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ORIGINAL RESEARCH

Association Between Dietary Taste Preferences and Primary Ovarian Insufficiency: A Mendelian Randomization Study

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Purpose: To investigate the effects of dietary taste preferences on primary ovarian insufficiency (POI) by two-sample Mendelian randomization analysis, excluding confounding factors.

Patients and Methods: Single nucleotide polymorphisms (SNPs) associated with 139 dietary taste preferences were obtained from GWAS results provided by May-Wilson S et al. Data for POI were obtained from the FinnGen Biobank. The relationship between dietary taste preferences and POIs was explored using IVW as the primary method. The MR-Egger intercept term test and Cochran's Q test examined sensitivity, multiplicity, and heterogeneity. The analyses were visualized by plotting scatterplots, funnel plots, and leave-one-out plots.

Results: IVW analysis showed that preference for sweet food (p=0.034), preference for cake (p=0.040), preference for white wine (p=0.048) was positively associated with the risk of developing POI, preference for bitter food (p=0.048), preference for Mackerel (p=0.031), preference for Gherkins (p=0.024), preference for Cream (p= 0.009) and preference for Soya milk (p=0.042) were negatively associated with the risk of developing POI, while there was no significant association between preference for salty food (p=0.350) and preference for spicy food (p=0.827) and POI.

Conclusion: This study suggests that food preference is a heritable trait, that food preference is the primary reason people choose their food intake, and that alterations in taste-related receptor genes may affect ovarian function. These findings could help guide improved dietary guidelines and thus control the progression of POI.

Keywords: primary ovarian insufficiency, taste preferences, diet, Mendelian randomization

Introduction

Primary Ovarian Insufficiency (POI) is a condition of diminished ovarian function with amenorrhea, high gonadotropins (eg, elevated FSH), and low estrogen levels before the age of 40 years, which was previously referred to as Premature Ovarian Failure (POF), but the term "failure" is easily misinterpreted to mean "irreversible". The term "failure" has been misinterpreted as "irrecoverable", and some patients may have intermittent ovarian activity.[1] In recent years the use of POI has been prioritized according to the recommendations of the International Federation of Gynecology and Obstetrics (FIGO) and the European Society of Human Reproduction and Embryology (ESHRE) to reduce patient anxiety and reflect the dynamic nature of the disease.[2] The pathogenesis of POI is the result of a multifactorial combination of genetic, immunologic, infectious, environmental, and medical factors.[3–5] Currently, there is a lack of effective therapies for ovarian failure that can achieve physiologic reestablishment of function. Although hormone replacement therapy (HRT) is widely used to alleviate the symptoms of hypoestrogenism, its long-term use may be associated with the risk of endometrial hyperplasia and even cancer and therefore requires strict individualized risk assessment and monitoring.[6,7] Given the limitations and low efficacy of existing treatments, there is an urgent need for new therapeutic approaches to restore ovarian viability.

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Dietary interventions have been incorporated into global priority strategies for chronic disease prevention and control as low-cost health management tools that can be scaled up.[8,9] Existing studies have emphasized the important role of dietary nutrition in influencing reproductive health, for example, the high-fat, high-sugar (HFHS) dietary pattern has been significantly associated with diminished ovarian reserve, which may elevate the risk of POI by inducing oxidative stress, disrupting steroid hormone synthesis, and contributing to chronic inflammation, among other multiple pathological pathways.[10–12] Therefore, dietary interventions based on nutritional metabolic regulation may be incorporated into the primary prevention system of POI to slow down the pathologic process in women who are genetically susceptible to POI or who are chronically exposed to risk factors such as environmental toxins and medically induced ovarian damage.[13]

