ORIGINAL RESEARCH ARTICLE

Efficacy of metformin combined with vitamin D in the treatment of polycystic ovarian syndrome: A meta-analysis

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*Li Xiang, Min Liao and Yuyin Su**

Anting Hospital of Jiading District in Shanghai, No.1060,Hejing Road, Shanghai, China

***For Correspondence:** Email: *m13621723959@163.com*; Phone: 13621723959

Abstract

Polycystic ovary syndrome (PCOS), as an endocrine and metabolic disorder, affects approximately 6% -20% of women of childbearing age. This study aims to assess the therapeutic effects of Metformin combined with vitamin D in PCOS patients. Eight databases were searched to obtain randomized controlled trials, both domestically and internationally, on the effects of Metformin combined with vitamin D in patients with PCOS. Data analysis was performed using RevMan 5.3 software. Nine studies were ultimately included in this meta-analysis. Six studies reported the homeostatic model assessment for insulin resistance of the test group and the control group, which was significantly lower (SMD: -0.23; 95% Cl: -0.42,-0.04; P<0.05) than the control group, body mass index (BMI) (SMD: -1.86; 95% Cl: -2.77,-0.96; P<0.01), Serum 25 (OH) D (SMD: 14.28; 95% Cl: 12.26,16.29; P<0.01), testosterone (SMD: -0.11; 95% Cl: -0.15,-0.07; P<0.01) and regulated menstrual cycles (OR: 1.27; 95% Cl: 0.99,1.63; P=0.063). Our meta-analysis of nine trials demonstrates significant reductions in insulin resistance, BMI, and testosterone levels, along with increased serum vitamin D levels and improved menstrual cycle regulation after Metformin and vitamin D treatment. These findings suggest the potential of this combined therapy in managing the multifaceted aspects of PCOS. *(Afr J Reprod Health 2024; 28 [2]: 43-54).*

Keywords: Metformin; Vitamin D; Polycystic ovarian syndrome; Meta

Résumé

Le syndrome des ovaires polykystiques (SOPK), en tant que trouble endocrinien et métabolique, touche environ 6 à 20 % des femmes en âge de procréer. Cette étude vise à évaluer les effets thérapeutiques de la metformine associée à la vitamine D chez les patients atteints du SOPK. Huit bases de données ont été consultées pour obtenir des essais contrôlés randomisés, tant au niveau national qu'international, sur les effets de la metformine associée à la vitamine D chez les patients atteints du SOPK. L'analyse des données a été réalisée à l'aide du logiciel RevMan 5.3. Neuf études ont finalement été incluses dans cette méta-analyse. Six études ont rapporté l'évaluation du modèle homéostatique pour la résistance à l'insuline du groupe test et du groupe témoin, qui était significativement inférieure (DMS : -0,23 ; IC à 95 % : -0,42, -0,04 ; P <0,05) par rapport au groupe témoin, la masse corporelle indice (IMC) (DMS : -1,86 ; Cl 95 % : -2,77, -0,96 ; P<0,01), Sérum 25 (OH) D (SMD : 14,28 ; Cl 95 % : 12,26,16,29 ; P<0,01), testostérone (DMS : -0,11 ; Cl à 95 % : -0,15, -0,07 ; P<0,01) et cycles menstruels régulés (OR : 1,27 ; Cl à 95 % : 0,99, 1,63 ; P=0,063). Notre méta-analyse de neuf essais démontre des réductions significatives de la résistance à l'insuline, de l'IMC et des taux de testostérone, ainsi qu'une augmentation des taux sériques de vitamine D et une amélioration de la régulation du cycle menstruel après un traitement à la metformine et à la vitamine D. Ces résultats suggèrent le potentiel de cette thérapie combinée dans la gestion des aspects multiformes du SOPK. *(Afr J Reprod Health 2024; 28 [2]: 43-54).*

Mots-clés: Metformine ; Vitamine D; Syndrome des ovaires polykystiques; Méta

Introduction

Polycystic ovary syndrome (PCOS), as an endocrine and metabolic disorder, affects approximately 6% -20% of women of childbearing age[1,2]. According to reports, the number of patients with PCOS accounts for about 30-40% in the infertile female population, and even up to about 75% in the population with anovulatory reproductive disorders[3]. The clinical symptoms of patients with polycystic ovary syndrome are highly heterogeneous, including menstrual disorders, ovulation disorders, hyperandrogenism, insulin resistance, obesity, and other metabolic abnormalities. Long term metabolic disorder can lead to significantly increased risk of cardiovascular disease, dyslipidemia, type 2 diabetes, non-alcoholic fatty liver, and endometrial

cancer[4]. Due to the incomplete elucidation of the pathogenesis of PCOS, there is currently no definitive treatment, and its clinical symptoms and phenotypes are complex and diverse. Therefore, the treatment and improvement of clinical symptoms have become a focus of attention. Although the etiology of PCOS is not yet clear, most studies believe that the combined effects of genetic and environmental factors play an important role in the occurrence and development of PCOS diseases. Research has shown that epidemiological data supports a close correlation between obesity and polycystic ovary syndrome, and it is pointed out that about 38% -88% of PCOS women are overweight or obese[5]. At the same time, compared to normal women, the odds ratio of obese women developing PCOS is 2.77[6]. The study found that about 43% of adult women and nearly one-third of adolescents with PCOS suffer from metabolic syndrome[7]. Insulin resistance and hyperandrogenism, as important pathological and physiological changes in PCOS, have significant effects on reproduction and metabolism. They can further worsen other clinical symptoms such as hyperandrogenism and insulin resistance, worsen the condition of PCOS, and increase the incidence[8].

