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Causal association between metabolic syndrome and ovarian dysfunction: a bidirectional two-sample mendelian randomization

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Abstract

Background The relationship between Metabolic Syndrome (MetS) and ovarian dysfunction has been widely reported in observational studies, yet it remains not fully understood. This study employs genetic prediction methods and utilizes summary data from genome-wide association studies (GWAS) to investigate this causal link.

Methods We employed a bidirectional two-sample Mendelian Randomization (MR) analysis utilizing MetS and ovarian dysfunction summary data from GWAS. Inverse variance weighted (IVW) was employed as the primary MR method, supplemented by Weighted Median, Weighted Mode, and MR-Egger methods. The robustness of the results was further assessed through sensitivity analyses including MR-Egger regression, MR-PRESSO, Cochran's Q, and leave-one-out test.

Results Our MR analysis identified a causal relationship between genetically determined insulin resistance (OR = 0.26, 95% CI: 0.08–0.89, $P = 0.03$), waist circumference (OR = 2.14, 95% CI: 1.45–3.15, $P < 0.001$), BMI (OR = 2.1, 95% CI: 1.56–2.83, $P < 0.001$) and ovarian dysfunction. Conversely, reverse MR analysis confirmed causal effects of ovarian dysfunction on metabolic syndrome (OR = 0.98, 95% CI: 0.97–0.99, $P < 0.001$) and waist circumference (OR = 0.99, 95% CI: 0.98–0.99, $P = 0.02$). The results of MR-Egger regression test indicated that the whole analysis was not affected by horizontal pleiotropy. Additionally, the MR-PRESSO test identified outliers in SNPs, but after removal of outliers, results remained unchanged.

Conclusion This study reveals a bidirectional causal connection between metabolic syndrome and ovarian dysfunction via genetic prediction methods. These findings are crucial for advancing our understanding of the interactions between these conditions and developing strategies for prevention and treatment.

Keywords Metabolic syndrome, Ovarian dysfunction, Mendelian randomization, Causal Association, Genetic analysis

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Background

Ovarian dysfunction is a prevalent issue in women's reproductive health, affecting approximately 26% of patients undergoing assisted reproductive treatments, who are diagnosed with diminished ovarian reserve. The prevalence of these conditions is increasing, and the age of onset is decreasing [1]. Ovarian dysfunction is characterized by the reduced ovarian function, which, if left untreated, can progress to ovarian atrophy and ultimately lead to premature ovarian failure. This progression is associated with significant risks, including infertility, cardiovascular diseases, and increased mortality [2, 3]. Current interventions for ovarian dysfunction, such as hormone replacement therapy, oral contraceptives, ovulation induction therapies, and assisted reproductive technologies, are often hindered by long-term side effects [4]. While metabolic syndrome has been linked to both ovarian dysfunction and primary ovarian failure, the precise causal mechanisms remain elusive.

Metabolic syndrome encompasses a group of metabolic disorders including obesity, hypertension, hyperglycemia, and dyslipidemia [5]. Clinical observational studies have consistently demonstrated a correlation between metabolic syndrome and conditions such as ovarian dysfunction and premature ovarian failure. Specifically, individuals with ovarian dysfunction frequently present with symptoms typical of metabolic syndrome, such as increased waist circumference, elevated fasting blood glucose (FBG) levels, and high triglyceride levels [6]. These observations underscore metabolic syndrome as a potential major contributor to ovarian dysfunction. Additionally, ovarian dysfunction could promote metabolic syndrome by impacting hormone secretion, inflammatory response, and oxidative stress pathways [2]. This suggests a possible bidirectional relationship between ovarian dysfunction and metabolic syndrome. Nevertheless, these studies are observational in nature, limiting their ability to definitively establish causality between ovarian dysfunction and metabolic syndrome.

Mendelian Randomization (MR) serves as a powerful tool for exploring causal relationships in diseases, utilizing the associations between genetic variants and exposure factors to mimic randomized controlled trials [7]. This method effectively reduces the interference of confounding factors and enables a more accurate assessment of the impact of exposure factors on diseases. Previous research has confirmed genetic causal associations between inflammatory regulators [8], gut microbiota [9], autoimmune diseases [10], and ovarian dysfunction using the MR method, validating the reliability of MR in exploring risk factors for ovarian dysfunction. This study employs a bidirectional MR approach to elucidate the causal relationships of metabolic syndrome, waist circumference, insulin resistance, FBG, high-density lipoprotein cholesterol, and triglycerides, and ovarian dysfunction. And by doing so, it aims to provide new insights and scientific evidence regarding the association between metabolic syndrome components, such as insulin resistance, FBG, HDL levels, and triglycerides, and ovarian dysfunction, thereby contributing to the development of targeted prevention and treatment strategies with significant clinical value.

