as $[(R^2 \times (N-2))/(1-R^2)]$, where R^2 represents the variance in the exposure explained by the SNPs, and N is the sample size. These steps were integral to enhancing the precision and reliability of our MR findings.

Statistical analyses

Statistical analyses were performed using R software (version 4.2.2) with specialized packages, including "ggplot2," "LDlinkR," "MendelianRandomization," "MRPRESSO," and "TwoSampleMR." The primary analytical method was the Inverse Variance Weighted (IVW) approach, widely regarded for its robustness in the absence of pleiotropic effects in instrumental variables. To enhance precision and account for potential biases from horizontal pleiotropy, additional methods such as MR-Egger, Maximum Likelihood, and Weighted Median Regression were employed. The MR-Egger intercept P-value was used to detect directional pleiotropy, with values above 0.05 suggesting no significant pleiotropic bias, thereby supporting the validity of the causal inference.

In cases where horizontal pleiotropy could confound IVW estimates, MR-Egger regression was used to identify and adjust for pleiotropic effects, enhancing the accuracy of causal estimates. The MR-PRESSO method was also used to validate results; when significant pleiotropy was detected (P-value below the MR-PRESSO outlier test threshold), analyses were rerun excluding outlying SNPs (Table 1), while Supplementary Table 1 shows the results of the horizontal pleiotropy test. To ensure robustness, sensitivity analyses were performed by systematically excluding certain SNPs. Results are presented as Odds Ratios (ORs) with 95% Confidence Intervals (CIs), clarifying causal links between dietary exposures and outcomes [27].

Result

Dietary preferences promoting the development of POI

As illustrated in Fig. 3, the analysis demonstrated that specific dietary preferences were linked to an elevated risk of developing primary ovarian insufficiency (POI). One notable finding was the significant correlation between butter and butter-like spreads and an elevated risk of POI. The data showed that women who consumed these products were significantly more likely to develop POI than those who preferred oil-based spreads (OR = 9.535, $p = 0.048$). In addition, a preference for whole milk was also significantly associated with an increased risk of POI (OR = 29.22, $p = 0.018$). It is noteworthy that semi-skimmed milk, despite its lower fat content, also exhibited a significant correlation with elevated POI risk (OR > 100, $p = 0.008$). This observation implies that factors beyond fat content, potentially including hormonal influences from dairy products, may be contributing to the risk of POI.

Dietary preferences inhibiting the development of POI

Conversely, as shown in Fig. 3, certain dietary preferences were protective against the development of POI. Regular consumption of oily fish, which is rich in omega-3 fatty acids, was associated with a significantly reduced risk of POI (OR = 0.180, $p = 0.008$). In addition, women who reported never eating eggs also had a lower risk of POI compared with those who did not restrict their egg intake

Table 1 Heterogeneity test and pleiotropy test in the mendelian randomization study

Exposures	Outcome	Menthod	Heterogeneity.Test.*P*	Egger intercept	MR.Egger.Intercept.*P*	MR.PRESSO. Global.Test.*P*
spread type: butter and butter-like spreads vs. oil-based spreads	Primary ovarian insufficienc	MR Egger	0.219	-	-	-
		Inverse variance weighted	0.243	0.027	0.584	0.571
never eat eggs vs. no eggs restrictions	Primary ovarian insufficienc	MR Egger	0.300	-	-	-
		Inverse variance weighted	0.415	0.015	0.908	0.971
milk type: semi-skimmed vs. any other	Primary ovarian insufficienc	MR Egger	0.985	-	-	-
		Inverse variance weighted	0.973	0.062	0.174	0.233
milk type: full cream vs. any other	Primary ovarian insufficienc	MR Egger	0.483	-	-	-
		Inverse variance weighted	0.516	-0.042	0.554	0.618
overall pork intake	Primary ovarian insufficienc	MR Egger	0.849	-	-	-
		Inverse variance weighted	0.866	-0.015	0.701	0.559
overall oily fish intake	Primary ovarian insufficienc	MR Egger	0.378	-	-	-
		Inverse variance weighted	0.340	0.056	0.102	0.328