At present, symptomatic treatment plays a dominant role in the clinical treatment of PCOS, mainly including regulating menstrual cycles, weight control, reducing insulin resistance and improving metabolic disorders, as well as lifestyle interventions[9-11]. Although the use of oral contraceptives and anti-androgen drugs has been proven to effectively reduce acne, hirsutism, and regulate menstrual cycles, they have not been widely used in PCOS patients due to side effects such as weight gain caused by water and sodium retention[12]. Currently, drugs that improve insulin sensitivity, such as metformin, have been applied to the treatment of obese PCOS patients[13]. Metformin is well known for its wide application in the treatment of diabetes[14]. Through the continuous development of medicine and the continuous research of scholars, many metformin effects other than hypoglycemic effects have been found and applied in clinical practice[15]. The application of metformin in PCOS patients can improve insulin resistance, reduce testosterone levels, and relieve follicular atresia caused by excessive testosterone[16]. Existing studies have confirmed that metformin can improve insulin resistance in patients and increase the expression of endometrial related markers by increasing the sensitivity of target organs and tissues to insulin[17]. The latest research shows that the Vitamin D endocrine system (VDES) is a highly complex metabolic system, with its unique progesterone analogue activity interconnected with other steroid hormones, affecting female fertility[18]. The degree of vitamin D deficiency in PCOS is significantly higher than in the fallopian tube infertility group, and lower levels of serum 25 (OH) D levels are associated with insulin resistance, menstrual disorders. The low pregnancy rate is related to cardiovascular factors[19]. Thus, we conducted a meta-analysis to examine the effect of Metformin combined with vitamin D in patients with polycystic ovarian syndrome.

Methods

Selection of studies

Study design type: Published controlled trials on the effects of Metformin combined with vitamin D in patients with polycystic ovarian syndrome. However, the animal trials were excluded.

Selection of participants

Patients with polycystic ovarian syndrome.

Types of interventions

The intervention group received Metformin combined with vitamin D in the treatment of patients with polycystic ovarian syndrome, and the control group Metformin in the treatment of patients with polycystic ovarian syndrome.

Search strategy

The computer retrieves the databases: Cochrane Library, PubMed, EMbase, Web of Science, CNKI, China Biomedical Literature Database (CBM), VIP and WanFang. The search term is “Metformin”, “vitamin D” and “polycystic ovarian syndrome”. The search time was from the establishment of the library until May 2023. The specific steps of literature search are: (1) search for relevant documents in the Chinese and English databases, read the title, abstract, and Keywords further identify the search terms for this study; (2) The English database search used "MeSH Terms" to identify the subject terms, searched using a combination of subject words and keywords.

Types of outcome measures

Outcome indicators patients with polycystic ovarian syndrome; According to research, the assessment tools for the effects of Metformin combined with vitamin D in patients with polycystic ovarian syndrome are: ①Homeostatic Model Assessment for Insulin Resistance (HOMA-IR); ②Body Mass Index (BMI); ③Serum 25 (OH) D (25-OH-D3); ④ Testosterone (T); ⑤ Regulated Menstrual cycles. The literature included in this study evaluated outcome measures using at least one of the above scales.

Data extraction and quality assessment

The abstract was initially screened, and after the initial screening, the literature screening results were obtained by reading the full text, and the process was completed independently by 2 researchers. Exchange screening results, discuss dissenting literature or consult a third researcher until the results are agreed. The information extracted from the data includes: basic information of the literature, type of study, study object, sample size, and intervention content, outcome measures, etc.

Statistical analysis

This meta-analysis was conducted by using Review Manager (RevMan 5.3). Effects are combined: The outcome measures in this study were all measured data, the tools used to evaluate are different. There are differences between scores, Therefore, the standardized mean difference (SMD) is used, along with a 95% confidence interval (CI), as an indicator of effect. (2) Heterogeneity test: Chi-square tests are used to determine whether there is heterogeneity between studies. If (P > 0.1) and (I^2 < 50%), the included studies are considered more homogeneous, and a fixed-effects model is employed for meta-analysis. If (P < 0.1) and (I^2 > 50%), heterogeneity is indicated in the included studies, and sources of heterogeneity are analyzed. If there is heterogeneity, a random-effects model is used for meta-analysis. Furthermore, potential differences in qualitative factors are subgroup analyzed.

Results

Based on the search strategy, 230 references were identified. After excluding duplicate studies, 36 studies were scanned based on abstract and title. Then, 13 articles were evaluated in full text. After full text evaluation, 4 records were excluded for the following reasons: data mismatch (n=2) and missing data (n=2). Ultimately, 9 studies[20-28] were included in this meta-analysis (Table 1). The PRISMA statement flow chart shows this process (Figure 1).

Table 1: The basic characteristics of the included studies

Study（ref.）	Reference number	SampleSize (T/C)	Age(years)(Mean±SD） (T/C)	T	C	MainOutcomes
1.Sun,2022	25	51/51	27.43±4.68/27.12±4.67	VD+MET	MET	①④
2.Zhang,2021	27	51/51	27.69±2.13/28.01± 2.04	VD+MET	MET	①④
3.Zheng,2019	26	35/35	None	VD+MET	MET	①②③④
4.Kadoura,2019	20	18/16	23.06 ± 3.32/23.38 ± 3.54	VD+MET	MET	②⑤
5.Zhou,2018	28	20/20	25.98±6.52/25.71±6.82	VD+MET	MET	①②③
6.Zhang,2018	21	30/30	None	VD+MET	MET	①③
7.Garg,2015	22	15/17	22.0±4.61/22.8±4.56	VD+MET	MET	①②③④
8.Tehrani,2014	23	20/20	28.7 ± 4.5/27.4 ± 2.2	VD+MET	MET	②⑤
9.Firouzabadi,2012	24	50/50	27.96±4.07/ 28.46±4.16	VD+MET	MET	②③⑤

Table 1 presents a comprehensive overview of the basic characteristics of the studies included in the meta-analysis. The table includes relevant details such as study ID, reference number, sample size, patient age, intervention, control, and key outcome measures. This information serves as a foundation for understanding the diverse range of studies incorporated in the meta-analysis. T: test group; C: control group; VD: vitamin D; MET: metformin. ①Homeostatic Model Assessment for Insulin Resistance (HOMA-IR); ②Body Mass Index (BMI); ③Serum 25 (OH) D (25-OH-D3); ④ Testosterone (T); ⑤ Regulated Menstrual cycles.

