Metabolic disturbances in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis

Shiqin Zhu, M.D.,[a,b,c] Bingqian Zhang, M.D.,[a,b,c] Xiao Jiang, M.D.,[a,b,c] Zeyan Li, M.D.,[d] Shigang Zhao, M.D., Ph.D.,[a,b,c] Linlin Cui, M.D., Ph.D.,[a,b,c] and Zi-Jiang Chen, M.D., Ph.D.[a,b,c,e,f]

[a] Center for Reproductive Medicine, Shandong Provincial Hospital Affiliated to Shandong University, [b] National Research Center for Assisted Reproductive Technology and Reproductive Genetics, [c] The Key Laboratory of Reproductive Endocrinology (Shandong University), Ministry of Education, Jinan; and [d] Department of Urology, Qilu Hospital of Shandong University, [e] Center for Reproductive Medicine, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University and [f] Shanghai Key Laboratory for Assisted Reproduction and Reproductive Genetics, Shanghai, People's Republic of China

Objective: To explore metabolic disturbances in nonobese women with polycystic ovary syndrome (PCOS) compared with nonobese healthy controls.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Nonobese women with PCOS and nonobese healthy controls.
Intervention(s): None.
Main Outcome Measure(s): Prevalence of metabolic disturbances including hyperinsulinemia, insulin resistance (IR), impaired fasting glucose (IFG), impaired glucose intolerance (IGT), prediabetes, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, and low high-density lipoprotein (low-HDL), as well as other metabolic outcomes such as type 2 diabetes mellitus (T2DM), hypertension, metabolic syndrome (Mets), myocardial infarction, stroke, cerebrovascular accident, arterial occlusive disease, and coronary heart disease.
Result(s): Compared to nonobese controls, nonobese women with PCOS showed a higher prevalence of hyperinsulinemia (odds ratio [OR], 36.27; 95% confidence interval [CI] 1.76–747.12), IR (OR, 5.70; 95% CI 1.46–22.32), IGT (OR, 3.42; 95% CI 1.56–7.52), T2DM (OR, 1.47; 95% CI 1.11–1.93), hypertriglyceridemia (OR, 10.46; 95% CI 1.39–78.56), low-HDL (OR, 4.03; 95% CI 1.26–12.95), and Mets (OR, 2.57; 95% CI 1.30–5.07). No significant difference was observed for IFG, pre-DM, dyslipidemia, hypercholesterolemia, and hypertension. In subgroup analysis, Whites exhibited increased risks of IR, IGT, IFG, T2DM, hypertension, and Mets, whereas no significant metabolic change was found in Asians. No study reported specifically an incidence of myocardial infarction, stroke, cerebrovascular accident, arterial occlusive disease, and coronary heart disease in nonobese women with PCOS.
Conclusion(s): Nonobese women with PCOS also suffer from metabolic disturbances and the risk of long-term metabolic complications. Further efforts should be made to elucidate underlying mechanisms and possible interventions in the early phase. (Fertil Steril® 2019;111:168–77. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Polycystic ovary syndrome, lean, metabolic syndrome, diabetes mellitus, systematic review

Received May 19, 2018; revised and accepted September 25, 2018.
S.Z. has nothing to disclose. B.Z. reports grant from Shandong Provincial Hospital Affiliated to Shandong University. X.J. reports grant from Shandong Provincial Hospital Affiliated to Shandong University. Z.L. has nothing to disclose. S.Z. reports grant from Shandong Provincial Hospital Affiliated to Shandong University. L.C. reports grant from Shandong Provincial Hospital Affiliated to Shandong University. Z.-J.C. reports grant from Shandong Provincial Hospital Affiliated to Shandong University.
Funded by The National Key Research and Development Program of China (No. 2017YFC1001000), National Natural Science Foundation of China (No. 81501223), and Young Scholars Program of Shandong University.
Reprint requests: Linlin Cui, M.D., Ph.D., Center for Reproductive Medicine, Shandong Provincial Hospital Affiliated to Shandong University, Jingliu Road 157, 250001 Jinan, People's Republic of China (E-mail: fdclear3@126.com).

Fertility and Sterility® Vol. 111, No. 1, January 2019 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.09.013

Polycystic ovary syndrome (PCOS), as one of the most common gynecological endocrine diseases, affects 6%–8% of women of reproductive age (1, 2). In addition to typical reproductive endocrinal changes, namely oligoovulation and anovulation, hyperandrogenism, and polycystic ovaries (PCOs) morphology and metabolic disturbances are also identified in most patients (3, 4). Accumulated evidence has demonstrated increasing risks of metabolic complications including insulin resistance (IR), type 2 diabetes mellitus (T2DM), metabolic syndrome (Mets), and cardiovascular disease (CVD) in this group of women (5, 6).

Obesity is extensively considered as the key basis of these metabolic complications, which can be observed in approximately half of women with PCOS. However, the metabolic features of patients with PCOS, but without obesity, are controversial. Some studies (3, 7, 8) demonstrated that patients with PCOS are still at increased risk of metabolic dysfunctions after the adjustment of body mass index (BMI). A previous meta-analysis (3) also indicated an elevated prevalence of impaired glucose tolerance (IGT) and Mets especially in lean women (BMI <25 kg/m^2) with PCOS compared with BMI-matched controls. Whereas, Cheung et al. (9) and Ollila et al. (10) suggested equivalent metabolic risks between nonobese women with PCOS and BMI-matched healthy controls.

Polycystic ovary syndrome is complex with heterogeneous manifestation and complicated etiology. Revealing the metabolic condition of nonobese women with PCOS can guide clinical screening and treatment, and indicate the possible metabolic pathway in this patient group. The aim of the present systematic review and meta-analysis is to estimate the differences in prevalence of glucose metabolic profiles, cardiovascular risk factors, and Mets between nonobese women of reproductive age with and without PCOS and to access the effect of the confounding factors such as PCOS definition and ethnicity.

