International Journal of Women's Health

Dovepress
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ORIGINAL RESEARCH

Bidirectional and Multivariable Mendelian Randomization Study of PCOS and VTE

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Background: We used bidirectional and multivariable Mendelian randomization (MR) to test whether polycystic ovary syndrome (PCOS) is causally related to venous thromboembolism (VTE).

Methods: Using European-ancestry GWAS summary statistics, we performed bidirectional two-sample univariable MR and multivariable MR adjusting for diabetes, body mass index (BMI), hormone replacement therapy, and oral contraceptive use. Robustness was assessed with Cochran's Q, MR-Egger intercept, MR-PRESSO, and leave-one-out analyses.

Results: Univariable MR showed no causal effect of PCOS on VTE (IVW OR 1.008, 95% CI 0.974–1.042; $p = 0.653$), and reverse-direction MR provided no evidence that VTE causally influences PCOS. In multivariable MR, PCOS remained not associated with VTE (IVW OR 1.016, 95% CI 0.987–1.045; $p = 0.285$), whereas BMI had a clear independent positive effect on VTE risk (IVW OR 1.358, 95% CI 1.262–1.461; $p < 0.001$).

Conclusion: Genetic evidence does not support a causal relationship between PCOS and VTE. BMI is independently associated with VTE risk and appears to be a key determinant of VTE risk.

Keywords: polycystic ovary syndrome, venous thromboembolism, mendelian randomization, body mass index, genetic epidemiology, multivariable analysis

Background

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder in women of reproductive age and is closely linked to obesity and insulin resistance.[1–4] In European populations, prevalence estimates vary substantially across studies, largely reflecting differences in diagnostic criteria (eg, NIH vs Rotterdam/ESHRE ASRM) and ascertainment strategies.[5,6] Venous thromboembolism (VTE) is a major, preventable vascular event.[7] Observational studies have reported an association between PCOS and VTE,[8,9] but interpretation is complicated by shared risk factors such as higher BMI and hormonal exposures, as well as residual confounding and potential reverse causation.[8–13]

Mendelian randomization (MR) uses genetic variants as instrumental variables to strengthen causal inference. Bidirectional and multivariable MR can further assess directionality and estimate direct effects while accounting for correlated risk factors.[13–15] In this study, we used European ancestry genome-wide association summary statistics to conduct bidirectional two-sample and multivariable MR analyses to evaluate the causal relationship between PCOS and VTE and to determine whether any association persists after accounting for BMI, diabetes, and hormone related exposures.

Methods

Study Design

We conducted a bidirectional two-sample MR study to assess the causal relationship between PCOS and VTE. We performed univariable MR (UVMR) as the primary analysis and multivariable MR (MVMR) to estimate the independent effect of PCOS on VTE while jointly adjusting for major risk factors, including diabetes, body mass index (BMI),

https://doi.org/10.2147/IJWH.S586045
Received: 2 December 2025
Accepted: 9 February 2026
Published: 28 March 2026

hormone replacement therapy (HRT) use, and oral contraceptive (OC) use. MR analyses relied on three core assumptions: (1) a robust association between exposure and the selected single nucleotide polymorphisms (SNPs); (2) independence of instrumental variables (IVs) from confounders; and (3) IVs influence outcomes solely via the exposure. Figure 1 presents the study workflow.

Data Sources

Data were extracted from publicly available GWAS datasets. PCOS data were sourced from the 2021 FinnGen project (finn-b-E4_PCOS; 642 cases, 118,228 controls). Diabetes data originated from the EBI database (ebi-a-GCST90038633; 24,659 cases, 459,939 controls, 2021). BMI, HRT, and oral contraceptive use data were drawn from the 2018 UK Biobank (ukb-b-19953, n=461,460; ukb-b-18541, 97,920 cases, 152,381 controls; ukb-b-9509, 205,516 cases, 44,924 controls, respectively). VTE summary statistics were also derived from FinnGen (finn-b-I9_VTE, 9,176 cases, 209,616 controls, 2021). All participants were of European descent. As all summary-level data were collected from previously published, open-access studies, neither additional ethical approval nor informed consent was required. Per China's Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (Feb 18, 2023), Article 32 (1)–(2), this study using publicly available, de-identified summary data is exempt from ethics review. The GWAS sources, IDs, ancestry, and sample sizes (cases/controls where applicable) are summarized in Table S1.