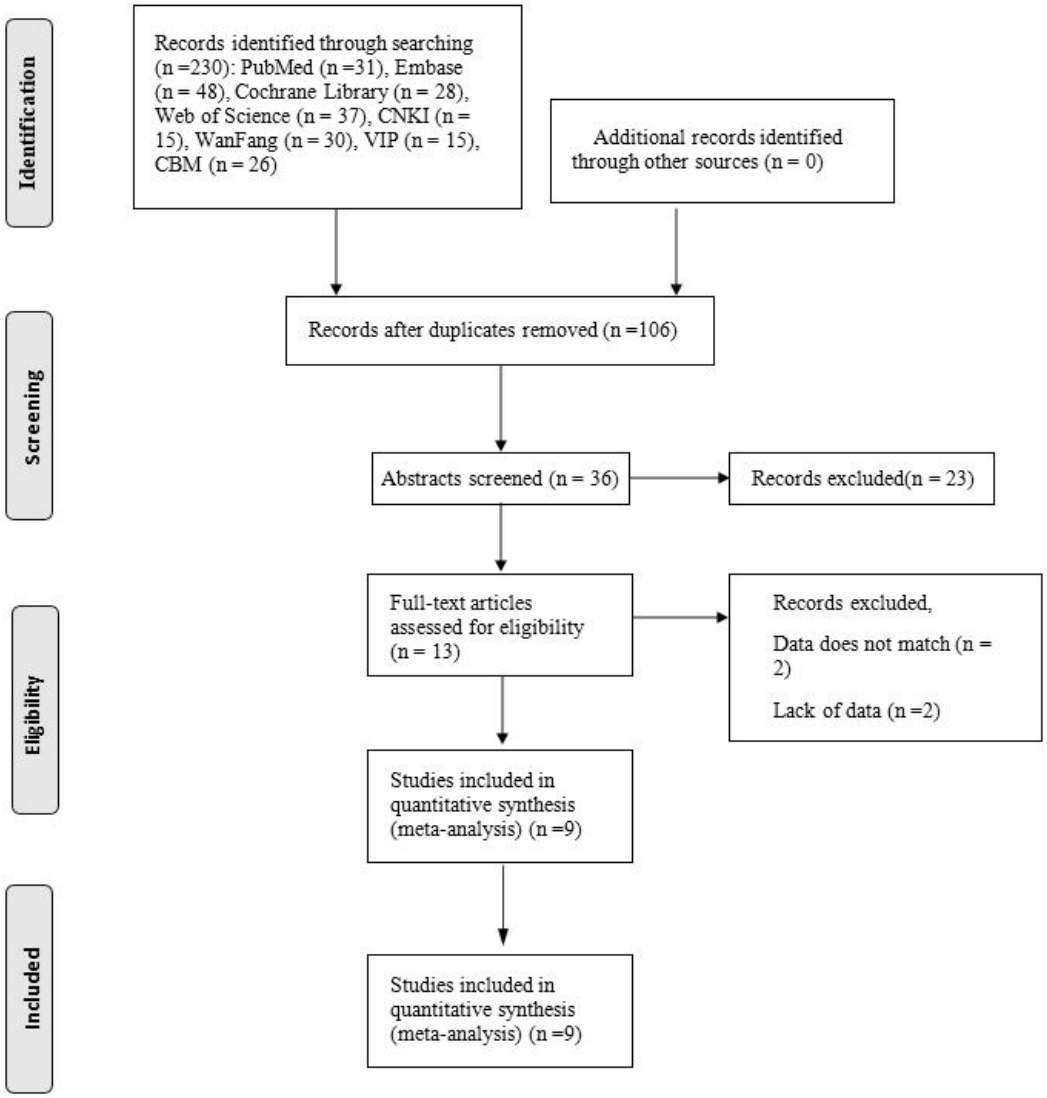

Figure 1 illustrates the systematic literature screening process conducted for study inclusion in the meta-analysis. The flow chart delineates the step-by-step procedure, starting with the initial identification of relevant publications through electronic searches, followed by the application of inclusion and exclusion criteria. The figure visually guides the reader through the screening process, depicting the number of studies at each stage and the rationale for exclusions, ultimately leading to the final selection of studies for the meta-analysis

Figure 1: Literature screening flow chart

Homeostatic model assessment for insulin resistance (homa-ir)

Six studies reported the HOMA-IR of the test group and the control group. Meta-analysis showed that the HOMA-IR of the test group was significantly lower (SMD: -0.23; 95% Cl: -0.42, -0.04; P<0.05, Figure 2) than the control group. The results of all these trials showed high heterogeneity, and a sensitivity analysis was conducted (Figure 3). Compared with the control group, Metformin combined with vitamin D in the treatment of patients with polycystic ovarian syndrome decrease the level of HOMA-IR. The Begg's Test is 0.707 and the Egger's test is 0.936, so this research results are relatively stable and there is no obvious publication bias.

