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ORIGINAL ARTICLE

Observational Study

Effect of vitamin supplementation on polycystic ovary syndrome and key pathways implicated in its development: A Mendelian randomization study

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Abstract

BACKGROUND

Many epidemiologic investigations have explored the relationship between viatmins and polycystic ovary syndrome (PCOS). However, the effectiveness of vitamin, vitamin-like nutrient, or mineral supplementation in reducing the risk of PCOS remains a subject of debate.

AIM

To investigate the impact of plasma levels of vitamins A, B12, D, E, and K on PCOS and key pathways implicated in its development, namely, insulin resistance, hyperlipidemia, and obesity, through Mendelian randomization (MR) analysis.

METHODS

Single nucleotide polymorphisms associated with vitamin levels were selected from genome-wide association studies. The primary analysis was performed using the random-effects inverse-variance-weighted approach. Complementary analyses were conducted using the weighted median, MR-Egger, MR-robust adjusted profile score, and MR-PRESSO approaches.

RESULTS

The results provided suggestive evidence of a decreased risk of PCOS with genetically predicted higher levels of vitamin E (odds ratio [OR] = 0.118; 95%

confidence interval [CI]: 0.071–0.226; $P < 0.001$) and vitamin B12 (OR = 0.753, 95%CI: 0.568–0.998, $P = 0.048$). An association was observed between vitamin E levels and insulin resistance (OR = 0.977, 95%CI: 0.976–0.978, $P < 0.001$). Additionally, genetically predicted higher concentrations of vitamins E, D, and A were suggested to be associated with a decreased risk of hyperlipidemia. Increased vitamins K and B12 levels were linked to a lower obesity risk (OR = 0.917, 95%CI: 0.848–0.992, $P = 0.031$).

CONCLUSION

The findings of this MR study suggest a causal relationship between increased vitamins A, D, E, K, and B12 levels and a reduced risk of PCOS or primary pathways implicated in its development.

Key Words: Vitamin levels; Polycystic ovary syndrome; Key pathways; Mendelian randomization; Casual effect

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Core Tip: Higher vitamins A, D, E, K, and B12 levels were casually related to a reduced risk of polycystic ovary syndrome (PCOS) or main pathways implicated in its development, as suggested by our Mendelian randomization investigation. More prospective and functional *in vivo* and *in vitro* trials are required to clarify the role of vitamin supplements in the onset of PCOS and main pathways implicated in its development.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a widespread endocrine disease that affects a large number of sexually mature women globally[1,2]. The prevalence of PCOS according to the diagnostic criteria ranges from 6% to 10%[3]. Patients with PCOS are at an increased risk of diabetes mellitus, atherogenic dyslipidemia, systemic inflammation, hypertension, and coagulation disorders[4,5].

PCOS arises from a combination of hereditary and epigenetic vulnerability, insulin resistance, and adiposity-related mechanisms[6,7]. Modifying one's lifestyle is among the recommended options for PCOS treatment and is highly advised for women seeking to improve their quality of life[8]. In recent years, there has been growing interest in nutritional supplements[9,10]. However, the potential of vitamin, vitamin-like nutrient, or mineral supplementation to reduce the risk of PCOS remains debatable. A meta-analysis found no evidence that vitamin D supplementation improved or alleviated metabolic and hormonal dysregulations in PCOS[11]. Nevertheless, convincing conclusions cannot be drawn at this point, and vitamin K may be a viable option for alleviating oxidative stress and improving glycemic control in PCOS [12].

The supplementation of specific nutrients and complementary treatments may improve the health conditions of women with PCOS by modulating critical pathways implicated in PCOS development, such as insulin signaling, insulin resistance, and lipid metabolism. However, observational studies largely constitute the primary evidence regarding the correlation between vitamin supplements and PCOS, which can be influenced by confounding or reverse causation. Mendelian randomization (MR) has emerged as an effective technique to identify the causal relationship of risk factors with diseases by using genetic variants as instrumental variables (IVs)[13]. MR enables stronger causal inferences than typical observational studies due to the random assignment of genetic variations during conception between parents and offspring.

To date, no MR analysis has explored the causal effect of vitamin supplements on PCOS. In this study, we aimed to conduct a two-sample MR analysis to assess the impact of plasma levels of vitamins A, B12, D, E, and K on PCOS and key pathways implicated in its development, namely, insulin resistance, hyperlipidemia, and obesity.

