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 ClinialTrails.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.

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 an important criterion for the diagnosis of PCOS. PCOS symptoms 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 the conflicting results with increasing blood androgens or not reach 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 reported that statins could reduce the DHEA levels in PCOS, but it included a nonrandom study[29] 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[30].

Literature search

Two authors (Chen, Deng) independently searched databases including PubMed, EMBASE, the Web of Science, the ClinialTrails.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 excluded 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 used statins continued for at least one week; 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 and 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[31] and the Jadad score[32]. 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[33], we chose the fixed-effect model; otherwise, we chose the randomized-effect model [34]. 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 **Figure. 1.**

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, 35]. 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 are shown in **Figures. 2 and 3**.

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(20mg/d) +Metformin(1.5g/d)	Metformin(1.5g/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
Banaszewska 2011[27]	Poland	3	Simvastatin(20mg/d) +Metformin(1.7g/d)	Metformin(1.7g/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,Acne	not report/ ng/dl
Rashidi 2011[20]	Iran	5	Simvastatin(20 mg/d)	placebo	2 months	32/29	T,DHEAS	chemiluminescence assays/ pg/ml
Kazerooni 2010[21]	Iran	5	Simvastatin(20mg/d) +Metformin(1.5g/d)	Metformin(1.5g/d)	3 months	42/42	T,DHEA,Hirsutism	Radioimmunoassay/ ng/ml
Duleba 2005[23]	Poland	2	simvastatin, 20 mg +OCP	OCP	3 month	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.

Effects of statins therapy on androgens levels

We choose random-effects model because substantial heterogeneities were observed. Effects of statins on Androgens includes testosterone, DHEA, androstenedione were analysed 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, I^2 = 68%)**(Figure. 4).** DHEA levels were reduced by statins in seven studies (SMD=-0.51; 95% CI, -0.97–-0.05; P = 0.03; I^2 = 84%)(**Figure. 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; I^2 = 67%) (**Figure. 6**) .

Effects of statin therapy on cutaneous manifestations

Four studies provided data on the change in hirsutism score, and 3 provided data on ance 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; I^2 = 86%)(Figure. 7) and acne (SMD=-0.92; 95% CI, -1.49–-0.34; P = 0.002, I^2 = 86%) (Figure. 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; I^2 = 71%) or metformin (SMD=-0.43; 95% CI, -0.84–-0.02; P = 0.04; I^2 = 65%) implied in the 9 studies. The two statins simvastatin (SMD=-0.48; 95% CI, -0.77–-0.18; P = 0.002; I^2 = 66%) and atorvastatin (SMD=-0.39; 95% CI, -1.38 – 0.61; P = 0.45; I^2 = 80%) also revealed no significant difference in reducing testosterone and DHEA (Table 2**)**. We did not conduct subgroup analysis in effects of statins on cutaneous manifestations, because less than 2 studies in each subgroup.

Table 2
Subgroup analysis in testosterone and DHEA.

Subgrouped by	No. of trials	WMD (95% CI)	P Value	P for heterogeneity	I^2 (%)	P for between Subgroup heterogeneity
Testosterone						
total	9	-0.47[-0.76,-0.18]	0.002	68	0.002	
Statin type						0.86
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	
Contol type						0.90
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						0.79
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	
Contol type						0.70
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	

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(95CI:-0.85 − 0.21) to -0.39 (95CI:-0.66 − 0.12), and DHEA with SMD range from − 0.61 (95CI: -1.10−-0.17) to -0.33 (95CI:-0.73 − 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 (**Figure. 9**). We did not perform sensitivity analysis and publication bias assessment in other outcomes because less than 5 studies were included.

Table 3
Sensitivity analysis of Testosterone and DHEA.

Excluded study	Testosterone		DHEA	
	SMD	95CI	SMD	95CI
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]
Rashidi 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]

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[36]. This article provided evidence that using statins may offer additional benefits for women with PCOS by improving hyperandrogenism.

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. There was no statistical change about androstenedione in statin treatment, possibly attributed to the small sample size with only 48 patient pooled from 2 trials. Results also show that statins relieved cutaneous symptoms hirsutism and acne. Sensitivity analyses confirmed the robustness of the main results.

