The effects of statins on hyperandrogenism in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials

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Abstract
Several clinical studies showed that statins were potential to treat polycystic ovary syndrome (PCOS). Through comprehensive search PubMed, EMBASE, the Web of Science, BIOSIS, the ClinicalTrials.gov, and the Cochrane Library database up to 14 Feb 2020, we identified the randomized controlled trials about the treatment of statins on hyperandrogenism in PCOS women, and performed a systematic review and meta-analysis. The quality of the included studies was assessed by the Cochrane risk of bias tool and the Jadda score. Subgroup analysis and sensitivity analysis were conducted to analyze the pooled results. Nine trials included 682 PCOS patients were identified. Statins showed a significant potential to reduce testosterone (SMD = -0.47; 95% CI, −0.76 −−−−0.18; P = 0.002) and dehydroepiandrosterone (SMD = -0.51; 95% CI, −0.97 −−−−0.05; P = 0.03) levels, compared to the control treatments. The cutaneous symptoms hirsutism (SMD = -0.61; 95% CI, −1.13 −−−−0.10; P = 0.02) and acne (SMD = -0.92; 95% CI, −1.49 −−−−0.34; P = 0.002) were significantly improved by statins in PCOS women. Subgroup analysis showed that the two types of statins, and the different control treatments as well, presented no significantly different effect on testosterone and dehydroepiandrosterone. Sensitivity analysis confirmed the stability of the findings from the meta-analysis. In conclusion, statin treatment could significantly reduce androgen levels and improve cutaneous manifestations of hyperandrogenism of PCOS.

Keywords: Hyperandrogenism, Hydroxymethylglutaryl-CoA Reductase inhibitors, Polycystic ovary syndrome, Randomized controlled trials, Meta-analysis

Introduction
Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, irregular menses, hirsutism, anovulation, dyslipidemia, hypertension, insulin resistance, and polycystic ovaries when other etiologies are excluded [1–3]. There are 10–15% of reproductive-aged women affected with PCOS [4]. Up to 60–80% of women with PCOS appear hyperandrogenism [1]. Hyperandrogenism is a medical condition characterized by excessive levels of androgens in the periphery or systemically. Hyperandrogenism also corresponds to an important criterion for the diagnosis of PCOS. PCOS symptoms of hirsutism, seborrhea, acne, androgenetic alopecia, and virilization are caused by hyperandrogenism [5–7]. The cutaneous symptoms of hirsutism, acne cause great psychological distress for patients [8, 9]. Pharmacologic treatment is...
usually used to attenuate PCOS symptoms and prevent long-term adverse effects [10, 11].

Recently, statins emerge a potential to improve the metabolic complications and reproductive endocrine function of PCOS [12–14]. Statins are 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and are the first-line drugs to treat hyperlipidemia and dyslipidemia [15]. As steroid hormones derived from cholesterol, statins are considered to inhibit the product of androgens in PCOS patients [16–18]. However, the open clinical randomized controlled trials (RCTs) displayed inconsistent outcomes about the effect of statins on androgens. Some studies showed statins decreased the blood androgens, including testosterone [19–23], dehydroepiandrosterone (DHEA) [19, 24, 25], and androstenedione [25] in PCOS women with hyperandrogenism. Other individual studies however yielded conflicting results with increasing blood androgens or not reaching the statistic difference [21, 23–27].

Ten years ago, a meta-analysis, based on 3 original trials, suggested that statins could reduce testosterone levels in PCOS, but the testosterone levels were not assigned as the primary outcome, and the bias of the trials and stability of the results were not assessed [28]. Another meta-analysis [29] reported that statins could reduce the DHEA levels in PCOS, but it included a nonrandom study [30] in the pooled studies, which limited the reliability of the conclusion. Additionally, those meta-analyses did not pay attention to assessing the effect of statins on the clinical manifestations associated with hyperandrogenism. On the basis of the more RCT studies recently published, we undertook a meta-analysis on the clinical effect of statins on hyperandrogenism, especially the cutaneous symptoms, to obtain more precise evidence of the effects of statins on blood androgens and cutaneous symptoms in women with PCOS.

Materials and methods
We implemented this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31].

Literature search
Two authors (Chen, Deng) independently searched databases including PubMed, EMBASE, the Web of Science, the ClinicalTrials.gov, the Cochrane Library, BIOSIS from inception to 14 Feb 2021 to identify relevant published RCTs. The following terms were used for comprehensive literature search: hydroxymethylglutaryl-CoA reductase inhibitors, Polycystic Ovary Syndrome (as MeSH terms) combined with statins*, fluvastatin, pravastatin, lovastatin, simvastatin, atorvastatin, rosuvastatin, lipid-lowering drugs, Sclerocystic Ovaries, ovary polycystic disease (as text words). We also performed a manual retrieval of the reference cited in the reviews and meta-analyses. The initial search results were checked for any duplicate publications by titles and abstracts, and then we screened articles according to the inclusion criteria to identify the most relevant studies. We excluded the case reports, editorials, letters to the editor, retrospective studies, and review articles. After excluding the nonrelevant articles by screening titles and abstracts, a further detailed review of the full text was conducted to carry out the final qualitative and quantitative analysis. Ethical approval is not required because no patient was recruited or personal information was collected.