The selection of food by humans is an inherently multifaceted decision-making process, in which numerous variables such as individual taste preferences, physiological health requirements, cultural values, and resource availability interact to influence the ultimate dietary pattern.[14] In modern societies where food is readily available, food preference is the primary factor influencing food choice and food intake.[15] Food preference is a complex process, and evidence from genetics suggests that food preference is influenced to some degree by heredity, that liking food is also non-negligibly heritable, and that it is twice as common as food consumption, which is consistent with the idea that liking food is more influenced by biology than actual behavior.[16] Given the central regulatory role of the taste-olfactory system in food discrimination and preference formation, genetic variation in its associated genes (eg, TAS2R3 bitter taste receptor gene, OR7D4 olfactory receptor gene) can be an important molecular basis for explaining individual differences in dietary choices by altering the thresholds of chemoreceptor function.[17,18]

Mendelian randomization (MR) uses an instrumental variable (IV) consisting of genetic variation, which reduces the effect of confounding factors and has advantages over other research methods.[19] Investigating taste receptor genes, there are relatively few studies investigating the correlation between dietary taste preferences and POI; therefore, our study focused on exploring the causal relationship between various dietary taste preferences and POI through MR studies and discussed the role played by the relevant taste receptor genes.

Material and Methods

Study Design

This study explored the causal relationship between 139 dietary taste preferences and POI through Mendelian randomization. In MR analysis, three core assumptions must be met to obtain valid results. Specifically, to serve as an IV for risk factors, genetic variants must satisfy the assumptions that they are (1) reliably associated with the risk factor under study (correlation assumption), (2) independent of any known or unknown confounders (independence assumption), and (3) affect the outcome only through the risk factor rather than through any other direct causal pathway (exclusionary restriction assumption).[20] An overview of the study is depicted in detail in Figure 1. Our research methods and reports are based on the STROBE-MR guidelines, which are detailed in Supplementary Table 1.

Data Sources

Genetic instrumental variables (IVs) associated with dietary taste preferences were derived from GWAS data provided by May-Wilson S et al.[21] This study examined dietary taste preference profiles of more than 150,000 participants in the UK Biobank cohort and replicated in up to 26,154 individuals in 11 separate cohorts. Data on POI were extracted from the FinnGen biobank (https://r11.finngen.fi/pheno/E4_OVARFAIL) and included 599 POF cases and 241,998 controls. Exposures and outcomes were obtained from different databases with little overlap in the populations involved. The populations also included were all European, fulfilling the requirement that both samples be from the same genetic background in MR studies.

Instrumental Variables Selection

SNPs for outcome and 139 dietary taste preferences were identified by a significance threshold of $p<5\times10^{-8}$. Next, we clustered SNPs to eliminate linkage disequilibrium (kb = 10,000, $r^2= 0.001$). During the harmonization process, SNPs