Instrumental Variable Selection

P-value thresholds. SNPs associated with PCOS, diabetes, BMI, and HRT were selected as instrumental variables at genome-wide significance ($p < 5 \times 10^{-8}$). For ever use of OCs, the threshold was relaxed to $p < 5 \times 10^{-7}$ due to the lack of genome-wide significant variants at $p < 5 \times 10^{-8}$.

LD clumping. To ensure independence, SNPs were clumped using linkage disequilibrium (LD) criteria of $r^2 < 0.001$ within a 10,000-kb window, retaining the variant with the lowest p-value in each LD block.

Instrument strength. Instrument strength was assessed using F-statistics, and weak instruments were excluded ($F < 10$).

Harmonization

We harmonized exposure and outcome summary statistics to ensure consistent effect allele orientation. (1) Effect alleles were aligned across datasets. (2) SNPs requiring strand flipping were recoded so that the estimated effects corresponded to the same allele. (3) Palindromic SNPs (A/T or C/G) with ambiguous strand orientation were excluded to avoid misalignment. (4) SNPs with non-matching alleles or incomplete information were removed before downstream MR analyses.

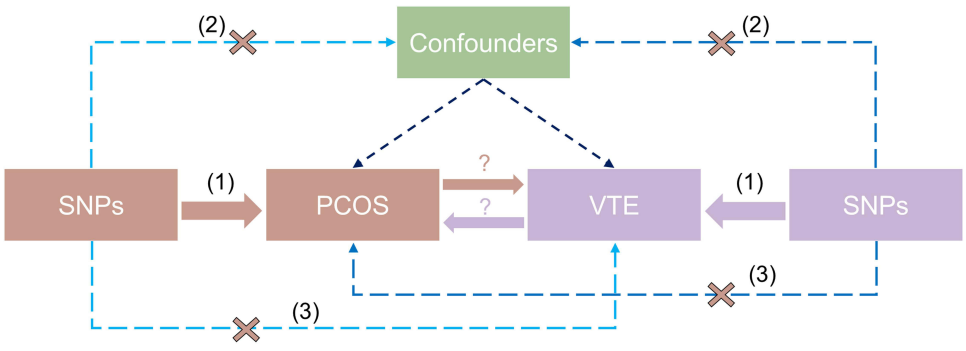

Figure 1 Overview of the present Mendelian randomization study. (1) relevance, genetic variants are associated with the exposure; (2) Independence, genetic variants are not associated with confounders; (3) exclusion restriction, genetic variants affect the outcome only through the exposure, with no direct or pleiotropic pathway. The cross (×) denotes an assumed absent association or pathway, and the question mark (?) denotes the hypothesized and uncertain causal direction tested in the bidirectional analysis between PCOS and VTE.

Univariable Mendelian Randomization

A two-sample MR framework was implemented to assess the effect of PCOS on VTE. We applied five estimators: inverse-variance weighted (IVW, primary), MR-Egger, weighted median, simple mode, and weighted mode. The IVW estimator provides the most precise estimate when all instruments are valid (or when any horizontal pleiotropy is balanced). MR-Egger allows for directional pleiotropy under the InSIDE assumption, with a non-zero intercept indicating average pleiotropic effects. The weighted median estimator yields a consistent estimate if at least 50% of the total instrument weight comes from valid variants. Mode-based estimators (simple and weighted mode) are consistent when the largest cluster of SNP-specific causal estimates corresponds to valid instruments. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), with $p < 0.05$ considered statistically significant.

Multivariable Mendelian Randomization

MVMR was performed with PCOS, diabetes, BMI, HRT use, and OC use entered jointly to estimate the direct effect of PCOS on VTE conditional on these covariates. These covariates were pre-specified a priori (Gariani et al).[12] because they are established VTE-related factors and are also linked to PCOS, which may induce correlated exposures and alternative pathways affecting VTE.