Years ago, two reviews employed few RCTs and implied a positive effect of statin treatment reducing testosterone and DHEA levels of PCOS women. Now, more RCTs included in our meta-analysis made this conclusion solid. First, through broad search strategy and system review, our study had amended several limitations in previous reviews. Second, 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. In the end, our study fully considered the effects of statins on hyperandrogenism by assessing blood indicators and the related manifestations. So far, no previous meta-analysis has assessed the effects of statins on the manifestation of hyperandrogenism among women with PCOS. Clinical manifestations of PCOS such as hypertrichosis, acne are closely related to the increase of androgens. Up to 70% of women with PCOS have dyslipidemia, depicted by elevated low-density lipoprotein and triglycerides levels with decreased high-density lipoprotein levels[37]. Statins are generally recommended for treating dyslipidemia. A Cochrane meta-analysis of 4 RCTs found that a 6 to 12-week course of statins could improve hyperlipidemia in women with PCOS when compared with placebo[13]. In the general patient without PCOS, the reduction of androgens levels is also observed during lipid-reducing interventions, including statins treatment, and is considered an adverse side effect[38]. Obviously, this is helpful for women with PCOS because the risk of bias is in the opposite direction in these two clinical settings. Our pooled results provide valuable evidence that statin could decrease levels of androgens and improve the symptom of hyperandrogenism, indicating that PCOS patients may benefit from statins.

Cholesterol is a key substrate for the production of androgens, inhibition of the biosynthesis of cholesterol will lead to a decrease of androgens[39–41]. In this way, a competitive inhibition of statin to HMG-CoA reductase, a key enzyme of cholesterol biosynthesis, possibly lead to a decrease of androgens [42, 43]. However, in men, some trials reported that statins treatment reduced androgen modestly, and some displayed no significant changes [44–46]. Accordingly, a meta-analysis demonstrated no significant difference between atorvastatin and placebo on the levels of testosterone in males[47]. This means the action of statins on men is much less than that on PCOS women, suggested a different mechanisms existing in women with PCOS.

It is believed that increased androgen production in PCOS primarily originates from the ovaries and adrenal glands. The excessive androgens from ovaries are considered as the most crucial inducer of PCOS[5], although adrenal hyperandrogenism emerges in 20–30% PCOS women.[48] Statins are supposed to act primarily on the ovaries. First, statins had been confirmed not to take any effects on androgen levels in postmenopausal women, in whom it is well-known that the major origin of androgens is extra-ovarian.[49–51] Second, the delivery of LDL from the adrenal cortex is markedly impaired in patients with heterozygous familial hypercholesterolemia, statins still could significantly decrease cholesterol levels. [13, 52, 53] Third, in vitro studies reported that statins could decrease ovarian theca interstitial cellular proliferation and subsequent androgen production[54–56]. Fourth, surgical resection of a part or all of ovary leads to a significant reduction of androgen[57]. Another possible explanation is that statins could induce apoptosis of rat and human theca cells and reduce proliferation, and inhibit androgen production [58, 59]. This may partially explain the dramatic decrease of ovarian volume and manifestations of hyperandrogenism.

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 various study, which might result in incomparable and heterogeneous 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 system 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, provided evidence for supporting the statins as a potential treatment for women with PCOS.

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JC and XD accomplish the literature search, identification of eligible studies. JC and WG complete 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.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare no competing interests in this study.

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Tables

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(20mg/d) +Metformin(1.5g/d)	Metformin(1.5g/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
Banaszewska 2011[27]	Poland	3	Simvastatin(20mg/d) +Metformin(1.7g/d)	Metformin(1.7g/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,Acne	not report/ ng/dl
Rashidi 2011[20]	Iran	5	Simvastatin(20 mg/d)	placebo	2 months	32/29	T,DHEAS	chemiluminescence assays/ pg/ml
Kazerooni 2010[21]	Iran	5	Simvastatin(20mg/d) +Metformin(1.5g/d)	Metformin(1.5g/d)	3 months	42/42	T,DHEA,Hirsutism	Radioimmunoassay/ ng/ml
Duleba 2005[23]	Poland	2	simvastatin, 20 mg +OCP	OCP	3 month	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.

Table 2: Subgroup analysis in testosterone and DHEA.