Study eligibility and exclusion criteria
Eligible studies were considered to meet the following criteria: studies assessed the effects of statins on androgen levels or manifestations of hyperandrogenism in women with PCOS; randomized clinical trials; studies that reported adequate information to extract data we interested; the full text of the article was available to acquire. The exclusion criteria included interventional studies without the appropriate control treatment, studies lacking adequate baseline or post-intervention data, and studies that were not written in English. When duplicate data of the same study were found, we choose the publication which had the maximum population or duration of treatment.

Data extraction
Two reviewers (Chen and Gong) extracted the details for each study independently; if disagreement occurred, two authors discussed and arrived at a consensus with a third author (Guo), data extracted included: name of the first authors; publication year; the country where the study was performed; sample capacity; study design; patient characteristics; rates and reasons of drop out from the study, the type of statin, dose and duration of statin use; mean and standard deviation (SD) of the change in androgen levels or manifestations of hyperandrogenism during the trial.

Quality evaluation
Two independent authors (Zhang and Liu) evaluated the quality of the eligible studies using the Cochrane risk of bias tool for RCTs [32] and the Jadad score [33]. The assessment of quality by the Cochrane risk of bias tool includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome data, incomplete outcome data, and selective reporting. The overall Jadad score ranges from 0 to 5 points based on random sequence, blind method,
lost to follow-up, and withdrawal of included studies. The higher scores represented the higher the quality of the study.

**Statistical analysis**
In this meta-analysis, we assessed several outcomes. The change of testosterone level was the primary outcome; other outcomes included changes of DHEA level, hirsutism score, acne score. All outcomes extracted from the literature were continuous data. The outcomes were presented as mean values and SD. Considering the different units of the included studies, we choose standardized mean difference (SMD) and 95% confidence interval (CI) to assess the degree of the effects, the effect with $P<0.05$ was considered to be statistically significant. When studies did not directly report the SD or variance, the variance was calculated using the 95% CI. The Q-test and the $I^2$ index were used to assess study heterogeneity. Q-test with $P<0.1$ or $I^2$ values $\leq 50\%$ represents statistical homogeneity [34], we chose the fixed-effect model; otherwise, we chose the randomized-effect model [35]. To explore the origin of heterogeneity, We performed subgroup analysis based on the statin type and therapy of the control group. However, the pooled analyses on subgroups were carried out only when there were at least 2 studies in each subgroup; sensitivity analysis was performed by sequentially removing one study at a time. Publication bias was assessed by funnel plot analysis. All the analytic process was performed by Revman 5.4 software (Nordic Cochrane Centre, Cochrane Collaboration).

**Results**

**Literature search**
We identified 243 RCTs through initial database searches. According to our purpose, we excluded 197 irrelevant studies by screening the titles and abstracts. Among the remaining 37 trials, 28 publications were further excluded due to the absence of outcome details ($n=23$), no appropriate control group ($n=2$), or duplicated data ($n=3$). Finally, 9 studies were screened out for the meta-analysis. A flowchart of the study selection is shown in Fig. 1.

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**Fig. 1** Flowchart of the selection of studies
Study characteristics and quality evaluation
In the 9 RCTs, 347 out of 682 PCOS patients were involved in the statin treatment group and the other 335 patients in the control treatment group. Two kinds of statins were used in the 9 RCTs, simvastatin for 6 studies [19–21, 23, 24, 27] and atorvastatin for three studies [22, 25, 26, 36]. About the controls, placebo was used for five studies, metformin for 3 studies, oral contraceptive pills (OCP) for 1 study. The specific characteristics of all 9 studies are summarized in Table 1. The median points of the Jadad score were 4, and the findings of the quality of each trial were evaluated by the Cochrane risk of bias tool is shown in Figs. 2 and 3.

Effects of statins therapy on androgens levels
We choose random-effects model because substantial heterogeneities were observed. Effects of statins on Androgens include testosterone, DHEA, androstenedione were analyzed in the pooled studies. Meta-analysis showed that compared with control treatment, statins reduced blood testosterone levels in nine studies (SMD = -0.47; 95% CI, -0.76—-0.18; P = 0.002, I² = 68%) (Fig. 4). DHEA levels were reduced by statins in seven studies (SMD = -0.51; 95% CI, -0.97—-0.05; P = 0.03; I² = 84%) (Fig. 5), but two studies reported androstenedione change were not reach the statistic difference (SMD = -0.50; 95% CI, -1.56—-0.56; P = 0.36; I² = 67%) (Fig. 6).

Effects of statin therapy on cutaneous manifestations
Four studies provided data on the change in hirsutism score, and 3 provided data on acne score. Results show that compared to control treatment, statin treatment could relieve the manifestations of hirsutism (SMD = -0.61; 95% CI, -1.13—-0.10; P = 0.02; I² = 86%) (Fig. 7) and acne (SMD = -0.92; 95% CI, -1.49—-0.34; P = 0.002, I² = 86%) (Fig. 8).