MATERIALS AND METHODS

Study design

Vitamin supplementation has the potential to improve health outcomes in women with PCOS by influencing crucial pathways such as insulin resistance, lipid metabolism, and obesity. We conducted a two-sample MR analysis to identify the effect of plasma levels of vitamins A, B12, D, E, and K on PCOS and its associated pathways, including insulin resistance, hyperlipidemia, and obesity. Figure 1 provides a detailed overview of the study design.

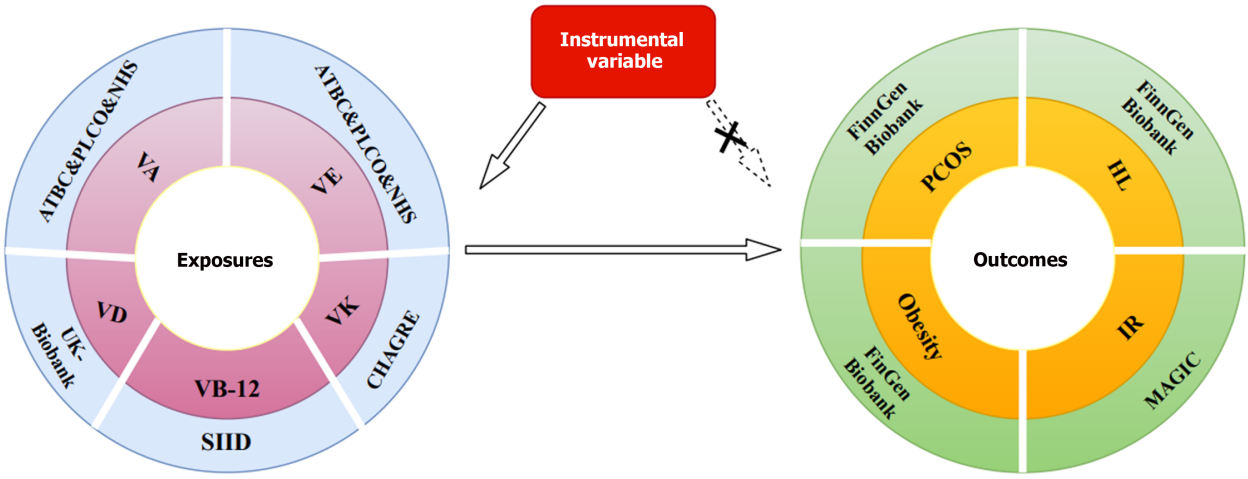

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Figure 1 Summary of the Mendelian randomization investigation. Genetic variations associated with plasma vitamin levels were used as instrumental variables to examine the correlation between exposures and outcomes.

Study participants

The genetic association data for vitamin D were analyzed using blood samples obtained twice from the United Kingdom Biobank, a major population cohort[14] comprising volunteers aged 37-73 years from 22 evaluation centers across the United Kingdom, aiming to enhance disease prevention[15]. Genetic association data for vitamin B12 were obtained from sequencing initiatives in Iceland and Denmark involving European populations, explaining 5.1% of the variation in circulating vitamin B12 levels[16]. Genetic instruments for vitamins A and E concentration were obtained from three cohorts: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Study; and the Nurses' Health Study[17]. Data for vitamin K were obtained from the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium Nutrition Working Group, which involved 2138 individuals. Genetic correlations were examined using linear models adjusted for key components, sex, age, and study-specific factors[18]. To mitigate potential bias stemming from ancestry, participation was limited to individuals of European heritage. All analyses of this study were based on publicly accessible databases; thus, no additional ethical approval or informed consent was required. The genome-wide association studies (GWAS) included in the analysis are presented in Table 1.

Outcome data source

The primary measure in this MR study was PCOS. Table 1 provides a summary of the specific sources of outcome data. Summary statistics for PCOS in individuals of European ancestry were obtained from the FinnGen Biobank consortium, which includes 118870 participants. The FinnGen project is a unique research endeavor that integrates genetic data with digital healthcare information from over 500000 Finnish biobank participants[19]. Hyperlipidemia, obesity, and insulin resistance are key pathways related to PCOS. Hyperlipidemia and obesity data were also sourced from the FinnGen Biobank consortium. Insulin resistance data were retrieved from the Meta-Analyses of Glucose and Insulin-related traits Consortium, involving up to 37037 participants[20].