Subgrouped by	No. of trials	WMD (95% CI)	P Value	P for heterogeneity	I^2 (%)	P for between Subgroup heterogeneity
Testosterone						
total	9	-0.47[-0.76,-0.18]	0.002	68	0.002	
Statin type						0.86
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	
Contol type						0.90
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						0.79
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	
Contol type						0.70
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.
Table 3: Sensitivity analysis of Testosterone and DHEA.

Excluded study	Testosterone		DHEA	
	SMD	95CI	SMD	95CI
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]
Rashidi 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]

Figures

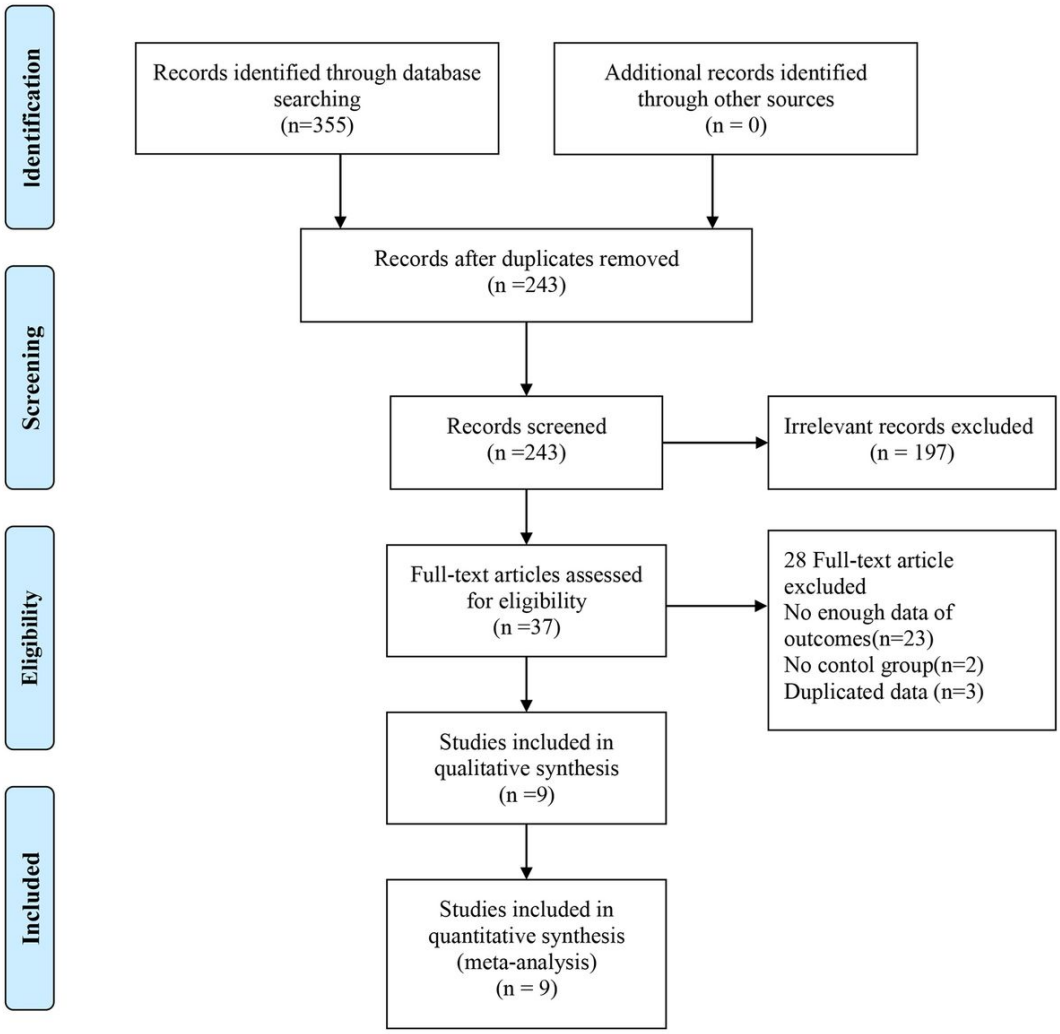

Figure 1

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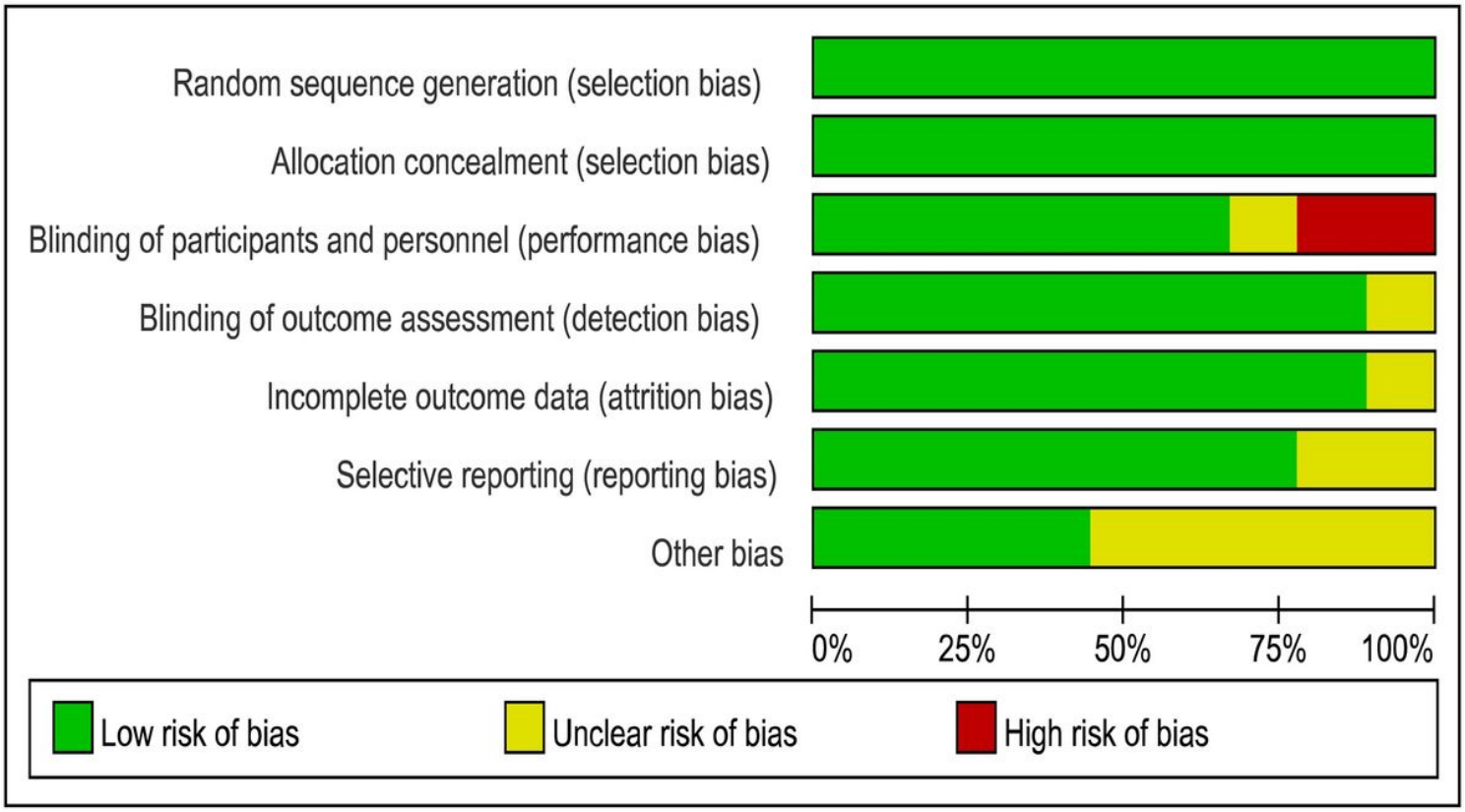