Methods

Study design

As depicted in Supplementary Fig. 1, our study employs a bidirectional two-sample MR design. We use exposure factors such as metabolic syndrome, waist circumference, body mass index (BMI), insulin resistance, FBG, high-density lipoprotein cholesterol (HDL-C), and triglycerides, with ovarian dysfunction and primary ovarian failure as the outcome variables for bidirectional MR analysis. The MR analysis adheres to three core assumptions [11]. The required GWAS summary data are sourced from public databases, which require no additional ethical approval.

Data sources

The GWAS summary data for ovarian dysfunction and primary ovarian failure are derived from the FinnGen cohort. Specifically, the ovarian dysfunction dataset comprises 254 cases and 118,228 controls of European ancestry, with a total of 16,379,677 SNPs. Ovarian dysfunction in this study is defined according to ICD-10 code E28, which includes various conditions such as polycystic ovary syndrome, primary ovarian failure, estrogen excess, androgen excess, and other ovarian dysfunctions, excluding isolated gonadotropin deficiency, postprocedural ovarian failure, and certain other specific disorders. For primary ovarian failure, defined according to ICD-10 code E28.3, the dataset includes 942 cases matched with an equal number of controls, encompassing 16,379,685 SNPs. Additionally, the UK Biobank provides GWAS summary data for metabolic syndrome, featuring 59,677 cases and 231,430 controls [12]. The harmonized NCEP criteria for metabolic syndrome include the presence of at least three of the following five conditions: blood pressure ≥ 130/85 mmHg or on antihypertensive treatment; FBG ≥ 6.1 mmol/L or on glucose-lowering treatment; triglyceride levels ≥ 1.7 mmol/L; waist circumference > 102 cm in men, > 88 cm in women; HDL cholesterol levels below 1.0 mmol/L in men and below 1.3 mmol/L in women [12]. GWAS data for waist circumference [13], BMI, insulin resistance [14], FBG [15], HDL cholesterol, and triglycerides [16] involve significant cohorts of 407,661, 461,460, 53,334, 200,622, 94,595, and 94,595 individuals of European descent, respectively, as detailed in Supplementary Table 1.

Instrumental variable (IV) selection

In this study, the selection of IVs adheres to rigorous criteria: First, we select SNPs that are significantly associated with the metabolic syndrome genome-wide, i.e., with P less than 5×10^{-8} [17]. For insulin resistance where suitable SNPs are challenging to identify, the selection criterion is relaxed to P less than 5×10^{-6}. SNPs must also exhibit a minor allele frequency (MAF) greater than 0.01. To mitigate the effects of linkage disequilibrium (LD) between SNPs, we apply a criterion of R^2 less than 0.001 within a window size of 10,000kb [18]. If an IV does not exist in the outcome's summary data, we identify a proxy SNP with high LD (R^2 greater than 0.8) with the IV [19]. Furthermore, we calculate the F-value of each SNP in the IV to assess the strength of the IV and eliminate the risk of weak instrument bias. The formula for F-value is: $F = R^2(N-2)/(1-R^2)$, where R^2 is the proportion of exposure variance explained by the IV, and the F-value must be greater than 10 [20].

MR analysis

The primary method of analysis in this study is the Inverse Variance Weighted (IVW) method, which evaluates the causal relationship between exposure and outcome by calculating the odds ratio (OR) and 95% confidence interval (CI) [21]. The IVW method computes a weighted average of effect sizes, using the inverse variance of each SNP as a weight. To ensure robustness, additional methods such as MR-Egger [22], weighted median [23], and weighted mode method [24] are employed. The MR-Egger method incorporates an intercept term, allowing for the estimation of accurate causal effects even in the presence of pleiotropy. The weighted median method, which assumes that at least half of the instruments are valid, is specifically used to analyze the causal link between exposure and outcome. All analyses are conducted by R (version 4.0.5) using the "TwoSampleMR" package (version 0.5.6, https://github.com/mrcieu/TwoSampleMR) [25], and results are visualized through scatter plots and sensitivity analysis graphs.

Sensitivity analysis

Sensitivity analysis is crucial for detecting potential heterogeneity and pleiotropy in MR studies. Cochran's Q test assesses heterogeneity among IVs, with P greater than 0.05 suggesting low heterogeneity [26]. The MR-Egger regression is employed to investigate horizontal pleiotropy; an intercept term close to zero or not statistically significant indicates an absence of pleiotropy bias [22]. Furthermore, the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method is utilized to identify potential outliers, specifically SNPs with P less than 0.05 [27]. After removing these outliers, the causal association is re-estimated to correct for any horizontal pleiotropy. Leave-one-out analysis is employed to identify and mitigate the influence of outliers or individual variants that may affect the overall analysis.