Sensitivity Analyses

Heterogeneity was assessed using Cochran's Q (IVW; MR-Egger where applicable). Directional pleiotropy was evaluated by the MR-Egger intercept test. MR-PRESSO was used to perform the global test, identify outliers, and re-estimate effects after outlier removal (including distortion testing). Leave-one-out analyses (IVW) were conducted to evaluate single-SNP influence. Collectively, these sensitivity analyses were used to support the consistency and robustness of causal estimates across MR methods.

Statistical Analysis

All analyses were conducted in R (version 4.3.3) using TwoSampleMR (v0.6.29), MendelianRandomization (v0.10.0), MVMR (v0.4.2), and MR-PRESSO (v1.0). Unless otherwise specified, functions were run with default settings. LD clumping and instrument-selection thresholds followed the prespecified criteria described above ($r^2 < 0.001$, 10,000 kb window; *p*-value thresholds as stated). For MR-PRESSO, we enabled both the outlier and distortion components (OUTLIERtest = TRUE, DISTORTIONtest = TRUE) with SignifThreshold = 0.05 and NbDistribution = 1000 (default), and a fixed random seed when applicable to ensure reproducibility.

Statistical Power

Given the limited number of PCOS cases in the FinnGen GWAS, statistical power may be reduced for detecting modest causal effects, particularly in MVMR where instruments are partitioned across multiple exposures. Therefore, null findings should be interpreted cautiously as they may reflect limited power rather than absence of a causal effect.

Table 1 Results of Mendelian Randomization Analyses Evaluating the Causal Effect of PCOS on VTE Risk

Exposure	Outcome	Methods	No. of SNPs	OR (95% CI)	*p* value
PCOS	VTE	IVW (fixed effects)	7	1.008 (0.974–1.042)	0.653
		IVW (random effects)	7	1.008 (0.962–1.056)	0.745
		MR Egger	7	1.100 (0.998–1.212)	0.114
		Weighted median	7	1.035 (0.991–1.082)	0.123
		Simple mode	7	1.040 (0.981–1.103)	0.236
		Weighted mode	7	1.038 (0.986–1.093)	0.201

Abbreviations: PCOS, polycystic ovary syndrome; VTE, venous thromboembolism; SNP, single nucleotide polymorphism; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

Table 2 Sensitivity Analyses for Heterogeneity and Pleiotropy in the Mendelian Randomization Study of PCOS and VTE

Exposure	Outcome	Heterogeneity Test (MR-Egger)			Heterogeneity Test (IVW)			Horizontal Pleiotropy Test (MR-Egger)		MR-PRESSO
		Cochran's Q	Q_df	*p*	Cochran's Q	Q_df	*p*	Intercept	*p*	*p*
PCOS	VTE	6.55	5	0.256	11.360	6	0.078	−0.025	0.113	0.091

Abbreviations: PCOS, polycystic ovary syndrome; VTE, venous thromboembolism; MR-Egger, Mendelian randomization-Egger regression; IVW, inverse variance weighted; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier test; Q, Cochran's Q statistic; df, degrees of freedom.

Results

Genetic Variants as Instrumental Variables

Seven SNPs were selected as IVs for PCOS, all with F-statistics > 10 (range: 30.829–116.213). Detailed SNP information is provided in Tables S2 and S3. The GWAS sources and sample sizes for all exposures and outcomes are summarized in Table S1.

Bidirectional Two-Sample Mendelian Randomization Between PCOS and VTE

The comprehensive results of the MR analyses are presented in Table 1. Both fixed-effects and random-effects IVW analyses showed no evidence of a causal effect of PCOS on VTE risk (OR = 1.008, 95% CI: 0.974–1.042, $p = 0.653$; OR = 1.008, 95% CI: 0.962–1.056, $p = 0.745$, respectively). Consistent results were observed using MR-Egger, weighted median, simple mode,