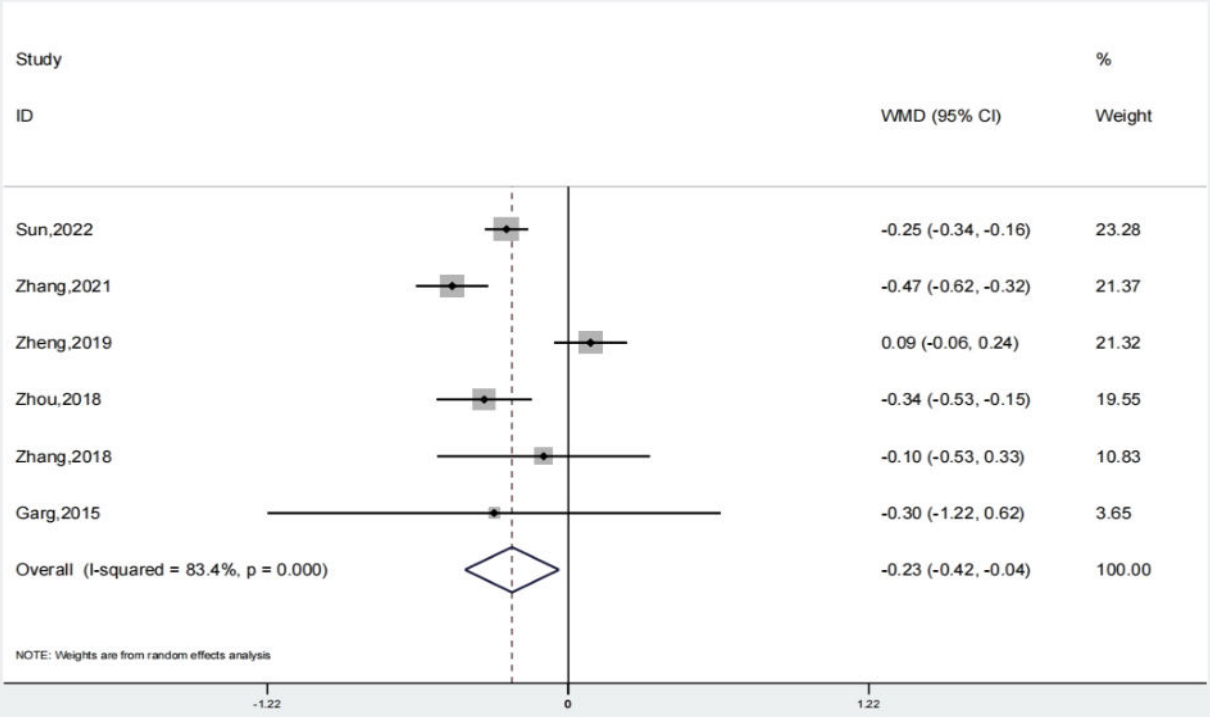

Figure 2: Forest illustration of the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

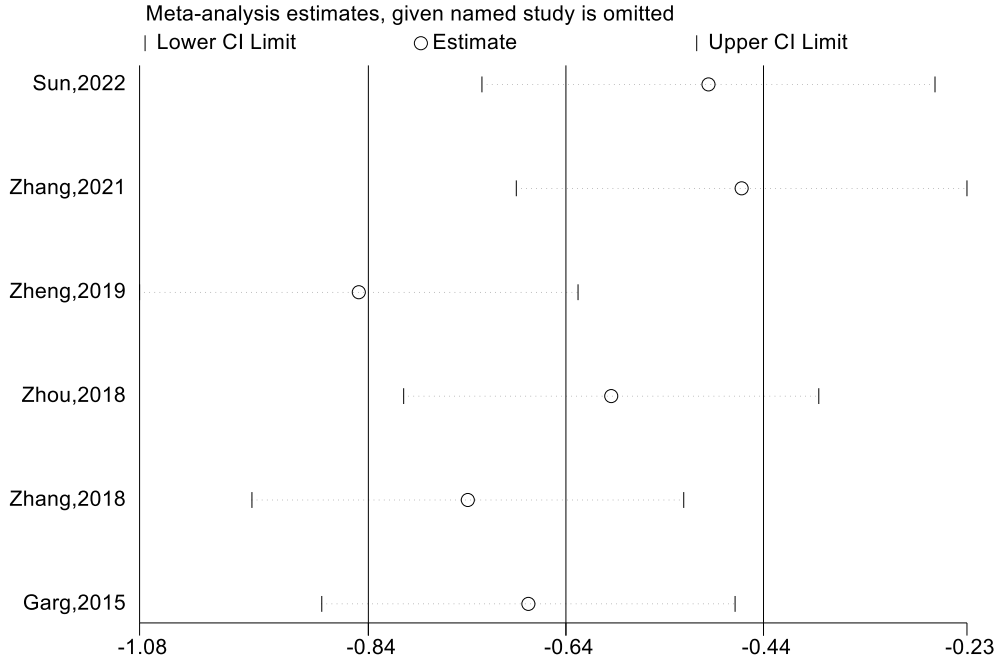

Figure 3: Sensitivity analysis of the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