Subgroup analysis
There is no significant difference between the effects on testosterone of the two control treatments placebo (SMD = -0.39; 95% CI, -0.86—-0.09; P = 0.11; I² = 71%) or metformin (SMD = -0.43; 95% CI, -0.84—-0.02; P = 0.04; I² = 65%) implied in the 9 studies. The two

Table 1  Characteristics of the studies included in the meta-analysis

| Publication author, year | Country        | Jadad score | Treatment arm A | Treatment arm B | Time of therapy | Sample size | Outcomes | Assessment method/Unit of primary outcome |
|--------------------------|----------------|-------------|----------------|----------------|----------------|-------------|---------|----------------------------------------|
| Seyam 2018 [19]          | Egypt          | 5           | Simvastatin (20 mg/d) + Metformin (1.5 g/d) | Metformin (1.5 g/d) | 12 months     | 70/65       | T, DHEA, Hirsutism                  | ELISA assay/ ng/ml |
| Seyam 2017 [24]          | Egypt          | 4           | Simvastatin (20 mg/d) | Placebo       | 6 months      | 100/100     | T, DHEA, Hirsutism, Acne            | Chemiluminescence assays/ ng/ml |
| Puurunen 2013 [26]       | Finland        | 5           | Atorvastatin (20 mg/d) | Placebo       | 6 months      | 15/13       | T, DHEA, And                        | Liquid mass spectrometry/ nmol/l |
| Sathyapalan 2009 [22]    | United Kingdom | 5           | Atorvastatin (20 mg/d) | Placebo       | 3 months      | 19/18       | T                                    | Immunoassay/ nmol/l |
| Banasiewska 2011 [27]    | Poland         | 3           | Simvastatin (20 mg/d) + Metformin (1.7 g/d) | Metformin (1.7 g/d) | 6 months      | 36/33       | T, DHEA, Hirsutism, Acne            | Enzymatic colorimetric assays/ ng/ml |
| Raja 2011 [25]           | American       | 4           | Atorvastatin (40 mg/d) | Placebo       | 1.5 months    | 9/11        | T, DHEA, And, Hirsutism             | Not report/ ng/dl |
| Rashidi 2011 [20]        | Iran           | 5           | Simvastatin (20 mg/d) | Placebo       | 2 months      | 32/29       | T, DHEA                              | Chemiluminescence assays/ pg/ml |
| Kazerooni 2010 [21]      | Iran           | 5           | Simvastatin (20 mg/d) + Metformin (1.5 g/d) | Metformin (1.5 g/d) | 3 months      | 42/42       | T, DHEA, Hirsutism                  | Radioimmunoassay/ ng/ml |
| Duleba 2005 [23]         | Poland         | 2           | Simvastatin, 20 mg + OCP | OCP          | 3 months      | 24/24       | T, DHEA                              | Chemiluminescence assays/ ng/dl |

T testosterone, DHEA dehydroepiandrosterone, And androstenedione, OCP oral contraceptive pills; containing 20 μg ethinyl E2 and 150 μg desogestrel
statins simvastatin (SMD = -0.48; 95% CI: -0.77 to -0.18; P = 0.002; I² = 66%) and atorvastatin (SMD = -0.39; 95% CI: -1.38 to 0.61; P = 0.45; I² = 80%) also revealed no significant difference in reducing testosterone and DHEA (Table 2). We did not conduct subgroup analysis in effects of statins on androstenedione and cutaneous manifestations, because less than 2 studies were in each subgroup.

Sensitivity analysis and publication bias
Sensitivity analysis was performed to evaluate the stability of the meta-analysis. When any single study was removed, the overall statistical significance did not change in testosterone with SMD range from -0.53 (95% CI: -0.85 to -0.21) to -0.39 (95% CI: -0.66 to -0.12), and DHEA with SMD range from -0.61 (95% CI: -1.10 to -0.17) to -0.33 (95% CI: -0.73 to -0.06), which indicated that the results of this meta-analysis were relatively stable (Table 3). The study publication bias was assessed by funnel plot, which showed no significant bias in testosterone and DHEA (Fig. 9). We did not perform sensitivity analysis and publication bias assessment in other outcomes because less than 5 studies were included.

Discussion
Statins appear to be safe, especially for long-term use. They are widely used to improve hyperlipidemia and protect from long-term cardiovascular morbidity [37]. This article provided evidence that using statins may offer additional benefits for women with PCOS by improving hyperandrogenism.

Years ago, two reviews employed few RCTs and implied a positive effect of statin treatment reducing testosterone and DHEA levels of PCOS women [28, 29]. Now, more RCTs included in our meta-analysis made this conclusion solid. Compared with the previous reviews, our findings provided the most up-to-date evidence on this topic and expanded the sample size, which enhanced statistical power and provided more precise and reliable results. Through broad search strategy and system review, our study had amended several limitations in previous reviews. This systematic review and meta-analysis of randomized controlled trials combined the outcomes of 682 women with PCOS from 9 individual studies, indicating that statins can reduce the levels of testosterone and DHEA. However, there was no statistical change about androstenedione in statin treatment, possibly attributed to the small sample size with only 48 patients pooled from two trials.