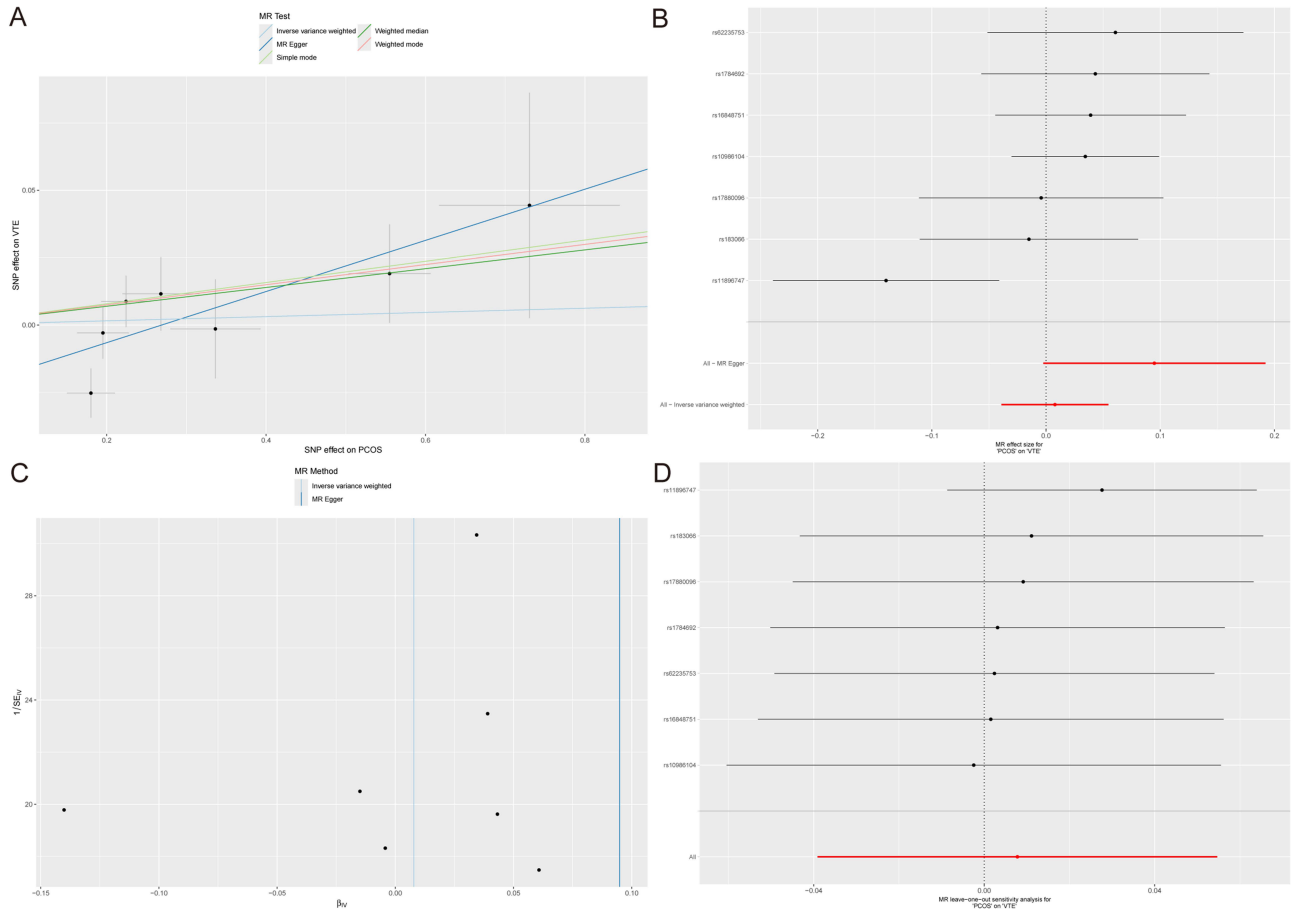

Figure 2 Results of Mendelian randomization analyses evaluating the effect of PCOS on VTE: (**A**) scatter plot, (**B**) forest plot, (**C**) funnel plot, and (**D**) leave-one-out sensitivity analysis.

and weighted mode. Cochran's Q provided no evidence of heterogeneity (MR-Egger: Q = 6.55, $p = 0.256$; IVW: Q = 11.360, $p = 0.078$) (Table 2 and Figure 2). The MR-Egger intercept did not indicate directional pleiotropy (intercept = −0.025, $p = 0.113$), and MR-PRESSO global test did not indicate horizontal pleiotropy ($p = 0.091$), and no outliers were identified (Table 2). Leave-one-out analyses suggested that no single SNP disproportionately influenced the IVW estimate. Overall, estimates were directionally consistent across MR methods and supported by sensitivity analyses indicating no material heterogeneity, directional pleiotropy, outliers, or single-variant influence.