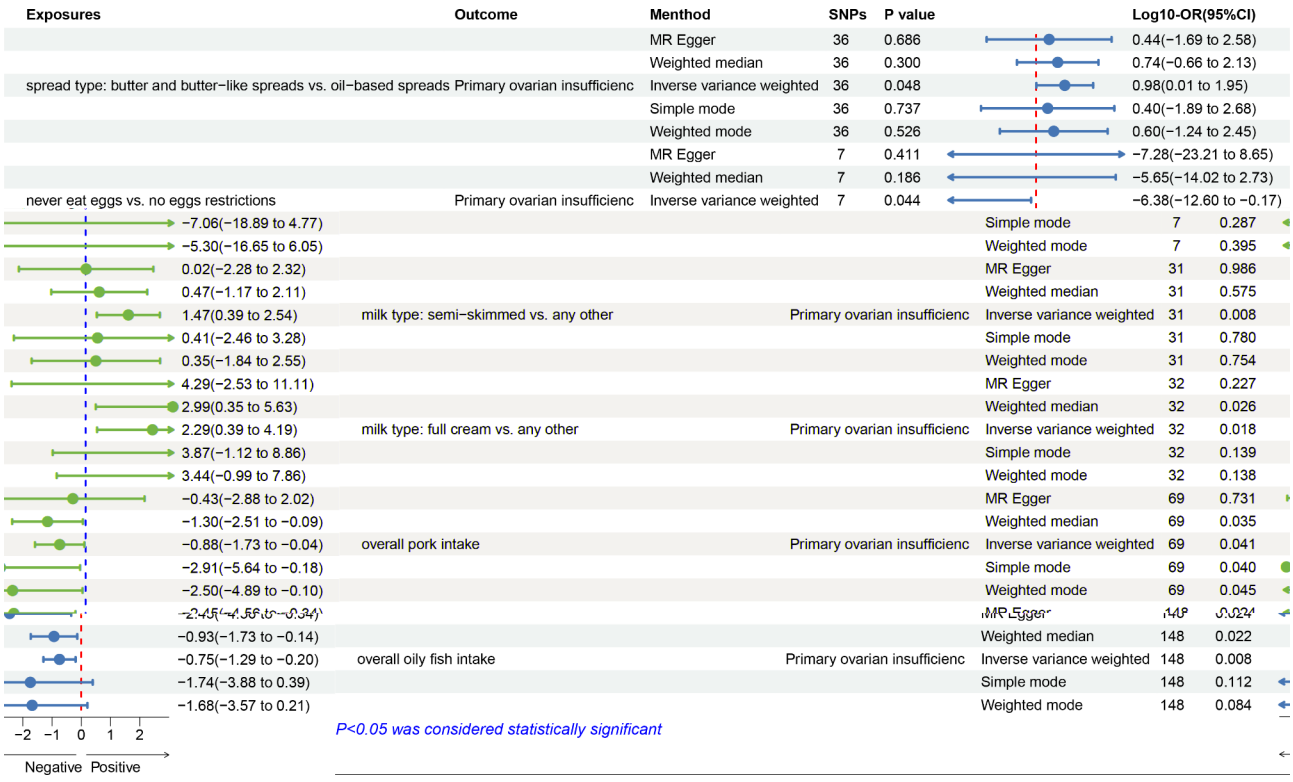

Fig. 3 Significant Associations between Dietary Preferences and Primary Ovarian Insufficiency (POI) Risk. This figure highlights dietary preferences showing statistically significant associations with POI risk, identified using the Inverse Variance Weighted (IVW) method as the primary analysis tool, alongside MR Egger, Weighted Median, Simple Mode, and Weighted Mode methods for robustness checks. Dietary exposures include butter-based spreads vs. oil-based spreads, egg consumption restrictions, milk type (semi-skimmed or full cream), pork intake, and oily fish intake. Odds ratios (ORs) with 95% confidence intervals (CIs) are displayed, with $p < 0.05$ indicating significance

(OR < 0.001, $p = 0.044$). While eggs are rich in essential nutrients, their exclusion in this study suggests that specific dietary patterns associated with low egg consumption may confer protective effects on ovarian health, although the exact mechanisms remain unclear. Interestingly, pork consumption also emerged as a protective factor against POI (OR = 0.131, $p = 0.041$).