MATERIALS AND METHODS

Search Strategy

This systematic review and meta-analysis was reported based on the Preferred Reporting Item for Systematic Reviews and Meta-analyses statement (11). Electronic literature search was performed in MEDLINE, Web of Science, Embase, and Cochrane library databases up to November 2017. The following terms were used in automatic search: polycystic ovary syndrome, PCOS, Stein Leventhal Syndrome, hyperlipidemia, hypertension, cardiovascular disease, CVD, Diabetes Mellitus, T2DM, Prediabetes, impaired glucose tolerance, IGT, impaired fasting glucose, impaired fasting glucose (IFG), insulin resistance, IR, hyperinsulinemia, Metabolic Syndrome, Mets, lean, non-obese, and normal weight. Detailed search strategy was shown in Supplemental Table 1 (available online). Languages were limited to English and Chinese.

Reference lists and relevant reviews were also manually searched to avoid omission of potential eligible studies. First authors and corresponding authors were contacted for additional information if necessary. Abstracts containing necessary information were considered.

Inclusion and Exclusion Criteria

Two independent reviewers (S.Z. and L.C.) identified and selected the articles according to the inclusion and exclusion criteria. The articles that compared the prevalence of metabolic abnormities between nonobese women with PCOS and BMI-matched controls were considered as eligible studies. The inclusion criteria were as follows: [1] observational studies; [2] studies focused on evaluating prevalence of any metabolic abnormities between the nonobese premenopausal women with PCOS and nonobese premenopausal controls; [3] dichotomous data were reported or sufficient data were available to extrapolate the odds ratio (OR) and its 95% confidence interval (CI); [4] the most recent and complete study was selected when overlapped datasets appeared; and [5] studies reporting two independent cohorts were included separately.

Polycystic ovary syndrome was defined in accordance with the National Institutes of Health (NIH) criteria (12), or the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria (13, 14), or the Androgen Excess and PCOS Society (AES) criteria (15). For some studies before the 21st century, definitions of PCOS based on the original articles were also accepted. Nonobesity was defined as a BMI <30 kg/m^2 for Whites and BMI <25 kg/m^2 for Asians, according to World Health Organization criteria (WHO 1998, WHO 2000) (16). Studies with BMI cutoff values <30 in Whites and 25 in Asians were included. Definitions of outcomes were based on the descriptions of original studies. Detailed definitions of outcomes in each study were listed in Supplemental Table 2 (available online). The exclusion criteria were as follows: [1] animal studies, [2] participants were investigated after certain treatments, [3] lack of BMI classification, [4] invalid definition of PCOS, [5] <20 observations, and [6] studies involving data from adolescents.

Data Extraction

Data were extracted from all eligible articles. These included sample size, age, race, study location, study design, baseline health state, definition of PCOS, BMI category, outcomes, definition of outcomes, calculated OR and its 95% CI, and adjusted confounders.

Quality Assessment

Included studies were critically assessed according to the Newcastle-Ottawa Quality Assessment Scale (NOS) (17), a valid tool recommended by the Cochrane Working Group to appraise the risk of bias of nonrandomized studies. As for cross-sectional studies, an adapted NOS scale was used. This modified scale, proposed by Barry et al. (18), adjusted the item of "ascertainment of diagnosis" to "ascertainment of exposure," which made NOS applicable for cross-sectional studies. Studies were graded into low quality (0–3 points), medium quality (4–6 points), and high quality (7–9 points) according to NOS score. Two reviewers (S.Z. and L.C.)

independently participated in quality assessment. Consensus was reached to resolve the disagreements.

Outcomes of Interest

Some outcomes of interest were the prevalence of metabolic disturbances, which included hyperinsulinemia (HIN), IR, IFG, IGT, pre-diabetes (pre-DM), dyslipidemia, hypercholesterolemia (high-TC), hypertriglyceridemia (high-TG), and low high-density lipoprotein (low-HDL). Other metabolic outcomes included T2DM, hypertension, Mets, myocardial infarction, stroke, cerebrovascular accident, arterial occlusive disease, and coronary heart disease.

Statistical Analysis

The OR and its 95% CI were used to estimate outcomes in nonobese women with PCOS versus nonobese healthy controls. Hazard ratio was considered equivalent to OR (19). Studies with zero events in both groups were omitted automatically from meta-analysis because of their limited contribution to the pooled estimation (20). Pooled ORs were calculated using the fixed-effects model and heterogeneity between studies was measured by the Q-test and I^2 statistics. $P<.1$ and $I^2>50\%$ indicated significant heterogeneity, where the random-effects model was applied instead. Subgroup analyses were stratified by ethnic, age, different definitions, BMI category, study design, NOS quality, adjusted waist circumference, and adjusted age. Sensitivity analyses were performed to test the stability of overall analysis by omitting single research or changing effect model. Publication bias was assessed by Egger's regression test (21, 22). Nonparametric trim-and-fill method was conducted to test publication bias when Egger's regression test was not applicable. Significant publication bias was defined as $P<.1$. Two-tail P value was adopted in this review and $P<.05$ was considered significant. All statistical analyses were accomplished in STATA 12.0.

RESULTS

Search Results

Search results are illustrated in the flow chart (Fig. 1). A total of 7,432 articles were yielded in the electronic search and 27 articles were searched from reference list or reviews. After title and abstract screening based on prior selection criteria, 118 articles were identified for full text assessment. In further examination, 35 studies were excluded for irrelevant outcomes, 43 were excluded for undesirable participants, 9 were excluded for foreign languages, 7 were excluded for involving adolescents, and 2 were excluded for overlapped datasets. Eventually, 22 full-text studies were included in the present meta-analysis.

Studies Characteristics

Characteristics of all 22 included studies are displayed in Supplemental Table 2. All eligible studies investigated the prevalence of metabolic abnormities in nonobese premenopausal women with PCOS and nonobese women without PCOS. Among them, 16 studies focused on glucose metabolic disturbances including IR, HIN, IGT, IFG, pre-DM, and T2DM (7–10, 23–34); 7 reported CVD risk factors, including dyslipidemia, hypertension, high-TC, high-TG, and low-HDL (9, 25, 27, 30, 35–37) and 7 assessed Mets (7, 9, 27, 32, 38–40). No study investigated the prevalence of myocardial infarction, stroke, cerebrovascular accident, arterial occlusive disease, and coronary heart disease in nonobese women with PCOS. Studies were published from 1986 to 2017 and overall 9,967 participants were recruited. Multiple ethnic groups were included in the present review as follows: White (n = 16) (7, 8, 10, 23, 27–31, 33–37, 39, 40), Mediterranean (n = 2) (26, 32), East Asian (n = 2) (9, 24), and Indian (n = 1) (38). Definitions of PCOS were mainly according to the NIH criteria (n = 6) (23, 25–27, 37, 40) and the Rotterdam criteria (n = 11) (7, 9, 24, 32–35, 37–40). Four studies adopted original definitions (28–31) and 2 studies were based on structured interview and self-reports (10, 36).