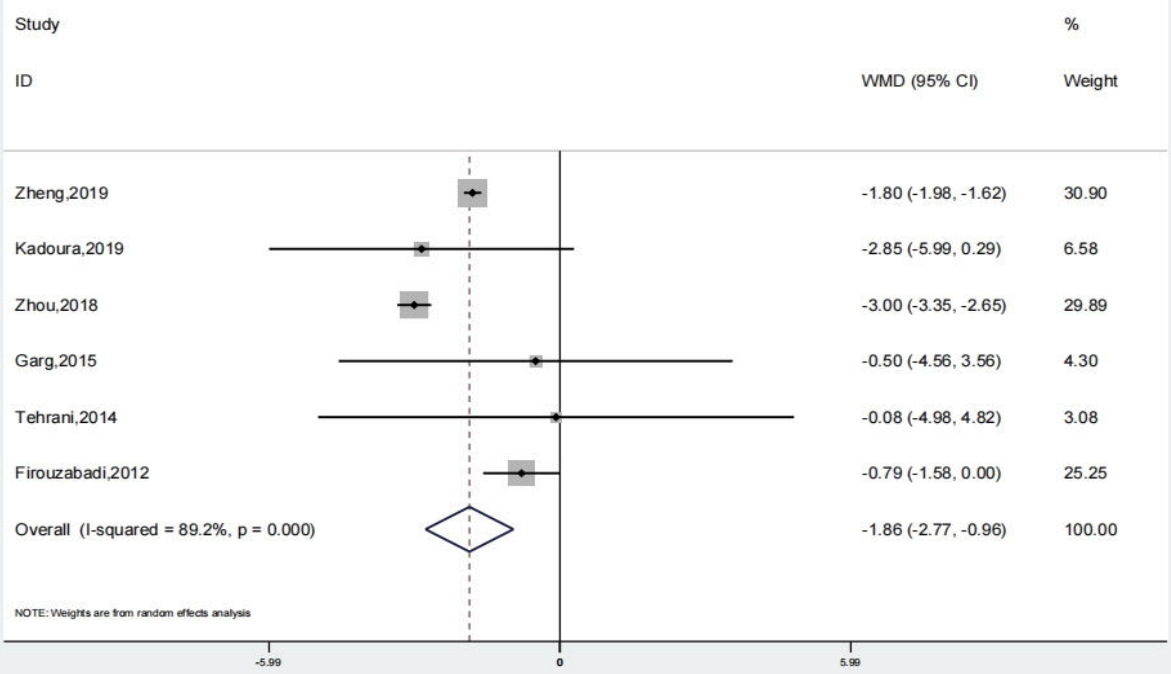

Figure 4: Forest illustration of the Body Mass Index (BMI)

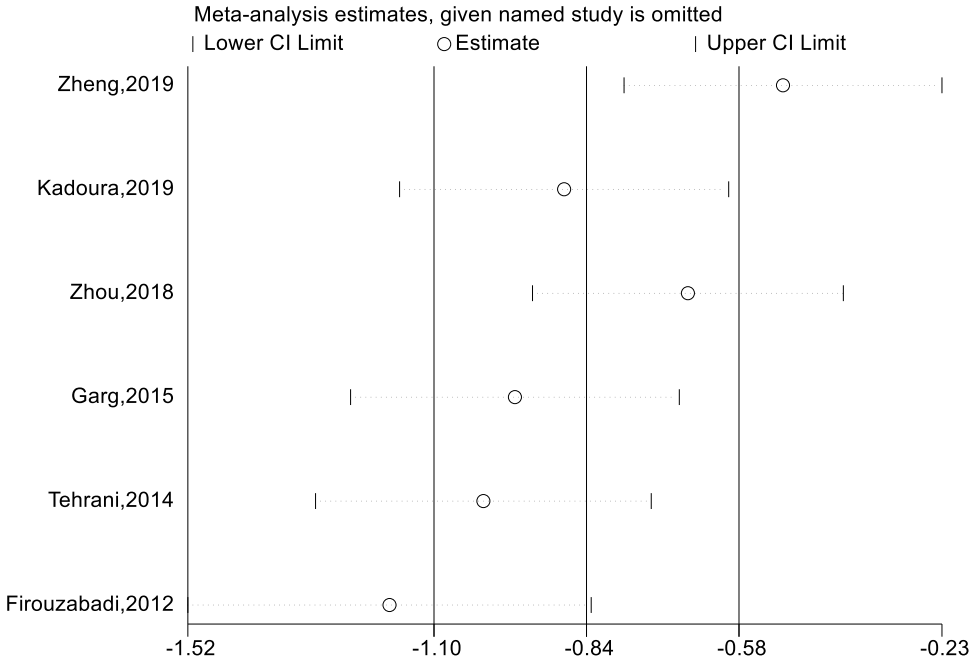

Figure 5: Sensitivity analysis of the Body Mass Index (BMI)

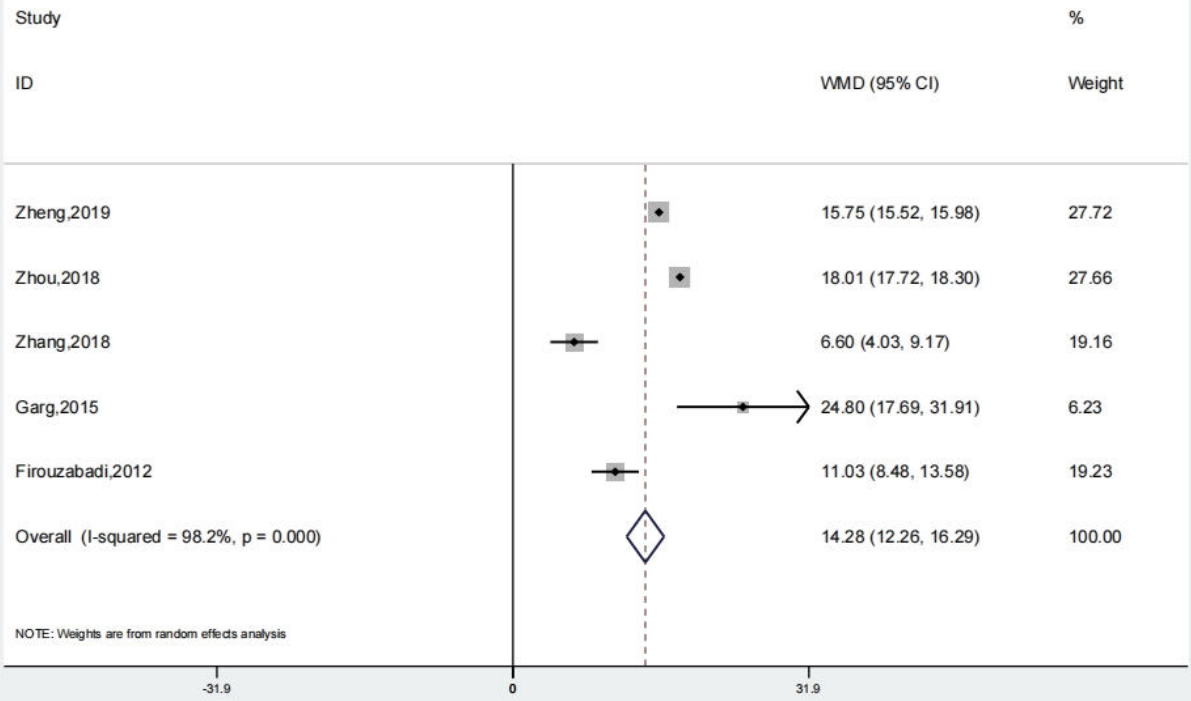

Figure 6: Forest illustration of the Serum 25 (OH) D (25-OH-D3)

