

Relationships Between Biochemical Markers of Hyperandrogenism and Metabolic Parameters in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis

Authors

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 **Supplementary material** for this article is available online at <http://www.thieme-connect.de/products>.

ABSTRACT

While several studies have documented an increased risk of metabolic disorders in patients with polycystic ovary syndrome (PCOS), associations between androgenic and metabolic parameters in these patients are unclear. We aimed to investigate the relationships between biochemical markers of hyperandrogenism (HA) and metabolic parameters in women with PCOS. In this systematic review and meta-analysis, a literature search was performed in the PubMed, Scopus, Google Scholar, ScienceDirect, and Web of Science from 2000 to 2018 for assessing androgenic and metabolic parameters in PCOS patients. To assess the relationships between androgenic and metabolic parameters, meta-regression analysis was used. A total number of 33 studies involving 9905 patients with PCOS were included in this analysis. The associations of total testosterone (tT) with metabolic parameters were not significant; after adjustment for age and BMI, we detected associations of this androgen with low-density lipoproteins cholesterol (LDL-C) ($\beta = 0.006$; 95% CI: 0.002, 0.01), high-density lipoproteins cholesterol (HDL-C) ($\beta = -0.009$; 95% CI: -0.02, -0.001), and systolic blood pressure (SBP) ($\beta = -0.01$; 95% CI: -0.03, -0.00). We observed a positive significant association between free testosterone (fT) and fasting insulin ($\beta = 0.49$; 95% CI: 0.05, 0.91); this association remained significant after adjustment for confounders. We also detected a reverse association between fT and HDL-C ($\beta = -0.41$; 95% CI: -0.70, -0.12). There was a positive significant association between A4 and TG ($\beta = 0.02$; 95% CI: 0.00, 0.04) after adjustment for PCOS diagnosis criteria. We also found significant negative associations between A4, TC, and LDL-C. Dehydroepiandrosterone sulfate (DHEAS) had a positive association with LDL-C ($\beta = 0.02$; 95% CI: 0.001, 0.03) and a reverse significant association with HDL-C ($\beta = -0.03$; 95% CI: -0.06, -0.001). This meta-analysis confirmed the associations of some androgenic and metabolic parameters, indicating that measurement of these parameters may be useful for predicting metabolic risk in PCOS patients.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder characterized by chronic anovulation, clinical and/or biochemical hyperandrogenism (HA), and/or polycystic ovaries [1]. The Androgen Excess-PCOS (AE-PCOS) Society Task Force considered HA as an essential criteria for diagnosing PCOS [2]. High blood levels of several androgens including serum total testosterone (tT), free testosterone (fT), androstenedione (A4), dehydroepiandrosterone sulfate (DHEAS), and calculated free androgen index (FAI) may be used to detect biochemical HA [3].

It is well-documented that PCOS is associated with increased risk of metabolic disorders [1, 4], which may be attributed to HA, obesity, dyslipidemia, impaired glucose tolerance, insulin resistance, and/or type 2 diabetes mellitus (T2DM) [5, 6]. In particular, high insulin levels secondary to insulin resistance may participate to the increased androgen production of women with PCOS, which can aggravate clinical symptoms of HA [7]. Biochemical markers of HA may be correlated with fasting blood sugar (FBS), fasting insulin, insulin resistance, lipids levels and blood pressure (BP) [5, 7]. However, a limited number of studies have investigated the relationships between HA and metabolic parameters in women with PCOS and different results have been reported [7, 8]. In addition, the role of androgens on the development of hypertension in women is controversial [9], especially in patients with obesity and insulin resistance [10].

In this systematic review and meta-analysis, we aimed to re-evaluate, in women with PCOS, the relationships between biochemical parameters of HA and metabolic findings. Because commercial assays of androgens, and in particular of tT and fT have been criticized for being inaccurate, we conducted a sub-analysis trying to differentiate the results on the basis of the assay used for androgen measurement. In fact, it has been reported that many methods for measuring androgens have low sensitivity for female HA and that only some methods including mass spectrometry/liquid chromatograph (LC/MS) may produce accurate and reliable assessment of androgen circulating levels [11].

Materials and Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12] to investigate the relationships between androgenic, and metabolic parameters in women with PCOS. The study has been approved as a research project by the Research Institute for Endocrine Sciences (RIES), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Registration number: IR.SBMU.RIES.RES.1394.90.

The PICO question of this study was in reproductive age women with PCOS; what are the relationships between biochemical markers of HA and metabolic parameters?

Eligibility criteria

We searched randomized controlled trials (RCTs), non-randomized studies (NRS), prospective or retrospective cohort studies, and case-control studies restricted to published papers in English from 2000 to 2018. Studies were eligible if they had: (1) a study population including PCOS women, diagnosed by criteria of the Rotterdam,

National Institutes of Health (NIH) or the Androgen Excess Society (AES); (2) assessed at least one metabolic parameter, including FBS, fasting insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), triglycerides (TG), total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C), high-density lipoproteins cholesterol (HDL-C) and BP, and at least one androgenic profile, including tT, fT, A4, and DHEAS. We also excluded: (1) non-human studies, reviews, commentaries, editorials, letters, meeting abstracts, case reports, (2) studies that had a population with idiopathic hirsutism or the other types of HA, diabetes, cardiometabolic, or thyroid disorders, and (3) studies that did not provide accurate and clear data or methods. Clinical HA is identified by hirsutism, acne, and alopecia [13]. High levels of serum total testosterone (tT), free testosterone (fT), free androgen index (FAI), androstenedione (A4) and dehydroepiandrosterone sulfate (DHEAS) also indicate biochemical HA [3].

Search strategy

Before initiation of the study, we conducted the search strategy with the assistance of a professional healthcare librarian. All authors performed searches separately. PubMed, Scopus, Google Scholar, ScienceDirect, and Web of Science were searched for studies documented from 2000 to May 2018 assessing androgenic and metabolic parameters in patients with PCOS, using the following terms: ["polycystic ovary syndrome" OR "polycystic ovary" AND "hyperandrogenism" OR "androgen" OR "hormone"]; ["polycystic ovary syndrome" OR "polycystic ovary" AND "metabolic" OR "insulin" OR "carbohydrate"]. We also identified additional studies through a manual search of the bibliographic references of relevant articles and existing reviews. Search strategy was almost similar for all databases. We also searched databases using free-text terms synonyms.

Study selection

In the initial screening stage, investigators independently reviewed the titles, abstracts, and keywords to exclude studies that clearly did not fulfill inclusion criteria. In the second step, they independently read the full text of remaining papers to identify eligible articles. Disagreements between reviewers were resolved by discussion or, if necessary, by all reviewers. Journals and authors were not blinded during study selection.

Data extraction

Data were extracted from full text articles by 2 reviewer (MA and SBG) in close consultation with the second one reviewer (FRT). For each eligible study, the following data were extracted: First author, publication date, country of study, study design, total number of patients, diagnostic criteria for PCOS, patient's characteristics including age and BMI, outcome measurements including FG score, tT (nanograms per milliliter, ng/ml), fT (pico grams per milliliter, pg/ml), A4 (ng/ml), DHEAS (micro grams per milliliter, µg/ml), FBS (milligrams per milliliter, or mg/ml), fasting insulin (micro Unit/milliliter, µU/ml), HOMA-IR, TG (mg/ml), TC (mg/mL), LDL-C (mg/ml), HDL-C (mg/ml), SBP and DBP (millimeters of mercury, mmHg). Baseline data of all studies were collected as mean and standard deviation (SD). To prevent extraction errors, a control check between the final data used in the meta-analysis and the original publications was performed by all authors.