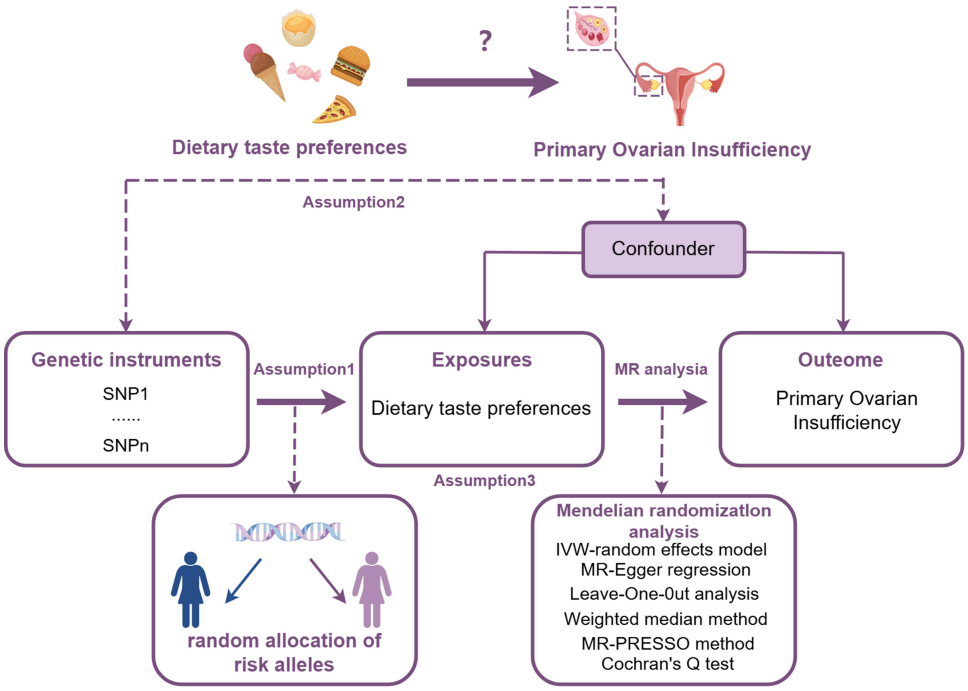

Figure 1 Overview of Mendelian randomization.

were excluded if they did not overlap with intermediate allele frequencies or palindromes. Finally, we calculated the intensity of each SNP using the following formula:

$$F = \frac{R^2 \times (N - 1 - K)}{K \times (1 - R^2)}$$

$$R^2 = \frac{2 \times EAF \times (1 - EAF) \times \beta^2}{2 \times EAF \times (1 - EAF) \times \beta^2 + 2 \times EAF \times (1 - EAF) \times N \times S_{\overline{X}}^2}$$

Where N is the sample size of the exposure factor, K is the number of instrumental variables, R2 is the proportion of the variance in the exposure factor explained by the instrumental variables, EAF is the effect allele frequency, and β is the effect value, which is the standard error of the β value. Since SNPs with an F-statistic greater than 10 were considered strongly correlated, SNPs with an F-statistic less than 10 were excluded.[22–26]

Mendelian Randomization Analysis

Random-effects inverse variance weighting (IVW) was used as the primary research method, supplemented by MR-Egger, weighted median, Simple mode, and Weighted mode methods, and results are shown as OR and 95% CI. A p-value below 0.05 was considered statistically consistent. Cochran's Q statistic evaluated heterogeneity among IVs. MR-Egger was performed using the MR polytomies test and intercept values were returned to assess horizontal polytomies. To check the stability of effect sizes and to find specific SNPs that had a disproportionate effect on the relationship, sensitivity analyses were performed by deleting each SNP and applying the IVW method to the effects of the remaining SNPs. All analyses were performed using the TwoSampleMR package in R 4.3.3.

Results

The MR results of the relationship between 139 dietary flavor preferences and POI can be seen in Supplementary Table 2, and Figure 2 demonstrates the relationship between major dietary preferences and the risk of developing POI. The data showed that preference for sweet foods (OR=2.32; 95% CI=1.06–5.67; P=0.034), cake (OR=2.17; 95% CI=1.04–4.55;