Discussion

Our Mendelian randomization (MR) analysis provides new insights into the causal relationships between specific dietary preferences and the risk of primary ovarian insufficiency(POI). As a major contributor to infertility and various metabolic disorders, POI poses a significant challenge to women's health [28]. Current treatment strategies, such as hormone replacement therapy (HRT), are primarily symptomatic and fail to restore fertility or halt disease progression. Therefore, the identification of modifiable factors, such as diet, may open new avenues for the prevention and management of POI [29].

Dietary spread and egg consumption

The significant association between butter and butter-like spreads and POI risk highlights the potential role of dietary fat composition in ovarian function. Butter, rich in saturated fats, may contribute to metabolic dysregulation, which in turn impacts reproductive health [30]. The replacement of butter with oil-based spreads, which are typically higher in unsaturated fats, could be a potential dietary intervention to reduce POI risk [31]. The hypothesis is supported by indirect evidence from studies on cardiovascular health and hormonal balance. Butter and butter-like spreads, rich in saturated fats and potential trans fats, are associated with increased cardiovascular risk, which may contribute to ovarian aging and increase POI risk [32]. Elevated cholesterol levels and impaired vascular function, both linked to high saturated fat intake, could negatively impact ovarian function [33, 34].

Oil-based spreads, which are higher in unsaturated fats, have beneficial effects on cardiovascular health and may support ovarian function, reducing POI risk [35]. Furthermore, the nutritional composition of these spreads influences metabolic and hormonal status. Saturated fats in butter can disrupt estrogen synthesis and regulation, extending periods of estrogen deficiency and contributing to ovarian dysfunction [36]. On the other hand, unsaturated fats in oil-based spreads are linked to

improved metabolic outcomes and hormone balance, potentially lowering POI risk [37].

Our analysis indicates that abstaining from egg consumption may offer a protective effect against primary ovarian insufficiency (POI) when compared to unrestricted egg intake. While eggs are widely recognized for their nutritional value providing high quality protein, choline, and essential vitamins this finding might be influenced by broader dietary patterns associated with lower egg consumption [38, 39]. It is also plausible that specific bioactive components in eggs, such as cholesterol and certain fatty acids, could impact ovarian function, potentially contributing to the development of POI [40].

Oily fish and pork consumption

The protective association of oily fish consumption with POI reinforces the established benefits of omega-3 fatty acids, including their anti-inflammatory properties and their reported role in enhancing oocyte quality in women [41, 42]. Omega-3 fatty acids, abundant in oily fish, have well-established benefits for cardiovascular and metabolic health, and these properties may extend to ovarian function [43, 44]. Omega-3 fatty acids have been widely studied for their beneficial effects on inflammation and metabolic health, as demonstrated in a randomized, double-blind, placebo-controlled trial involving women with polycystic ovary syndrome (PCOS) [42]. This study revealed that 12 weeks of fish oil supplementation significantly upregulated peroxisome proliferator-activated receptor gamma (PPAR-γ) expression and downregulated pro-inflammatory cytokines interleukin-1 (IL-1) and interleukin-8 (IL-8) in peripheral blood mononuclear cells (PBMCs) of PCOS patients. Given these effects, increased oily fish intake or omega-3 supplementation may serve as a practical, dietary-based preventive strategy for women at risk of POI.

Interestingly, the consumption of pork was also associated with a reduced risk of POI. While red meat consumption is often associated with negative health outcomes, pork may provide essential nutrients such as iron, B vitamins, and high-quality protein, all of which are crucial for maintaining metabolic and reproductive health [45, 46]. The lower POI risk observed in pork consumers could be attributed to these nutritional benefits. However, this finding requires careful interpretation, as the type and quality of pork consumed (e.g., lean versus processed pork) could lead to varying health outcomes [47, 48]. Further research is needed to distinguish the effects of processed versus lean pork on reproductive health and to explore how pork consumption may reduce POI risk.