Quality assessment

The studies included for the meta-analysis were appraised for the quality of their methodological and result presentation. Two reviewers (MA and RBY) assessed the quality of the studies separately. They were blinded to study author, institution, and journal name. Disagreement was resolved and adjusted by the senior reviewer (FRT).

We used the modified consolidated standards of reporting trials (CONSORT) as a validated quality assessment checklist for RCTs. We also used CONSORT checklist for NRS after modification of it. For scoring of the quality of items, one point was given if the information for each item was stated in the study and 0 point if the information was not stated or was unclear. Studies with scores $\geq 70\%$ of the highest level of CONSORT checklist were considered as high, 40–70% as moderate, 20–40% as low and $< 20\%$ as very low quality [14].

In addition, observational studies including cohort, case-control, cross-sectional were appraised according to the Newcastle-Ottawa scale [15]. In this respect, 3 domains were scored for selection and comparability of study cohorts, and determination of the outcome of interest. If a study obtained $\geq 70\%$ of the highest level of the Newcastle-Ottawa scale, it was considered as high quality, 40–70% as moderate, and 20 to 40% as low and $< 20\%$ as very low quality.

Risk of bias assessment

Risk of bias in each study included was assessed using the Cochrane collaboration's tools; these tools were designed for various methodological studies including for RCTs and observational studies (cohorts, cross-sectional, and case-control) [16]. NRS were assessed by ROBINS tool [17]. Review authors' judgments were categorized as "low risk," "high risk," and "unclear risk" of bias [16].

Statistical analysis

First, we conducted this meta-analysis to obtain the pooled effect size of androgenic parameters including tT, fT, A4 and DHEAS, and metabolic parameters including FBS, fasting insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, SBP, and DBP. Heterogeneity test were assessed by I-squared and Chi-squared test. Random effect estimation method was applied for significant test result (p -value < 0.05) or I-squared greater than 50%. Forest plots were also drawn to show pooled effect size and its relevant 95% confidence intervals (CIs) [18, 19].

To assess publication bias, Egger's [20] test were used. For significant results the trim and fill method was used to identify and correct for publication bias by adding certain study measures [21, 22].

Second, to estimate the observational relationships of androgenic parameters with metabolic parameters, random effect meta-regression models were fitted. The association between means of androgens and means of metabolic parameters were obtained as regression coefficients of the univariate models, without adjusting for confounding variables. Moreover, we fitted meta-regression models to investigate the associations between androgens and metabolic parameters, adjusted for age and BMI, diagnostic criteria for PCOS (Rotterdam, NIH, and AES), quality assessment (low and moderate vs. high), study design (RCT vs. Non-RCT) and, ethnic groups (Western, Middle East, Eastern, African) and methods

of hormonal assay (Chemi/electrochemi, radioimmunoassay, Enzyme, unknown). Bubble plots were also drawn to show the direction of observational relationships between androgenic and metabolic parameters, which were adjusted according to the within-study variance show by circles. We also performed a subgroup analysis based on the hormonal assay methods. For all results, p -values < 0.05 were considered significant. Statistical analysis was done using STATA software (version 10; STATA, INC., college station, TX, USA).

Results

Search results and study selection and study characteristics

► **Fig. 1** illustrates the literature search and its results. Among the 33 studies (with 55 study groups) selected, 13 were RCTs [23–35], 6 NRS [36–41], 6 cross-sectionals [5, 13, 42–45], 3 case-controls [46–48], and 5 cohorts [3, 49–52]. The study population consisted of 9905 PCOS patients with a mean age of 25.16 (range: 20.9–31.00) years and a mean BMI of 27.61 (range: 20.90–36.40) kg/m². Main characteristics of the studies included are listed in ► **Table 1**.

Results of meta-regression analyses

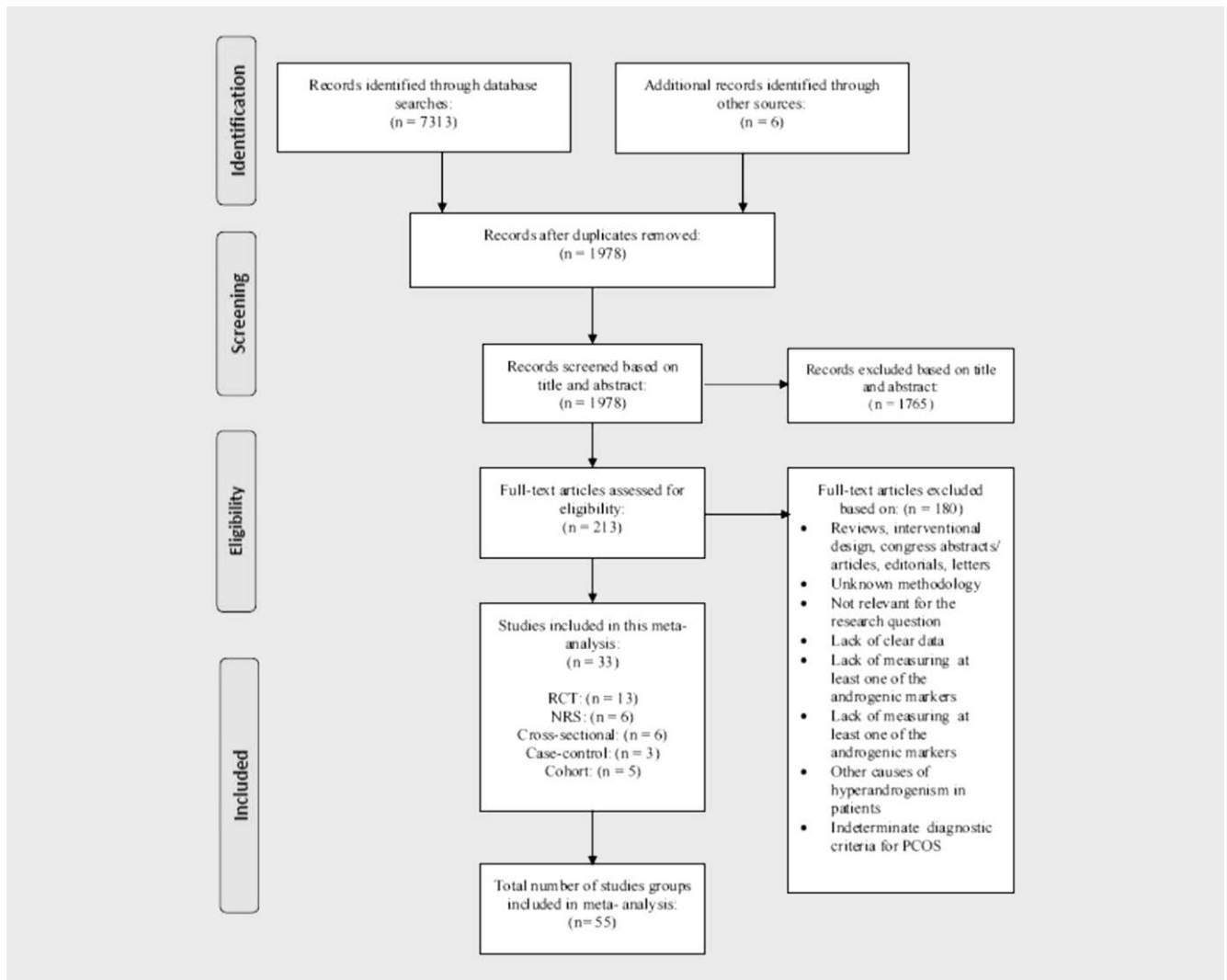
Results of univariate weighted linear meta-regression analyses did not show any significant relationships between of androgens and some metabolic parameters including FBS and HOMA-IR. However, we found significant relationships between androgenic markers, and insulin and lipid profiles.