Genetic instruments for vitamin concentration

Single nucleotide polymorphisms (SNPs) associated with vitamins D, E, A, and B12 were defined at the genome-wide significance threshold ($P < 5 \times 10^{-8}$). Owing to the limited number of SNPs for vitamin K, SNPs at a level of genome-wide significance of $P < 5 \times 10^{-6}$ were chosen as IVs. To ensure instrument validity, SNPs were filtered within a 1000 kb window with an $r^2 < 0.01$ threshold[21]. Through a search of the *GWAS* Catalog (https://www.ebi.ac.uk/gwas/), we identified pleiotropic IV SNPs associated with any confounding factor related to the outcome. Estimates of the effects of these vitamin-related genetic variations on outcome datasets were collected. Additionally, SNP harmonization was conducted to restore allele orientation. The final selection of SNPs used in this MR is presented in Supplementary Tables 1-20.

SNP-based Mendelian randomization estimates

The primary analyses were performed using the random-effects inverse-variance-weighted (IVW) approach, assuming all SNPs as valid IVs. The IVW method is considered highly reliable when there is no evidence of directional pleiotropy among the selected IVs (P value for MR-Egger intercept > 0.05)[22]. Complementary analyses were conducted using the weighted median[23] and MR-Egger[23] methods as supplements to the IVW approach. The weighted median model generates consistent causal findings when over 50% of the weights are derived from valid SNPs. The MR-Egger regression method can detect and adjust for directional pleiotropy[24].

Table 1 Details of the genome-wide association studies included in this Mendelian randomization analysis

Exposures/Outcomes	Consortium	Ethnicity	Participants	Number of SNPs
Vitamin D	United Kingdom Biobank	European	496946	6896093
Vitamin K	CHAGRE	European	2138	/
Vitamin E	ATBC&PLCO&NHS	European	7781	/
Vitamin A	ATBC&PLCO&NHS	European	7778	/
Vitamin B12	SIID	European	45576	/
Polycystic ovarian syndrome	FinnGen Biobank	European	118870	16379676
Hyperlipidaemia	FinnGen Biobank	European	201497	16380389
Obesity	FinnGen Biobank	European	218735	16380465
Insulin resistance	MAGIC	European	37037	2435028

SNPs: Single nucleotide polymorphisms.

Furthermore, we performed MR-robust adjusted profile score (MR-RAPS) using the "Huber" loss function to model a random-effects distribution of the pleiotropic effects of genetic variants[25]. Additionally, the MR-PRESSO approach was used to identify outlier SNPs and provide causal estimations after removing probable outliers, assuming that the employed SNPs are valid[26].

Heterogeneity and pleiotropy analysis

We used Cochran's Q test to analyze the heterogeneity of the estimations from each SNP. When there was no statistically significant heterogeneity ($P > 0.05$), we used the fixed-effects model; however, the random-effects model was used to produce highly conservative estimations. Pleiotropy analysis was conducted using the MR-Egger intercept test. A zero intercept for MR-Egger ($P > 0.05$) indicates no presence of pleiotropic bias[27].

All tests were performed using the statistical program "R" v3.5 with the "TwoSampleMR," "MR-PRESSO," "Mr.raps," and "Forestplot" packages. All analyses were two-sided, and statistical significance was set at $P < 0.05$.

RESULTS

Association of vitamin E supplementation with PCOS and key pathways implicated in its development

In the fixed-effects IVW estimations, genetically projected higher values of vitamin E were associated with a reduced risk of PCOS (Figure 2 and Supplementary Table 21). For 1-SD increase in genetically projected vitamin E concentrations, the combined odds ratio (OR) was 0.118 (95% confidence interval [CI]: 0.071–0.226, $P < 0.001$). The association remained consistent in complementary analyses when using the random-effects IVW and weighted median techniques. Higher vitamin E levels were correlated with a decreased risk of hyperlipidemia (OR = 0.259, 95%CI: 0.111–0.608, $P = 0.002$) and insulin resistance (OR = 0.977, 95%CI: 0.976–0.978, $P < 0.001$). However, no impact of vitamin E on obesity was observed *via* the fixed-effects IVW approach.

Association of vitamin D supplementation with PCOS and key pathways implicated in its development

Genetically anticipated higher vitamin D concentrations were suggestive of a decreased risk of hyperlipidemia, as indicated *via* the random-effects IVW approach (OR = 0.749, 95%CI: 0.592–0.948, $P = 0.016$; Figure 3 and Supplementary Table 21). The results remained consistent in the fixed-effects IVW approach (OR = 0.749, 95%CI: 0.647–0.868, $P = 0.001$). However, other complementary analyses yielded negative results. Additionally, all MR methods did not support a link between genetically projected vitamin D concentrations and PCOS, obesity, and insulin resistance.