Results

Causal effects of metabolic syndrome on primary ovarian failure and ovarian dysfunction

In our MR analysis, we utilized exposure factors such as metabolic syndrome, waist circumference, BMI, insulin resistance, FBG, HDL-C, and triglycerides. The number of IVs for these factors were 85, 329, 457, 18, 66, 87, and 54 respectively. During the analysis of primary ovarian failure as an outcome, there were mismatches in the summary data, with 2, 9, 3, 0, 0, 0, and 0 SNPs respectively. To mitigate this, we substituted rs7755248 for rs10945840 in the metabolic syndrome analysis, and rs34020954, rs1861410, rs77483079 for rs146322930, rs4671328, and rs4790841 in waist circumference; rs57086307 replaced rs58925536 in FBG, rs247617 substituted rs247616 in HDL-C, and rs247617, rs9297994 replaced rs247616, rs4738684 in triglycerides. In cases analyzing ovarian dysfunction, there were mismatches in 9 and 3 SNPs for waist circumference and BMI, respectively, with no suitable proxy SNPs found. All F-statistics were greater than 10, confirming the effectiveness of the IVs. All the IVs were detailed in Supplementary Tables 2–9.

The results of IVW revealed significant causal associations. Insulin resistance demonstrated an OR of 0.26 (95% CI: 0.08–0.89, $P = 0.03$), waist circumference an OR of 2.14 (95% CI: 1.45–3.15, $P < 0.001$), and BMI an OR of 2.1 (95% CI: 1.56–2.83, $P < 0.001$) with the risk of primary ovarian failure and ovarian dysfunction respectively (Table 1; Fig. 1). Specifically, the analyses for waist circumference, using both MR-Egger and Weighted Median methods, confirmed a statistical correlation with ovarian dysfunction. For BMI, MR-Egger, Weighted Median, and Weighted Mode methods all indicated consistent causal associations. Additionally, analyses for HDL-C using MR-Egger, Weighted Median, and Weighted Mode methods also found a statistical association with ovarian dysfunction (Table 1). For other exposure-outcome combinations, no statistically significant associations were observed (Table 1).

The robustness of our results is supported by several tests: Cochran's Q test indicated no significant heterogeneity and MR-Egger regression test showed no pleiotropy (Supplementary Table 10, Supplementary Fig. 2A-C). MR-PRESSO analysis did not identify any outliers, and MR-PRESSO global test revealed no horizontal pleiotropy (Supplementary Table 11). Furthermore, the leave-one-out test demonstrated that the links were not driven by single SNPs (Supplementary Fig. 2D-F). These tests confirmed the robustness of our MR analysis.

Table 1 The causal relationship between metabolic syndrome and ovarian dysfunction using mendelian randomization