Cutaneous symptoms hirsutism of PCOS are complications due to the combined effect of excessive androgen and the sensitive response of the hair follicle. Up to 75% of PCOS women with hirsutism have measurable hyperandrogenemia [38], however, suppression of androgen production by oral contraceptives, the first-line treatment, is not so effective. Moreover, the severity of hirsutism is not well-correlated with the inordinate level of androgen excess, though the cutaneous symptoms of PCOS are theoretically a result of hyperandrogenism. It indicates the intricacy of those cutaneous comorbidities. Cumulating evidence shows that a single agent is not satisfactory, and combination therapy is recently recommended [39, 40]. Statins are effective for reducing androgen levels in PCOS women, but their use to control skin comorbidities is still uncertain. A previous meta-analysis displayed that there was insufficient evidence supporting the therapeutic efficacy of statins on hirsutism in premenopausal women [41]. With the addition of the recent
RCTs, our meta-analysis demonstrated that statins could relieve cutaneous symptoms of hirsutism and acne. Simvastatin presented more active treatment on both hirsutism and acne than metformin, probably on account of DHEA sulphate (DHEAS) that inhibited by simvastatin while elevated by metformin [27]. A meta-analysis included 55 study groups with a total of 6593 PCOS patients documents that DHEAS and androstenedione are positively associated with Ferriman-Gallwey (FG) score, which is well accepted as a gold standard for hirsutism diagnosis to determine the density of terminal hairs at nine different body sites [38]. Whereas the other

![Summary of risk of bias](image-url)
Fig. 4  Forest plot of the effect of statins on the levels of testosterone

| Study or Subgroup | Statins Mean | SD | Total | Control Mean | SD | Total | Weight | IV. Random, 95% CI | Year |
|-------------------|--------------|----|-------|--------------|----|-------|--------|---------------------|------|
| Seyam 2018        | -1.21        | 3.35 | 70    | -0.25        | 0.08 | 65    | 14.4%  | -0.40 [-0.74, -0.05] | 2018 |
| Seyam 2017        | -0.41        | 5   | 100   | 0.05         | 0.1  | 100   | 15.4%  | -0.13 [-0.41, 0.15]  | 2017 |
| Puurunen 2013     | -0.1         | 0.75 | 15    | -0.2         | 0.26 | 13    | 8.3%   | 0.17 [-0.58, 0.91]   | 2013 |
| Raja 2011         | -14.2        | 19.54 | 9     | -17.6        | 47.01 | 11    | 6.8%   | 0.06 [-0.82, 0.95]   | 2011 |
| Banaszewska 2011  | -0.16        | 0.18 | 36    | -0.15        | 0.23 | 33    | 12.2%  | -0.05 [-0.52, 0.42]  | 2011 |
| Rashidi 2011      | -22.05       | 25.53 | 32    | -8.63        | 9.46 | 29    | 11.5%  | -0.68 [-1.19, -0.16] | 2011 |
| Kazerooni 2010    | -0.22        | 0.99 | 42    | -0.14        | 0.1  | 42    | 12.6%  | -0.83 [-1.28, -0.39] | 2010 |
| Sathyapalan 2009  | -1.2         | 0.75 | 19    | -0.1         | 0.85 | 18    | 8.6%   | -1.35 [-2.07, -0.62] | 2009 |
| Duleba 2005       | -34.7        | 22   | 24    | -10.9        | 22.93 | 24    | 10.1%  | -1.04 [-1.65, -0.44] | 2005 |

Total (95% CI): 347, 335, 100.0%: -0.47 [-0.76, -0.18]

Heterogeneity: Tau² = 0.12; Ch² = 24.68, df = 8 (P = 0.002); I² = 68%

Test for overall effect: Z = 3.14 (P = 0.002)

Fig. 5  Forest plot of the effect of statins on the levels of dehydroepiandrosterone (DHEA)

| Study or Subgroup | Statins Mean | SD | Total | Control Mean | SD | Total | Weight | IV. Random, 95% CI | Year |
|-------------------|--------------|----|-------|--------------|----|-------|--------|---------------------|------|
| Seyam 2018        | -1.96        | 1.67 | 70    | -0.09        | 0.81 | 65    | 16.1%  | -1.40 [-1.78, -1.02] | 2018 |
| Seyam 2017        | -1.26        | 2   | 100   | 0.02         | 1   | 100   | 16.8%  | -0.81 [-1.09, -0.52] | 2017 |
| Puurunen 2013     | -0.8         | 1.65 | 15    | -0.4         | 1.47 | 13    | 12.3%  | -0.12 [-0.87, 0.62]  | 2013 |
| Raja 2011         | -296.5       | 282.31 | 9     | 67.8        | 288.7 | 11    | 9.9%   | -1.22 [-2.20, -0.24] | 2011 |
| Banaszewska 2011  | 0.59         | 1.86 | 36    | 0.54         | 2.13 | 33    | 15.1%  | 0.02 [-0.45, 0.50]   | 2011 |
| Kazerooni 2010    | -7.55        | 68.76 | 42    | -0.54        | 66.14 | 42    | 15.6%  | -0.10 [-0.53, 0.33]  | 2010 |
| Duleba 2005       | -0.98        | 1.39 | 24    | -0.96        | 1.33 | 24    | 14.2%  | -0.01 [-0.58, 0.55]  | 2005 |