No evidence of directional pleiotropy was observed, but heterogeneity was present for vitamin D analysis on the key pathways of PCOS (Table 2). Furthermore, outlier SNPs were identified using the MR-PRESSO test, and the causal effect estimates of vitamin E on the risk of PCOS and key pathways implicated in its development were not statistically significant (Table 3).

Association of vitamin K supplementation with PCOS and key pathways implicated in its development

Figure 4A presents the MR estimation for the association of vitamin E supplementation with PCOS and key pathways implicated in its development. According to the fixed-effects IVW method, increased vitamin E levels were associated with a reduced risk of obesity (OR = 0.917, 95%CI: 0.848–0.992, $P = 0.031$; Figure 4A and Supplementary Table 21). However, no causal effect of vitamin E on PCOS, hyperlipidemia, and insulin resistance was observed. No evidence was observed of horizontal pleiotropy (P value for intercept > 0.05; Table 2) or heterogeneity as measured using Cochran's Q test (P value for Cochran's Q > 0.05; Table 3).

Table 2 Heterogeneity and pleiotropy tests of the Mendelian randomization analysis

Exposure/Outcome	Heterogeneity		Pleiotropy	
	Cochran's Q	*P* value	Egger-intercept	*P* value
Vitamin D/PCOS	180.692	0.368	-0.006	0.487
Vitamin D/Hyperlipidaemia	449.648	< 0.001	-0.004	0.425
Vitamin D/Obesity	402.633	< 0.001	0.002	0.494
Vitamin D/Insulin resistance	169.312	0.001	-0.002	0.059
Vitamin K/PCOS	2.926	0.570	0.029	0.752
Vitamin K/Hyperlipidaemia	5.151	0.272	0.044	0.290
Vitamin K/Obesity	7.086	0.131	0.049	0.150
Vitamin K/Insulin resistance	7.932	0.094	-0.008	0.469
Vitamin B12/PCOS	1.284	0.973	0.004	0.930
Vitamin B12/Hyperlipidaemia	3.346	0.764	-0.022	0.297
Vitamin B12/Obesity	5.046	0.540	0.003	0.858
Vitamin B12/Insulin resistance	3.578	0.466	-0.003	0.451

PCOS: Polycystic ovary syndrome.

Table 3 Mendelian randomization PRESSO estimates for effect of vitamin supplements on risk of polycystic ovary syndrome and its risk factors

Exposure trait	Outcome trait	*N*	Beta	*P* value
Vitamin D	PCOS	172	-0.092	0.645
Vitamin D	Hyperlipidaemia	169	-0.141	0.126
Vitamin D	Obesity	174	-0.031	0.618
Vitamin D	Insulin resistance	117	-0.005	0.789
Vitamin B12	PCOS	6	-0.284	0.005
Vitamin B12	Hyperlipidaemia	6	-0.103	0.063
Vitamin B12	Obesity	6	-0.088	0.048
Vitamin B12	Insulin resistance	6	-0.015	0.319

PCOS: Polycystic ovary syndrome.

Association of vitamin B12 supplementation with PCOS and key pathways implicated in its development

The fixed-effects IVW estimations suggested a link between genetically anticipated higher vitamin B12 Levels and a lower risk of PCOS (OR = 0.753, 95%CI: 0.568–0.998, P = 0.048) and obesity (OR = 0.917, 95%CI: 0.843–0.995, P = 0.037; Figure 4B and Supplementary Table 21). However, no correlation was observed between vitamin B12 levels and hyperlipidemia or insulin resistance.

No evidence of horizontal pleiotropy (P value for intercept > 0.05; Table 2) or heterogeneity as indicated by the Cochran's Q test (P value for Cochran's Q > 0.05; Table 3) was found. After correcting for the outline SNPs, the causal effect estimates of vitamin B12 on the risk of PCOS (P = 0.005) and obesity (P = 0.048) remained statistically significant (Table 3).