Exposure	Outcome	*N*.SNPs	Methods	OR (95% CI)	*P*
metabolic syndrome	Primary ovarian failure	79	IVW	1.01 (0.71–1.43)	0.97
			MR-Egger	1.24 (0.59–2.57)	0.57
			Weighted Median	1.07 (0.63–1.82)	0.81
			Weighted Mode	1.32 (0.54–3.18)	0.54
Waist circumference		299	IVW	1.66 (0.81–3.41)	0.17
			MR-Egger	1.37 (0.17–11.19)	0.77
			Weighted Median	1.11 (0.37–3.37)	0.85
			Weighted Mode	0.32 (0.04–2.68)	0.29
Body mass index (BMI)		432	IVW	1.25 (0.72–2.14)	0.43
			MR-Egger	0.67 (0.15–3)	0.60
			Weighted Median	1.45 (0.6–3.53)	0.41
			Weighted Mode	1.13 (0.2–6.34)	0.89
insulin resistance		18	IVW	0.26 (0.08–0.89)	**0.03**
			MR-Egger	2.83 (0.14–58.73)	0.51
			Weighted Median	0.22 (0.04–1.26)	0.09
			Weighted Mode	0.06 (0–1.39)	0.10
fasting blood glucose (FBG)		63	IVW	0.5 (0.17–1.54)	0.23
			MR-Egger	0.48 (0.07–3.56)	0.48
			Weighted Median	0.48 (0.1–2.46)	0.38
			Weighted Mode	0.42 (0.09–2.1)	0.3
HDL cholesterol		86	IVW	1.33 (0.86–2.07)	0.2
			MR-Egger	1.52 (0.74–3.12)	0.25
			Weighted Median	1.87 (0.92–3.79)	0.08
			Weighted Mode	1.55 (0.86–2.8)	0.15
Triglycerides		54	IVW	1.14 (0.62–2.07)	0.67
			MR-Egger	0.93 (0.35–2.5)	0.89
			Weighted Median	0.74 (0.3–1.79)	0.5
			Weighted Mode	0.83 (0.38–1.8)	0.64
metabolic syndrome	Ovarian dysfunction	81	IVW	1.11 (0.92–1.34)	0.29
			MR-Egger	0.82 (0.56–1.21)	0.33
			Weighted Median	1.06 (0.81–1.4)	0.68
			Weighted Mode	1.03 (0.71–1.49)	0.88
Waist circumference		299	IVW	2.14 (1.45–3.15)	**< 0.001**
			MR-Egger	4.54 (1.48–13.9)	**0.01**
			Weighted Median	1.91 (1.06–3.46)	**0.03**
			Weighted Mode	0.76 (0.16–3.67)	0.74
Body mass index (BMI)		432	IVW	2.1 (1.56–2.83)	**< 0.001**
			MR-Egger	3.06 (1.34–6.99)	**0.01**
			Weighted Median	2.35 (1.48–3.71)	**< 0.001**
			Weighted Mode	5.34 (1.63–17.51)	**0.01**
insulin resistance		18	IVW	1.16 (0.61–2.23)	0.65
			MR-Egger	3.36 (0.67–16.71)	0.16
			Weighted Median	1.3 (0.54–3.1)	0.56
			Weighted Mode	1.16 (0.3–4.44)	0.83
fasting blood glucose (FBG)		63	IVW	1.74 (0.97–3.13)	**0.06**
			MR-Egger	1.87 (0.65–5.35)	0.25
			Weighted Median	1.19 (0.45–3.12)	0.72
			Weighted Mode	0.83 (0.28–2.46)	0.74
HDL cholesterol		86	IVW	1.2 (0.96–1.52)	0.12
			MR-Egger	1.5 (1.03–2.19)	**0.04**
			Weighted Median	1.53 (1.03–2.27)	**0.04**
			Weighted Mode	1.46 (1.03–2.07)	**0.04**
Triglycerides		54	IVW	1.01 (0.75–1.37)	0.94

Table 1 (continued)

Exposure	Outcome	*N*.SNPs	Methods	OR (95% CI)	*P*
			MR-Egger	0.74 (0.45–1.21)	0.24
			Weighted Median	0.89 (0.57–1.4)	0.62
			Weighted Mode	0.86 (0.57–1.29)	0.47