Total (95% CI): 296, 288, 100.0%: -0.51 [-0.97, -0.05]

Heterogeneity: Tau² = 0.31; Ch² = 38.33, df = 6 (P < 0.00001); I² = 84%

Test for overall effect: Z = 2.18 (P = 0.03)

Fig. 6  Forest plot of the effect of statins on the levels of androstenedione

| Study or Subgroup | Statins Mean | SD | Total | Control Mean | SD | Total | Weight | IV. Random, 95% CI | Year |
|-------------------|--------------|----|-------|--------------|----|-------|--------|---------------------|------|
| Puurunen 2013     | -1.4         | 4.39 | 15    | -1.4         | 3.4  | 13    | 54.0%  | 0.00 [-0.74, 0.74]   |      |
| Raja 2011         | -0.9         | 0.8644 | 9     | 0.3         | 1.2  | 11    | 48.0%  | -1.08 [-2.04, -0.13] |      |

Total (95% CI): 24, 24, 100.0%: -0.50 [-1.56, 0.56]

Heterogeneity: Tau² = 0.40; Ch² = 3.07, df = 1 (P = 0.08); I² = 67%

Test for overall effect: Z = 0.92 (P = 0.36)

Fig. 7  Forest plot of the effect of statins on the hirsutism

| Study or Subgroup | Statins Mean | SD | Total | Control Mean | SD | Total | Weight | IV. Random, 95% CI | Year |
|-------------------|--------------|----|-------|--------------|----|-------|--------|---------------------|------|
| Seyam 2018        | -2.1         | 2.51 | 70    | -0.6         | 1.61 | 65    | 25.8%  | -0.70 [-1.05, -0.35] | 2018 |
| Seyam 2017        | -1.3         | 1   | 100   | 0.7         | 2    | 100   | 26.5%  | -1.26 [-1.56, -0.96] | 2017 |
| Banaszewska 2011  | -1           | 0.9 | 36    | -0.64        | 2.01 | 33    | 23.5%  | -0.10 [-0.58, 0.37]  | 2011 |
| Kazerooni 2010    | -1.1         | 1.2  | 42    | -0.6         | 1.9  | 42    | 24.3%  | -0.31 [-0.74, 0.12]  | 2010 |

Total (95% CI): 248, 240, 100.0%: -0.61 [-1.13, -0.10]

Heterogeneity: Tau² = 0.24; Ch² = 22.07, df = 3 (P < 0.0001); I² = 86%

Test for overall effect: Z = 2.33 (P = 0.02)
biochemical hyperandrogenism parameters including total testosterone, free testosterone, free androgen index, sex hormone binding globulin (SHBG) are negatively associated with FG scores, although the effects of simvastatin or metformin on SHBG is akin to DHEAS [27]. In fact, serum concentrations of DHEA and DHEAS, rather than testosterone, are significantly higher in axillary hair-positive than in -negative women over 50 years old [42]. Furthermore, oral administration of DHEA to young females with central adrenal insufficiency or adult hypopituitary women exhibits significant progress in pubic and/or axillary hair growth [43]. However, this effect of DHEA needs more experimental evidence to understand the mechanism, because DHEA inhibits hair follicle

Table 2 Subgroup analysis in testosterone and DHEA

| Subgrouped by       | No. of trials | WMD (95% CI) | P Value | P for heterogeneity | I² (%) | P for between Subgroup heterogeneity |
|---------------------|---------------|--------------|---------|---------------------|--------|-------------------------------------|
| **Testosterone**    |               |              |         |                     |        |                                     |
| total               | 9             | -0.47 [-0.76, -0.18] | 0.002   | 0.002               | 68     |                                     |
| Statin type         |               |              |         |                     |        |                                     |
| Simvastatin         | 6             | -0.48 [-0.77, -0.18] | 0.002   | 0.002               | 66     |                                     |
| Atorvastatin        | 3             | -0.39 [-1.38, 0.61] | 0.45    | 0.007               | 80     |                                     |
| Control type        |               |              |         |                     |        |                                     |
| Placebo             | 5             | -0.39 [-0.86, 0.09] | 0.11    | 0.008               | 71     |                                     |
| Metformin           | 3             | -0.43 [-0.84, -0.02] | 0.04    | 0.06                | 65     |                                     |
| **DHEA**            |               |              |         |                     |        |                                     |
| total               | 7             | -0.51 [-0.97, -0.05] | 0.03    | <0.001              | 84     |                                     |
| Statin type         |               |              |         |                     |        |                                     |
| Simvastatin         | 5             | -0.46 [-1.02, 0.09] | 0.10    | <0.001              | 89     |                                     |
| Atorvastatin        | 2             | -0.62 [-1.70, 0.45] | 0.25    | <0.001              | 67     |                                     |
| Control type        |               |              |         |                     |        |                                     |
| Placebo             | 3             | -0.49 [-1.44, 0.46] | 0.31    | <0.001              | 93     |                                     |
| Metformin           | 3             | -0.70 [-1.20, -0.21] | 0.005   | 0.15                | 47     |                                     |