Association of vitamin A supplementation with PCOS and key pathways implicated in its development

The IVW estimate showed a significant association between genetically predicted vitamin A levels and hyperlipidemia risk (OR = 0.287, 95%CI: 0.258–0.320, P < 0.001; Figure 4C and Supplementary Table 21). This association was consistent with complementary analyses using the random-effects IVW method. However, no statistically significant causal effect estimates of vitamin A on the risk of PCOS, obesity, and insulin resistance were observed.

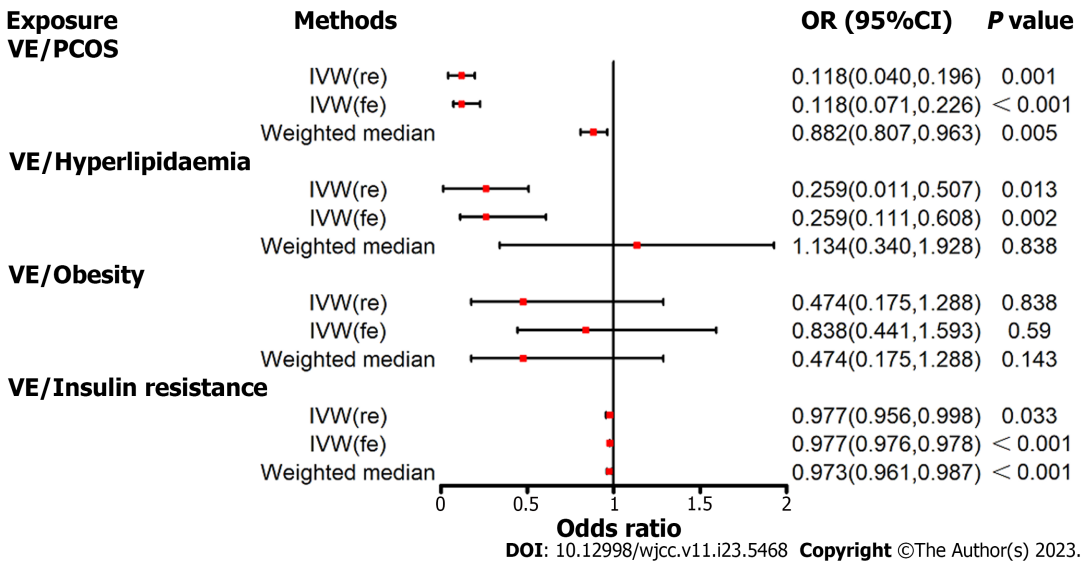

Figure 2 Association of vitamin E supplementation with polycystic ovary syndrome, hyperlipidemia, obesity, and insulin resistance. IVW (re): Inverse variance weighted with random effect; IVW(fe): Inverse variance weighted with fixed effect; VE: Vitamin E; OR: Odds ratio; PCOS: Polycystic ovary syndrome.