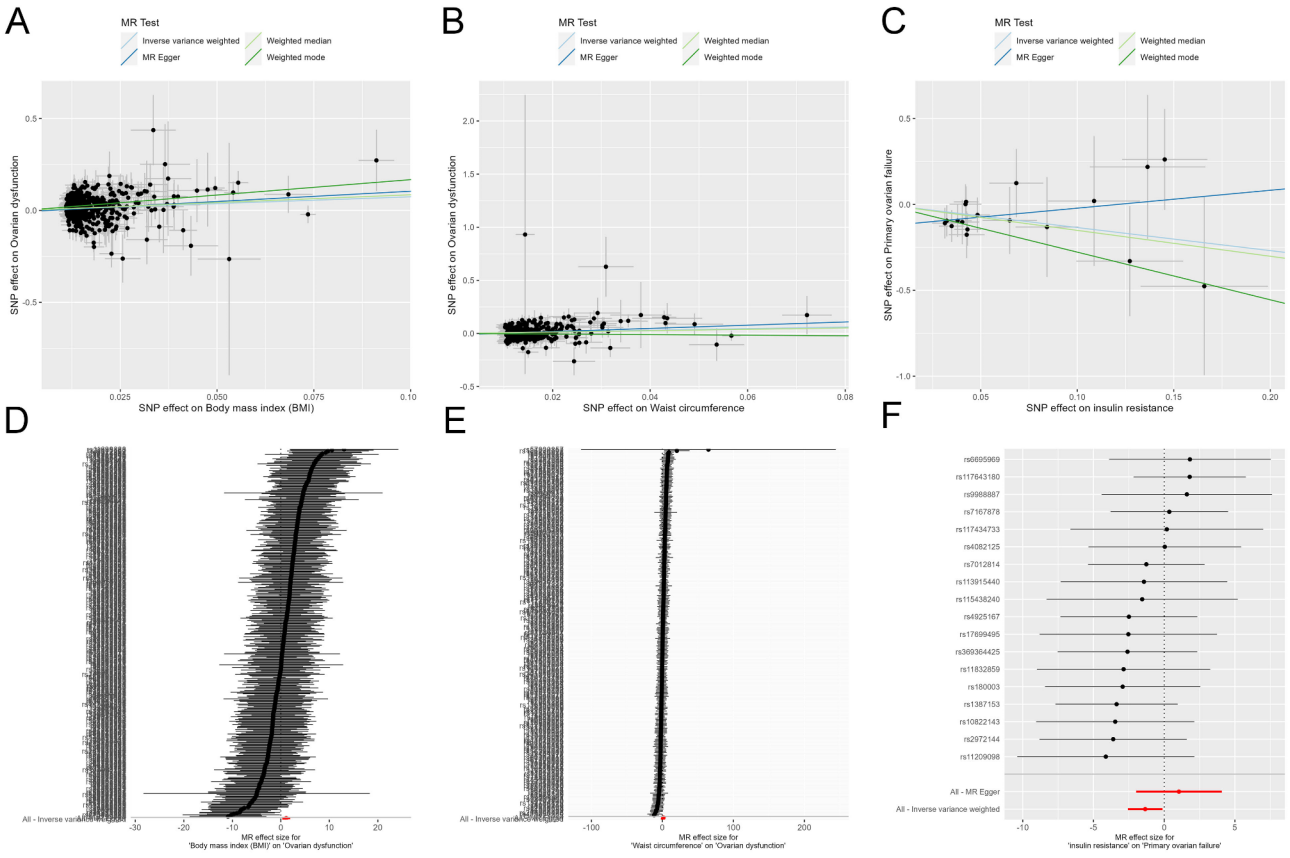

Fig. 1 Causal effects of MetS on primary ovarian failure and ovarian dysfunction. Scatter plots of BMI (**A**) and waist circumference (**B**) on ovarian dysfunction; and insulin resistance (**C**) on primary ovarian failure. Forest plots of BMI (**D**) and waist circumference (**E**) on ovarian dysfunction; and insulin resistance (**F**) on primary ovarian failure

Causal effects of primary ovarian failure and ovarian dysfunction on metabolic syndrome

For primary ovarian failure as the exposure factor, 13 IVs were identified. The outcomes analyzed included metabolic syndrome, waist circumference, BMI, insulin resistance, FBG, HDL-C, and triglycerides. In the analyses for metabolic syndrome, BMI, insulin resistance, and HDL-C, mismatches of 1, 1, 1, and 9 SNPs respectively were noted. For HDL-C and triglycerides, rs7691064 substituted for rs72664690 due to mismatched SNPs. The F-statistics for these IVs were all above 10.

For ovarian dysfunction as the exposure, 9 IVs were used. The outcome factors analyzed were metabolic syndrome, waist circumference, BMI, insulin resistance, FBG, HDL-C, and triglycerides, with mismatched SNPs totaling 1, 5, and 5 respectively in the analyses of insulin resistance, HDL-C, and triglycerides. The substitute SNP, rs7691064 for rs72664690, was utilized for HDL-C and triglycerides. All associated F-statistics exceeded 10. The details of the IVs were presented in Supplementary Tables 12–13.

As shown in Table 2, IVW analysis indicated a causal relationship between ovarian dysfunction and metabolic syndrome (OR = 0.98, 95% CI: 0.97–0.99, $P < 0.001$) and waist circumference (OR = 0.99, 95% CI: 0.98–0.99, $P = 0.02$). The weighted median method also supported the genetic correlation between ovarian dysfunction and both waist circumference and BMI (Fig. 2). However, no significant genetic correlations were found between other exposures and outcomes (Table 2).

With ovarian dysfunction as the exposure, Cochran's Q test indicated heterogeneity in BMI and FBG ($P < 0.001$ and $P = 0.035$, respectively) (Supplementary Table 14, Supplementary Fig. 3A-B). However, this heterogeneity

Table 2 The causal relationship between ovarian dysfunction and metabolic syndrome using mendelian randomization