Total testosterone was not significantly related to metabolic parameters; after adjustment for age and BMI, it was significantly associated with LDL-C ($\beta = 0.006$; 95% CI: 0.002, 0.01), HDL-C ($\beta = -0.009$; 95% CI: -0.02 , -0.001) and SBP ($\beta = -0.01$; 95% CI: -0.03 , -0.00). Other relationships between tT and metabolic parameters were not significant (► **Table 2** and ► **Fig. 2**).

The association between fT and fasting insulin was significant ($\beta = 0.49$; 95% CI: 0.05, 0.91); it was also associated with fasting insulin after adjustment for confounders. In addition, we found a reverse significant relationship between fT and HDL-C ($\beta = -0.41$; 95% CI: -0.70 , -0.12); this relationship remained after adjustment for confounders. Other associations between fT and metabolic parameters were not significant (► **Table 2** and ► **Fig. 2**).

We found a significant association between A4 and TG after adjustment for PCOS diagnostic criteria ($\beta = 0.02$; 95% CI: 0.00, 0.04). We also observed a significant association between A4 and TC ($\beta = -0.05$; 95% CI: -0.08 , -0.007); this relationship remained after adjustment for quality assessment, ethnicity and hormonal assay methods. A reverse significant association was observed between A4 and HDL-C after adjustment for PCOS diagnostic criteria, and hormonal assay methods. Other relationships between A4 and metabolic parameters were non-significant (► **Table 2** and ► **Fig. 3**).

There was a significant association between DHEAS and TC after adjustment for age and BMI ($\beta = 0.03$; 95% CI: 0.006, 0.05). We observed a significant association between DHEAS and LDL-C ($\beta = 0.02$; 95% CI: 0.001, 0.03); this relationship remained after adjustment for confounders. There was also a significant negative relationship between DHEAS and HDL-C ($\beta = -0.03$; 95% CI: -0.06 ,



► Fig. 1 Flow diagram of study selection.

–0.001); this relationship remained after adjustment for study design, ethnicity and hormonal assay method (► Table 2 and ► Fig. 3).

No significant association was found between blood pressure and androgenic markers except tT after adjustment for age and BMI ($\beta = -0.01$; 95% CI: $-0.03, -0.00$). We found significant heterogeneities for androgenic and metabolic parameters (supplementary files 1 and 2).

Results of subgroup analysis

Results of subgroup analysis based on the hormonal assay methods showed that when measurements were done by Radioimmunoassay, or chemi-/electrochemiluminescence, some associations between androgenic and metabolic parameters (in particular fasting insulin, TC and HDL-C) were significant, confirming our previous results. See detailed results in the supplementary file 3.

Publication bias

Egger’s test did not show any significant statistical publication bias among studies included for parameters measured; therefore, trim and fill correction were not applied (Supplementary file 1).

Risk of bias assessment

Supplementary file 4 shows details of risk of bias of published studies. Most RCT studies were at low risk of bias of random sequence generation, incomplete outcome data and selective outcome reporting; in these studies, some biases were more probable like blinding of allocation concealment, blinding of participant and personnel and outcome assessment.

Most NRS were at low risk of bias of confounding, selection of participants, interventions classification, and selection of the reported results. While most cross-sectional and case control studies were not at high risk of bias of assessment of exposure, development of outcome of interest in case and controls and selection of cases, some studies included had high risk of bias in selection of controls and adjustment for prognostic variables.

Although cohort studies were at low risk of bias of selection, assessment of exposure, present of outcome of interest at start of study, outcome assessment and adequacy of duration follow-ups, some studies included had serious risk biases in control of prognostic variables.

▶ **Table 1** Baseline characteristics of studies included in the meta-analysis.