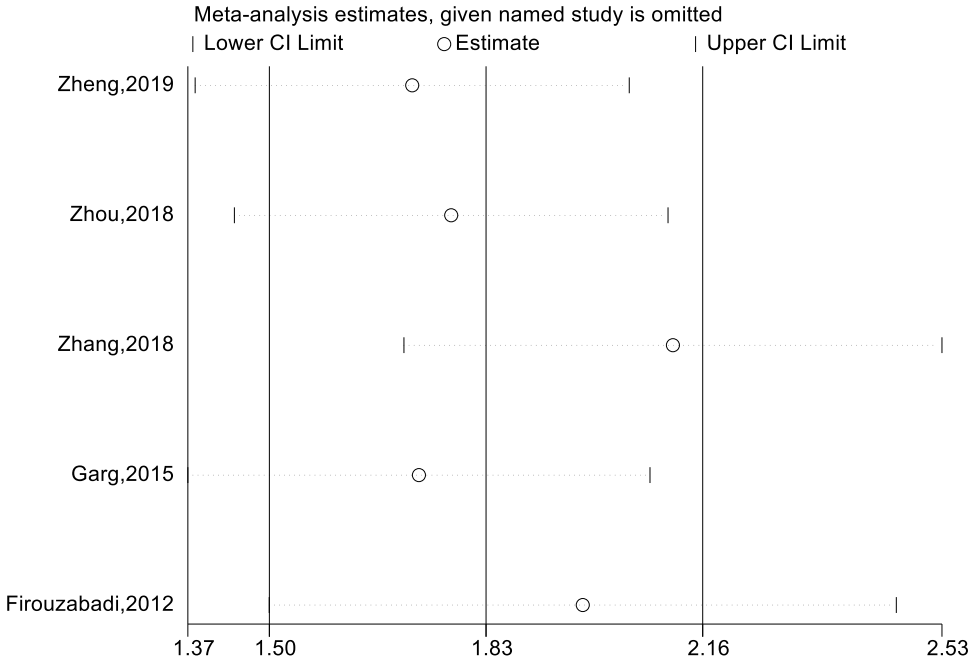

Figure 7: Sensitivity analysis of the Serum 25 (OH) D (25-OH-D3)