Reverse MR Analysis

For the reverse MR analysis assessing the impact of VTE on PCOS risk (excluding palindromic SNP rs2844543), IVW showed no evidence of a causal effect (fixed-effects OR = 0.998, 95% CI: 0.904–1.101, $p = 0.962$; Table S4 and Figure 3). Heterogeneity and pleiotropy assessments are detailed in Table S5.

Multivariable MR Analysis

Figure 4 summarizes the results of the MVMR estimating associations between PCOS, diabetes, BMI, HRT, oral contraceptive use, and VTE. No significant causal effect of PCOS on VTE was found (IVW: OR = 1.016, 95% CI: 0.987–1.045, $p = 0.285$). However, a significant association was observed between BMI and VTE (IVW: OR = 1.358, 95% CI: 1.262–1.461, $p < 0.001$). No significant associations were found for diabetes, HRT, or oral contraceptive use with VTE, with consistent findings across MVMR-Egger, MVMR-Lasso, and MVMR-Median analyses.

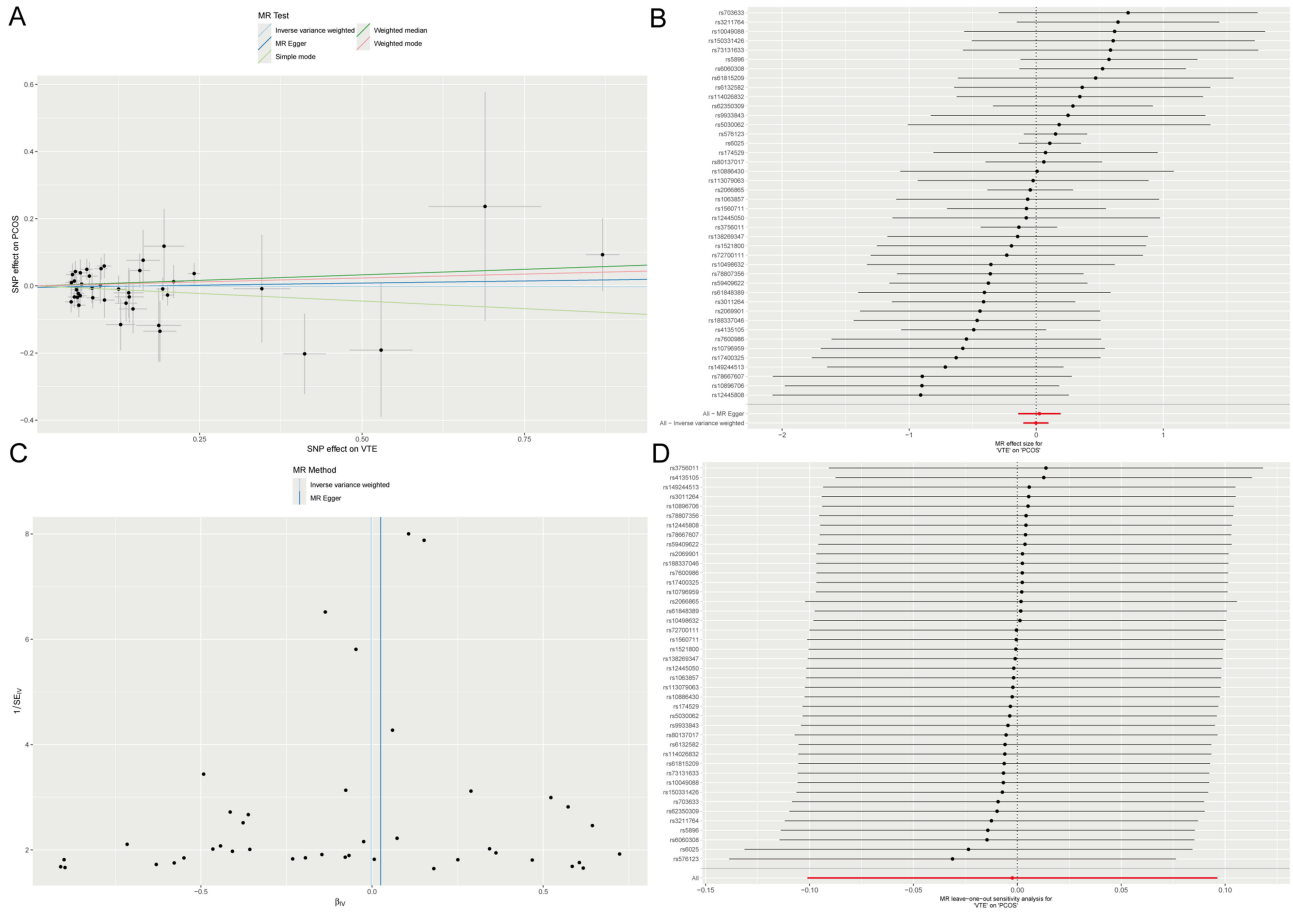

Figure 3 Results of Mendelian randomization analyses evaluating the effect of VTE on PCOS: (**A**) scatter plot, (**B**) forest plot, (**C**) funnel plot, and (**D**) leave-one-out sensitivity analysis.