First author, year ref.	Country	PCOS diagnostic criteria	Study design	Sample size (n)	Metabolic parameters measured	Androgenic parameters measured	Age (mean ±SD)	BMI (mean±SD)	FG score (mean±SD)	QA
Elter, 2002[23]	Turkey	RTM	RCT	20	FBS, Insulin, TG, TC, LDL-C, HDL-C	t ^{1b} , t ^{1c} , A4 ^b , DHEAS ^a	23.45±6.07	21.83±1.40	12.06±5.25	High
Elter, 2002[23]	Turkey	RTM	RCT	20	FBS, Insulin, TG, TC, LDL-C, HDL-C	t ^{1b} , t ^{1c} , A4 ^b , DHEAS ^a	24.90±6.62	22.74±2.66	9.47±5.48	High
Mastorakos, 2002[24]	Greece	NIH	RCT	14	FBS, Insulin, TG, TC, LDL-C, HDL-C	t ^{1b} , t ^{1c} , A4 ^b , DHEAS ^b	17.53±0.51	25.50±1.79	15.71±1.63	Moderate
Mastorakos, 2002[24]	Greece	NIH	RCT	14	FBS, Insulin, TG, TC, LDL-C, HDL-C	t ^{1b} , t ^{1c} , A4 ^b , DHEAS ^b	17.46±0.43	24.84±1.09	16.78±1.15	Moderate
Hahn, 2005[46]	Germany	NIH	Case-control	120	HOMA-IR	t ^{1a}	17.46±0.43	31.00±9.30	9.20±5.80	Moderate
Palep-Singh, 2004[36]	UK	RTM	NRS	17	FBS, TG, TC, LDL-C, HDL-C	t ^{1d}	26.40±5.30	29.00±3.70	18.50±2.74	Moderate
Amato, 2006[49]	Italy	RTM	Cohort	75	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1c} , t ^{1e} , A4 ^b , DHEAS ^a	24.72±5.83	31.19±7.36	17.94±9.27	Moderate
Amato, 2006[49]	Italy	RTM	Cohort	55	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1c} , t ^{1e} , A4 ^b , DHEAS ^a	24.35±4.28	28.70±6.16	6.50±2.02	Moderate
Pehlivanov, 2007[37]	Bulgaria	RTM	NRS	20	FBS, HOMA-IR	t ^{1c} , DHEAS ^c	23.00±4.10	26.45±0.65	11.60±0.90	Moderate
Chae, 2008[47]	Korea	RTM	Case-control	87	FBS, Insulin, HOMA-IR, TG, TC, HDL-C, BP	t ^{1b} , t ^{1c} , DHEAS ^b	25.40±5.70	22.80±5.10	8.70±3.10	High
Chae, 2008[47]	Korea	RTM	Case-control	52	FBS, Insulin, HOMA-IR, TG, TC, HDL-C, BP	t ^{1b} , t ^{1c} , DHEAS ^b	25.70±4.90	20.90±4.40	3.10±3.00	High
Chae, 2008[47]	Korea	RTM	Case-control	23	FBS, Insulin, HOMA-IR, TG, TC, HDL-C, BP	t ^{1b} , t ^{1c} , DHEAS ^b	23.40±6.90	23.10±4.80	10.50±3.00	High
Wu, 2008[25]	China	RTM	RCT	7	Insulin	t ^{1a}	25.00±4.30	25.30±0.80	8.30±1.00	Moderate
Wu, 2008[25]	China	RTM	RCT	12	Insulin	t ^{1a}	26.10±4.60	21.40±1.60	7.80±1.30	Moderate
Wu, 2008[25]	China	RTM	RCT	6	Insulin	t ^{1a}	24.50±2.40	25.20±1.00	8.20±1.40	Moderate
Wu, 2008[25]	China	RTM	RCT	10	Insulin	t ^{1a}	25.80±4.00	21.60±1.40	7.80±2.10	Moderate
Ozdemir, 2008[26]	Turkey	RTM	RCT	32	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1b} , t ^{1c}	22.70±3.80	22.70±3.80	10.40±3.60	Low
Adali, 2008[50]	Turkey	RTM	Cohort	42	FBS, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1b} , DHEAS ^a	23.54±3.13	28.42±4.30	12.42±3.40	Moderate
Landay, 2009[42]	USA	NIH	Cross-sectional	749	FBS, Insulin	t ^{1b} , t ^{1c} , DHEAS ^b	27.50±7.40	33.60±9.30	8.23±4.92	High
Mahmood, 2009[27]	Egypt	AES	RCT	21	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1a} , DHEAS ^a	26.05±2.44	29.42±2.02	9.71±1.85	Low
Kriplani, 2010[28]	India	RTM	RCT	30	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1b} , DHEAS ^c	22.50±4.70	22.70±2.30	12.60±4.50	Moderate
Naka, 2011[38]	Greece	RTM	NRS	13	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1a}	20.90±3.70	23.00±4.00	8.50±2.20	Moderate
Liang, 2011[51]	Taiwan	RTM	Cohort	453	FBS, Insulin, HOMA-IR	t ^{1b} , DHEAS ^b	27.90±4.70	25.70±6.60	3.80±3.80	High
Coskun, 2011[3]	Turkey	RTM	Cohort	43	Insulin	t ^{1b} , DHEAS ^a	26.05±0.76	29.27±0.84	11.20±4.20	Moderate
Misichronis, 2012[48]	Greece	RTM	Case-control	1087	FBS, Insulin	t ^{1b} , A4 ^b , DHEAS ^b	23.40±5.60	26.70±7.00	8.50±4.70	Moderate
Alanbay, 2012[43]	Turkey	RTM	Cross-sectional	25	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1c} , t ^{1e}	27.30±4.00	23.10±1.00	10.10±3.90	High
Alanbay, 2012[43]	Turkey	RTM	Cross-sectional	54	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{1c} , t ^{1e}	25.30±3.70	27.80±1.90	10.20±3.20	High
Ilie, 2012[39]	Romania	AES	NRS	25	FBS, Insulin, HOMA-IR, TG, TC, BP	t ^{1c}	22.76±0.83	28.44±1.24	9.72±1.06	Moderate
Karabulut, 2012[40]	Turkey	RTM	NRS	6	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BP	t ^{1d} , DHEAS ^d	22.40±6.30	28.55±4.24	12.00±3.40	Low
Bhattcharia, 2012[29]	India	RTM	RCT	58	FBS, Insulin, HOMA-IR, BP	t ^{1a}	22.24±4.47	25.41±4.49	5.55±4.51	High
Bhattcharia, 2012[29]	India	RTM	RCT	56	FBS, Insulin, HOMA-IR, BP	t ^{1a}	22.32±4.17	26.41±3.81	6.84±5.17	High
Bhattcharia, 2012[29]	India	RTM	RCT	57	FBS, Insulin, HOMA-IR, BP	t ^{1a}	22.33±4.76	26.47±4.65	6.14±5.15	High

► **Table 1** Continued.

First author, year ref.	Country	PCOS diagnostic criteria	Study design	Sample size (n)	Metabolic parameters measured	Androgenic parameters measured	Age (mean±SD)	BMI (mean±SD)	FG score (mean±SD)	QA
Aydin, 2013 [41]	Turkey	RTM	NRS	28	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{†d} , A4 ^d , DHEAS ^d	21.40±4.20	21.80±3.40	9.25±8.03	Moderate
Panidis, 2013 [13]	Greece	RTM	Cross-sectional	780	FBS, Insulin, HOMA-IR	t ^{†b} , A4 ^b , DHEAS ^b	23.80±5.60	27.30±7.00	11.40±2.50	High
Panidis, 2013 [13]	Greece	RTM	Cross-sectional	517	FBS, Insulin, HOMA-IR	t ^{†b} , A4 ^b , DHEAS ^b	25.10±5.90	25.90±6.80	3.40±2.40	High
Quinn, 2014 [44]	USA	RTM	Cross-sectional	56	FBS, Insulin, HOMA-IR	t ^{†b} , A4 ^b , DHEAS ^b	28.80±5.67	30.90±8.45	9.27±6.43	High
Quinn, 2014 [44]	USA	RTM	Cross-sectional	198	FBS, Insulin, HOMA-IR	t ^{†b} , A4 ^b , DHEAS ^b	27.80±6.10	30.10±8.17	8.13±6.04	High
Kahraman, 2014 [30]	Turkey	AES	RCT	19	TG, TC, LDL-C, HDL-C	t ^{†b} , FT ^b , A4 ^b , DHEAS ^b	22.30±3.20	23.20±3.30	15.80±7.30	Moderate
Kahraman, 2014 [30]	Turkey	AES	RCT	20	TG, TC, LDL-C, HDL-C	t ^{†b} , FT ^b , A4 ^b , DHEAS ^b	22.40±2.70	23.20±5.50	15.30±7.30	Moderate
Sales, 2015 [5]	Brazil	RTM	Cross-sectional	50	FBS, Insulin, TC, LDL-C, HDL-C	t ^{†a}	31.00±5.00	28.90±5.30	11.00±7.00	Moderate
Yildizhan, 2015 [31]	Turkey	RTM	RCT	60	HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{†b} , DHEAS ^b	25.36±2.91	24.82±1.08	9.98±4.86	Moderate
Yildizhan, 2015 [31]	Turkey	RTM	RCT	60	HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{†b} , DHEAS ^b	24.82±3.20	23.56±3.32	5.56±3.44	Moderate
Diri, 2015 [32]	Turkey	RTM	RCT	18	HOMA-IR	t ^{†b} , A4 ^b , DHEAS ^b	22.40±0.90	22.10±0.50	14.70±0.90	Moderate
Diri, 2015 [32]	Turkey	RTM	RCT	19	HOMA-IR	t ^{†b} , A4 ^b , DHEAS ^b	25.10±1.80	23.30±0.60	12.70±1.10	Moderate
Wang, 2016 [33]	China	RTM	RCT	50	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BP	t ^{†a}	23.50±4.90	23.38±1.74	2.25±1.45	Low
Wang, 2016 [33]	China	RTM	RCT	49	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BP	t ^{†a}	24.30±4.00	24.10±1.49	2.75±0.88	Low
Gobl, 2016 [45]	Austria	NIH	Cross-sectional	35	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{†d} , A4 ^d , DHEAS ^d	23.75±2.26	25.75±2.07	12.00±2.02	Moderate
Gobl, 2016 [45]	Austria	RTM	Cross-sectional	18	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C	t ^{†d} , A4 ^d , DHEAS ^d	26.75±3.20	24.25±2.70	5.20±2.080	Moderate
Alpanes, 2017 [34]	Spain	AES	RCT	24	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BP	t ^{†b} , A4 ^b , DHEAS ^a	25.00±5.00	30.60±7.90	10.00±5.00	High
Alpanes, 2017 [34]	Spain	AES	RCT	22	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BP	t ^{†b} , A4 ^b , DHEAS ^a	23.00±6.00	31.20±9.00	13.00±7.00	High
Katulski, 2017 [52]	Poland	RTM	Cohort	2511	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BP	t ^{†c} , DHEAS ^c	25.00±5.00	26.10±6.90	19.00±7.00	Moderate
Katulski, 2017 [52]	Poland	RTM	Cohort	1366	FBS, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BP	t ^{†c} , DHEAS ^c	24.00±4.00	26.50±6.70	20.00±7.00	Moderate
Engmann, 2017 [35]	USA	RTM	RCT	476	FBS, Insulin, HOMA-IR, TG, LDL-C, HDL-C, BP	t ^{†b} , A4 ^b	28.80±4.20	35.10±9.80	17.00±8.70	High
Engmann, 2017 [35]	USA	RTM	RCT	98	FBS, Insulin, HOMA-IR, TG, LDL-C, HDL-C, BP	t ^{†b} , A4 ^b	28.70±4.90	35.70±7.90	15.80±8.50	High
Engmann, 2017 [35]	USA	RTM	RCT	128	FBS, Insulin, HOMA-IR, TG, LDL-C, HDL-C, BP	t ^{†b} , A4 ^b	29.20±4.10	36.40±7.90	17.60±7.50	High

