



Plasma Lipoprotein(a) Levels in Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis

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Abstract

Introduction The polycystic ovary syndrome (PCOS) may represent an important model of lipid alterations. Lipoprotein(a) [Lp(a)] has emerged as a new marker of cardiovascular risk.

Aim The main objective of this meta-analysis was to analyze the available evidence on Lp(a) levels in patients with PCOS compared to a control group.

Methods This meta-analysis was performed according to PRISMA guidelines. A literature search was performed to detect studies that have quantified Lp(a) levels in women with PCOS compared to a control group. The primary outcome was Lp(a) levels expressed in mg/dL. Random effects models were used.

Results Twenty-three observational studies including 2,337 patients were identified and considered eligible for this meta-analysis. In the overall analysis, the quantitative analysis showed that patients with PCOS have a higher Lp(a) levels (SMD: 1.1 [95% CI: 0.7 to 1.4]; $I^2=93%$) compared to the control group. The results were similar in the analysis of the subgroups of patients according to body mass index (normal weight group: SMD: 1.2 [95% CI: 0.5 to 1.9], $I^2=95%$; overweight group: SMD: 1.2 [95% CI: 0.5 to 1.8], $I^2=89%$). Sensitivity analysis showed that the results were robust.

Conclusions This meta-analysis shows that women with PCOS had higher levels of Lp(a) compared to healthy women used as a control group. These findings were observed in both overweight and non-overweight women.

Keywords Lipoprotein(a) · Polycystic ovary syndrome · Overweight · Meta-analysis

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1 Introduction

The polycystic ovary syndrome (PCOS) is a prevalent chronic endocrine disorder that affects women of reproductive age [1]. It is a multifaceted disease involving several pathophysiological mechanisms, among which are hormonal imbalance, chronic low-grade inflammation, insulin resistance (IR), and hyperandrogenism [2]. In addition, the key clinical characteristics of PCOS are menstrual dysfunction, infertility, hirsutism, acne, and obesity [3].

PCOS may represent an important model of lipid alterations starting during adolescence or fertile age. Previous data showed that dyslipidemia is common in PCOS [4]. This is characterized by higher levels of triglycerides, low-density lipoprotein (LDL)-cholesterol and non-high-density lipoprotein (HDL)-cholesterol, and lower levels of HDL-cholesterol compared to subjects without PCOS.

Lipoprotein(a) [Lp(a)] is a lipid-carrying particle composed of a LDL-like particle containing apolipoprotein

B-100 linked by a disulfide bond to apolipoprotein(a) and is mainly determined by genetic variability at the LPA locus [5]. High levels of Lp(a) are an independent risk factor for atherosclerotic cardiovascular diseases through mechanisms associated with inflammation, thrombosis, and atherogenesis [6]. Therefore, knowing the peculiarities of this lipoprotein in patients with PCOS could be important to understand the complex pathophysiology of this clinical entity, as well as the associated comorbidities.

Several studies have evaluated the Lp(a) levels in PCOS patients [7–29]. In addition, a previously reported meta-analysis evaluated several markers of cardiovascular disease risk, including Lp(a) levels. However, this study analyzed data from only four studies [30]. On the other hand, another meta-analysis evaluated different lipid markers in PCOS patients although it did not evaluate Lp(a) levels [4].

Therefore, the main objective of this updated meta-analysis was to analyze all the available evidence on Lp(a) levels in patients with PCOS compared to a control group.

2 Methods

2.1 Data Extraction and Quality Assessment

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]. This systematic review was registered in PROSPERO CRD42023403549.

A literature search was performed to detect studies that have evaluated the Lp(a) levels in PCOS patients. Two reviewers searched the electronic PubMed/MEDLINE, Embase, Science Direct, Scopus, and Cochrane Controlled Trials databases using “polycystic ovary syndrome” or “polycystic ovarian syndrome” terms combined with the following terms: “lipoprotein(a)”, “apolipoprotein(a)”, “LPA locus” and “dyslipidemia”. The final article search ended on 31 January 2023.

The following inclusion criteria were used to select eligible studies: (1) Experimental or observational studies developed in humans; (2) Studies that reported Lp(a) values in patients with PCOS and control groups.

There were no idiomatic, geographical or publication restrictions. Excluded studies included expert opinions, reviews and case-series. Study characteristics were extracted by two independent investigators. Discrepancies among investigators were resolved by consensus.

The primary outcome of interest was Lp(a) levels expressed in mg/dL. The diagnosis of PCOS was based on clinical, laboratory and ovarian ultrasound findings considered by each study.

Potential risks of bias were evaluated for all included experimental studies, using the Cochrane tool developed

for this purpose [32]. The ROBINS-I tool assesses bias in seven different domains: bias due to confounding, bias due to selection to participants, bias in classification of interventions, bias due to deviations from intended intervention, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Each domain was rated as “Serious”, “Moderate” or “Low” depending on the judgment of the authors.

2.2 Statistical Analysis

The summary effect on the primary endpoint was estimated. Measures of effect size were expressed as standardized mean difference (SMD), and the I^2 statistic was calculated to quantify between trial heterogeneity and inconsistency. Depending on the value of I^2 , a fixed effects model ($I^2 < 40\%$) or a random effects model ($I^2 > 40\%$) was chosen. To compare mean effects between subgroups, a Z test was used. When the summary/dispersion measures were not mean and standard deviation, conversion tools previously suggested by the literature were used [33]. In this meta-analysis, we performed a global analysis (all studies) as well as a sub-analysis of studies that reported data on patients with or without overweight (body mass index < 25 or > 25 kg/m²).