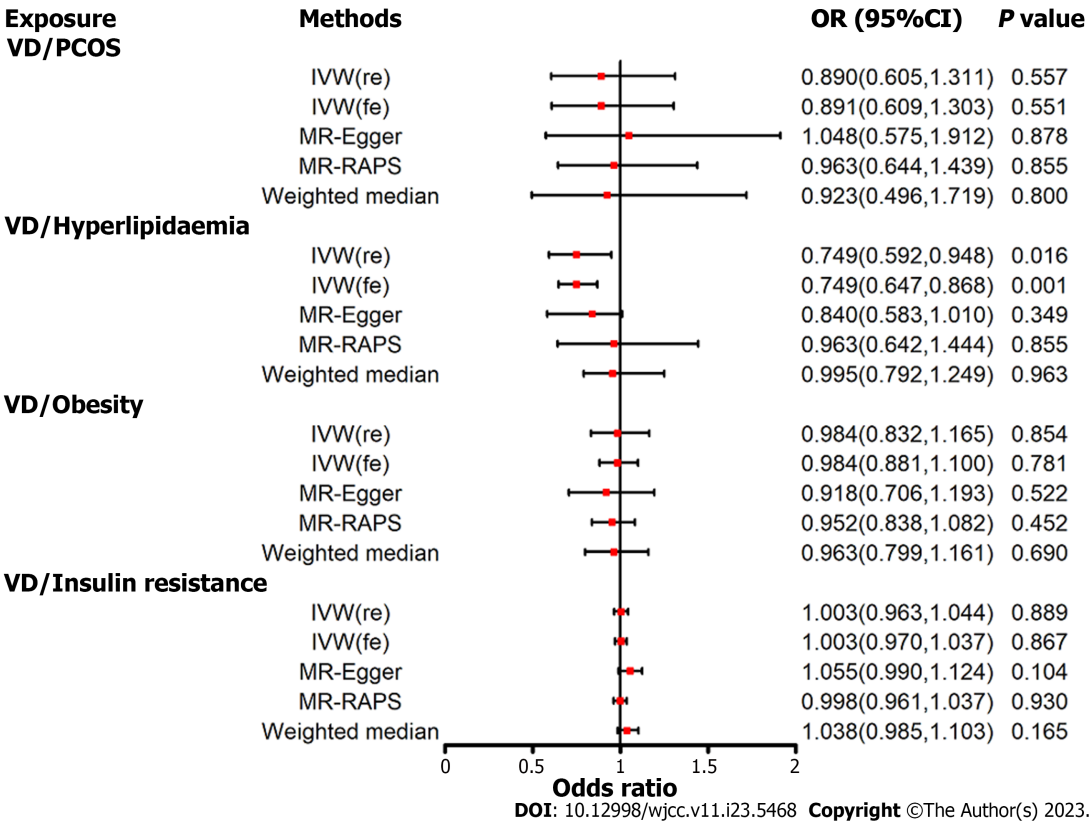

Figure 3 Association of vitamin D supplementation with polycystic ovary syndrome, hyperlipidemia, obesity, and insulin resistance. MR-RAPS: MR-robust adjusted profile score; OR: Odds ratio; PCOS: Polycystic ovary syndrome; VD: Vitamin D.

DISCUSSION

Supplementation with individual nutrients may improve health outcomes in women with PCOS by altering crucial PCOS-related pathways, such as insulin signaling, insulin resistance, and lipid metabolism. This MR analysis, based on large-scale genetic consortia, provides suggestive evidence supporting a causal effect of higher vitamins E and B12 levels on a decreased risk of PCOS. Our findings indicated that genetically predicted levels of vitamins K and B12 were related to a lower risk of obesity. Additionally, genetically predicted higher levels of vitamins E, D, and A were suggestively