Exposure	Outcome	*N*.SNPs	Methods	OR (95% CI)	*P*
Primary ovarian failure	metabolic syndrome	12	IVW	1 (0.99–1.01)	0.46
			MR-Egger	0.99 (0.97–1.01)	0.46
			Weighted Median	1 (0.99–1.01)	0.8
			Weighted Mode	1 (0.98–1.01)	0.87
	Waist circumference	13	IVW	1.0002 (0.9978–1.0026)	0.874
			MR-Egger	0.9994 (0.9949–1.004)	0.814
			Weighted Median	0.999 (0.9964–1.0016)	0.467
			Weighted Mode	0.9991 (0.996–1.0022)	0.577
	Body mass index (BMI)	12	IVW	1.0005 (0.9975–1.0034)	0.763
			MR-Egger	0.9987 (0.9924–1.005)	0.685
			Weighted Median	0.9998 (0.9966–1.0031)	0.918
			Weighted Mode	1.0002 (0.9957–1.0046)	0.938
	insulin resistance	12	IVW	1.002 (0.9932–1.0108)	0.663
			MR-Egger	1.0041 (0.984–1.0247)	0.698
			Weighted Median	1.0002 (0.9892–1.0113)	0.974
			Weighted Mode	1.0024 (0.9878–1.0172)	0.752
	fasting blood glucose (FBG)	13	IVW	0.9976 (0.995–1.0002)	0.073
			MR-Egger	0.9949 (0.989–1.0009)	0.126
			Weighted Median	0.9968 (0.9933–1.0003)	0.073
			Weighted Mode	0.9964 (0.9906–1.0023)	0.252
	HDL cholesterol	4	IVW	1.0023 (0.9906–1.0141)	0.703
			MR-Egger	1.039 (0.892–1.2103)	0.672
			Weighted Median	0.9996 (0.9859–1.0135)	0.960
			Weighted Mode	0.9957 (0.9761–1.0156)	0.697
	Triglycerides	4	IVW	0.9921 (0.9787–1.0057)	0.256
			MR-Egger	1.0928 (0.9479–1.2599)	0.346
			Weighted Median	0.996 (0.9827–1.0095)	0.563
			Weighted Mode	1.0022 (0.9784–1.0265)	0.872
Ovarian dysfunction	metabolic syndrome	9	IVW	0.98 (0.97–0.99)	**< 0.001**
			MR-Egger	0.98 (0.96–1)	**0.05**
			Weighted Median	0.98 (0.96–1)	**0.01**
			Weighted Mode	0.98 (0.96–1)	**0.04**
	Waist circumference	9	IVW	0.9931 (0.9872–0.9991)	**0.02**
			MR-Egger	0.9979 (0.9909–1.0049)	0.57
			Weighted Median	0.9944 (0.9897–0.9991)	**0.02**
			Weighted Mode	0.9944 (0.9898–0.999)	**0.04**
	Body mass index (BMI)	9	IVW	0.9938 (0.9867–1.0009)	0.09
			MR-Egger	0.9984 (0.9893–1.0076)	0.74
			Weighted Median	0.9941 (0.9891–0.9992)	**0.02**
			Weighted Mode	0.9942 (0.9894–0.999)	**0.05**
	insulin resistance	8	IVW	1.0047 (0.9905–1.0191)	0.52
			MR-Egger	0.9924 (0.9728–1.0125)	0.49
			Weighted Median	0.9937 (0.9751–1.0126)	0.51
			Weighted Mode	0.9959 (0.9787–1.0134)	0.66
	fasting blood glucose (FBG)	9	IVW	1.0019 (0.9962–1.0076)	0.52
			MR-Egger	1.0002 (0.9921–1.0084)	0.95
			Weighted Median	1.0021 (0.997–1.0072)	0.43
			Weighted Mode	1.0023 (0.9974–1.0073)	0.38
	HDL cholesterol	4	IVW	0.9994 (0.9767–1.0225)	0.96
			MR-Egger	0.9593 (0.8922–1.0314)	0.38
			Weighted Median	1.0044 (0.9771–1.0324)	0.76
			Weighted Mode	1.0064 (0.9743–1.0396)	0.73
	Triglycerides	4	IVW	0.9867 (0.9651–1.0087)	0.23

Table 2 (continued)

Exposure	Outcome	*N.*SNPs	Methods	OR (95% CI)	*P*
			MR-Egger	1.0177 (0.9495–1.0908)	0.67
			Weighted Median	0.9884 (0.9622–1.0153)	0.39
			Weighted Mode	0.9878 (0.9562–1.0205)	0.51