Statistical analyses were performed using the R software for statistical computing version 3.5.1 with additional specific packages [34]. A two-tailed p value > 0.05 was considered statistically significant.

2.3 Reporting Bias Assessment

A funnel plot using the standard error (SME) for mean difference was created. In addition, modified Egger’s regression intercept tests were done [35]. A p-value less than 0.1 was considered significant for the linear regression test.

2.4 Sensitivity Analyses

A sensitivity analysis was performed. It consists of replicating the results of the meta-analysis, excluding in each step 1 of the studies included in the review (Table 1).

3 Results

The search included 965 potentially relevant articles after title/abstract screening, and 906 studies were excluded because they were duplicate publications or because they did not assess the purpose of this study. After a careful reading of the remaining articles, 44 studies were removed, because these studies did not report the exposure/event of interest. A flow diagram of the study’s screening process has been shown in Fig. 1.

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

Study (year)	Design	PCOS population	Control group used	Lp(a) assay
Velazquez (1997) [7]	Controlled before-and-after study.	Non-diabetic women aged 18–34 years. Mean BMI: 26.7 (3.6) kg/m ²	Healthy non-diabetic women aged 18–34 years not matched by BMI	Enzyme immunoassay
Dejager (2001) [8]	Cross-sectional study.	Women aged 18–41 years with a BMI between 18 and 35 kg/m ² . Mean age, 25.7 (6) years; mean BMI, 26.7 (5.5) kg/m ²	Healthy women not matched by age or BMI	Nephelometry method
Yildiz (2002) [9]	Cross-sectional study.	Women without impaired fasting glucose, impaired glucose tolerance, or diabetes. Mean age, 22.9 (4.4) years; mean BMI, 23.0 (2.4) kg/m ²	Healthy women matched by age and BMI	Nephelometry method
Yilmaz M 1 (2005) [10]	Cross-sectional study.	Non-diabetic women. Mean age, 23.2 (4.9) years. Mean BMI: overweight and obese group, 31.6 (5.8) kg/m ² ; non-obese group, 21.0 (2.1) kg/m ²	Healthy women not matched by age or BMI	Nephelometry method
Yilmaz M 2 (2005) [11]	Controlled before-and-after study.	Non-diabetic women with BMI < 25 kg/m ² . Mean age, 24.1 (4.9) years; mean BMI: 21.9 (3.2) kg/m ²	Healthy women matched by age and weight	Nephelometry method
Bickerton (2005) [12]	Cross-sectional study.	Women aged 18–50 years (premenopausal women). Mean age, 33.5 (6.1) years; mean BMI: 35.3 (6.8) kg/m ² .	Healthy women matched by age and weight	Nephelometry method
Macut (2006) [13]	Cross-sectional study.	Women without impaired fasting glucose Overweight group: mean age, 24.9 (5.9) years; mean BMI 30.2 (4.4) kg/m ² Normal weight group: mean age 23.8 (4) years; mean BMI 21.4 (2) kg/m ²	Healthy women matched by age and BMI	Nephelometry method
Hu (2006) [14]	Cross-sectional study.	Mean age, 29.6 (3.2) years; mean BMI: 24.7 (4.5) kg/m ²	Women with a BMI < 25 kg/m ² not matched for age	Not reported
Yilmaz S (2007) [15]	Controlled before-and-after study.	Non-obese women. Mean age, 21.6 (3.7) years; mean BMI: 22.4 (2.1) kg/m ²	Healthy women matched by age and BMI	Not reported
Berneis (2009) [16]	Cross-sectional study.	Women without diabetes. Mean age, 28 (7) years; mean BMI: 27 (5) kg/m ² .	Healthy women matched by age and BMI	Immunturbidimetric assay
Rizzo (2009) [17]	Cross-sectional study.	Anovulatory* women without diabetes aged 18–40 years. Mean age, 25 (6) years; mean BMI: 28 (6) kg/m ²	Healthy women matched by age and BMI.	Immunturbidimetric assay
Yilmaz M (2009) [18]	Cross-sectional study.	Women without diabetes Mean age, 24.1 (5.3) years Obese group: mean BMI 30.5 (4.4) kg/m ² Non-obese group: mean BMI 21.4 (3.1) kg/m ²	Healthy women without diabetes, not matched by age or BMI	Nephelometry method
Arikan (2010) [19]	Cross-sectional study.	Young non-obese/overweight women without impaired fasting glucose, impaired glucose tolerance, or diabetes. Mean age, 21.8 (5.4) years; mean BMI, 23.8 (6.6) kg/m ²	Healthy women matched by age and BMI	Immunoimetric assay

Table 1 (continued)