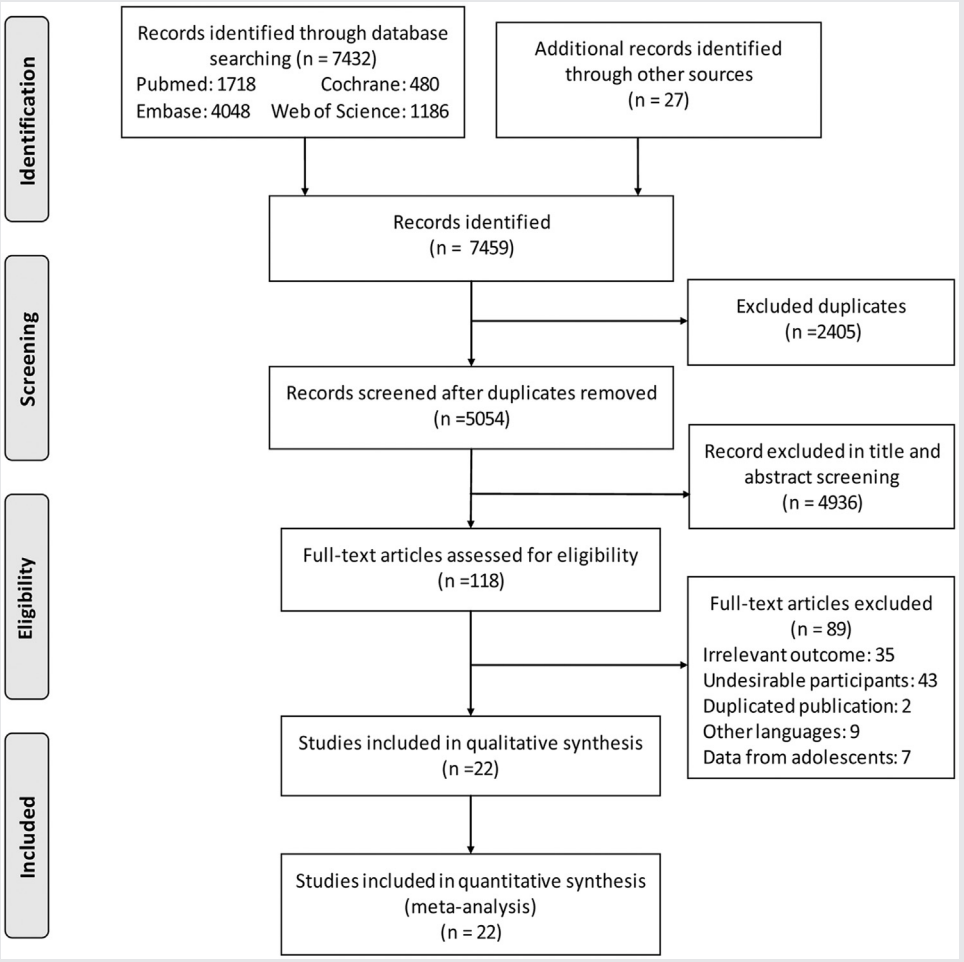
Methodological Quality

Assessment of risk of bias is illustrated in Supplemental Table 3 (available online). Overall, 9 studies were graded into high quality. One study was recognized as low quality because of limited data for NOS score. Seventeen studies recruited subjects matching for confounders such as age, BMI, and waist and hip circumference. No history of medication was declared in 11 studies, whereas 2 studies adjusted the condition of treatments. In 10 studies, early events were excluded before cases recruitment. In 9 studies, other relevant information such as smoking, alcohol use, and family history of metabolic diseases, was also recorded (Supplemental Table 4, available online). Given the remarkable between-studies heterogeneity of clinical characteristics, sensitivity analyses and publication bias assessment were conducted for each analysis.

Comparison in Glucose Metabolism Outcomes

According to meta-analysis, increased risks of IR (OR, 5.70; 95% CI 1.46–22.32; $P=.012$; $P_h = .005$; $I^2 = 81.1\%$) and IGT (OR, 3.42; 95% CI 1.56–7.52; $P=.002$; $P_h = .310$; $I^2 = 16.3\%$) were found in nonobese premenopausal women with PCOS. One study reported higher prevalence of HIN in nonobese women with PCOS (OR 36.27; 95% CI 1.76–747.12) (29). In addition, nonobese women with PCOS also showed increased risk of T2DM (OR 1.47; 95% CI 1.11–1.93; $P=.007$; $P_h = .555$; $I^2 = 0$). When the design of the study was restricted to cohort, pooled OR remained significant (OR 1.48; 95% CI 1.12–1.95; $P=.007$; $P_h = .245$; $I^2 = 29.0\%$). However, there was no remarkable difference of prevalence in IFG and pre-DM (for IFG: OR 1.08; 95% CI 0.46–2.53; $P=.864$; $P_h = .109$ $I^2 = 50.4\%$; for pre-DM: OR 1.39; 95% CI 0.73–2.63; $P=.317$; $P_h = .459$; $I^2 = 0$) (Table 1, Fig. 2). Subgroups with increased risks of metabolic disturbances were listed in Supplemental Table 5 (available online). In subgroup analyses, the risks of IR, IGT, IFG, and T2DM were elevated in nonobese White patients ($P<.05$), whereas in other ethnic groups, only elevated risk of IR was identified in Mediterraneans. Except

FIGURE 1



Flow diagram for study selection.