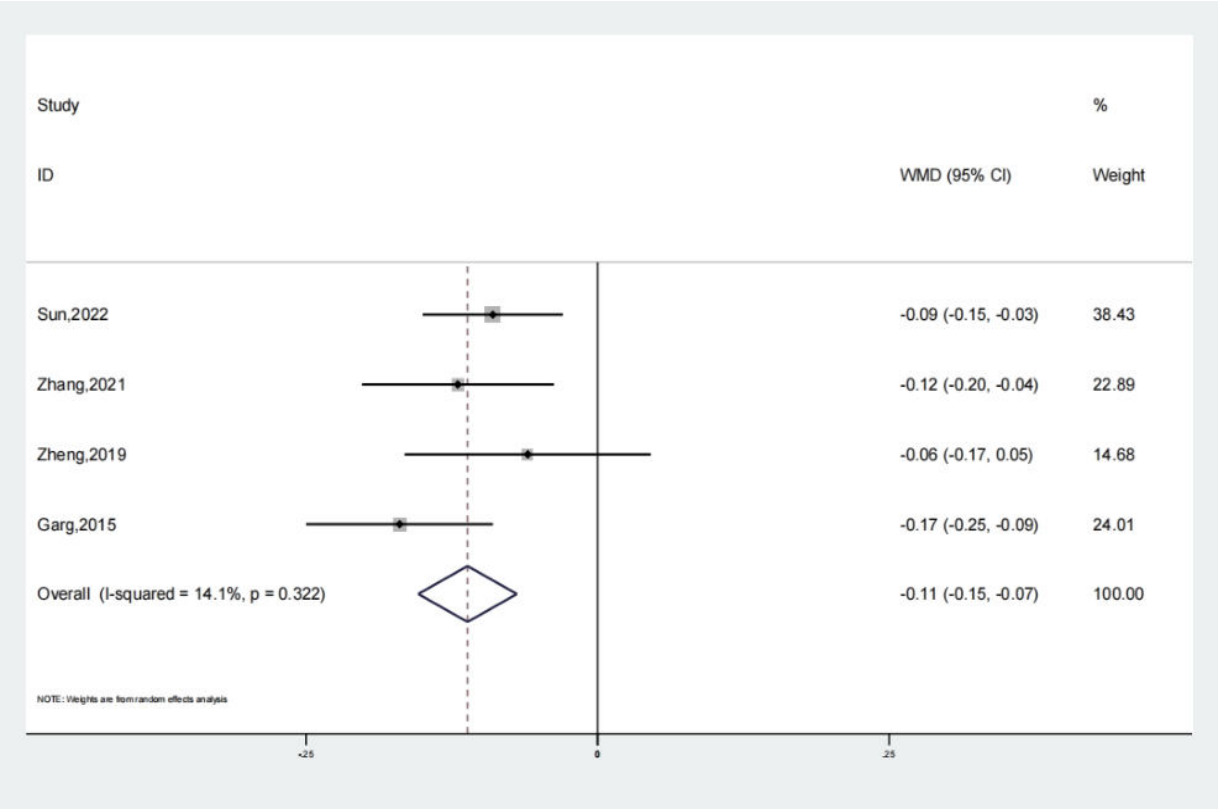

Figure 8: Forest illustration of the Testosterone

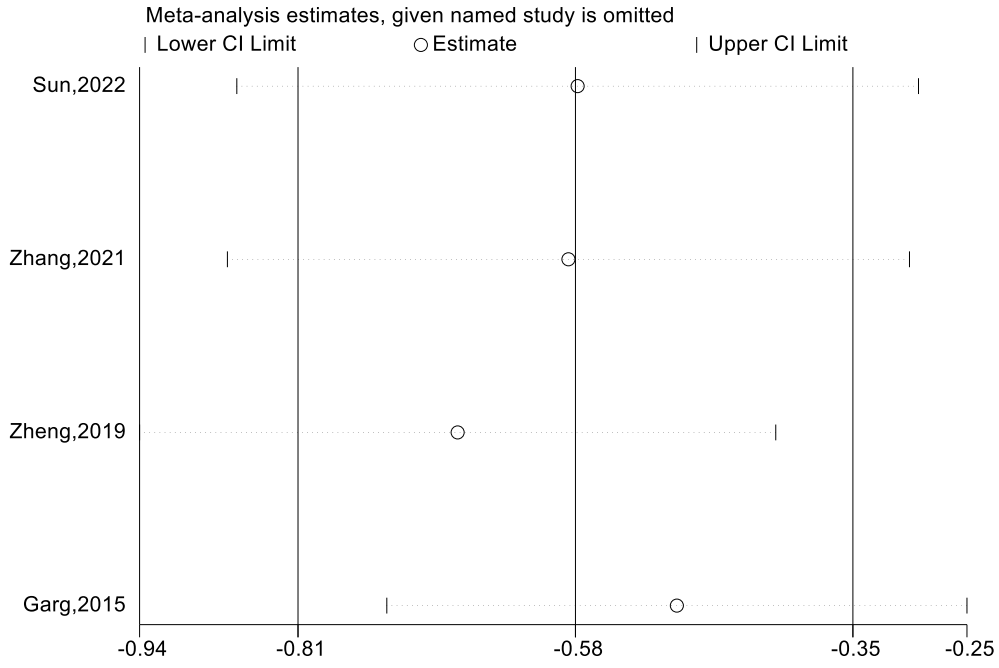

Figure 9: Sensitivity analysis of the Testosterone

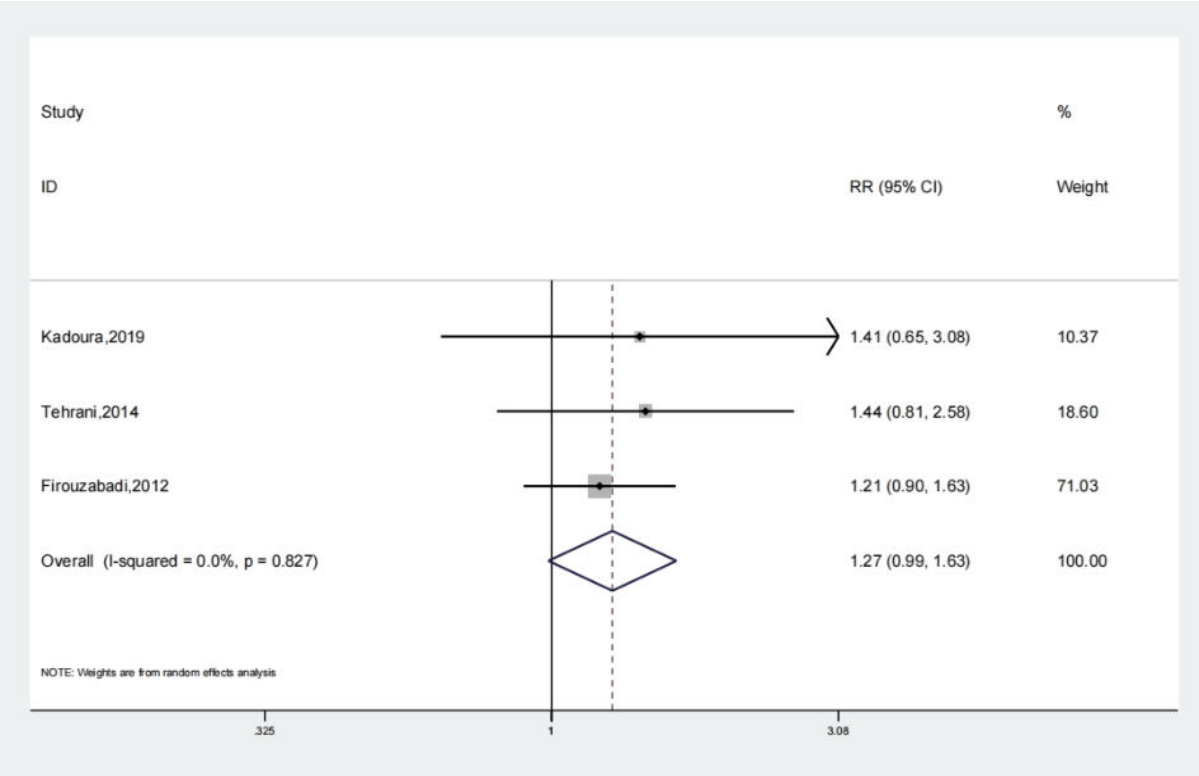

Figure 10: Forest illustration of the Regulated Menstrual cycles

Body mass index (BMI)

Six studies reported the BMI of the test group and the control group. Meta-analysis showed that the BMI of the test group was significantly lower (SMD: -1.86; 95% Cl: -2.77, -0.96; P<0.01, Figure 4) than the control group. The results of all these trials showed high heterogeneity, and a sensitivity analysis was conducted (Figure 5). Compared with the control group, Metformin combined with vitamin D in the treatment of patients with polycystic ovarian syndrome decrease the level of BMI. The Begg's Test is 1.000 and the Egger's test is 0.939, so this research results are relatively stable and there is no obvious publication bias.