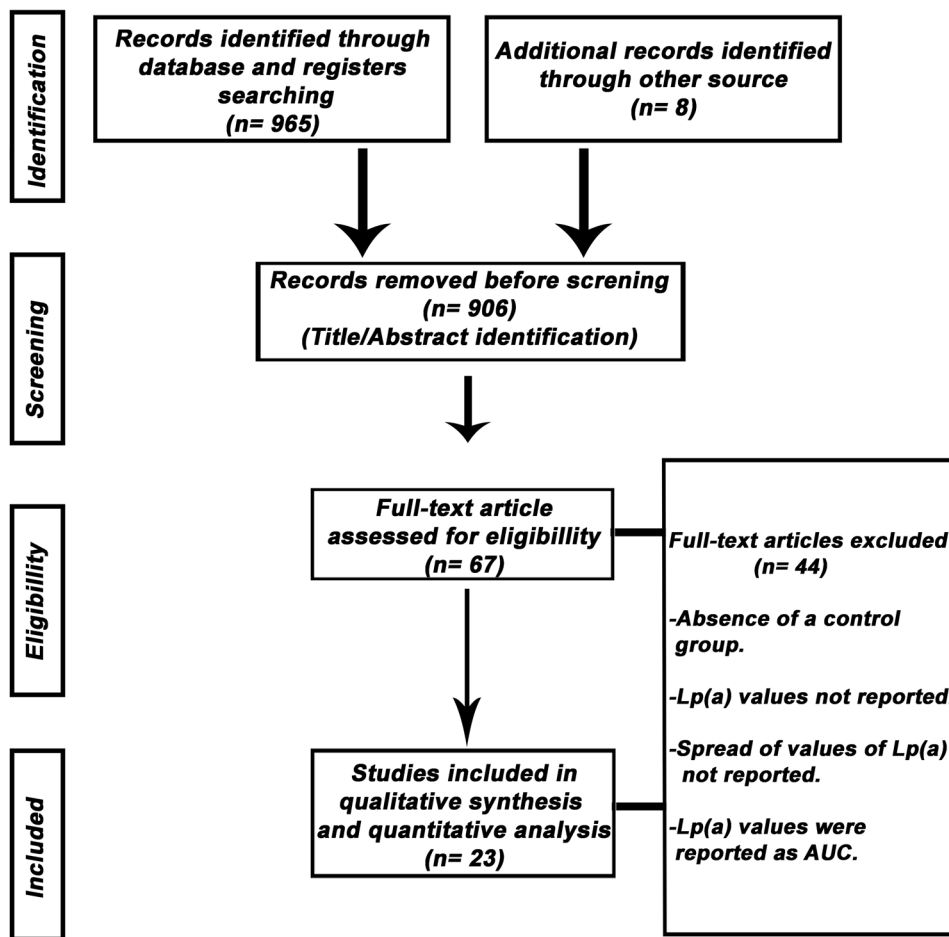
Study (year)	Design	PCOS population	Control group used	Lp(a) assay
Güdülcü 1 (2009) [20]	Cross-sectional study.	Women without diabetes. Mean age, 24.7 (4.4) years, mean BMI, 23.9 (5) kg/m ²	Healthy women not matched by age or BMI	Not reported
Güdülcü 2 (2009) [21]	Cross-sectional study.	Women without diabetes analyzed according to BMI (> or < 25 kg/m ²). Mean age, 24.8 (4.9) years, mean BMI, 23.9 (5) kg/m ²	Healthy women analyzed according to BMI (> or < 25 kg/m ²) not matched by age.	Not reported
Kim (2013) [22]	Case-control study.	Women aged 18 to 40 years with a BMI <25 kg/m ² . Mean age, 24.9 (6) years, median BMI, 21.2 kg/m ²	Healthy women matched by age and BMI	Immunoturbidimetric assay
Tsouma 1 (2014) [23]	Cross-sectional study.	Overweight group: mean age, 32.1 (3.8) years; median BMI, 26.2 kg/m ² Normal weight group: mean age 31.9 (4.3) years; median BMI, 22.2 kg/m ²	Healthy women matched by age and weight.	Immunoturbidimetric assay.
Tsouma 2 (2014) [24]	Cross-sectional study.	Overweight group: mean age, 32.2 (3.9) years. Normal weight group: mean age 32.4 (3.7) years	Healthy women matched by age and weight	Immunoturbidimetric assay
Kumar (2014) [25]	Cross-sectional study.	Women aged 15–30 years. Mean BMI, 26.2 (2.9) kg/m ²	Healthy women matched by age	Enzyme-linked immunoassay
Tsouma 3 (2014) [26]	Cross-sectional study.	Overweight group: median age, 32 years; median BMI, 26.6 kg/m ² . Normal weight group: median age 31 years; median BMI, 22.2 kg/m ²	Healthy women matched by age and weight	Immunoturbidimetric assay
Tu** (2016) [27]	Controlled before-and-after study.	Women with infertility aged 20–39 years. Mean age: 25.9 years	Healthy volunteers not matched by age and BMI	Immunoturbidimetric assay
Bousmpoula(2018) [28]	Cross-sectional study.	Overweight group: mean age, 32.2 (3.9) years; mean BMI, 26.9 (1.5) kg/m ² Normal weight group: mean age 32.1 (4.2) years; mean BMI, 22.4 (1) kg/m ²	Healthy women matched by age and weight	Immunoturbidimetric assay
Shah (2022) [29]	Cross-sectional study.	Women aged 18–35 years. Mean age, 23.3 (4.3); mean BMI, 25.2 (3.3) kg/m ²	Healthy women not matched by age or BMI	Not reported

BMI body mass index, Lp(a) lipoprotein(a), PCOS polycystic ovary syndrome

*We used this group because it had a larger number of patients compared to the ovulation group

**Group "A" of this study was arbitrarily used for this meta-analysis, as data from the total PCOS population was not reported

Fig. 1 Flow diagram of the study screening process.



Twenty-three observational studies including 2,337 patients were identified and considered eligible for this meta-analysis [7–29]. There were a total of 1,338 women in the PCOS group and 999 individuals in the respective control group. Seven studies reporting data on groups of women with or without overweight (with independent control groups) were included separately in the quantitative analysis [10, 13, 21, 23, 24, 26, 28]. Globally, 18 cross-sectional studies, 4 studies with a controlled before-after design and one case-control study were included.

In total, 20 studies were assessed as being at moderate risk of bias and 3 studies were assessed as being at high risk of bias. Those studies that were of high risk of bias had methodological issues principally within the domains related to selection of participants or measurement of outcomes. The quality of the selected studies can be detailed in Fig. 2.

In the overall analysis, the quantitative analysis showed that patients with PCOS have a higher Lp(a) levels (SMD: 1.1 [95% CI: 0.7 to 1.4]; I²=93%) compared to the control group (Fig. 3).