Table 3 Sensitivity analysis of Testosterone and DHEA

| Excluded study     | Testosterone | DHEA |
|--------------------|--------------|------|
|                    | SMD 95%CI     | SMD 95%CI |
| None               | -0.47 [-0.76, -0.18] | -0.51 [-0.97, -0.05] |
| Seyam 2018         | -0.48 [-0.84, -0.13] | -0.33 [-0.73, 0.06] |
| Seyam 2017         | -0.53 [-0.85, 0.21]  | -0.46 [-1.04, 0.13] |
| Puurunen 2013      | -0.53 [-0.83, 0.22]  | -0.57 [-1.07, -0.06] |
| Banaszewska 2011   | -0.53 [-0.85, 0.21]  | -0.61 [-1.10, -0.12] |
| Raja 2011          | -0.51 [-0.81, 0.20]  | -0.43 [-0.92, 0.06] |
| Rashi 2011         | -0.44 [-0.76, 0.12]  | - | |
| Kazerooni 2010     | -0.41 [-0.72, 0.11]  | -0.59 [-1.09, -0.09] |
| Sathyapalan 2009   | -0.39 [-0.66, 0.12]  | - | |
| Duleba 2005        | -0.40 [-0.70, 0.11]  | -0.60 [-1.05, -0.16] |
Acne affects 15–25% of PCOS women [10]. Acne score declines over 60% after oral or topical statin treatment for patients with or without PCOS [27]. Reviewed the published knowledge, we also find lessening DHEA is probably a reason why statins are more capable of acne than metformin. DHEAS in scalp hair and blood are higher in acne women than in the normal controls, but serum testosterone levels are comparable in the two populations [45, 46]. Moreover, serum DHEAS is correlated to the severity of acne, and its increase implies an aggravating effect on the risk of acne [45, 47]. DHEAS is considered to be a key role in the pathogenesis of adult-onset acne [48]. Although the target gene of statins is 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme of cholesterol production, and is responsible for cholesterol metabolism of skin sebaceous glands and hair follicles [49]. However, the mechanisms that undertake the therapeutic effect of statins on hirsutism are enigmatic. In contrast to this, several reports display the therapeutic potential of statins for hair loss [50]. Simvastatin and atorvastatin are commonly used drugs with different effectiveness in lowering blood lipid levels and fat solubility, an animal study reported that statins vary greatly with regard to their effects on steroidogenesis of rat ovarian theca-interstitial cells. Compare to atorvastatin, simvastatin may exert greater inhibitory effects on the number of viable cells and production of androgens [51], a RCT also indicated simvastatin was more effective in reducing the serum testosterone level (by 27% vs. 16%) [52]. However, on subgroup analysis, the two kinds of statins showed similar effects on hyperandrogenism in women with PCOS, the effects of different statins on hyperandrogenism need more studies to certain, In addition, we performed sensitivity analyses, which confirmed the robustness of the main results.

However, there are some limitations in this meta-analysis. First, the heterogeneity among the studies probably limited the credibility of the study, but we did not find the origin of heterogeneity partially because of few RCTs included. Second, the levels of androgens were measured by different methods in the various study, which might result in incomparability and heterogeneity between the data from different RCTs. Third, the score of cutaneous manifestation of hirsutism and acne was subjective based on various standards. Finally, this study was constrained to studies published in English only. So publication bias cannot be excluded.

**Conclusion**

This systematic review and meta-analysis of 9 RCTs indicated that statins could reduce the levels of androgens and improve the cutaneous manifestations of hyperandrogenism in women with PCOS, providing evidence for supporting the statins as a potential treatment for women with PCOS. It appears crucial to confirm the additional beneficial effects of statins on hyperandrogenism when aiming to improve health conditions for women with PCOS. To achieve this, more high validity trials, with more comprehensive outcomes of hyperandrogenism and more focus on the subgroups are required to explore the origin of heterogeneity and determine the effects of statins on hyperandrogenism.
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Authors’ contributions
JC and XD accomplished the literature search, identification of eligible studies. JC and WG completed the data extraction. JL and TZ achieved the assessment of the quality of the literature. CH, and JC, HL completed manuscript preparation. All authors reviewed and approved the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests in this study.