Figure 2

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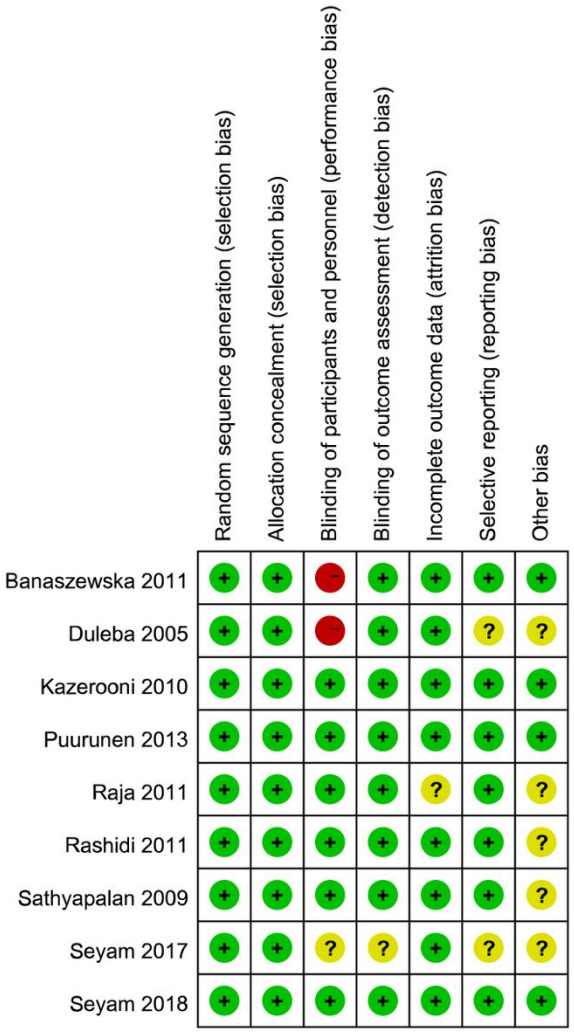

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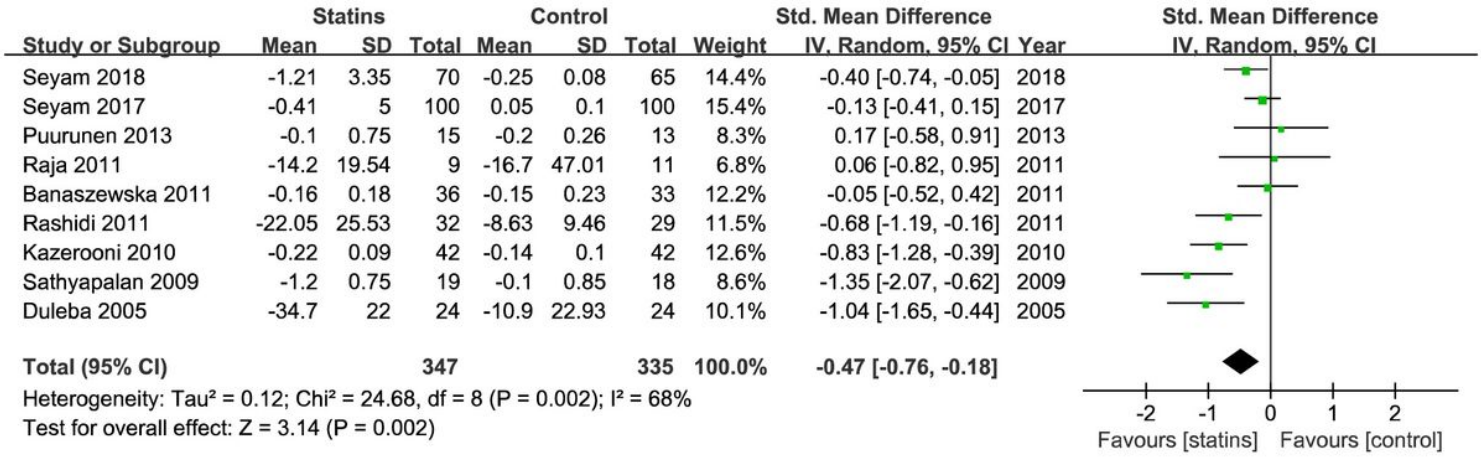