The results were similar in the analysis of the subgroups of patients with or without overweight. When evaluating the studies that included only patients with normal weight, the

results showed that women with PCOS have a higher Lp(a) levels (SMD: 1.2 [95% CI: 0.5 to 1.9], I²=95%) compared to the control group. Similarly, overweight women also showed higher lipid levels compared to healthy women (SMD: 1.2 [95% CI: 0.5 to 1.8], I²=89%). The graphical representation of the subgroup analysis can be seen in Fig. 4.

The graphical (Fig. 5) and analytical evaluation do not suggest publication bias (p=0.197).

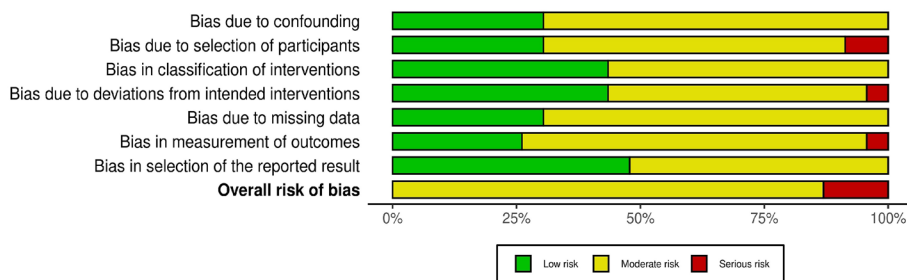
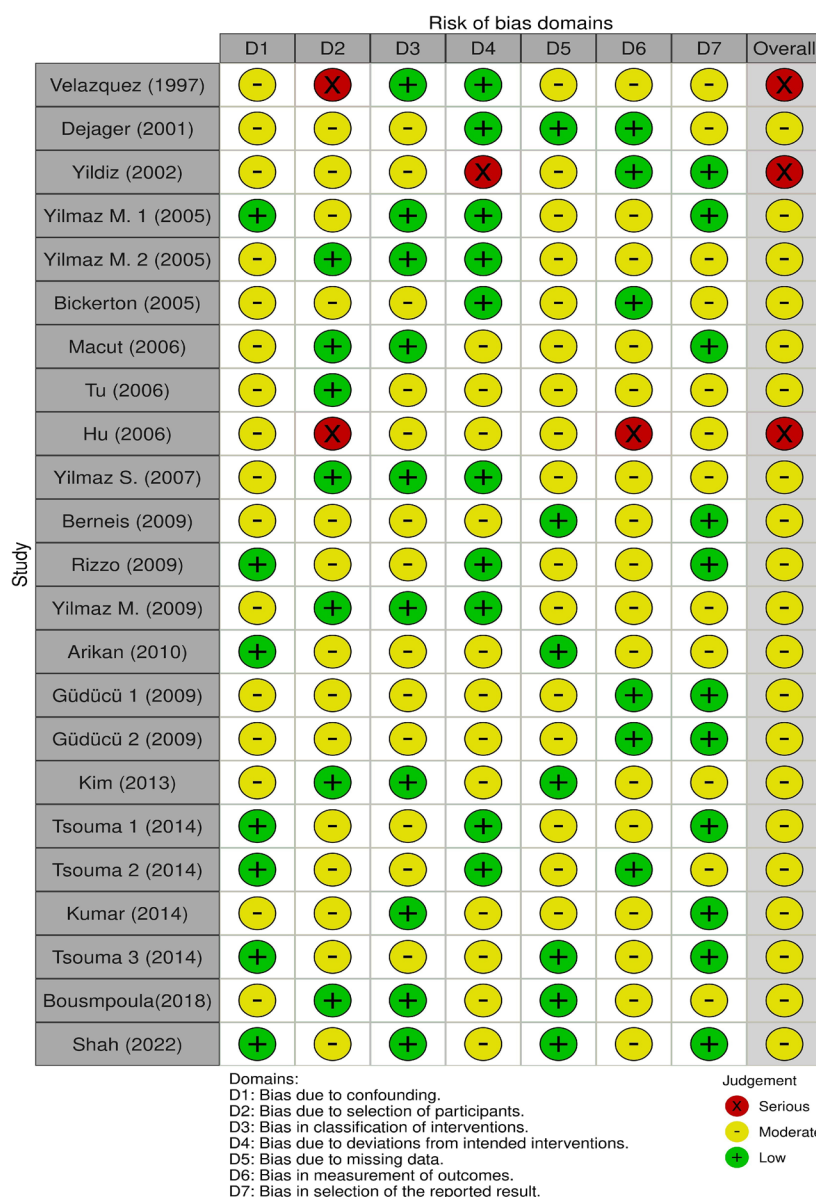
Sensitivity analysis showed that the results were robust (Figs. 6 and 7).

4 Discussion

This systematic review and meta-analysis included a growing body of evidence that examined the Lp(a) values in patients with PCOS.

PCOS is the most common endocrinopathy of women of reproductive age [3]. The pathogenesis of PCOS is complex and is influenced by multiple genetic, environmental, and hormonal factors [36]. Women with PCOS display a range of classic and non-classic cardiovascular risk factors, including central obesity, insulin resistance,

Fig. 2 Bias assessment of included studies.



hypertension, and dyslipidemia [37]. Additionally, PCOS has been associated with diabetes mellitus and cardiovascular disease [38, 39].

Recently, Lp(a) was recognized as one of the new cardiovascular risk factors for cardiovascular disease [40]. In addition, the relevance of the contribution of Lp(a) to

cardiovascular risk stratification has been highlighted in current guidelines [5].