PCOS: Polycystic ovary syndrome; n: Number of study participants; SD: Standard deviation; HOMA-IR: Homeostasis model assessment; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; BP: Blood pressure; BMI: Body mass index; QA: Quality assessment; RCT: Randomized controlled trial; P-cohort: Prospective cohort; R-cohort: Retrospective cohort; RTM: Rotterdam criteria (2003); NIH: National Institutes of Health (1990); AES: Androgen Excess Society (2006); ^a Measured by chemi-/electrochemiluminescence method; ^b Measured by radioimmunoassay method; ^c Measured by enzyme method; ^d Method unknown.

Table 2 Meta-regression results for univariate and multiple (adjusted effect) models to assess the observational relationships between androgenic and metabolic parameters.

Parameter	Models	tT	fT	A4	DHEAS
		β (95% CI for β)	β (95% CI for β)	β (95% CI for β)	β (95% CI for β)
FBS	unadjusted model	0.00 (-0.01, 0.02)	0.25 (-0.43, 0.92)	-0.04 (-0.12, 0.03)	0.004 (-0.02, 0.03)
	adjusted for age and BMI	0.01 (-0.006, 0.02)	0.13 (-0.67, 0.94)	-0.04 (-0.11, 0.03)	0.009 (-0.02, 0.05)
	adjusted for PCOS diagnosis criteria	0.00 (-0.007, 0.02)	0.22 (-0.48, 0.93)	-0.02 (-0.09, 0.05)	0.006 (-0.02, 0.04)
	adjusted for quality assessment	0.00 (-0.008, 0.01)	0.24 (-0.47, 0.95)	-0.06 (-0.14, 0.01)	0.008 (-0.02, 0.04)
	adjusted for study design	0.00 (-0.009, 0.02)	0.19 (-0.48, 0.86)	-0.02 (-0.08, 0.03)	0.006 (-0.02, 0.04)
	adjusted for ethnic	0.01 (-0.007, 0.02)	0.26 (-0.53, 1.0)	-0.06 (-0.15, 0.03)	0.01 (-0.02, 0.04)
	adjusted for hormonal assay methods	0.00 (-0.009, 0.02)	0.28 (-0.62, 1.1)	0.04 (-0.12, 0.04)	0.005 (-0.03, 0.03)
Fasting insulin	unadjusted model	0.007 (-0.006, 0.022)	0.49 (0.05, 0.91)*	0.02 (-0.07, 0.10)	-0.001 (-0.04, 0.03)
	adjusted for age and BMI	0.01 (-0.003, 0.03)	0.51 (0.003, 1.01)*	0.02 (-0.08, 0.12)	-0.007 (-0.04, 0.03)
	adjusted for PCOS diagnosis criteria	0.008 (-0.005, 0.02)	0.48 (-0.006, 0.96)	0.05 (-0.03, 0.14)	-0.005 (-0.04, 0.03)
	adjusted for quality assessment	0.01 (-0.001, 0.03)	0.48 (0.02, 0.94)*	0.009 (-0.10, 0.12)	0.001 (-0.03, 0.03)
	adjusted for study design	0.005 (-0.01, 0.02)	0.45 (0.02, 0.87)*	-0.05 (-0.12, 0.02)	0.006 (-0.04, 0.03)
	adjusted for ethnic	0.004 (-0.01, 0.02)	0.50 (0.05, 0.95)*	0.02 (-0.09, 0.13)	-0.004 (-0.04, 0.03)
	adjusted for hormonal assay methods	0.02 (-0.02, 0.06)	0.50 (0.02, 0.95)*	0.03 (-0.06, 0.12)	-0.008 (-0.05, 0.03)
HOMA-IR	unadjusted model	0.004 (-0.07, 0.08)	0.38 (-1.90, 2.70)	-0.002 (-0.33, 0.32)	-0.08 (-0.28, 0.10)
	adjusted for age and BMI	0.00 (-0.09, 0.08)	-0.93 (-3.71, 1.80)	-0.27 (-0.77, 0.21)	-0.08 (-0.30, 0.13)
	adjusted for PCOS diagnosis criteria	0.01 (-0.06, 0.08)	-0.67 (-2.76, 1.40)	0.12 (-0.21, 0.46)	-0.07 (-0.27, 0.12)
	adjusted for quality assessment	0.008 (-0.06, 0.08)	0.16 (-2.35, 2.60)	-0.11 (-0.49, 0.26)	-0.08 (-0.27, 0.11)
	adjusted for study design	0.009 (-0.07, 0.08)	0.65 (-1.99, 3.29)	0.02 (-0.26, 0.29)	-0.09 (-0.29, 0.11)
	adjusted for ethnic	-0.04 (-0.10, 0.04)	0.20 (-2.31, 2.70)	-0.006 (-0.47, 0.45)	-0.09 (-0.28, 0.10)
	adjusted for hormonal assay methods	0.02 (-0.26, 0.31)	0.40 (-2.17, 2.90)	0.02 (-0.33, 0.36)	-0.09 (-0.30, 0.11)
TG	unadjusted model	0.006 (-0.002, 0.003)	0.04 (-0.03, 0.11)	0.01 (-0.01, .04)	0.003 (-0.003, 0.01)
	adjusted for age and BMI	0.006 (-0.001, 0.002)	0.05 (-0.03, 0.12)	0.01 (-0.02, 0.05)	0.002 (-0.004, 0.009)
	adjusted for PCOS diagnosis criteria	0.00 (-0.002, 0.003)	0.04 (-0.03, 0.12)	0.02 (0.00, 0.04)*	0.003 (-0.002, 0.01)
	adjusted for quality assessment	0.00 (-0.002, 0.00)	0.05 (-0.03, 0.12)	0.009 (-0.03, 0.04)	0.003 (-0.004, 0.01)
	adjusted for study design	0.00 (-0.002, 0.003)	0.04 (-0.04, 0.11)	-0.003 (-0.03, 0.02)	0.003 (-0.003, 0.01)
	adjusted for ethnic	0.00 (-0.002, 0.002)	0.04 (-0.04, 0.12)	0.02 (-0.02, 0.04)	0.006 (-0.001, 0.01)