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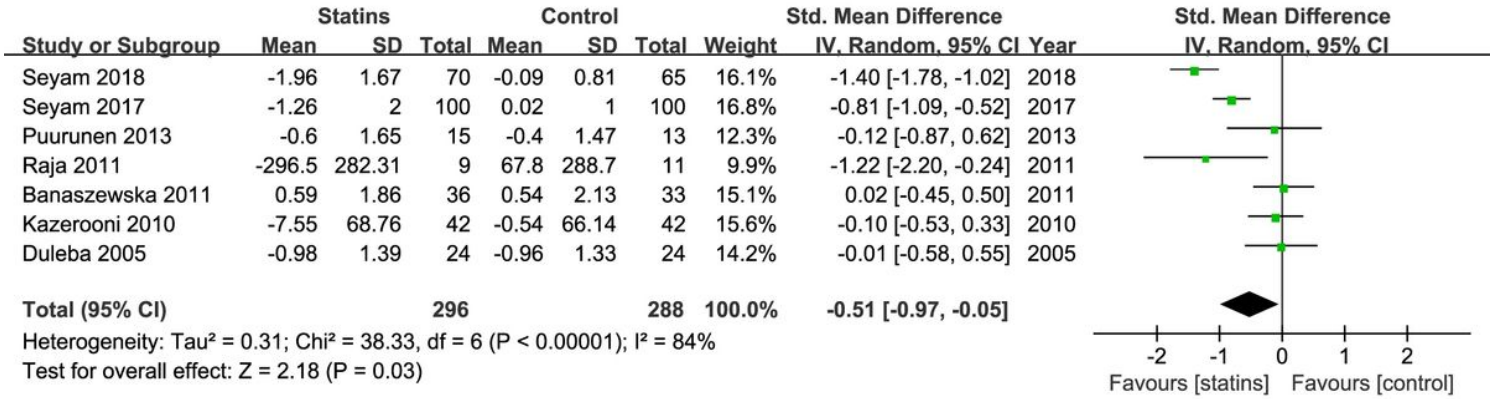

Figure 5

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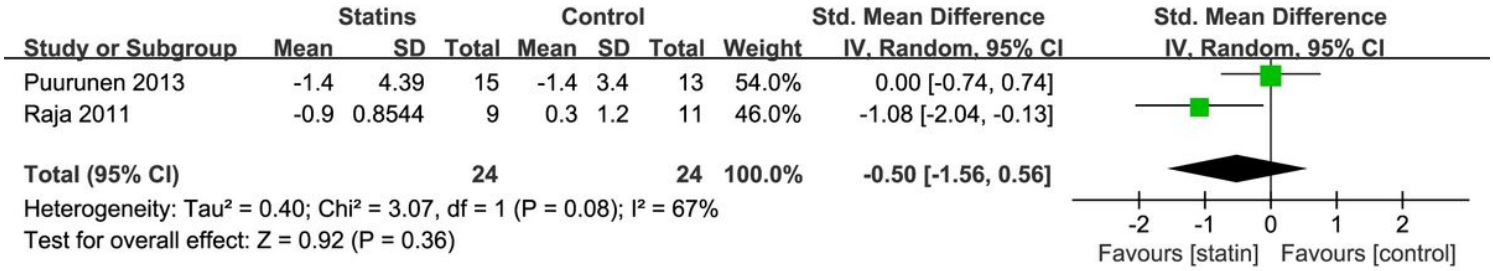

Figure 6

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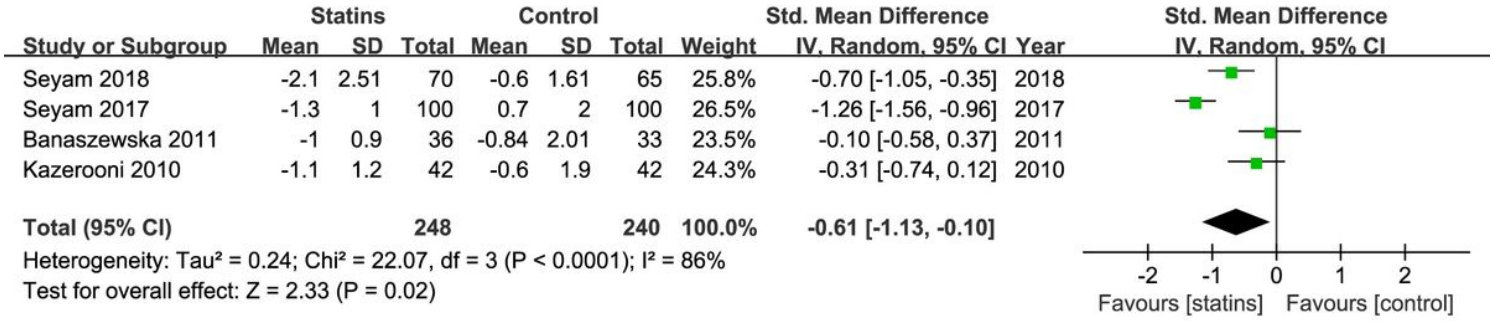