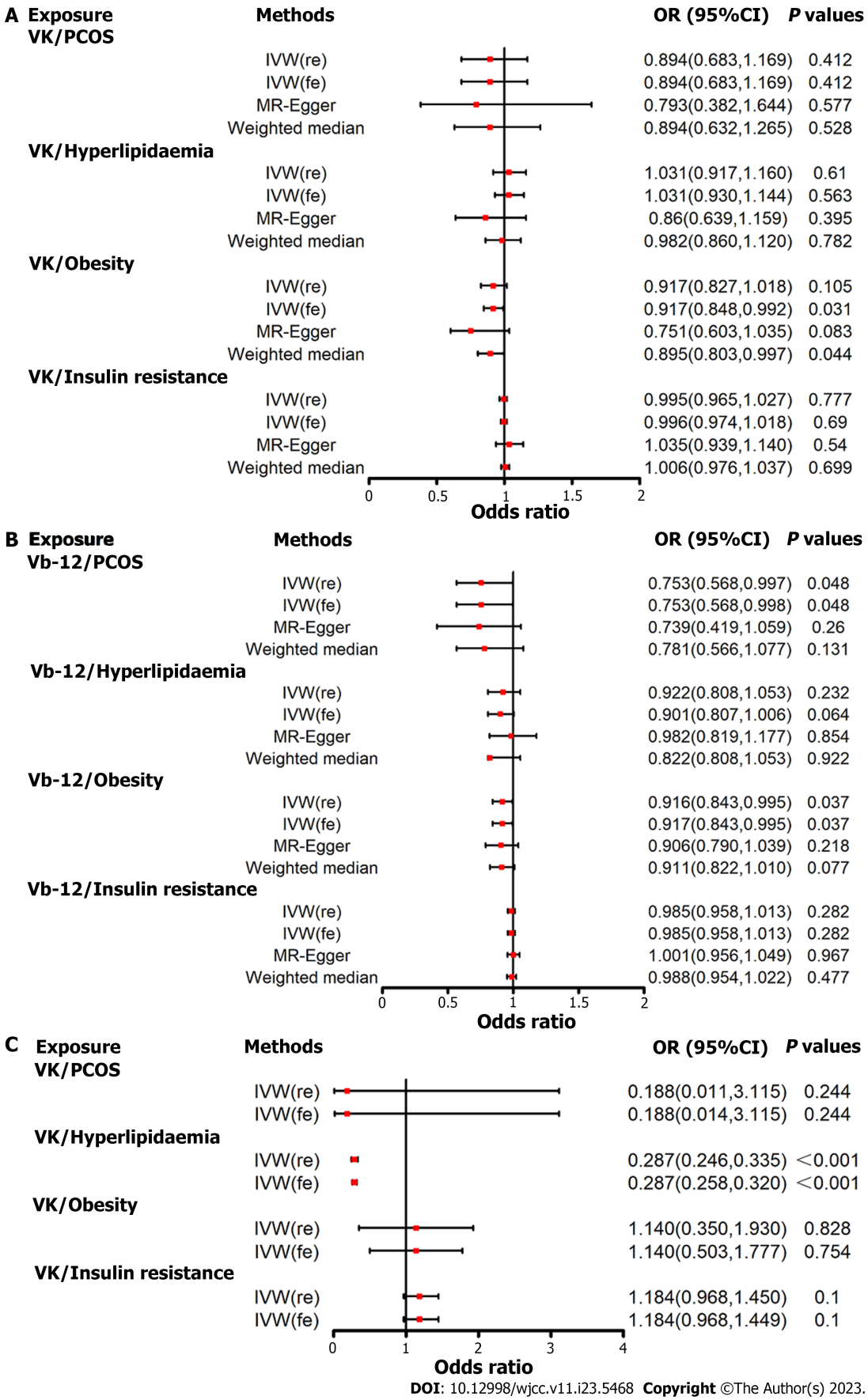

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Figure 4 Association of vitamin supplementation with polycystic ovary syndrome, hyperlipidemia, obesity, and insulin resistance. A: Vitamin K; B: Vitamin B12; C: Vitamin A. OR: Odds ratio; PCOS: Polycystic ovary syndrome.

associated with a decreased risk of hyperlipidemia, while higher vitamin E levels were suggestively linked to a lower risk of insulin resistance.

Previous studies have employed cross-sectional, case-control, and cohort designs to investigate the association between vitamin supplementation and the risk of PCOS. However, the findings remain disputed. For instance, Panidis *et al*[28] found that patients with PCOS had lower levels of vitamin D compared with controls. Hahn *et al*[29] demonstrated a link between low serum 25-hydroxyvitamin D values and insulin resistance and obesity in women with PCOS. However, a meta-analysis of 30 trials did not provide evidence that vitamin D supplementation reduces or alleviates metabolic and hormonal dysregulations in PCOS[11]. This discrepancy may be attributed to the limitations of observational investigations, which are prone to residual confounding and imprecise measurements of confounders. In contrast, MR analysis offers highly accurate causal conclusions by leveraging the random assignment of genetic variations from parents to children.

A recent systemic review of 12 articles indicated that vitamin E supplementation improves lipid profile, reduces insulin levels, and decreases HOMA-IR values[30,31]. This is consistent with our findings suggesting that increased vitamin E concentrations are associated with a decreased risk of PCOS, hyperlipidemia, and insulin resistance. The anti-oxidative property of vitamin E, along with its effects on oxidative stress metrics, may explain its positive effects on lipid profile enhancement and insulin resistance[30]. Vitamin E acts as a substantial fat antioxidant, neutralizing peroxyl radicals and preventing the oxidation of polyunsaturated fatty acids[32,33]. Coenzyme Q10 is often supplemented together with vitamin E due to its synergistic roles in sustaining mitochondrial activity and integrity[10]. Foreign studies have shown favorable effects of coenzyme Q10 and vitamin E supplementation on blood insulin, HOMA-IR, and total testosterone levels in women with PCOS[34,35].

The role of vitamin B12 on PCOS remains unclear. B-group vitamins are responsible for breaking down Hcy in the blood, which is associated with insulin resistance[36]. However, our study provides no evidence of a causal effect of vitamin B12 on insulin resistance. A randomized controlled trial with B-group vitamin supplementation indicated a reduction in Hcy concentrations but no changes in insulin resistance[37].

Lipid metabolism is a key pathway in PCOS. Our MR analysis revealed that genetically predicted higher levels of vitamins E, D, and A are suggestively associated with a decreased risk of hyperlipidemia. This finding suggests the potential benefits of supplementing these vitamins. However, further functional studies *in vivo* are necessary to explore the underlying mechanisms. Additionally, adipose tissue plays a role as a metabolic and endocrine organ, and its overabundance can lead to alterations in body homeostasis and vitamin deficiency[2,38]. Therefore, vitamin supplementation may be beneficial in improving health outcomes in women with PCOS and obesity.