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Exposure	No.of SNP	Method	OR(95% CI)	P
sweet food liking	12	Inverse variance weighted	2.32 (1.06 to 5.07)	0.034
		MR Egger	2.16 (0.08 to 56.50)	0.653
		Simple mode	2.57 (0.75 to 8.76)	0.160
		Weighted mode	1.94 (0.68 to 5.53)	0.242
		Weighted median	1.81 (0.78 to 4.18)	0.164
bitter food liking	6	Inverse variance weighted	0.33 (0.11 to 0.99)	0.048
		MR Egger	0.00 (0.00 to 5.60)	0.158
		Simple mode	0.17 (0.02 to 1.25)	0.142
		Weighted mode	0.17 (0.03 to 0.92)	0.096
		Weighted median	0.18 (0.05 to 0.72)	0.015
spicy food liking	16	Inverse variance weighted	0.76 (0.43 to 1.35)	0.350
		MR Egger	0.62 (0.02 to 24.02)	0.802
		Simple mode	1.28 (0.35 to 4.74)	0.714
		Weighted mode	1.32 (0.32 to 5.47)	0.704
		Weighted median	0.94 (0.45 to 1.94)	0.862
salty food liking	13	Inverse variance weighted	1.18 (0.27 to 5.04)	0.827
		MR Egger	0.01 (0.00 to 1913.97)	0.447
		Simple mode	0.49 (0.01 to 29.55)	0.738
		Weighted mode	0.39 (0.01 to 23.81)	0.658
		Weighted median	0.87 (0.12 to 6.39)	0.889
Mackerel liking	14	Inverse variance weighted	0.58 (0.35 to 0.95)	0.031
		MR Egger	0.25 (0.01 to 7.01)	0.428
		Simple mode	0.48 (0.17 to 1.35)	0.187
		Weighted mode	0.51 (0.18 to 1.47)	0.238
		Weighted median	0.54 (0.28 to 1.03)	0.061
Gherkins liking	19	Inverse variance weighted	0.61 (0.40 to 0.94)	0.024
		MR Egger	0.20 (0.03 to 1.26)	0.105
		Simple mode	1.00 (0.36 to 2.74)	0.997
		Weighted mode	0.56 (0.24 to 1.30)	0.190
		Weighted median	0.55 (0.30 to 1.01)	0.054
Cake liking	13	Inverse variance weighted	2.17 (1.04 to 4.55)	0.040
		MR Egger	1.70 (0.07 to 41.28)	0.750
		Simple mode	2.66 (0.50 to 14.13)	0.274
		Weighted mode	2.06 (0.58 to 7.36)	0.289
		Weighted median	1.79 (0.68 to 4.74)	0.241
Cream liking	3	Inverse variance weighted	0.14 (0.03 to 0.61)	0.009
		MR Egger	0.01 (0.00 to 93.62)	0.503
		Simple mode	0.10 (0.01 to 0.71)	0.149
		Weighted mode	0.18 (0.02 to 1.38)	0.241
		Weighted median	0.14 (0.03 to 0.75)	0.022
Soya milk liking	3	Inverse variance weighted	0.32 (0.10 to 0.96)	0.042
		MR Egger	0.45 (0.01 to 35.87)	0.780
		Simple mode	0.38 (0.09 to 1.62)	0.320
		Weighted mode	0.37 (0.09 to 1.55)	0.309
		Weighted median	0.36 (0.09 to 1.37)	0.132
White wine liking	5	Inverse variance weighted	3.02 (1.01 to 8.99)	0.048
		MR Egger	1.14 (0.07 to 18.83)	0.934
		Simple mode	1.43 (0.22 to 9.34)	0.729
		Weighted mode	1.57 (0.20 to 12.54)	0.693
		Weighted median	1.90 (0.46 to 7.82)	0.372

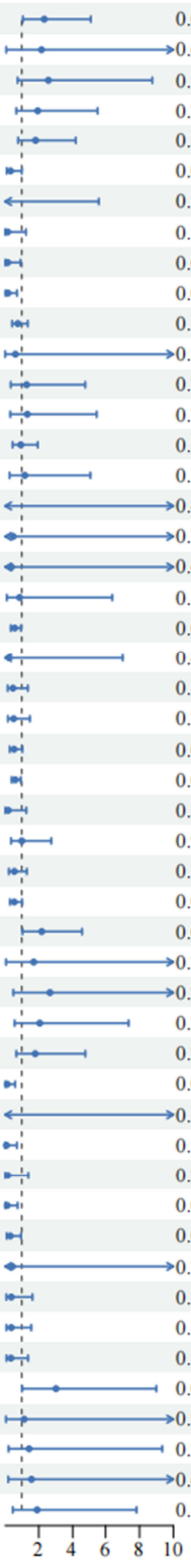

Figure 2 Forest plot of the relationship between 10 dietary flavour preferences and POI.