Figure 7

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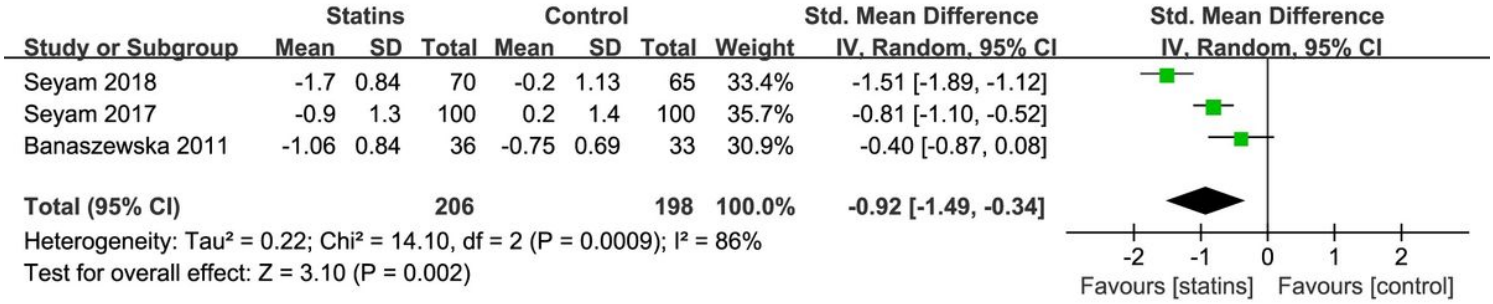

Figure 8

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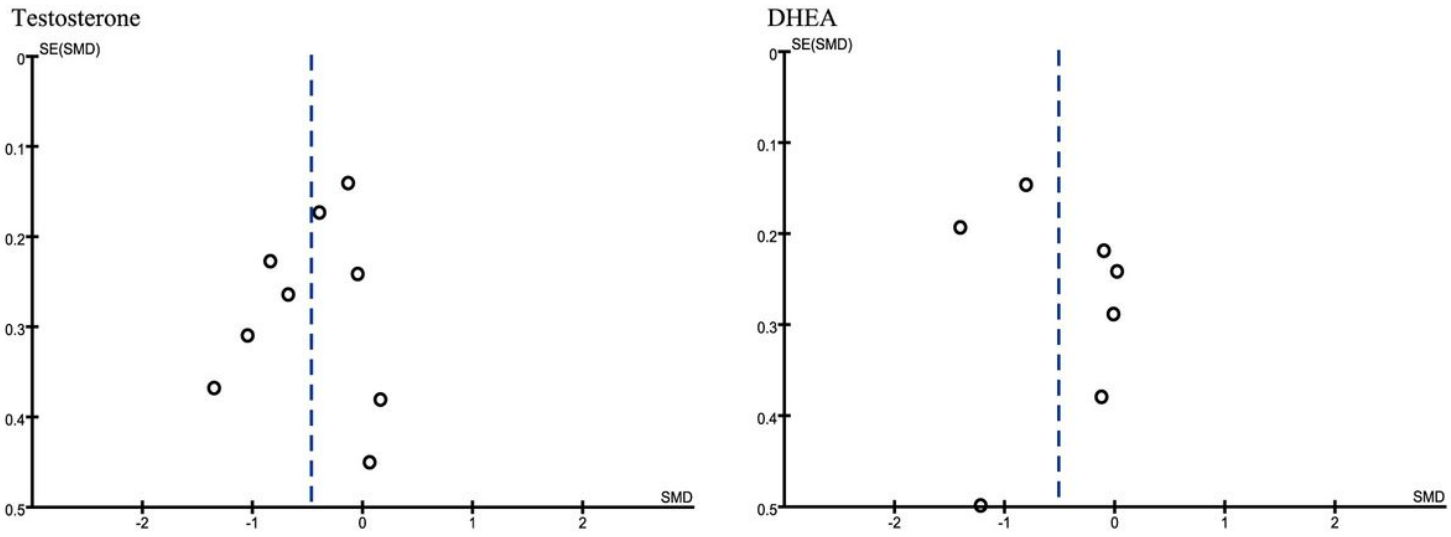

Figure 9

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