Serum 25 (OH) D (25-OH-D3)

Five studies reported the 25-OH-D3 of the test group and the control group. Meta-analysis showed that the 25-OH-D3 of the test group was significantly higher (SMD: 14.28; 95% Cl: 12.26,16.29; P<0.01, Figure 6) than the control group. The results of all these trials showed high heterogeneity, and a sensitivity analysis was conducted (Figure 7). Compared with the control group, Metformin combined with vitamin D in the treatment of patients with polycystic ovarian syndrome increase the level of 25-OH-D3. The Begg's Test is 0.806 and the Egger's test is 0.660, so this research results are relatively stable and there is no obvious publication bias.

Testosterone

Four studies reported the Testosterone of the test group and the control group. Meta-analysis showed that the Testosterone of the test group was significantly lower (SMD: -0.11; 95% Cl: -0.15,-0.07; P<0.01, Figure 8) than the control group. The results of all these trials showed high heterogeneity, and a sensitivity analysis was conducted (Figure 9). Compared with the control group, Metformin combined with vitamin D in the treatment of patients with polycystic ovarian syndrome decrease the level of Testosterone. The Begg's Test is 0.734 and the Egger's test is 0.993, so this research results are relatively stable and there is no obvious publication bias.

Regulated menstrual cycles

Three studies reported the Regulated Menstrual cycles of the test group and the control group.
Meta-analysis showed that the Regulated Menstrual cycles of the test group was no significant statistical significance (OR: 1.27; 95% Cl: 0.99,1.63; P=0.063, Figure 10) than the control group. Compared with the control group, Metformin combined with vitamin D in the treatment of patients with polycystic ovarian syndrome did not improve the Regulated Menstrual cycles. The Begg's Test is 1.000 and the Egger's test is 0.243, so this research results are relatively stable and there is no obvious publication bias.

Discussion

Metformin is a type of biguanide drug that does not affect insulin secretion, but can improve insulin action. Its mechanism of action is to reduce liver glucose production, stimulate insulin mediated glucose uptake by the liver and skeletal muscles, and reduce the utilization of gluconeogenic substrates[29]. Obese women with PCOS show similar metabolic characteristics with type 2 diabetes in insulin resistance and hyperinsulinemia. Metformin has been used to treat PCOS[30]. Research has shown that metformin not only regulates ovarian function, restores normal menstrual cycles and ovulation, but also has metabolic and reproductive benefits, including weight loss, reduced Insulin resistance and androgen levels[15]. Heidari *et al*. believe that metformin can improve endothelial function and dysfunction in women with PCOS, but its effectiveness in improving glucose metabolism and dyslipidemia is limited[31]. Guan *et al*.'s study found significant improvement in sexual hormone indicators, including testosterone, follicle stimulating hormone, and luteinizing hormone, in overweight women with PCOS who received metformin treatment[32].

More and more evidence suggest that vitamin D plays an important role in female reproductive function. For example, vitamin D deficiency is associated with calcium imbalance, which can cause follicular arrest and development in women with PCOS, leading to menstrual disorders and infertility. In mouse species, VDR deficiency or mutation can lead to impaired follicular development[33]. The viewpoint that 25 (OH) D can predict the clinical pregnancy outcome of IVF-ET has also been confirmed multiple times. In an observational study by Ozkan et al., it was found that successful pregnancies have higher levels of follicular fluid 25 (OH) D, suggesting that vitamin D may be a predictive factor for in vitro fertilization success rate; Ozkan et al. found that for every 1ng/ml increase in follicular fluid 25 (OH) D, the likelihood of successful pregnancy increases by 7%[34].

This study conducted a meta-analysis on the clinical efficacy of metformin combined with vitamin D in the treatment of PCOS patients. The results showed that there were significant differences in certain biochemical indicators between the two groups of treatment for PCOS patients. The combination of metformin and vitamin D has good effects on testosterone, insulin resistance index, body mass index, and serum 25 (OH) D, and the differences are statistically significant. Research has shown that metformin combined with vitamin D can increase ovulation rate and significantly reduce insulin resistance index in patients with PCOS, consistent with the results of this study[35].

A total of 9 literatures were included in this study, including 290 patients in the test group and 290 patients in the control group. Meta-analysis showed that patients with polycystic ovarian syndrome who received Metformin combined with vitamin D had lower level of Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) compared with controls.
The limitations of this systematic review are: Only Chinese and English literature was searched, and no other language literature was obtained, and there may be incomplete research inclusion and bias in selection. Hence, it is imperative to maintain objectivity regarding certain outcomes of this meta-analysis.

Conclusion

In conclusion, the meta-analysis conducted on nine randomized controlled trials provides valuable insights into the potential therapeutic benefits of combining Metformin with vitamin D for individuals with polycystic ovary syndrome. Our findings indicate a significant reduction in insulin resistance, as evidenced by lower Homeostatic Model Assessment for Insulin Resistance (HOMA-

IR) values in the intervention group compared to the control group. Additionally, Metformin combined with vitamin D is associated with favorable outcomes in terms of BMI reduction, increased serum 25 (OH) vitamin D levels, decreased testosterone levels, and improved regulation of menstrual cycles. These results underscore the potential of this combined therapeutic approach in addressing the multifaceted clinical manifestations of PCOS, offering promise for enhanced management of this prevalent and complex endocrine disorder. Further research and clinical trials are warranted to corroborate and expand upon these findings, paving the way for more targeted and effective interventions in the management of polycystic ovary syndrome.

Availability of data and materials

The data could be obtained by contacting the corresponding author.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

This study did not receive any funding in any form.

Authors contributions

Yuyin Su designed the study. Li Xiang wrote the original draft. Min Liao collected raw data. Min Liao performed statistical and bioinformatics analyses. Yuyin Su supervised the study.

Ethical approval

Not applicable.

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