	adjusted for hormonal assay methods	0.001 (-0.005, 0.006)	0.04 (-0.04, 0.12)	0.02 (-0.01, 0.04)	0.004 (-0.00, 0.01)
TC	unadjusted model	0.002 (-0.004, 0.007)	0.09 (-0.09, 0.26)	-0.05 (-0.08, -0.007)*	0.01 (-0.005, 0.03)
	adjusted for age and BMI	0.004 (-0.0003, 0.008)	0.07 (-0.13, 0.27)	-0.04 (-0.11, 0.01)	0.03 (0.006, 0.05)*
	adjusted for PCOS diagnosis criteria	0.002 (-0.004, 0.006)	0.08 (-0.10, 0.27)	-0.02 (-0.05, 0.00)	0.02 (-0.001, 0.04)
	adjusted for quality assessment	0.00 (-0.004, 0.006)	0.10 (-0.09, 0.28)	-0.06 (-0.09, -0.01)*	0.01 (-0.006, 0.03)
	adjusted for study design	0.003 (-0.002, 0.008)	0.07 (-0.10, 0.25)	-0.04 (-0.07, -0.005)	0.01 (-0.006, 0.03)
	adjusted for ethnic	-0.001 (-0.006, 0.003)	0.08 (-0.11, 0.27)	-0.05 (-0.09, -0.00)*	0.01 (-0.004, 0.03)
	adjusted for hormonal assay methods	-0.02 (-0.03, 0.002)	0.09 (-0.10, 0.27)	-0.05 (-0.09, -0.00)*	0.01 (-0.00, 0.03)
LDL-C	unadjusted model	0.001 (-0.005, .006)	0.16 (-0.03, 0.34)	-0.006 (-0.04, 0.03)	0.02 (0.001, 0.03)*
	adjusted for age and BMI	0.006 (0.002, 0.01)*	0.13 (-0.06, 0.33)	-0.02 (-0.08, 0.04)	0.02 (0.005, 0.04)*
	adjusted for PCOS diagnosis criteria	0.00 (-0.004, 0.007)	0.14 (-0.05, 0.35)	0.01 (-0.03, 0.04)	0.02 (0.001, 0.03)*
	adjusted for quality assessment	0.00 (-0.004, 0.01)	0.17 (-0.006, 0.35)	-0.04 (-0.09, 0.007)	0.02 (0.000, 0.03)*
	adjusted for study design	0.00 (-0.004, 0.01)	0.16 (-0.05, 0.35)	-0.02 (-0.05, 0.01)	0.02 (0.00, 0.03)*
	adjusted for ethnic	-0.001 (-0.008, 0.004)	0.14 (-0.05, 0.30)	-0.008 (-0.05, 0.03)	0.02 (0.001, 0.03)*
	adjusted for hormonal assay methods	-0.009 (-0.03, 0.01)	0.15 (-0.05, 0.35)	-0.004 (-0.05, 0.04)	0.02 (0.003, .03)*
HDL-C SBP	unadjusted model	-0.006 (-0.02, 0.003)	-0.41 (-0.70, -0.12)*	-0.05 (-0.10, 0.002)	-0.03 (-0.06, -0.001)*
	adjusted for age and BMI	-0.009 (-0.02, -0.001)*	-0.45 (-0.76, -0.14)*	-0.07 (-0.15, 0.00)	-0.02 (-0.06, 0.01)
	adjusted for PCOS diagnosis criteria	-0.001 (-0.02, 0.002)	-0.44 (-0.74, -0.13)*	-0.06 (-0.10, -0.02)*	-0.03 (-0.06, 0.005)

► **Table 2** Continued.

Parameter	Models	tT	fT	A4	DHEAS
		β (95% CI for β)	β (95% CI for β)	β (95% CI for β)	β (95% CI for β)
	adjusted for quality assessment	-0.007 (-0.016, 0.001)	-0.45 (-0.75, -0.15)*	-0.06 (-0.13, 0.02)	-0.03 (-0.06, 0.00)
	adjusted for study design	-0.002 (-0.01, .007)	-0.38 (-0.73, -0.05)*	-0.02 (-0.08, 0.03)	-0.04 (-0.08, -0.009)*
	adjusted for ethnic	-0.002 (-0.01, 0.006)	-0.40 (-0.71, -0.10)*	-0.05 (-0.11, 0.007)	-0.04 (-0.07, -0.00)*
	adjusted for hormonal assay methods	-0.03 (-0.06, 0.0007)	-0.40 (-0.74, -0.10)*	-0.06 (-0.11, -0.00)*	-0.04 (-0.07, -0.00)*
	unadjusted model	-0.006 (-.02, .009)	0.18 (-0.29, 0.66)	0.08 (-0.12, 0.27)	0.12 (-0.02, 0.26)
	adjusted for age and BMI	-0.01 (-0.03, -0.00)*	-	0.20 (-1.09, 1.50)	0.22 (-0.18, 0.62)
	adjusted for PCOS diagnosis criteria	0.00 (-0.02, 0.015)	-	0.09 (-0.37, 0.55)	0.14 (-0.03, 0.31)
	adjusted for quality assessment	-0.003 (-0.02, 0.01)	-	-	0.11 (-0.05, 0.30)
	adjusted for study design	-0.01 (-0.04, 0.01)	-	0.08 (-0.12, 0.27)	0.14 (-0.03, 0.31)
	adjusted for ethnic	-0.004 (-0.02, 0.008)	-	-	0.03 (-0.14, 0.20)
DBP	adjusted for hormonal assay methods	-	-	0.09 (-0.37, 0.55)	0.12 (-0.04, 0.28)
	unadjusted model	-0.002 (-0.03, 0.02)	0.42 (-1.50, 2.30)	0.09 (-0.11, 0.30)	0.02 (-0.15, 0.19)
	adjusted for age and BMI	-0.02 (-0.04, 0.005)	-	0.20 (-0.90, 1.40)	-0.07 (-0.34, 0.19)
	adjusted for PCOS diagnosis criteria	0.005 (-0.02, 0.03)	-	0.10 (-0.30, 0.55)	0.02 (-0.18, 0.21)
	adjusted for quality assessment	-0.002 (-0.02, 0.02)	-	-	-0.03 (-0.28, 0.22)
	adjusted for study design	0.00 (-0.03, 0.033)	-	0.09 (-0.11, 0.30)	0.02 (-0.18, 0.20)
	adjusted for ethnic	0.002 (-0.02, 0.02)	-	-	-0.02 (-0.14, 0.09)
adjusted for hormonal assay methods	-	-	0.10 (-0.35, 0.55)	0.01 (-0.21, 0.22)	

* Statistical significance level $p < 0.05$; -: No data available.