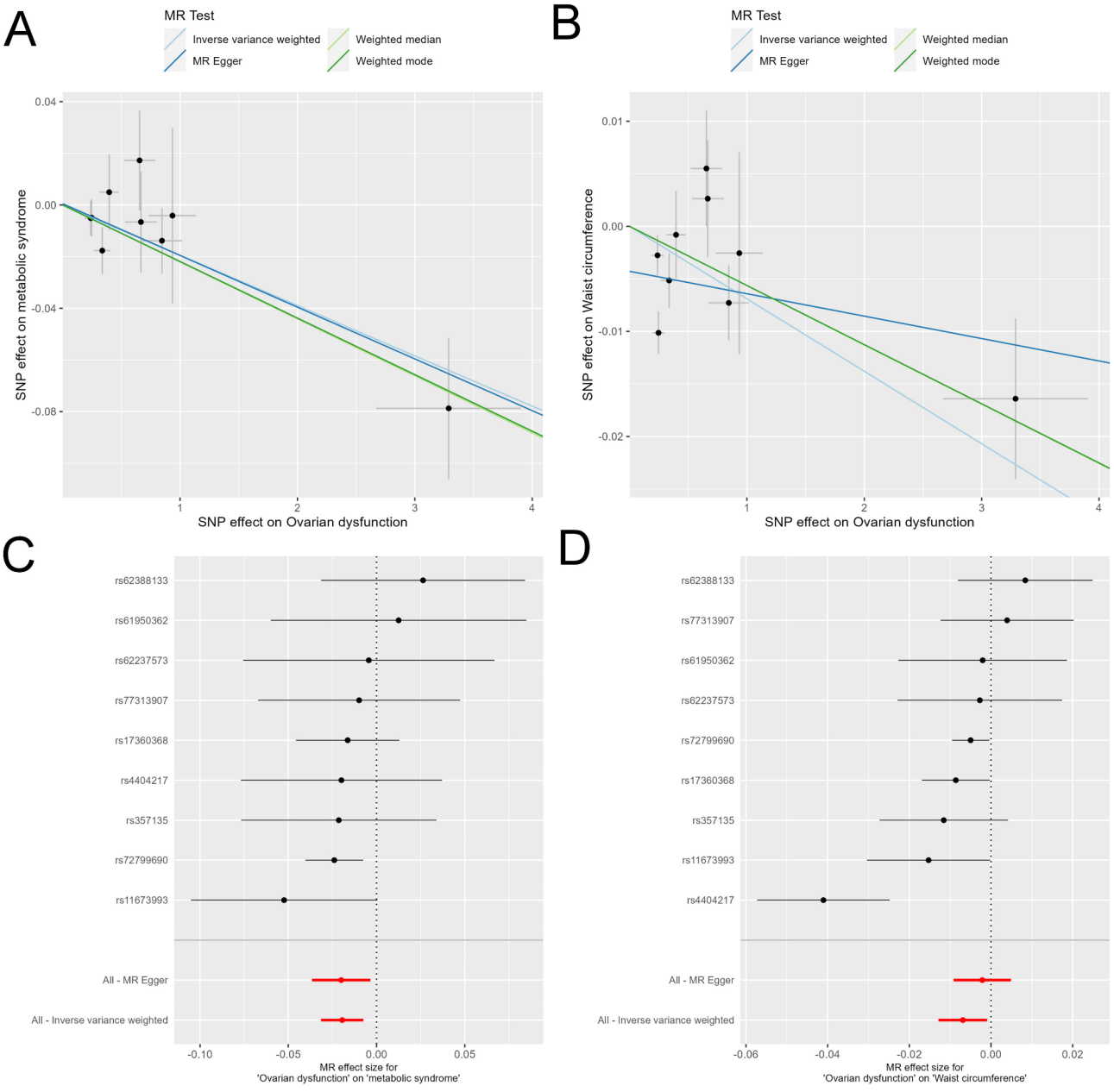

Fig. 2 Causal effects of primary ovarian failure and ovarian dysfunction on MetS. Scatter plots of ovarian dysfunction on MetS (**A**) and waist circumference (**B**). Forest plots of ovarian dysfunction on MetS (**C**) and waist circumference (**D**)

is acceptable given that the analysis was conducted using a random effects IVW method. MR-Egger regression confirmed no pleiotropy affecting the analysis (Supplementary Table 14); MR-PRESSO global test detected pleiotropy related to waist circumference and BMI ($P = 0.043$ and $P = 0.006$, respectively), suggesting potential outliers causing pleiotropy (Supplementary Table 15). As shown in Supplementary Fig. 3C-D, the leave-one-out test indicated that the MR result was not driven by any single SNP. After outlier removal, a statistically

significant causal relationship was revealed between waist circumference and ovarian dysfunction (OR = 0.99, 95% CI: 0.99–0.99, $P = 0.019$), which is consistent with the result of IVW analysis. Besides, other results remained unchanged after removal of outliers.

When primary ovarian failure as the exposure, Cochran's Q test indicated heterogeneity in metabolic syndrome ($P = 0.015$) (Supplementary Table 14). MR-Egger regression showed no impact of horizontal pleiotropy (Supplementary Table 14); MR-PRESSO tests identified outliers for SNPs related to metabolic syndrome and BMI ($P = 0.022$ and $P = 0.048$, respectively), while the MR-PRESSO outlier test showing no change after outlier removal (Supplementary Table 15). These sensitivity analyses ensure the reliability and stability of our results.