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References
1. Ye W, Xie T, Song Y, Zhou L. The role of androgen and its related signals in PCOS. J Cell Mol Med. 2021;25:1825–37.
2. Cooney LG, Dokras A. Cardiometabolic risk in polycystic ovary syndrome: current guidelines. Endocrinol Metab Clin N Am. 2021;50:83–95.
3. Cignarella A, Mioni R, Sabbadin C, Dassie F, Parolin M, Vettor R, Barbot M, Scarioni C. Pharmacological Approaches to Controlling Cardiometabolic Risk in Women with PCOS. Int J Mol Sci. 2020;21(24):9554.
4. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev. 2015;36:487–525.
5. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian Hyperandrogenism revisited. Endocr Rev. 2016;37:467–520.
6. Rodrigues JK, Navarro PA, Zelinski MB, Stouffer RL, Xu J. Direct actions of androgens on the survival growth and secretion of steroids and anti-Müllerian hormone by individual macaque follicles during three-dimensional culture. Hum Reprod. 2015;30:664–74.
7. Rosenfield RL, Ehrlich EN, Cleary RE. Adrenal and ovarian contributions to the elevated free plasma androgen levels in hirsute women. J Clin Endocrinol Metab. 1972;34:92–8.
8. Phillips TG, Slomiany WP, Allison R. Hair loss: common causes and treatment. Am Fam Physician. 2017;96:371–8.
9. Rittmaster RS, Lonaux DL. Hirotsu S. Ann Intern Med. 1987;106:95–107.
10. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The androgen excess and PCOS society criteria for the polycystic ovary syndrome: the complete task-force report. Fertil Steril. 2009;91:456–88.
11. Sirmanis SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;6:1–13.
12. Sokalska A, Potrovitski PC, Ryczynska I, Cress A, Duleba AJ. Statins inhibit growth of human theca-interstitial cells in PCOS and non-PCOS tissues independently of cholesterol availability. J Clin Endocrinol Metab. 2010;95:5390–4.
13. Raval AD, Hunter T, Stuckey B, Hart RJ. Statins for women with polycystic ovary syndrome not actively trying to conceive. Cochrane Database Syst Rev. 2011;10:Cd008565. https://doi.org/10.1002/14651858.CD008565.pub2.
14. Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Simvastatin improves biochemical parameters in women with polycystic ovary syndrome: results of a prospective, randomized trial. Fertil Steril. 2006;85:996–1001.
15. Schaff RA, Moe RW, Knirckbaum DW. An overview of cholesterol management. Am Health Drug Benefits. 2008;1:39–48.
16. Almalki HH, Alshbams TM, Alhifany AA, Almohammed QA. Comparative efficacy of statins, metformin, spironolactone and combined oral contraceptives in reducing testosterone levels in women with polycystic ovary syndrome: a network meta-analysis of randomized clinical trials. BMC Womens Health. 2020;20:68.
17. Carmena R, Bettendige DJ. Diabetogenic action of statins: mechanisms. Curr Atheroscler Rep. 2019;21:223.
18. Koch CA, Krabbe S, Hennmke B, Statis, metformin, proprotein-conversase-subtilisin-kexin type-9 (PCSK9) inhibitors and sex hormones: Immunomodulatory properties? Rev Endocr Metab Dsord. 2018;19:363–95.
19. Seyam E, Heyf E. Long-term effects of combined simvastatin and metformin treatment on the clinical abnormalities and ovulation dysfunction in single young women with polycystic ovary syndrome. Gynecol Endocrinol. 2018;34:1073–80.
20. Rashidi B, Abediasl J, Tehraninejad E, Rahmanpour H, Sills ES. Simvastatin effects on androgens, inflammatory mediators, and endogenous pituitary gonadotropins among patients with PCOS undergoing IVF: results from a prospective, randomized, placebo-controlled clinical trial. J Investig Med. 2011;59:912–26.
21. Kazerooni T, Shojaae-Baghini A, Dehshashi S, Asadi N, Ghaffarpasand F, Kazerooni Y. Effects of metformin plus simvastatin on polycystic ovary syndrome: a prospective, randomized, double-blind, placebo-controlled study. Fertil Steril. 2010;94:2208–13.
22. Sathyapalan T, Klipatrick ES, Coady AM, Atkin SL. The effect of atorvastatin in patients with polycystic ovarian syndrome: a randomized double-blind placebo-controlled study. J Clin Endocrinol Metab. 2009;94:103–8.
23. Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Simvastatin improves biochemical parameters in women with polycystic ovary syndrome: results of a prospective, randomized trial. J Fertility and Sterility. 2006;85(4):996–1001.
24. Seyam E, Al Gelany S, Abd Al Ghaney A, Mohamed MAA, Youseff AM, Ibrahim EM, et al. Evaluation of prolonged use of statins on the clinical and biochemical abnormalities and ovulation dysfunction in single young women with polycystic ovary syndrome. Gynecol Endocrinol. 2017;34:589–96.
25. Raja-Khan N, Kunselman AR, Hogeman CS, Stetter CM, Demers LM, Legro RS. Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled trial. Fertil Steril. 2011;95:1849–52.
26. Puurunen J, Pittonen T, Puukka K, Ruokonen A, Savolainen MJ, Boigu R, et al. Statin therapy worsens insulin sensitivity in women with polycystic ovary syndrome (PCOS): a prospective, randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2013;98:4798–807.
27. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Effects of simvastatin and metformin on polycystic ovary syndrome after six months of treatment. J Clin Endocrinol Metab. 2011;96:3493–501.
28. Gao L, Zhao FL, Li SC. Statin is a reasonable treatment option for patients with polycystic ovary syndrome: a meta-analysis of randomized controlled trials. Exp Clin Endocrinol Diabetes. 2012;120:367–75.