Discussion

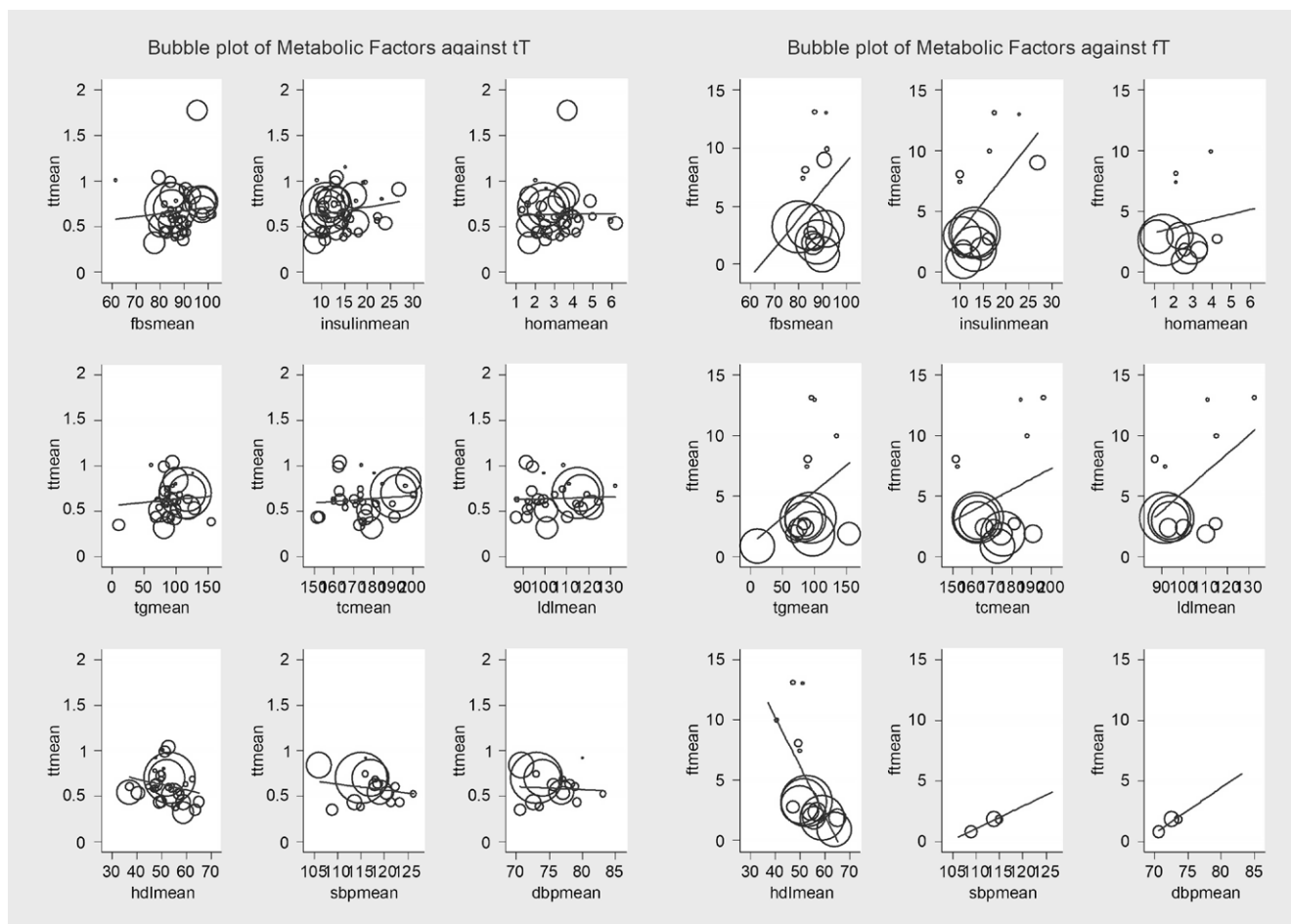
In this systematic review and meta-analysis, we assessed the possible relationships between androgenic markers of hyperandrogenism and metabolic findings in women with PCOS. Because it is well known that all these parameters may be affected by several factors such as age, BMI, ethnicity, and methods of hormonal of assay [1, 13, 53–58]; in performing the meta-analysis, we adjusted the results for all these important confounders.

The results for possible correlations between biochemical parameters of hyperandrogenism and metabolic findings were mixed, generally negative but with some significant correlation. In fact, some androgenic parameters but especially fT were significantly associated with insulin levels, HDL-C, and LDL-C. Interestingly, the significant association between fT and fasting insulin remained after adjustment for confounders including as age, BMI, quality assessment, study design, ethnicity and methods of assay. A significant reverse association between fT and HDL-C was also detected; adjusting for most confounders confirmed this result.

Of course, a simple explanation of these results is that circulating values of free testosterone are highly depending on sex hormone binding globulin (SHBG) levels that are low in presence of high insulin levels. Because of it, some experts have expressed doubts on the value of the assessment of free testosterone levels as an indicator of increased androgen production [59].

Insulin resistance is one of the most common metabolic disorders in women with PCOS [60, 61], which is observed in a large number of PCOS patients with HA. It has been reported that high insulin levels exert a direct positive effect on androgen production in women with PCOS [48, 62]. In addition, hyperinsulinemia increases the production of insulin growth factors I (IGF-I) and II in the liver [55], which lead to increase in androgen production [63]. IGF-I inhibits the aromatase enzyme that prevents the conversion of testosterone into estrogen. Insulin can also increase LH action in ovaries [64]. Moreover, hyperinsulinemia decreases liver production of SHBG, contributing to increased activity of free testosterone [65]. Also, insulin resistance reduces SHBG and raises free circulating testosterone [48, 62]. Insulin resistance is often associated with dyslipidemia as a common risk factor for CVD in patients with PCOS [66, 67]. PCOS patients with HA also have an increased risk for metabolic syndrome (MetS) [68]. A progressive accumulation of fat, which is often associated with dyslipidemia and an increase in fasting insulin and insulin resistance has been observed in PCOS patients with HA [4]. In fact, HA, related to PCOS, can aggravate metabolic and reproductive disorders associated with PCOS including dyslipidemia and MS [69].

At the contrary, the findings of this meta-analysis showed that tT was not significantly associated with any metabolic parameters. After adjustment for age and BMI, tT showed a positive significant



► **Fig. 2** Bubble plot of the univariate relationships between tT, fT, and metabolic parameters.

relationship with LDL-C and a reverse significant relationship with HDL-C and SBP.

However, adjusting for other confounders including diagnosis criteria for PCOS, study design, ethnicity, and methods of hormonal assay did not associate with any change in the relationships of tT and metabolic parameters. Particularly interesting is the finding that no correlation between tT and metabolic parameters of PCOS was observed also when we evaluated different subgroups of studies divided according the assay method of total testosterone. While there were minor associations between A4, TC, and HDL-C, in general we did not find significant associations between this androgenic marker and metabolic parameters.