The visceral fat accumulation observed in patients with PCOS causes low-grade chronic inflammation, resulting in insulin resistance, hyperinsulinemia, increase of testosterone and estradiol (hormonal changes). At the same time,

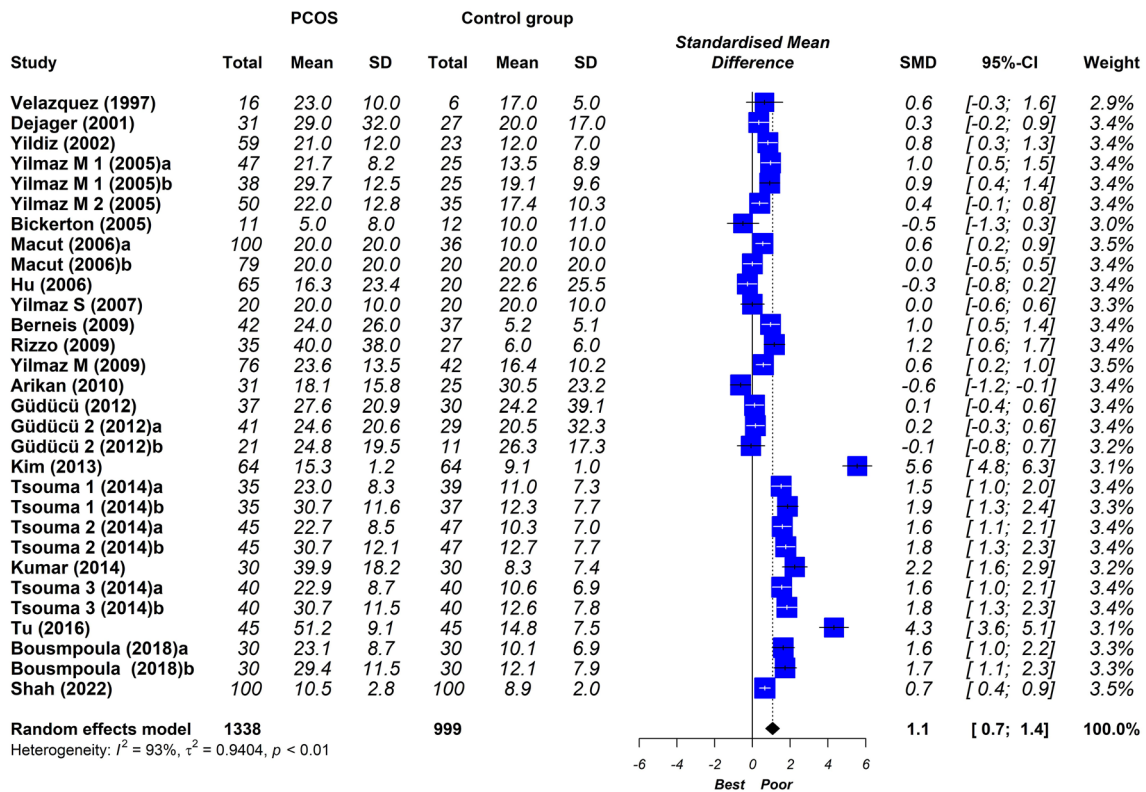


Fig. 3 Quantitative analysis in the total population. Lp(a) levels in PCOS and control groups. Random effects model. Standardized mean difference (SMD), standard deviation (SD), 95% confidence intervals (CI) and I^2 statistics

hormonal variations and insulin resistance can modulate the genetically determined Lp(a) production in the liver [41]. Additionally, non-obese PCOS patients may also develop visceral fat accumulation, generating pro-inflammatory and metabolic effects similar to those seen in overweight or obese women [42].

In this meta-analysis, we assess the data globally and by BMI. In total, 11 of the 23 studies used a cut-off value of BMI (25 Kg/m²) as inclusion criteria or analyzed lean and overweight patients separately. The remaining 12 studies, five of them matched controls for BMI or weight. Our findings revealed that Lp(a) levels were higher in women with PCOS, both in the overall analysis and in the analysis of the overweight/obese vs non-overweight/obese subgroups. Therefore, BMI is an insufficient biomarker of visceral adiposity, and would not fully explain the difference in Lp(a) levels observed in this group of patients.

Although many studies have shown conflicting results, there is a certain consensus that there would be an inverse relationship between the levels of sex hormones and the Lp(a) values [43, 44]. When we analyzed the studies included in this review, 15 studies reported testosterone levels. As expected, 14 of them showed that PCOS patients had significantly higher testosterone levels compared to the control group. However, high testosterone levels could

favor dysfunctional adipose tissue. In this sense, the results observed in the present meta-analysis could not be explained by the hormonal increases typically observed in patients with PCOS. However, high testosterone levels could favor dysfunctional adipose tissue, regulating the expression of adipocytokines such as adiponectin levels [45, 46]. In fact, testosterone reduces the adiponectin levels. An inverse relationship between adiponectin and Lp(a) has been previously reported [47]. Therefore, this phenomenon could be an additional pathophysiological mechanism that could partly explain the findings observed in patients with PCOS.