Zhu. Metabolic disturbances in non-obese PCOS. Fertil Steril 2018.

for IR, which was pooled from studies using only Rotterdam criteria, all other parameters of glucose metabolism were analyzed further after dividing by PCOS definition. Significant increase was still found in IGT in cases based on the Rotterdam criteria (OR 2.74; 95% CI 1.19–6.31; P=.018), and T2DM in cases based on the NIH criteria (OR 2.76; 95% CI 1.12–6.88; P=.030) and on medical record (OR 1.37; 95% CI 1.03–1.84; P=.034). There is no difference of IFG based on the Rotterdam criteria and pre-DM based on the NIH criteria. Impaired glucose intolerance and IFG based on the NIH criteria as well as T2DM based on the Rotterdam criteria were not meta-analyzed because of the limited amount of studies included, but no difference was reported in each of the above studies. Detailed results of subgroup analyses are illustrated in Supplemental Tables 6–10 (available online).

Comparison in CVD Risk Factors

Elevated prevalence of high-TG and low-HDL were showed in nonobese patients with PCOS (for high-TG: OR 10.46; 95% CI 1.39–78.56; P=.022; P_h = .554; I^2 = 0; for low-HDL: OR 4.03; 95% CI 1.26–12.95; P=.019; P_h = .626; I^2 = 0). But no significant difference was found in prevalence of high-TC, dyslipidemia, and hypertension (for high-TC: OR 5.78; 95% CI 0.31–107.92; for dyslipidemia: OR 1.87; 95% CI 0.85–4.13; P=.121; P_h = .913; I^2 = 0; for hypertension: OR 2.44; 95% CI 0.80–7.43; P=.117; P_h = .117; I^2 = 53.3%) (Table 1, Fig. 3). In subgroup analyses, between-studies heterogeneity for hypertension could be explained by ethnicity. Whites displayed a fourfold increased risk of hypertension (OR 4.27; 95% CI 2.04–8.96; P<.001; P_h = .812; I^2 = 0). After being divided by PCOS definition, elevated risk of hypertension remained in cases based on self-report (OR 4.37; 95% CI 2.04–9.38; P<.001), whereas no difference was found in cases diagnosed by the Rotterdam criteria (OR 1.22; 95% CI 0.42–3.60; P=.714). As for other parameters of CVD, both high-TG and low-HDL were pooled from studies using the Rotterdam criteria and only one study, which reported no difference in high-TC, was adopted the Rotterdam, the NIH, and the Androgen Excess and PCOS Society criteria. No difference

TABLE 1

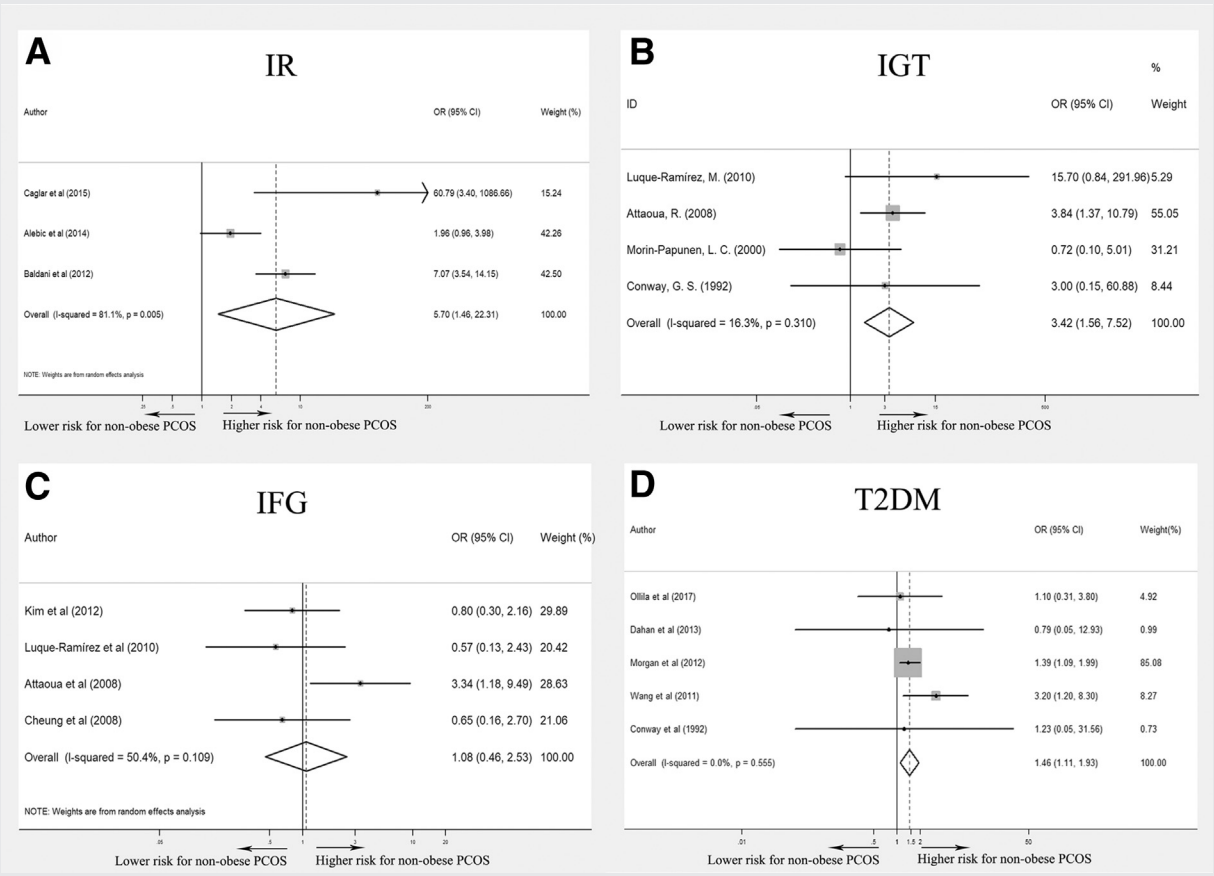
Meta-analysis results for glucose metabolic disturbances and cardiovascular disease risk factors.