29. Yang S, Gu YY, Jing F, Yu CX, Guan QY. The effect of statins on levels of Dehydroepiandrosterone (DHEA) in women with polycystic ovary syndrome: a systematic review and Meta-analysis. Med Sci Monit. 2019;25:S90–7.

30. Celik O, Acbay O. Effects of metformin plus rosuvastatin on hyperandrogenism in polycystic ovary syndrome patients with hyperlipidemia and impaired glucose tolerance. J Endocrinol Invest. 2012;35(10):905–10.

31. Mohrer D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.

32. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:CD000142.

33. Jadad AR, Moore RA, Carroll DJ, Jenkinson C, Maheu M, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.

34. Berman NG, Parker RA. Meta-analysis: neither quick nor easy. BMC Med Res Methodol. 2002;2:10.

35. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.

36. Sathyapalan T, Smith KA, Coady AM, Kilpatrick ES, Atkin SL. Atorvastatin therapy decreases androstenedione and dehydroepiandrosterone sulphate concentrations in patients with polycystic ovary syndrome: randomized controlled study. Ann Clin Biochem. 2012;49:80–5.

37. Claessen BE, Guedeney P, Gibson CM, Angiolillo DJ, Cao D, Lepor N, et al. Lipid Management in Patients Presenting with Acute Coronary Syndromes: a review. J Am Heart Assoc. 2020;9:e018897.

38. Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestirmar F, Moghetti P, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the androgen excess and polycystic ovary syndrome society. Hum Reprod Update. 2012;18:146–70.

39. Faison E, Kostova E, Moran LJ, Bilal S, Be CC, Venetis C, et al. Metformin versus the combined oral contraceptive pill for hirsutism, acne, and menstrual pattern in polycystic ovary syndrome. Cochrane Database Syst Rev. 2020;8:CD005552.

40. Barrionuevo P, Nabhan M, Altayar O, Wang Z, Erwin PJ, Asi N, et al. Treatment options for Hirsutism: a systematic review and network Meta-analysis. J Clin Endocrinol Metab. 2018;103:1258–64.

41. Somani N, Turvy D. Hirsutism: an evidence-based treatment update. Am J Clin Dermatol. 2014;15:247–66.

42. Ishihara F, Komatsu M, Yamada T, Aizawa T, Ichikawa K, Takezawa N, et al. Role of dehydroepiandrosterone and dehydroepiandrosterone sulfate for the maintenance of axillary hair in women. Horm Metab Res. 1993;25:34–6.

43. Johansson G, Burman P, Winin L, Engstrom BE, Nilsson AG, Ottosson M, et al. Low-dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. J Clin Endocrinol Metab. 2002;87:2046–52.

44. Azzi L, El-Alfy M, Martel C, Labrie F. Gender differences in mouse skin morphology and specific effects of sex steroids and dehydroepiandrosterone. J Invest Dermatol. 2005;124:22–7.

45. Chen MJ, Chen CD, Yang JH, Chen CL, Ho HN, Yang WS, et al. High serum cholesterol levels are associated with phenotypic acne and a reduced risk of abdominal obesity in women with polycystic ovary syndrome. J Endocrinol Invest. 2011;34:1196–200.

46. Timpatanapong P, Rojanasakul A. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. J Dermatol. 1997;24:223–9.

47. Saleh BO. Role of growth hormone and insulin-like growth factor-1 in hyperandro genesis and the severity of acne vulgaris in young males. Saudi Med J. 2012;33:1196–200.

48. Seirafi H, Farnaghi F, Vasheghani-Farahani A, Alienezee NS, Esfahani F, Firooz A, et al. Assessment of androgens in women with adult-onset acne. Int J Dermatol. 2007;46:1188–91.

49. Smythe CD, Greenall M, Kealey T. The activity of HMG-CoA reductase and acetyl-CoA carboxylase in human apocrine sweat glands, sebaceous glands, and hair follicles is regulated by phosphorylation and by exogenous cholesterol. J Invest Dermatol. 1998;111:139–48.

50. Palmer MA, Blakeborough L, Harries M, Haslam IS. Cholesterol homeostasis: links to hair follicle biology and hair disorders. Exp Dermatol. 2020;29:299–311.

51. Sokalska A, Stanley SD, Villanueva JA, Ortega I, Duleba AJ. Comparison of effects of different statins on growth and steroidogenesis of rat ovarian theca-interstitial cells. Biol Reprod. 2014;90:44.

52. Kaya C, Pabuccu R, Cengiz SD, Dunder I. Comparison of the effects of atorvastatin and simvastatin in women with polycystic ovary syndrome: a prospective, randomized study. Exp Clin Endocrinol Diabetes. 2010;118:161–6.