Table 1 Heterogeneity Test and Pleiotropy Test

Exposure	Outcome	Method	Q_pval	Egger_Intercept	Se	pval
Sweet food liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.066 0.096	0.004	0.100	0.965
Bitter food liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.565 0.359	0.591	0.371	0.187
Mackerel liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.965 0.974	0.061	0.121	0.624
Gherkins liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.692 0.651	0.085	0.069	0.236
Cake liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.257 0.326	0.013	0.084	0.879
Cream liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.978 0.844	0.169	0.292	0.665
Soya milk liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.673 0.903	−0.025	0.156	0.899
White wine liking	Primary ovarian failure	MR Egger Inverse variance weighted	0.454 0.531	0.063	0.086	0.514

P=0.040), and white wine (OR=3.02; 95% CI=1.01–8.99; P=0.048) were positively associated with the risk of developing POI and preference for bitter foods (OR=1.01–8.99; P=0.048) were positively associated with the risk of developing POI. Associated with the risk of developing POI, preference for bitter foods (OR=0.33; 95% CI=0.11–0.99; P=0.048), preference for Mackerel (OR=0.58; 95% CI=0.35–0.95; P=0.031), preference for Gherkins (OR=0.61; 95% CI=0.40–0.94; P=0.024), preference for Cream (OR=0.14; 95% CI=0.03–0.61; P=0.009) and preference for Soya milk (OR=0.32; 95% CI=0.10–0.96; P=0.042) were negatively associated with the risk of developing POI, whereas preference for savory foods (OR=1.18; 95% CI=0.27–5.04; P=0.827) and preference for spicy food (OR=0.76; 95% CI=0.43–1.35; P=0.350) were not significantly associated with POI. Scatter plots, funnel plots, and leave-one-out plots for the 10 MR findings can be seen in Supplementary Figure 1.

In addition, the MR-Egger intercept test for eight of the positive results did not indicate the presence of horizontal pleiotropy and heterogeneity (p> 0.05). The OR directions obtained by the five MR methods were consistent, which proved the accuracy of the results. Table 1 shows the results of the heterogeneity test and the polytropy test.

Discussion

The overall prevalence of POI is 3%, and its age distribution shows significant variability: about 2–3% of cases are concentrated in the 30–40 age group, while the prevalence in young women under 30 is only 0.1%.[27] It is worth noting that the disease has been on the rise in recent years, and its pathological effects go beyond the reproductive system - in addition to directly impairing fertility, it also triggers multi-system metabolic disorders through endocrine homeostatic imbalances, including but not limited to dysregulation of glucose and lipid metabolism, accelerated bone loss, and autonomic nervous system dysfunction.[28,29] The etiology of POI is highly heterogeneous, and its core pathological mechanisms have not been fully elucidated. In terms of treatment, recognized therapies for POI include in vitro activation, regenerative medicine, and hormone therapy; however, the efficacy of treatment is limited, and there is a certain likelihood of complications.[30,31] There is a lack of effective therapies for ovarian decline that can achieve physiological reestablishment of function, based on modifiable factors (eg, diet) that may be an effective measure to slow down the pathological process of POI.[32]

Genetic variants associated with taste receptors play a crucial role in individual differences in food preferences and ultimately influence food choice and health.[15] Taste receptors are expressed not only in taste buds but also in other non-taste tissues, including the reproductive system, and taste receptors can be activated by a variety of tastes to perform relatively physiological functions.[33] The results of our MR study showed that preference for sweet foods was positively associated with the risk of developing POI and preference for bitter foods was negatively associated with the risk of developing POI.TAS2RS are a class of type 2 sensing receptors responsible for the perception of bitter taste.A study by Bianca Semplici et al showed that TAS2R14 expression was significantly elevated in the ovarian thalamus and granulosa cells of the ovary in young women compared to older women, demonstrating its possible involvement in female fertility.[34] Resveratrol, a bitter natural polyphenol, specifically activates TAS2R14 and has anti-inflammatory and antioxidant effects.[35] Modern studies have shown that resveratrol protects oocytes by reducing the production of reactive oxygen species (ROS), suggesting that resveratrol, as a bitter supplement, may have potentially beneficial effects on reproductive function and the ovary by modulating TAS2R gene expression.[36] An animal study by Kavita et al showed that sweetener intake impaired reproductive indices in older mice.[37] TIR2 is a class of sweet taste receptors. Li et al suggested that T1R2 is significantly expressed in the guinea pig ovary and uterus, and that over-supplementation with non-nutritive sweeteners inhibited the ovarian expression of T1R2 and led to some adverse effects on the morphology of the ovary and uterus.[38] The results of a genome-wide meta-analysis by Kaoru et al showed a strong correlation between the 12q24 genetic locus and sweet taste preference, and the gene was also associated with alcohol metabolism and drinking behaviour.[39] An animal study by Van Thiel DH et al noted that alcohol intake produces histological and functional ovarian failure in rats.[40] And our MR study showed that preference for alcohol was positively associated with the risk of developing POI, as was preference for sweetened foods, which is consistent with our findings.