Discussion

Main findings

This study employed a bidirectional MR approach to investigate the relationship between metabolic syndrome-associated factors and ovarian dysfunction. The forward IVW analysis identified significant causal links between insulin resistance, waist circumference, and BMI, and the risk of ovarian dysfunction. Conversely, the reverse IVW analysis revealed causal connections from ovarian dysfunction to metabolic syndrome and waist circumference. Further, additional MR methods supported genetic correlations between HDL-C and ovarian dysfunction, as well as between ovarian dysfunction and BMI. This study is the first to reveal the bidirectional causal relationships between metabolic syndrome and ovarian dysfunction using a bidirectional MR approach, underscoring the pivotal role of metabolic syndrome in the development of ovarian dysfunction. These findings offer crucial insights and a scientific foundation for further exploration into the pathogenesis of ovarian dysfunction.

Interpretation

Observational clinical studies have previously highlighted associations between metabolic syndrome and ovarian dysfunction. For example, a study conducted in China involving 118 patients with ovarian dysfunction and 151 age and BMI-matched healthy female controls, demonstrated significantly higher rates of hypertriglyceridemia (17.8% vs. 9.3%, $P = 0.039$) and elevated FBG (16.9% vs. 6.6%, $P = 0.008$) in patients compared to controls. Additionally, the patients exhibited higher fasting insulin levels and insulin resistance indices (HOMA-IR), while other metabolic syndrome factors did not show significant differences [6]. Moreover, a meta-analysis that included 1573 women with primary ovarian insufficiency (POI) and 1762 controls, found that women with POI had significantly higher waist circumference, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, and fasting glucose levels than controls [28]. These observational findings lend partial support to our MR-based conclusions, suggesting that metabolic syndrome may play a crucial role in the onset and progression of ovarian dysfunction.

However, not all studies align with our findings. A research on 56 patients with ovarian insufficiency indicated that serum total cholesterol, high-density lipoprotein, and low-density lipoprotein levels were significantly higher than healthy controls, while triglycerides, glucose, insulin, and HOMA-IR showed no significant differences [29]. Another study highlighted that although the waist circumference of patients with ovarian dysfunction was significantly greater than that of healthy controls (90.0 vs. 80.7, $p < 0.01$), no significant differences were found in lipid and glucose levels or the prevalence of diabetes [30]. These inconsistencies may stem from the inherent limitations of observational studies, such as susceptibility to confounding factors including age, lifestyle, and geographical variations. To ascertain the causal relationships between metabolic syndrome-related factors and ovarian dysfunction more accurately, future research should employ randomized controlled trials and larger-scale cohort studies, aiming to minimize confounding influences and bolster the reliability and applicability of the findings.

Strengths and limitations

Our study elucidates a bidirectional causal relationship between metabolic syndrome-associated factors and ovarian dysfunction. Current mechanistic studies suggest that elements of metabolic syndrome, such as obesity and insulin resistance, may influence ovarian function through various pathways, including hormone secretion, lipid metabolism, and inflammatory responses [31, 32]. Conversely, ovarian dysfunction could lead to hormonal imbalances that affect metabolism and immune functions, thereby increasing the risk of insulin resistance and dyslipidemia associated with metabolic syndrome [33, 34]. These findings propose a dynamic interplay between ovarian dysfunction and metabolic syndrome. Our research offers valuable perspectives for further investigation into these complex interaction mechanisms.

In this study, we employed a bidirectional MR approach, establishing causal relationships between insulin resistance, waist circumference, and BMI with ovarian dysfunction, and confirming the bidirectional influence between metabolic syndrome and ovarian dysfunction. However, the study has several limitations: firstly, the sample selection is predominantly of European descent, which may limit the applicability of the findings to other populations. Secondly, the study relies on online public

databases, and future research should include validation across more diverse databases. Lastly, while the MR method enabled us to explore causal relationships, the specific molecular mechanisms underlying the interaction between ovarian dysfunction and metabolic syndrome require further investigation. In conclusion, our study elucidates the causal connections between metabolic syndrome-related factors and ovarian dysfunction, providing a foundation for a deeper understanding of their pathogenesis and the development of new therapeutic interventions. Nevertheless, additional clinical studies are necessary to confirm these results and to uncover more detailed mechanisms.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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None.

Author contributions
Ying Zhang and Jianfang Zhang carried out the studies and participated in its design. Ying He and Yanling Wei participated in collecting data, and drafted the manuscript. Haixia Liang participated in acquisition of data and draft the manuscript. Yi Wan performed the statistical analysis and interpretation of data. All authors read and approved the final manuscript.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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