The relationship between Lp(a) and inflammation is bidirectional as Lp(a) levels, besides being associated with inflammatory properties, are regulated by inflammatory stimuli or anti-inflammatory treatment [48]. When we assessed inflammatory markers in the studies included in this review, only 5 small studies reported C-reactive protein (CRP) levels as a marker of inflammation [12, 19–22]. In this case, one study showed higher CRP levels in women with PCOS [21], while three other studies showed a statistically non-significant trend [19, 20, 22]. A previously published meta-analysis showed that women with PCOS demonstrated significantly elevated CRP serum concentrations when compared with controls [30]. Again, testosterone would play an important role in the inflammatory process

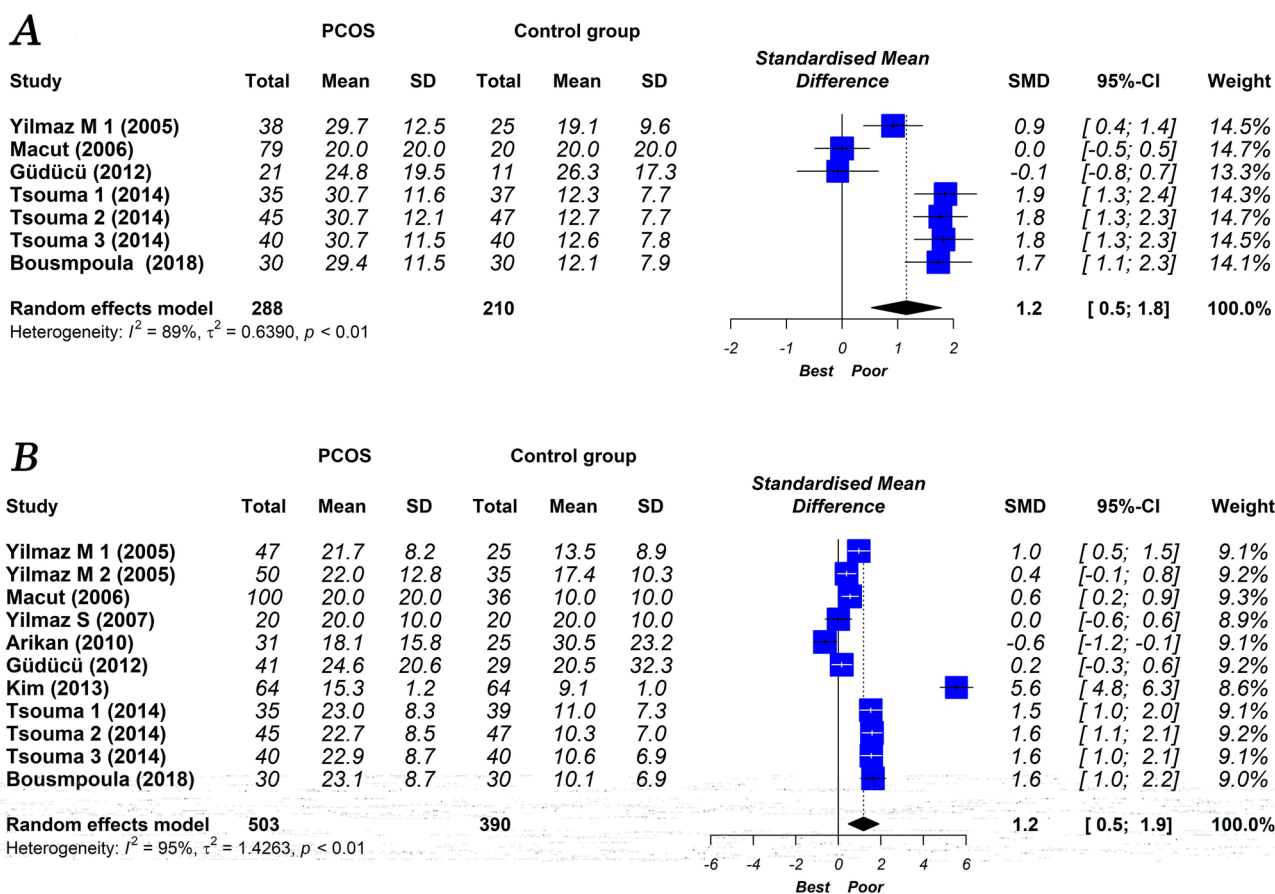


Fig. 4 Quantitative analysis according to body mass index (BMI). **A** BMI > 25 Kg/m². **B** BMI < 25 Kg/m². Random effects model. Standardized mean difference (SMD), standard deviation (SD), 95% confidence intervals (CI) and I² statistics