https://doi.org/10.2147/IJWH.S586045

Methods	Exposure	SNPs	aOR (95%CI)	P value
MRMV_IVW				
	PCOS	460	1.016(0.987-1.045)	0.285
	Diabetes	460	1.728(0.741-4.032)	0.206
	BMI	460	1.358(0.262-1.461)	<0.001
	HRT	460	0.912(0.532-1.561)	0.736
	Ever taken oral contraceptive pill	460	0.485(0.219-1.073)	0.074
MRMV_Egger				
	PCOS	460	1.021(0.981-1.063)	0.307
	Diabetes	460	1.739(0.744-4.064)	0.201
	BMI	460	1.359(1.263-1.463)	<0.001
	HRT	460	0.916(0.534-1.571)	0.751
	Ever taken oral contraceptive pill	460	0.483(0.218-1.07)	0.073
MRMV_Lasso				
	PCOS	460	1.009(0.985-1.034)	0.451
	Diabetes	460	1.398(0.676-2.891)	0.366
	BMI	460	1.372(1.288-1.462)	<0.001
	HRT	460	0.839(0.535-1.316)	0.445
	Ever taken oral contraceptive pill	460	0.563(0.287-1.104)	0.094
MRMV_Median				
	PCOS	460	1.014(0.984-1.045)	0.356
	Diabetes	460	2.408(0.812-7.139)	0.113
	BMI	460	1.357(1.242-1.482)	<0.001
	HRT	460	0.870(0.475-1.592)	0.651
	Ever taken oral contraceptive pill	460	0.510(0.213-1.221)	0.131

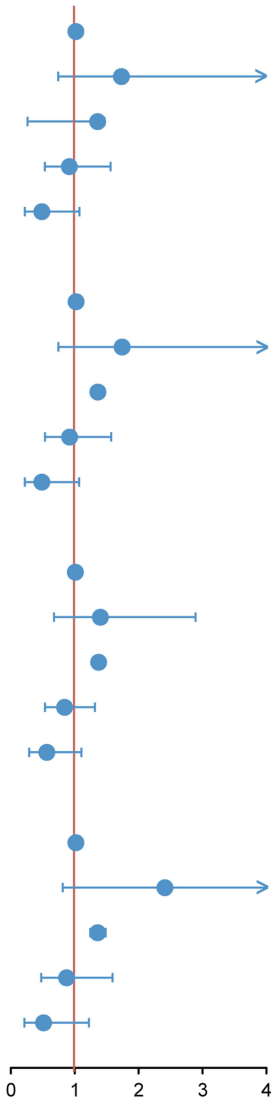

Figure 4 Multivariable Mendelian randomization.