Our study also showed that preference for Gherkins and preference for Soya milk were negatively associated with the risk of developing POI. A cohort study looking at diet and age at menopause in British women says that increased intake of fish and fresh pulses leads to a delay in the age of natural menopause and that vegetarian diets such as vegetables fruits and soya beans are rich in beneficial polyphenols, a source of phytoestrogens, which have anti-inflammatory and antioxidant properties.[41] An animal study showed that the phytoestrogen genistein ameliorated ovarian oxidative damage induced by radiotherapy, demonstrating the potential of phytoestrogens in improving POI.[42] A report examining risk factors for POI in Iranian populations reported that POI prevalence was associated with lower fish and red meat consumption.[43] Oily fish is a rich source of anti-inflammatory omega-3 fatty acids, which can potentially increase the antioxidant capacity to counteract ROS, thereby reducing the proportion of follicles with follicular atresia and delaying the onset of natural menopause.[44] In a study of normal weight women, supplementation with omega-31 for 31 months significantly reduced inflammation and significantly reduced FSH.[45] Another reported that fish supplementation was more biologically active than fish oil supplementation, ie, fish had a beneficial effect on delaying menopausal age and improving ovarian health.[46] This is consistent with our findings.

By parsing the potential association between dietary taste preferences and POI, this study provides a new theoretical basis for nutritional intervention strategies. However, given the significant geographic heterogeneity of dietary cultures, the evidence-based translation of the study findings needs to carefully assess the following characteristics of the target population: (1) the constraining effect of localized food accessibility on nutritional intake patterns; and (2) the differences in metabolic responses under gene-environment interactions. Therefore, the construction of an accurate nutritional recommendation system requires the integration of multi-omics data and regional dietary epidemiological surveys to achieve the practical goal of “localizing global evidence”.

Nonetheless, the inclusion of male participants in this analysis has significant methodological limitations. The inclusion of male participants was necessary due to the limitations of the available exposure data. Therefore, although MRI analyses suggest a potential causal relationship between certain dietary taste preferences and POI, these results must be interpreted with caution. Therefore, it is recommended that future studies focus on validating these associations in female-only cohorts to facilitate more targeted and appropriate dietary interventions.

Conclusion

In this study, we found that dietary taste preferences, as genetically regulated complex phenotypes, are dominant drivers of dietary intake patterns. Polymorphisms in key taste receptor genes (eg TAS2R family) not only regulate food choice behavior but also exist in the ovary and have an impact on ovarian function, a mechanism that provides a molecular target for precision nutritional interventions to optimize POI. Based on this, it is suggested to incorporate genotype-oriented dietary strategies into the secondary prevention system of POI and to evaluate the regulatory effects of nutritional interventions on ovarian reserve function in combination with epigenetic mechanisms.

Data Sharing Statement

The GWAS data for this article are available under public license.

Ethics Approval

The data in this study were obtained from published studies, of which all data had been approved by the institutional review committee. The ethical application for this study was approved by the Medical Ethics Committee of the Affiliated Hospital of Liaoning University of Traditional Chinese Medicine [ID: Y2023132CS(KT)-132-01].

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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 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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