Fig. 5 Funnel plot to assess publication bias

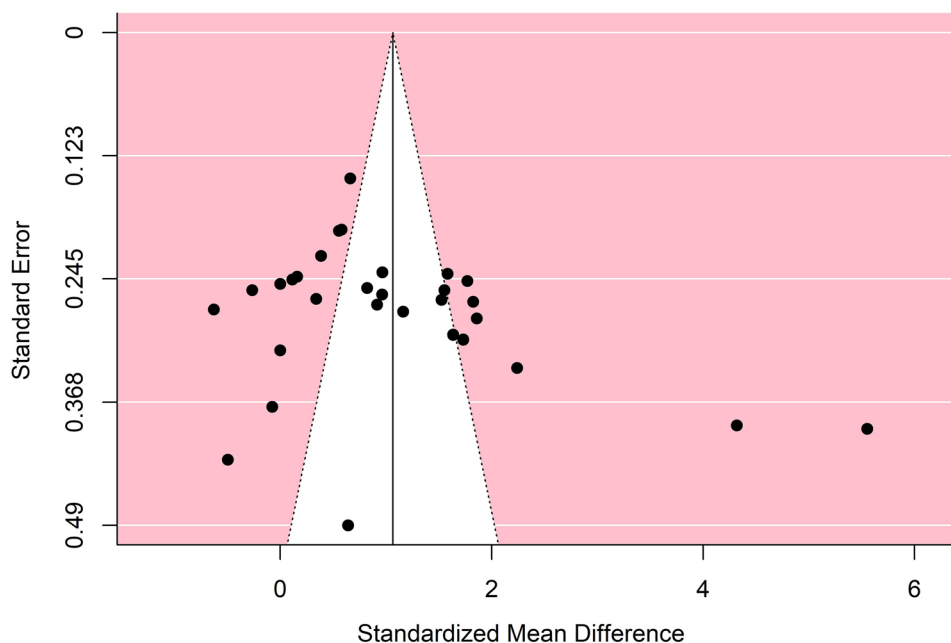
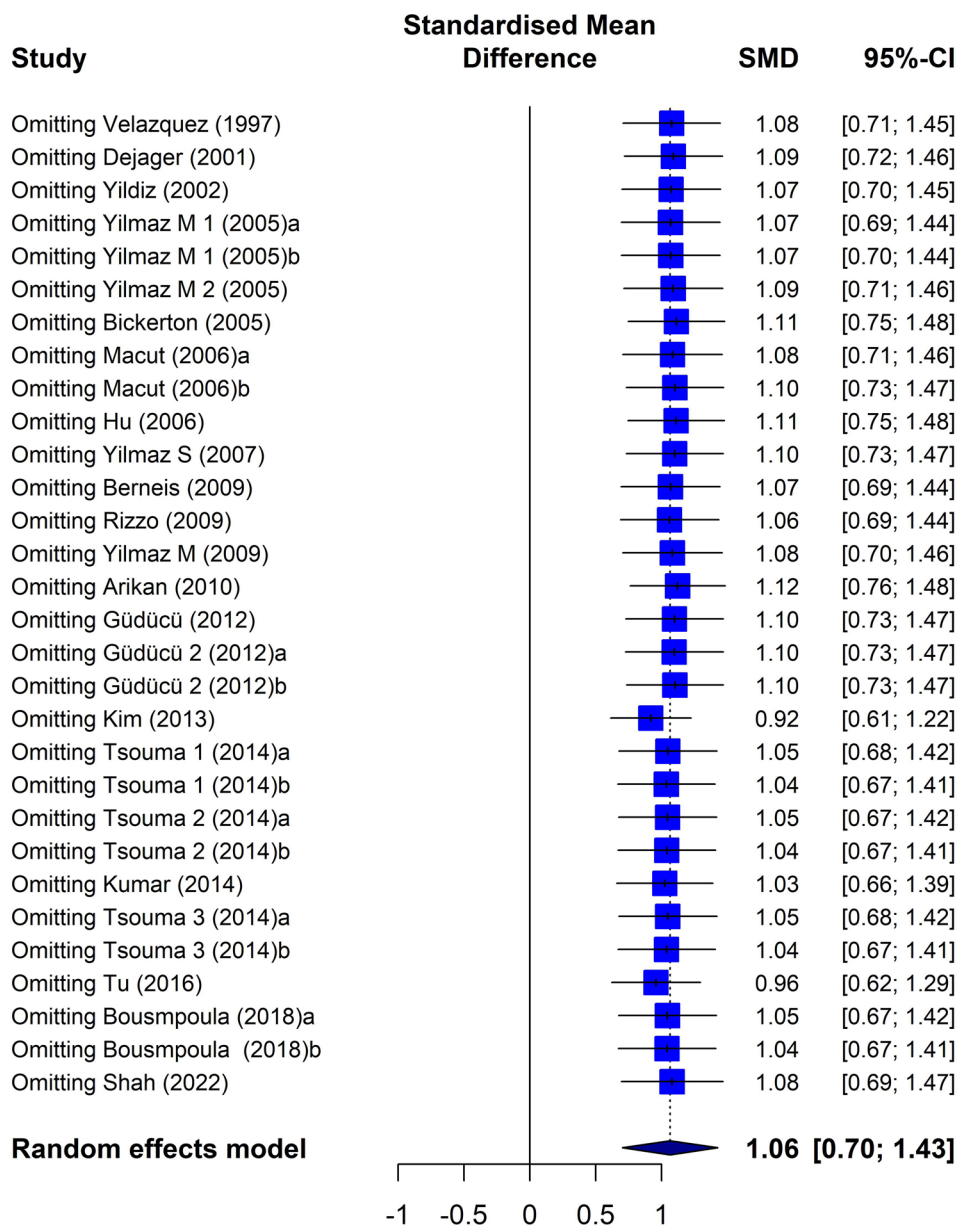


Fig. 6 Sensitivity analysis of all the studies evaluated. SMD standardized mean difference, CI confidence interval.



