REVIEW
5416 Recent progress in understanding mitokines as diagnostic and therapeutic targets in hepatocellular carcinoma
Wang J, Luo LZ, Liang DM, Guo C, Huang ZH, Jian XH, Wen J

ORIGINAL ARTICLE
Retrospective Cohort Study
5430 Clinical characteristics and risk factors of intracranial hemorrhage after spinal surgery
Yan X, Yan LR, Ma ZG, Jiang M, Gao Y, Pang Y, Wang WW, Qin ZH, Han YT, You XF, Ruan W, Wang Q

Retrospective Study
5440 Application effect of phloroglucinol injection in elderly patients with spastic abdominal pain in emergency department
Liu YF, Chen J

5447 Efficacy and prognosis of adjuvant treatment of endometrial cancer with medroxyprogesterone acetate COX regression analysis
Wang DR

5455 Serum vascular endothelial growth factor and cortisol expression to predict prognosis of patients with hypertensive cerebral hemorrhage
Zhang CY, Wang B, Hua XT, Fan K, Li YF

5462 Progress of ulcerative colitis patients during the COVID-19 pandemic
Suda T, Takahashi M, Katayama Y, Soga K, Kobori I, Kusano Y, Tamano M

Observational Study
5468 Effect of vitamin supplementation on polycystic ovary syndrome and key pathways implicated in its development: A Mendelian randomization study
Shen JY, Xu L, Ding Y, Wu XY

Prospective Study
5479 Evaluation of childhood developing via optical coherence tomography-angiography in Qamdo, Tibet, China: A prospective cross-sectional, school-based study

SYSTEMATIC REVIEWS
5494 Isolated left ventricular apical hypoplasia: Systematic review and analysis of the 37 cases reported so far
Bassareo PP, Duignan S, James A, Dunne E, McMahon CJ, Walsh KP
META-ANALYSIS

5504 Identification of key genes and biological pathways in lung adenocarcinoma by integrated bioinformatics analysis
Zhang L, Liu Y, Zhuang JG, Guo J, Li YT, Dong Y, Song G

CASE REPORT

5519 Clinical outcomes of robotic-assisted and manual total hip arthroplasty in the same patient: A case report
Hu TY, Lin DC, Zhou YJ, Zhang ZW, Yuan JJ

5525 Emphysematous sloughed floating ball after prostate water vaporization Rezum: A case report
Alnazari M, Bakhsh A, Rajih ES

5530 Imaged guided surgery during arteriovenous malformation of gastrointestinal stromal tumor using hyperspectral and indocyanine green visualization techniques: A case report

5538 Membranous nephropathy with systemic light-chain amyloidosis of remission after rituximab therapy: A case report
Zhang J, Wang X, Zou GM, Li JY, Li WG

5547 Rhabdomyolysis-induced acute kidney injury after administration of a red yeast rice supplement: A case report
Wang YH, Zhang SS, Li HT, Zhi HW, Wu HY

5554 Jackstone in the renal calyx: A rare case report
Song HF, Liang L, Liu YB, Xiao B, Hu WG, Li JX

5559 Critical respiratory failure due to pregnancy complicated by COVID-19 and bacterial coinfection: A case report
Zhou S, Liu MH, Deng XP

5567 Townes–Brocks syndrome with adult renal impairment in a Chinese family: A case report
Wu J, Zhang J, Xiao TL, He T

5573 Nasopharyngeal carcinoma with synchronous breast metastasis: A case report
Lei YY, Li DM

5580 Anti-melanoma differentiation-associated gene 5 and anti-Ro52 antibody-dual positive dermatomyositis accompanied by rapidly lung disease: Three case reports
Ye WZ, Peng SS, Hu YH, Fang MP, Xiao Y

5589 Anaphylactic shock induced by polyethylene glycol after bowel preparation for the colorectal cancer surgery: A case report
Park GW, Park N, Kuk JC, Shin EJ, Lim DR

5595 Knee locking caused by osteochondroma of the proximal tibia adjacent to the pes anserinus: A case report
Sonobe T, Hakozaki M, Matsuo Y, Takahashi Y, Yoshida K, Konno S
Contents

5602 Complex inferior vena cava reconstruction during ex vivo liver resection and autotransplantation: A case report
   Humaerhan J, Jiang TM, Aji T, Shao YM, Wen H

5610 Hemocholecyst caused by accidental injury associated with radiofrequency ablation for hepatocellular carcinoma: A case report
   Tan YW, Zhang XY

5615 Pancreatic cavernous hemangioma complicated with chronic intracapsular spontaneous hemorrhage: A case report and review of literature
   Li T

5622 Pyogenic liver abscess secondary to gastric perforation of an ingested toothpick: A case report
   Park Y, Han HS, Yoon YS, Cho JY, Lee B, Kang M, Kim J, Lee HW
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Observational Study

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

Jia-Yan Shen, Li Xu, Yang Ding, Xiao-Yun Wu

Abstract

BACKGROUND
Many epidemiologic investigations have explored the relationship between vitamins 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.
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

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

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 = 0.034; 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

<table>
<thead>
<tr>
<th>Exposure/Outcome</th>
<th>Heterogeneity</th>
<th>Pleiotropy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cochran's Q</td>
<td>P value</td>
</tr>
<tr>
<td>Vitamin D/PCOS</td>
<td>180.692</td>
<td>0.368</td>
</tr>
<tr>
<td>Vitamin D/Hyperlipidaemia</td>
<td>449.648</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vitamin D/Obesity</td>
<td>402.633</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vitamin D/Insulin resistance</td>
<td>169.312</td>
<td>0.001</td>
</tr>
<tr>
<td>Vitamin K/PCOS</td>
<td>2.926</td>
<td>0.570</td>
</tr>
<tr>
<td>Vitamin K/Hyperlipidaemia</td>
<td>5.151</td>
<td>0.272</td>
</tr>
<tr>
<td>Vitamin K/Obesity</td>
<td>7.086</td>
<td>0.131</td>
</tr>
<tr>
<td>Vitamin K/Insulin resistance</td>
<td>7.932</td>
<td>0.094</td>
</tr>
<tr>
<td>Vitamin B12/PCOS</td>
<td>1.284</td>
<td>0.973</td>
</tr>
<tr>
<td>Vitamin B12/Hyperlipidaemia</td>
<td>3.346</td>
<td>0.764</td>
</tr>
<tr>
<td>Vitamin B12/Obesity</td>
<td>5.046</td>
<td>0.540</td>
</tr>
<tr>
<td>Vitamin B12/Insulin resistance</td>
<td>3.578</td>
<td>0.466</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Exposure trait</th>
<th>Outcome trait</th>
<th>N</th>
<th>Beta</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>PCOS</td>
<td>172</td>
<td>-0.092</td>
<td>0.645</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Hyperlipidaemia</td>
<td>169</td>
<td>-0.141</td>
<td>0.126</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Obesity</td>
<td>174</td>
<td>-0.031</td>
<td>0.618</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Insulin resistance</td>
<td>117</td>
<td>-0.005</td>
<td>0.789</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>PCOS</td>
<td>6</td>
<td>-0.284</td>
<td>0.005</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Hyperlipidaemia</td>
<td>6</td>
<td>-0.103</td>
<td>0.063</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Obesity</td>
<td>6</td>
<td>-0.088</td>
<td>0.048</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Insulin resistance</td>
<td>6</td>
<td>-0.015</td>
<td>0.319</td>
</tr>
</tbody>
</table>

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.
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
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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Country/Territory of origin: China

ORCID number: Xiao-Yun Wu 0009-0001-0010-4286.
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Vitamins and polycystic ovary syndrome


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