Outcome	No. of studies	Effects model	OR (95%CI)	*P* value	Heterogeneity P_h value	Heterogeneity I^2 (%)
Comparison in glucose metabolism disturbances						
HIN	1		36.27 (1.76, 747.12)			
IR	3	Random	5.70 (1.46, 22.32)	.012	0.005	81.1
IFG	4	Random	1.08 (0.46, 2.53)	.864	0.109	50.4
IGT	4	Fixed	3.42 (1.56, 7.52)	.002	0.310	16.3
Pre-DM	3	Fixed	1.39 (0.73, 2.63)	.317	0.459	0
T2DM	5	Fixed	1.47 (1.11, 1.93)	.007	0.555	0
T2DM cohort	3	Fixed	1.48 (1.12, 1.95)	.007	0.245	29
Comparison in CVD risk factors						
Dyslipidemia	2	Fixed	1.87 (0.85, 4.13)	.121	0.913	0
high-TC	1		5.78 (0.31, 107.92)			
high-TG	2	Fixed	10.46 (1.39, 78.56)	.022	0.554	0
low-HDL	2	Fixed	4.03 (1.26, 12.95)	.019	0.626	0
Hypertension	3	Random	2.44 (0.80, 7.43)	.117	0.117	53.3

Note: CI = confidence interval; CVD = cardiovascular disease; high-TC = hypercholesterolemia; high-TG = hypertriglyceridemia; HIN = hyperinsulinemia; IFG = impaired fasting glucose; IGT = impaired glucose intolerance; IR = insulin resistance; low-HDL = low high-density lipoprotein; Pre-DM = IGT plus IFG; OR = odds ratio; T2DM = type 2 diabetes mellitus.

Zhu. Metabolic disturbances in non-obese PCOS. Fertil Steril 2018.

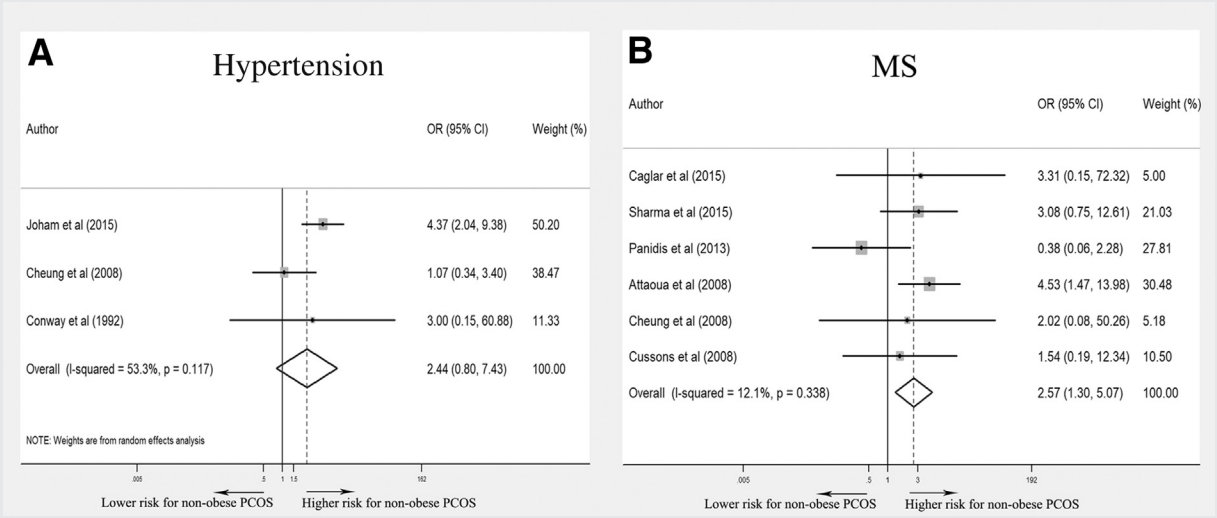
FIGURE 2



Meta-analysis on insulin resistance (IR), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and type 2 diabetes mellitus (T2DM): nonobese women with PCOS versus nonobese healthy controls. Forest plot displayed odds of IR **(A)**, IGT **(B)**, IFG **(C)**, and T2DM **(D)** in nonobese women with PCOS versus nonobese healthy controls.

Zhu. Metabolic disturbances in non-obese PCOS. Fertil Steril 2018.

FIGURE 3



Forrest plot displayed odds of hypertension and metabolic syndrome (Mets) in nonobese women with PCOS versus nonobese healthy controls. **(A)** Meta-analysis on hypertension; **(B)** meta-analysis on Mets.

Zhu. Metabolic disturbances in non-obese PCOS. Fertil Steril 2018.

was found in dyslipidemia on either the NIH or the Rotterdam criteria. Detailed results are shown in Supplemental Table 5 and Supplemental Tables 11–14, available online.

Comparison in Mets Risk

Using the fixed-effects model, a 2.6-fold increased risk of Mets was found in nonobese women with PCOS compared with nonobese controls (OR 2.57; 95% CI 1.30–5.07; $P=.007$; $P_h=.338$; $I^2=12.1\%$) (Fig. 3). In subgroup analyses, consistent results were observed in the White group (OR 2.40; 95% CI 1.05–5.49; $P=.039$) and the group in which Mets was defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria (OR 3.77; 95% CI 1.62–8.77; $P=.002$) (Supplemental Table 5). However, no difference was found in the non-White group and the group in which IDF was used as the definition for Mets. All eligible studies on Mets were based on the Rotterdam criteria (Supplemental Table 15, available online).

Sensitivity Analyses and Publication Bias

Sensitivity analyses verified the robustness of the results of all outcomes except for T2DM. Significant variations were introduced in pooled OR of T2DM after omitting one study (OR 1.96; 95% CI 0.95–4.02). No obvious publication bias was detected according to Egger's tests and trim and filled analyses (Supplemental Table 16, available online). A sensitivity analysis graph of Mets is shown in Supplemental Figure 1, available online.

DISCUSSION

The present meta-analysis showed that even without obesity, PCOS patients still presented an increased prevalence of glucose metabolic disturbances including HIN, IR, IGT, and T2DM compared with BMI-matched controls. In addition, frequencies of high-TG, low-HDL, and Mets were increased in nonobese women with PCOS, which indicated more risk of adverse metabolic outcomes such as CVD.