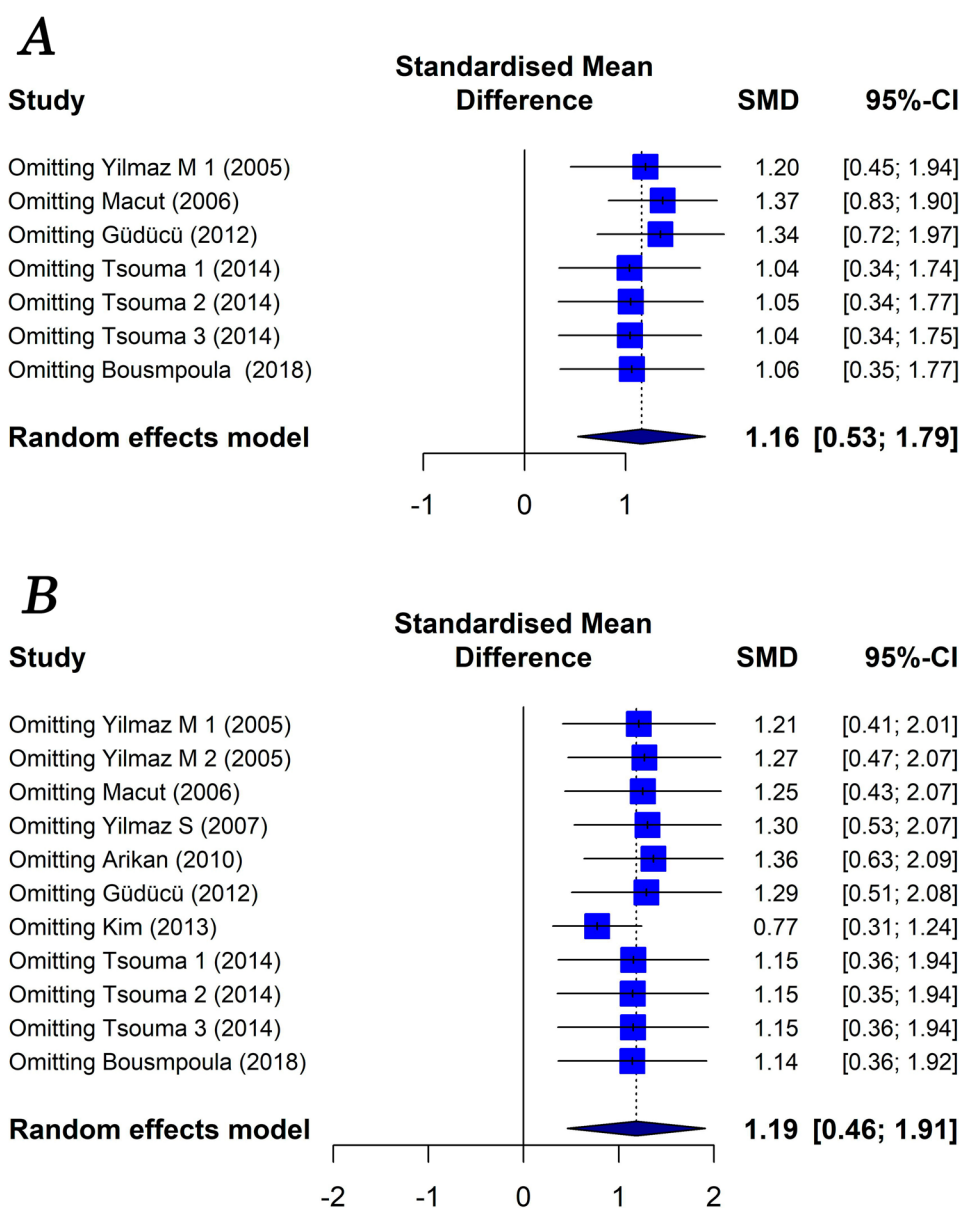
observed in patients with PCOS [49]. Probably, the chronic anti-inflammatory state related to increased visceral fat observed in patients with PCOS (not correctly assessed in the studies analyzed in this review) could partly explain the findings of this study.

Finally, another relevant point to analyze is the relationship between Lp(a) levels and insulin resistance, a phenomenon frequently observed in patients with PCOS. Insulin resistance is associated with changes in lipid and lipoprotein metabolism which result in atherogenic dyslipidemia [50]. These changes seem clear when we analyze the conventional lipid profile. However, there was a complex connection between hyperinsulinemia, insulin resistance and Lp(a) levels. The few studies that evaluated the association

between Lp(a) and metabolic syndrome have shown conflicting results [51–53]. Analysis of the studies included in this review shows that only 11 studies reported insulin and HOMA-R levels. In fact, 10 studies showed higher insulin and HOMA-R levels in PCOS patients compared to the control group. The mechanisms by which insulin resistance might affect Lp(a) levels are not fully understood. Therefore, we cannot affirm that the insulin resistance was an explanatory variable for our findings.

Considering the findings of this meta-analysis, it would seem appropriate to include Lp(a) among the laboratory studies that are usually indicated in patients with PCOS. Importantly, it would not be necessary to repeat the lipid measurement in this population if we rely on the general

Fig. 7 Sensitivity analysis in subgroups according to body mass index. **A** BMI > 25 Kg/m². **B** BMI < 25 Kg/m². SMD standardized mean difference, CI confidence interval



recommendations [5]. Physicians involved in the follow-up and treatment of patients with PCOS should act vigorously on modifiable risk factors, especially if they shows high levels of Lp(a).

This systematic review and meta-analysis presented several limitations. First, statistical heterogeneity was high in quantitative analysis. Despite its common use in the literature, I^2 is not an ideal measure for heterogeneity and its value still heavily depends on the precision and size of the included studies. In fact, almost all of the studies showed greater Lp(a) levels in patients with PCOS, suggesting in this case that the heterogeneity was more related to the magnitude of the effect than to the direction of the effect. Second, considering the origin and authors of some publications, we cannot rule out some degree of overlap in the patient

samples. However, the sensitivity analysis showed robust results. Finally, the qualitative analysis included all observational studies. Consequently, the presence of biases and confounders was highly expected. Despite these limitations, this study analyzed the best evidence available to date.

5 Conclusion

This meta-analysis shows that women with PCOS had higher levels of Lp(a) compared to healthy women used as a control group. These findings were observed in both overweight and non-overweight women, although the pathophysiological mechanisms are not entirely clear and require further investigation.

Declarations

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Conflict of Interest The authors declare that they have no conflict of interest.

Availability of Data and Material The data underlying this article are available in the article and in its online supplementary material.

Author Contributions WM and LB participated in the conception and design of the research. WM, LB and JPN participated in the data collection. The interpretation of the data and the statistical analysis was done by WM and ML. WM, ALC, PC and LB drafted the manuscript. All authors performed a critical review of the final document. All authors have read and agreed to the published version of the manuscript.

Ethical Approval This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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