This study is the first MR investigation exploring the association between vitamin supplementation and PCOS and key pathways implicated in its development. The MR design strengthens causal inference by reducing residual confounding and other biases[39]. The use of data obtained from independent large GWAS ensures the reliability of the results. Furthermore, to address the potential influence of pleiotropic SNPs on our data, we implemented various techniques such as weighted median and MR-RAPS to minimize violations of the MR assumptions. Additionally, we used MR-PRESSO to identify and assess the probable presence of pleiotropy among the SNPs. Lastly, the genetic variants used as IVs were located on different chromosomes, minimizing the potential gene-gene interactions in our findings.

Nevertheless, our study has some limitations. First, the vitamin levels analyzed were genetically predicted concentrations, approximating average effects over the life course. The concentration of vitamins is influenced by the diet. Second, the analysis was restricted to participants of European ancestry to minimize bias due to population stratification; this limits the generalizability of the findings to non-European populations. Third, weak instrument bias may be present, given the low variability of vitamin levels explained by the SNPs. Fourth, although our study incorporated data from extensive genetic epidemiology networks, it may not be adequately powered to detect considerably small effects. Fifth, we were unable to obtain data stratified by the PCOS phenotype, warranting further investigation into the effect of vitamin supplements on different PCOS phenotypes. Lastly, we were unable to assess linear associations between vitamin levels and PCOS. Further prospective and functional studies are warranted to elucidate the role of vitamin supplements in PCOS.

CONCLUSION

Our MR analysis suggests that higher levels of vitamins A, D, E, K, and B12 are causally related to a reduced risk of PCOS or key pathways implicated in its development. Further prospective population-based studies and *in vivo* and *in vitro* trials are required to clarify the precise role of vitamin supplements in the onset of PCOS and key pathways implicated in its development.

ARTICLE HIGHLIGHTS

Research background

Outcomes from conventional observational investigations are often based on the limited sample size and influenced by confounding factors.

Research motivation
To conduct a two-sample mendelian randomization (MR) analysis to assess the impact of plasma levels of vitamins A, B12, D, E, and K on polycystic ovary syndrome (PCOS) and key pathways implicated in its development, namely, insulin resistance, hyperlipidemia, and obesity.

Research objectives
To explore the causal relationship between increased vitamins A, D, E, K, and B12 values and a reduced risk of PCOS or primary pathways implicated in its development.

Research methods
The inverse variance weighted (IVW) method is considered highly reliable when there is no evidence of directional pleiotropy among the selected instrumental variables. Complementary analyses were conducted using the weighted median and MR-Egger methods as supplements to the IVW method. Furthermore, the MR-robust adjusted profile score (MR-RAPS) and MR-PRESSO approaches were used to identify outlier single nucleotide polymorphisms (SNPs) and provide causal estimations after removing probable outliers, assuming that the employed SNPs are valid.

Research results
This MR analysis, based on large-scale genetic consortia, provided suggestive evidence supporting a causal effect of higher vitamins E and B12 levels on a decreased risk of PCOS. Our findings indicated that genetically predicted levels of vitamins K and B12 were related to a lower risk of obesity. Additionally, genetically predicted higher levels of vitamins E, D, and A were suggestively associated with a decreased risk of hyperlipidemia, while higher vitamin E levels were suggestively linked to a lower risk of insulin resistance.

Research conclusions
Higher levels of vitamins A, D, E, K, and B12 are causally related to a reduced risk of PCOS or key pathways implicated in its development.

Research perspectives
Further prospective population-based studies and *in vivo* and *in vitro* trials are required to clarify the precise role of vitamin supplements in the onset of PCOS and key pathways implicated in its development.

FOOTNOTES

Author contributions: Shen JY, Xu L, Ding Y, and Wu XY designed the research study; Shen JY and Xu L performed the research; Shen JY and Ding Y contributed new reagents and analytic tools; Shen JY and Wu XY analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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Informed consent statement: The data was from large sample size GWAS, and no informed consent statement is required.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest to disclose.

Data sharing statement: The data can be accessed from the following website: https://gwas.mrcieu.ac.uk/. Additionally, we have presented the relevant data in Supplementary Tables 1–20.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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