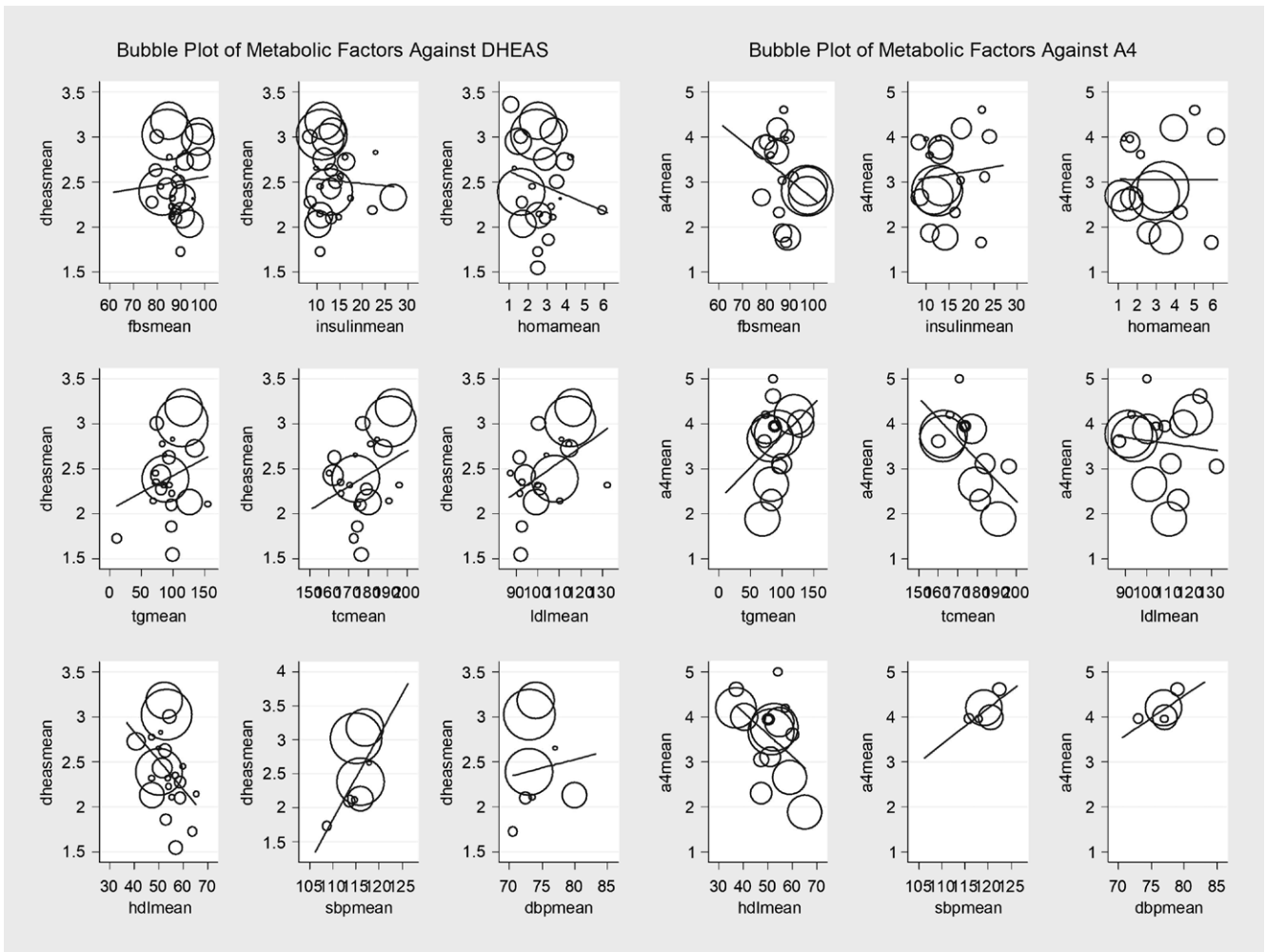
Finally, our study showed that DHEAS had a positive significant association with LDL-C and reverse significant association with HDL-C; after adjustment for the most important confounders such as age, BMI, and methods of assay, this associations remained. This finding is particularly provocative because it has been suggested that low DHEAS levels may be related to a worst metabolic pattern [70].

We did not find significant associations between FBS and androgens. We also did not detect any association between HOMA-IR and androgenic parameters. Our study results showed a reverse significant association between androgens and HDL-C and a positive significant association between LDL-C and androgens, where-

as we did not detect significant associations with other lipids such as TC and TG.

The limitations of this study should be considered in interpretation of the findings. Most studies in this meta-analysis recruited participants from different settings such as hospitals and clinics, which may represent a population with more severe manifestations of PCOS. In this study, we could not investigate the association between biochemical and metabolic parameters, considering all confounders simultaneously because of a limited number of included studies. Our findings can be also limited by variations in lifestyle factors in patients with PCOS that could have affected their metabolic profiles. We have used HOMA-IR as a surrogate marker for assessing of IR. In spite of the good correlation between HOMA-IR and gold standard clamp methods [71], this method might be inaccurate in PCOS subjects [72].

While we aimed to minimize all possible bias in this meta-analysis, it should be noted that there was a significant heterogeneity in androgenic and metabolic parameters among studies. These heterogeneities were partly predictable and may have resulted from clinical heterogeneity related to variability in age, BMI, PCOS diagnostic criteria, hormonal assay methods, race, and ethnicity. We used random effect analysis to deal with the problem. To reduce selection bias and heterogeneity, we excluded studies, that



► **Fig. 3** Bubble plot of the univariate relationships between A4, DHEAS, and metabolic parameters.

their study with populations including patients with chronic disease such as diabetes, cardiovascular, or thyroid disorders. It is important to consider that the majority of patients were young (mean age 25 years) without having obesity (mean BMI 27.61). So, caution should be applied in extrapolating these results for wider applications. Finally our meta-analysis could not include LC.MS methods for measuring androgens because no sufficient number of studies used this new methodology.

The present study provides some clues for better understanding of the pathophysiology of PCOS, which may be helpful in decision-making process and managing patients with this syndrome. Since no sufficient number of studies used LC.MS for measuring androgens, more researches are necessary to assess the androgens levels by this accurate method in patients with PCOS.

Conclusion

In conclusion, our meta-analysis shows few relationships between biochemical parameters of hyperandrogenism and metabolic findings in women with PCOS. Some correlation with serum lipids was observed but was similar to that found when analyzing the effect of androgens in general population (males and females). Only FT

showed a correlation with insulin levels and insulin resistance but it may depend on the well-known effect of insulin on SHBG. Probably, insulin excess has limited effects on androgen ovarian production.

Authors' Contributions

MA was involved in study design, search in databases, study selection, data analysis, manuscript drafting, and submitting the manuscript. FRT was involved in study design, data analysis, manuscript drafting, and critical discussion. SBG contributed searching the databases and study selection. RBY contributed in study selection, data analysis, and critical discussion. FA contributed to study design, execution and manuscript drafting. EC was involved in data analysis, manuscript drafting, revising and critical discussion. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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