Insulin resistance was supposed to be strongly correlated with obesity, but in our meta-analysis, it was also more frequently encountered in nonobese patients with PCOS than in nonobese controls. This suggested that the pathophysiological change may not only be a result consequent to obesity but also an intrinsic etiologic basis for PCOS regardless of obesity. Relative genes variations, defect of the certain signaling pathway, and the vicious circle between the two with hyperandrogenism are proposed as possible underlying mechanisms. Previous genome-wide association studies (41, 42) revealed that *INSR* and *DENND1A* conferred to a PCOS risk. In subsequent study (42) these two genes were demonstrated to be associated with IR in patients with PCOS, which suggested a genetic basis. In addition, tissue-specific defects in the insulin signal transduction were also involved in IR in PCOS. Except for well-accepted abnormality in the adipocyte of subjects with PCOS, myotubes also displayed impaired insulin responsiveness for glucose disposal. It was correlated with diminished insulin-stimulated Akt phosphorylation, a key step of insulin signaling pathway, in skeletal muscle of patients with PCOS (43, 44). It could in part explain IR in nonobese patient with PCOS. In addition, animal studies (45, 46) indicated that hyperandrogenism could contribute to IR by increasing serine phosphorylation on myotubes and facilitating visceral fat accumulation. The paralleled change of serum-free T and reduced insulin-stimulated glucose disposal were also confirmed in women with PCOS (44). Hyperinsulinemia was also observed in nonobese women with PCOS according to the present meta-

analysis. Except for a compensatory response to IR, reduced hepatic clearances of insulin provided correlative evidence as well (47, 48). The intrinsic abnormalities in IR contributed to elevated risk for adverse metabolic outcomes including IGT, T2DM, and Mets in nonobese women with PCOS, which was demonstrated by the present study.

According to the present study, nonobese patients with PCOS showed higher prevalence of high-TG and low-HDL compared with their counterparts. Dyslipidemia was one of the most frequent cardiovascular metabolic disturbances in women with PCOS, which could exaggerate the risk for CVD (35). The reason for abnormal lipid metabolism is multifactorial, and involves abnormal hormone changes such as insulin, androgen, and estrogen (E), as well as environmental factors (49). Enhanced ApoCI-mediated block of several enzymes and receptors within pathway of lipoprotein transfer and metabolism was supposed as the possible mechanism in normal-weight women with PCOS (50). The guidelines from the Androgen Excess and PCOS Society recommend that lipid pattern screening be performed in all women with PCOS (51). However, no difference was found in hypertension, another CVD risk factor, in nonobese women with and without PCOS. The relative young age of subjects enrolled might be an important confounding factor. Cohort studies with a longer duration of follow-up are needed.

Our study identified a significant increase in Mets incidence in nonobese patients with PCOS. Mets is a cluster of dysfunction in glucose and lipid metabolism including central obesity, glucose intolerance, dyslipidemia, and hypertension (52, 53). It is a well-documented risk factor for T2DM and CVD. Insulin resistance and central obesity are considered to play a common etiologic role in Mets and PCOS (54, 55). Impaired insulin sensitivity and responsiveness would result in hyperglycemia and hyperlipidemia by reducing adipocyte glucose uptake and stimulating adipocyte lipolysis (56, 57). Central obesity with excess visceral fat could exacerbate IR in normal weight subjects (58, 59). After adjustment for waist circumference, no difference was found for Mets incidence according to the results of subgroup analysis in the present study. It suggested that accumulation of visceral fat might be a key reason for the development of Mets in nonobese women with PCOS. Notably, various diagnostic criteria of Mets were adopted in the included literature, which was a great confounding factor. On subgroup analyses, increased frequency of Mets as defined only in Adult Treatment Panel III was maintained in nonobese women with PCOS.

Differences of ethnicity and PCOS diagnostic criteria were noted to result in significant clinical heterogeneity in the present study. Therefore, subgroup analyses based on these two variables were conducted. Differences were maintained for IR, IGT, IFG, T2DM, hypertension, and Mets in nonobese White, and IR in Mediterranean, but none in Asian. Specific genetic background (42, 60) and environmental exposures, such as high-fat diet and smoking (61, 62), were the most possible reasons. With regard to PCOS diagnostic criteria, some previous studies (63, 64) showed that women diagnosed with the NIH criteria had a higher prevalence of Mets. In our study, the prevalence of metabolic disturbances, including IR, IGT, high-TG, low-HDL, and Mets, were increased in nonobese women with PCOS, as diagnosed by the Rotterdam consensus. It was partly consistent with the study of Yildiz et al. (65), which reported a twofold increased risk of Mets in patients with PCOS regardless of diagnostic criteria adopted.

The results of the present study provided relative solid evidence for metabolic deterioration in nonobese women with PCOS based on systemic review and standard meta-analysis of all published studies. However, several limitations still existed. First, the heterogeneity caused by different definitions of nonobesity and metabolic disturbances in the studies, and lack of baseline information, including medical history, family history, smoking, and alcohol conditions, would still bring biases. As a remedy, subgroup analyses and sensitivity analyses were conducted in the present meta-analysis. Second, in most of the studies, the cutoff values of BMI were below the WHO criteria, which might shrink the case group and cover up the difference of outcomes to some extent. Prospective cohort studies based on homogeneous populations of large sample size with strict definition of nonobesity are still needed to verify the conclusion. Third, because the number of eligible studies in each subgroup was limited, the results of subgroup analyses should be explained with more caution. In addition, metabolic dysfunction is a life-long process that would exaggerate risk of adverse metabolic outcomes such as CVD with aging. The relative young age of the enrolled subjects in the study may conceal some outcomes of interest. Thus the conclusions should be confirmed in a well-designed longitudinal cohort study with confounding factors precisely controlled.

In conclusion, our study demonstrated that nonobese women with PCOS also suffered from glucose and lipid metabolic disturbances, as well as metabolic complications including T2DM and Mets. It suggested that early screening and intervention should be extended to this subset of patients. Future study should focus on elucidating the underlying mechanism and finding the optimal time point for screening and intervention.

Acknowledgments: The authors thank Professor Helena J. Teede and Professor Onno E. Janssen for providing the preliminary information.

REFERENCES

1. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab 1999; 84:4006–11.
2. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007;370:685–97.
3. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010;16:347–63.
4. Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2017;32:1075–91.

5. Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. Trends Endocrinol Metab 2015;26:136–43.
6. Ali AT. Polycystic ovary syndrome and metabolic syndrome. Ceska Gynekol 2015;80:279–89.
7. Attaoua R, El Mkadem SA, Radian S, Fica S, Hanzu F, Albu A, et al. FTO gene associates to metabolic syndrome in women with polycystic ovary syndrome. Biochem Biophys Res Commun 2008;373:230–4.
8. Morgan CL, Jenkins-Jones S, Currie CJ, Rees DA. Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched, reference controls: a retrospective, observational study. J Clin Endocrinol Metab 2012;97:3251–60.
9. Cheung L, Ma R, Lam P, Lok I, Haines C, So W, et al. Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. Hum Reprod 2008;23:1431–8.
10. Ollila M-M, West S, Keinänen-Kiukaanniemi S, Jokelainen J, Auvinen J, Puukka K, et al. Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus—a prospective, population-based cohort study. Hum Reprod 2017;32:423–31.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
12. Zawadski J. Diagnostic criteria for polycystic ovary syndrome, towards a rational approach. Polycystic ovary syndrome, 1992:39–50.
13. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. et al. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:417.
14. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97:28–38.e25.
15. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006;91:4237–45.
16. World Health Organization. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia; 2000 Feb.
17. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2009. Epub Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [cited 2009 Oct 19] 2013. Accessed January 23, 2018.
18. Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2011;26:2442–51.
19. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA 2011;306:1241–9.
20. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2011.
21. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
22. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
23. Dahan M, Morris D. The impact of body mass index (BMI) on the incidence of type 2 diabetes (DMII) in women with and without polycystic ovary syndrome (PCOS). Fertil Steril 2013;100:S348–9.
24. Kim JJ, Choi YM, Cho YM, Jung HS, Chae SJ, Hwang KR, et al. Prevalence of elevated glycated hemoglobin in women with polycystic ovary syndrome. Hum Reprod 2012;27:1439–44.
25. Wang ET, Calderon-Margalit R, Cedars MI, Daviglus ML, Merkin SS, Schreiner PJ, et al. Polycystic ovary syndrome and risk for long-term diabetes and dyslipidemia. Obstet Gynecol 2011;117:6.
26. Luque-Ramírez M, Alpañés M, Escobar-Morreale HF. The determinants of insulin sensitivity, β-cell function, and glucose tolerance are different in patients with polycystic ovary syndrome than in women who do not have hyperandrogenism. Fertil Steril 2010;94:2214–21.
27. Faloia E, Canibus P, Gatti C, Frezza F, Santangelo M, Garrapa G, et al. Body composition, fat distribution and metabolic characteristics in lean and obese women with polycystic ovary syndrome. J Endocrinol Invest 2004;27:424–9.
28. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Tapanainen JS. Insulin sensitivity, insulin secretion, and metabolic and hormonal parameters in healthy women and women with polycystic ovarian syndrome. Hum Reprod 2000;15:1266–74.
29. Dos Reis R, Foss M, de Moura MD, Ferriani R, Silva de Sa M. Insulin secretion in obese and non-obese women with polycystic ovary syndrome and its relationship with hyperandrogenism. Gynecol Endocrinol 1995;9:45–50.
30. Conway GS, Agrawal R, Betteridge D, Jacobs H. Risk factors for coronary artery disease in lean and obese women with the polycystic ovary syndrome. Clin Endocrinol (Oxf) 1992;37:119–25.
31. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989;38:1165–74.
32. Çağlar GS, Kiseli M, Seker R, Ozdemir ED, Karadag D, Demirtas S. Atherogenic dyslipidemia, subclinical atherosclerosis, non-alcoholic fatty liver disease and insulin resistance in polycystic ovarian syndrome/[Polikistik over sendromunda insülin direnci, aterojenik dislipidemi, subklinik aterosklerozis ve non-alkolik yağlı karaciğer hastalığı]. Turkish J Biochem 2015;40:24–30.
33. Alebić MŠ, Bulum T, Stojanović N, Duvnjak L. Definition of insulin resistance using the homeostasis model assessment (HOMA-IR) in IVF patients diagnosed with polycystic ovary syndrome (PCOS) according to the Rotterdam criteria. Endocrine 2014;47:625–30.
34. Pavicic Baldani D, Skrgatic L, Sprem Goldstajn M, Zlopasa G, Kralik Oguic S, Canic T, et al. Clinical and biochemical characteristics of polycystic ovary syndrome in Croatian population. Coll Antropol 2012;36:1413–8.
35. Blagojevic IP, Eror T, Pelivanovic J, Jelic S, Kotur-Stevuljevic J, Ignjatovic S. Women with polycystic ovary syndrome and risk of cardiovascular disease. J Med Biochem 2017;36:259–69.
36. Joham AE, Boyle JA, Zoungas S, Teede HJ. Hypertension in reproductive-aged women with polycystic ovary syndrome and association with obesity. Am J Hypertens 2014;28:847–51.
37. Rocha MP, Marcondes JA, Barcellos CR, Hayashida SA, Curi DD, da Fonseca ÂM, et al. Dyslipidemia in women with polycystic ovary syndrome: incidence, pattern and predictors. Gynecol Endocrinol 2011;27:814–9.
38. Sharma S, Majumdar A. Prevalence of metabolic syndrome in relation to body mass index and polycystic ovarian syndrome in Indian women. J Hum Reprod Sci 2015;8:202.
39. Panidis D, Tziomalos K, Macut D, Kandaraki EA, Tsourdi EA, Papadakis E, et al. Age-and body mass index-related differences in the prevalence of metabolic syndrome in women with polycystic ovary syndrome. Gynecol Endocrinol 2013;29:926–30.
40. Cussons AJ, Watts GF, Burke V, Shaw JE, Zimmet PZ, Stuckey BG. Cardiometabolic risk in polycystic ovary syndrome: a comparison of different approaches to defining the metabolic syndrome. Hum Reprod 2008;23:2352–8.
41. Chen ZJ, Zhao H, He L, Shi Y, Qin Y, Shi Y, et al. Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. Nat Genet 2011;43:55–9.
42. Shi Y, Zhao H, Shi Y, Cao Y, Yang D, Li Z, et al. Genome-wide association study identifies eight new risk loci for polycystic ovary syndrome. Nat Genet 2012;44:1020–5.
43. Ciaraldi TP, Aroda V, Mudaliar S, Chang RJ, Henry RR. Polycystic ovary syndrome is associated with tissue-specific differences in insulin resistance. J Clin Endocrinol Metab 2009;94:157–63.
44. Hojlund K, Glintborg D, Andersen NR, Birk JB, Treebak JT, Frosig C, et al. Impaired insulin-stimulated phosphorylation of Akt and AS160 in skeletal muscle of women with polycystic ovary syndrome is reversed by pioglitazone treatment. Diabetes 2008;57:357–66.
45. Manneras L, Cajander S, Holmang A, Seleskovic Z, Lystig T, Lonn M, et al. A new rat model exhibiting both ovarian and metabolic characteristics of polycystic ovary syndrome. Endocrinology 2007;148:3781–91.