Discussion

In this bidirectional two-sample MR study, with additional multivariable MR analyses, we examined the potential causal relationship between PCOS and VTE. Across univariable MR, reverse-direction MR, and multivariable MR adjusted for major correlated risk factors (BMI, diabetes, HRT use, and OC use), we did not find evidence that genetically predicted PCOS has a direct causal effect on VTE. BMI, however, remained independently associated with higher VTE risk in MVMR.

Our findings differ from several observational studies reporting increased VTE risk among women with PCOS. This difference is plausible.[8,9,16] Observational associations may be inflated by residual confounding and selection mechanisms that are difficult to fully address, particularly shared risk factors such as adiposity, insulin resistance or metabolic syndrome, and time-varying hormonal exposures (for example, OC use).[10,17,18] Surveillance or diagnostic bias may also play a role, as women with PCOS often have more healthcare contact for reproductive and metabolic concerns, which could increase the likelihood of VTE detection.[19] MR uses germline genetic variants as instruments for lifelong liability to the exposure, which helps reduce reverse causation and limits confounding relative to conventional observational designs.[13]

The association between BMI and VTE observed in our MVMR is consistent with epidemiologic evidence and prior MR studies supporting a causal role of adiposity in VTE.[10,20,21] Taken together, the elevated VTE risk reported in PCOS cohorts may largely reflect co-occurring adiposity-related metabolic pathways and residual cardiometabolic confounding rather than a direct effect of PCOS itself. Evidence that modifiable metabolic factors can influence PCOS risk, along with the causal role of adiposity in VTE, is consistent with a model in which cardiometabolic burden contributes to vascular risk among women with PCOS.[22–25] This also fits with clinical heterogeneity in insulin resistance across PCOS phenotypes.

From a clinical perspective, our results suggest a practical distinction. We found no evidence for a direct causal effect of PCOS on VTE, while BMI appears to be an independent causal risk factor. VTE prevention in women with PCOS may therefore benefit from focusing on modifiable cardiometabolic risk, particularly adiposity and related metabolic disturbances, rather than using PCOS diagnosis alone for thrombosis risk stratification.[24,26] This approach may help identify women with higher adiposity or metabolic burden, in whom absolute VTE risk is more likely to be clinically meaningful.

Several limitations should be noted. First, the PCOS GWAS included a relatively limited number of cases, which may have reduced statistical power, especially for detecting modest effects in MVMR. Second, although sensitivity analyses did not indicate major violations of MR assumptions, horizontal pleiotropy cannot be completely excluded. Third, our analyses were restricted to European-ancestry datasets, which limits generalizability, as PCOS prevalence and metabolic manifestations can vary across populations and may be influenced by diagnostic criteria and ascertainment. Finally, the PCOS summary statistics were based on registry or ICD-defined case status. Detailed phenotyping (for example, Rotterdam A to D) was not available, so we could not conduct phenotype-stratified analyses.

Future work would benefit from larger, ancestry-diverse PCOS GWAS with improved phenotypic resolution, including Rotterdam subtypes and key medication exposures such as hormonal therapies. Pleiotropy-robust approaches, including colocalization and robust MR methods, as well as replication in independent cohorts, will also be important.

Conclusion

This bidirectional and multivariable MR study suggests that PCOS is unlikely to directly increase VTE risk, while higher BMI appears to be a robust independent causal risk factor. These findings support a clinical focus on reducing adiposity-related risk and managing cardiometabolic burden, rather than relying on PCOS diagnosis alone for VTE risk assessment.

Data Sharing Statement

Data analyzed in this study were publicly available from GWAS datasets. More details are shown in the main text.

Ethical Approval and Consent to Participate

As all summary-level data were collected from previously published, open-access studies, neither additional ethical approval nor informed consent was required.

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.

Funding

This study was supported by the Medical and health research Project of Yuhang District (Grant No.2019007).

Disclosure

Lifang You and Hongyin Cui are co-first authors for this study. The authors declared that they have no conflict of interest.

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