Oily fish and pork consumption

A novel finding in our study was the association between increased risk of POI and preferences for both full cream and semi-skimmed milk, suggesting that both high-fat and lower-fat dairy products may negatively impact ovarian health, potentially due to exogenous hormones in dairy that may disrupt endogenous hormone regulation and contribute to early ovarian aging [49, 50]. Evidence supporting this includes a study indicating a negative correlation between total fat intake and anti-Müllerian hormone (AMH) concentrations, where higher trans fat consumption was associated with ovulatory infertility [51]. Additionally, data from the NHS II cohort and other studies suggest that higher dairy fat intake is linked to slower declines in AMH levels, while higher trans fats increase infertility risk [52, 53].

These findings have important implications for the prevention and management of primary ovarian insufficiency POI. While treatment options remain limited, dietary modifications offer a non-invasive strategy to reduce POI risk, particularly for women with family histories or other risk factors.

Generalizability and practical implications of dietary recommendations

This study providesinsights into dietary preferences and their association with primary ovarian insufficiency (POI), but the broader applicability of these findings across different populations requires careful consideration. For instance, our results show that a preference for butter and whole milk is significantly linked to an increased risk of POI, while consumption of oily fish and pork appears protective. These findings underscore the importance of considering local dietary habits, as food preferences and availability can vary greatly across regions and cultures. In populations where dairy consumption is high or where fatty foods are a staple, the generalizability of these results may be limited, and tailored dietary recommendations will be necessary to address regional differences in food habits and health outcomes.

The practical implications of these findings suggest that public health policies should focus not only on identifying risky dietary patterns, such as high butter or whole milk intake, but also on promoting the protective effects of foods like oily fish and lean meats. In terms of real-world application, these recommendations could be translated into dietary guidelines or health campaigns aimed at reducing the consumption of risk-associated foods and encouraging the inclusion of protective foods in everyday diets. However, such interventions must account for socio-economic factors, food accessibility, and cultural preferences to ensure that they are feasible and effective across different population groups.

Additionally, the potential for adverse consequences or challenges in modifying dietary habits, particularly in vulnerable populations, must be considered. For example, while excluding eggs from the diet showed a protective effect against POI in our study, the long-term impact of such dietary changes should be carefully assessed to avoid nutrient deficiencies or unintended health effects. Therefore, any dietary modifications recommended should be accompanied by comprehensive guidance to ensure nutritional balance and sustainability, especially in populations with limited access to diverse food options.

Limitations

Despite the strengths of this study, including the use of Mendelian randomization (MR) to infer causal relationships, several limitations must be acknowledged. The wide confidence intervals for certain dietary exposures, such as dairy products, suggest variability in the data, indicating that larger sample sizes are needed to improve the precision of these estimates. Furthermore, while MR allows for robust causal inferences, it relies on the availability of appropriate genetic variants as instrumental variables. Future observational studies should focus on identifying additional genetic instruments and integrating them with other omics approaches, like metabolomics, to provide a more comprehensive understanding of the impact of diet on ovarian function.

Conclusion

Our findings suggest that certain dietary factors, such as the consumption of butter and full-fat dairy, are associated with an increased risk of POI, while dietary choices like oily fish and pork appear to offer protective benefits. These results highlight the significant role that modifiable dietary habits play in influencing reproductive health, particularly in relation to POI risk.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-024-03488-z.

Supplementary Material 1

Supplementary Material 2

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Author contributions
Concept and design: ZQ, EYZH and JK. Acquisition, analysis, and interpretation of data: ZQ and YF. Drafting of the manuscript: ZQ, EYZH and YL. Critical revision of the manuscript for important intellectual content: ZQ, JD and JK. Statistical analysis: ZQ and JK. Visualization, ZQ, EYZH and JK. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data supporting the findings of this study are available from the corresponding authors upon reasonable request.

Declarations

Ethical approval
Not applicable.

Consent for publication
Not applicable.

Informed consent
Not applicable.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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