46. Allemand MC, Irving BA, Asmann YW, Klaus KA, Tatpati L, Coddington CC, et al. Effect of testosterone on insulin stimulated IRS1 Ser phosphorylation in primary rat myotubes—a potential model for PCOS-related insulin resistance. PLoS One 2009;4:e4274.
47. Ciampelli M, Fulghesu AM, Cucinelli F, Pavone V, Caruso A, Mancuso S, et al. Heterogeneity in beta cell activity, hepatic insulin clearance and peripheral insulin sensitivity in women with polycystic ovary syndrome. Hum Reprod 1997;12:1897–901.
48. Amato MC, Vesco R, Vigneri E, Ciresi A, Giordano C. Hyperinsulinism and polycystic ovary syndrome (PCOS): role of insulin clearance. J Endocrinol Invest 2015;38:1319–26.
49. Wild RA. Dyslipidemia in PCOS. Steroids 2012;77:295–9.
50. Huang S, Qiao J, Li R, Wang L, Li M. Can serum apolipoprotein C-I demonstrate metabolic abnormality early in women with polycystic ovary syndrome? Fertil Steril 2010;94:205–10.
51. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocr Metab 2010;95:2038–49.
52. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
53. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am 2014;43:1–23.
54. Alberti KGM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. Lancet 2005;366:1059–62.
55. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome. Circulation 2005;112:2735–52.
56. Boucher J, Kahn CR. Differential roles of insulin and IGF-1 receptor in brown and white adipose tissue and development of lipoatrophic diabetes. Diabetes 2013;62:A37.
57. Kumar A, Lawrence JC, Jung DY, Ko HJ, Keller SR, Kim JK, et al. Fat cell-specific ablation of rictor in mice impairs insulin-regulated fat cell and whole-body glucose and lipid metabolism. Diabetes 2010;59:1397–406.
58. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796–808.
59. Yudkin JS, Stehouwer C, Emeis J, Coppack S. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972–8.
60. Hayes MG, Urbanek M, Ehrmann DA, Armstrong LL, Lee JY, Sisk R, et al. Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. Nat Commun 2015;6:7502.
61. Garruti G, de Palo R, de Angelisc M. Weighing the impact of diet and lifestyle on female reproductive function. Curr Med Chem 2017;24:1. https://doi.org/10.2174/0929867324666170518101008.
62. Glintborg D, Mumm H, Hougaard D, Ravn P, Andersen M. Ethnic differences in Rotterdam criteria and metabolic risk factors in a multiethnic group of women with PCOS studied in Denmark. Clin Endocrinol (Oxf) 2010;73:732–8.
63. Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod Update 2009;15:477–88.
64. Anaforoglu I, Algun E, Incecayir O, Ersoy K. Higher metabolic risk with National Institutes of Health versus Rotterdam diagnostic criteria for polycystic ovarian syndrome in Turkish women. Metab Syndr Relat Disord 2011;9:375–80.
65. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod 2012;27:3067–73.

Alteraciones metabólicas en mujeres no obesas con síndrome de ovario poliquístico: Una revisión sistemática y meta-análisis

Objetivo: Comparar alteraciones metabólicas entre mujeres no obesas con síndrome de ovario poliquístico (PCOS) y controles sanos.

Diseño: Revisión sistemática y meta-análisis.

Entorno: No aplicable.

Paciente(s): mujeres no obesas con PCOS y controles sanos no obesas.

Intervención(es): Ninguna.

Principales medidas de resultado: Prevalencia de alteraciones metabólicas incluyendo hiperinsulinemia, resistencia a la insulina (IR), alteración de la glucosa en ayunas (IFG), alteración de la intolerancia a la glucosa (IGT), prediabetes, dislipidemia, hipercolesteloremia, hipertrigliceridemia, niveles bajos de la lipoproteína de alta densidad (low-HDL), así como, otros resultados metabólicos como la diabetes mellitus tipo II (T2DM), hipertensión, síndrome metabólico (Mets), infarto de miocardio, apoplejía, accidente cerebrovascular, enfermedad arterial oclusiva, y enfermedad coronaria.

Resultados: Comparado con controles no obesas, las mujeres no obesas con PCOS mostraron una prevalencia más alta de hiperinsulinemia (Odds Ratio [OR] 36.27; 95% intervalo de confianza[CI] 1.76–747.12), IR (OR, 5.70; 95% CI 1.46–22.32), IGT (OR, 3.42; 95% CI 1.56–7.52), T2DM (OR, 1.47; 95% CI 1.11–1.93), hipertrigliceridemia (OR, 10.46; 95% CI 1.39–78.56), low-HDL (OR, 4.03; 95% CI 1.26–12.95), y Mets (OR, 2.57; 95% CI 1.30–5.07). No se observaron diferencias significativas para IFG, pre-DM, dislipidemia, hipercolesterolemia ni hipertensión. En el análisis de subgrupos, las mujeres blancas mostraron un riesgo incrementado de IR, IGT, IFG, T2DM, hipertensión y Mets, mientras que en las mujeres asiáticas no se encontraron cambios metabólicos. Ningún estudio ha informado específicamente de la incidencia de infarto de miocardio, apoplejía, accidente cerebrovascular, enfermedad arterial oclusiva ni enfermedad coronaria en mujeres no obesas con PCOS.

Conclusión: Las mujeres no obesas con PCOS también sufren alteraciones metabólicas y tienen riesgo de complicaciones metabólicas a largo plazo. Se deben realizar más esfuerzos para aclarar los mecanismos subyacentes y las posibles intervenciones en la fase inicial.