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RESEARCH ARTICLE

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Asprosin levels in women with and without the polycystic ovary syndrome: a systematic review and meta-analysis

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ABSTRACT

Objective: This systematic review and meta-analysis aimed at summarizing the evidence concerning circulating asprosin, and related endocrine and metabolites in women with and without the polycystic ovary syndrome (PCOS).

Method: We performed a comprehensive literature search in Pubmed, Web of Science, Scielo, and Chinese National Knowledge Infrastructure for studies published until May 20, 2022, that evaluated circulating asprosin levels in women with and without PCOS, regardless of language. The quality of studies was assessed with the Newcastle-Ottawa Scale. Random-effects models were used to estimate mean differences (MD) or standardized MD (SMD) and their 95% confidence interval (CI).

Results: We evaluated eight studies reporting 1,050 PCOS cases and 796 controls of reproductive age. Participants with PCOS were younger (MD = −2.40 years, 95% CI −2.46 to −2.33), with higher values of asprosin (SMD = 2.57, 95% CI 1.64–3.50), insulin (SMD = 2.73, 95% CI 1.18–4.28), homeostatic model assessment of insulin resistance (SMD = 2.70, 95% CI 0.85–4.55), luteinizing hormone (SMD = 2.33, 95% CI 0.60–4.06), total testosterone (SMD = 4.06, 95% CI 1.89–6.22), dehydroepiandrosterone sulfate (SMD = 2.38, 95% CI 0.37–4.40), and triglycerides (SMD = 1.20, 95% CI 0.13 to 2.27). Moreover, PCOS women had lower circulating levels of sex hormone-binding globulin (SMD = −3.36, 95% CI −4.92 to −1.80), and high-density lipoprotein-cholesterol (SMD = −0.85, 95% CI −1.69 to −0.01); with no significant differences observed for glucose, total cholesterol, and low-density lipoprotein-cholesterol levels.

Conclusion: Circulating asprosin levels were significantly higher in women with PCOS as compared to those without the syndrome.

Abbreviations: BMI: Body mass index; CI: Confidence interval; DHEA-S: dehydroepiandrosterone sulfate; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment of insulin resistance; IGF: insulin growth factor; LDL-C: Low density lipoprotein-cholesterol; MD: Mean difference; NOS: Newcastle–Ottawa Scale; PCOS: polycystic ovary syndrome; SD: Standard deviation; SMD: Standardized mean difference; T2DM: type 2 diabetes mellitus.

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Introduction

Adipose tissue has been considered an inert energy storage organ that provides insulation from the cold. However, it is also an endocrine organ because it synthetizes adipokines or adipose-derived hormones. Asprosin (derived from the Greek word 'aspros' which means white) is one of the most recently identified fat hormones that stimulate the liver to release glucose to the circulatory system. It is a 140-amino-acid fragment from the C-terminal of profibrillin (encoded by the FBN1 gene) that stimulates appetite, insulin production, and the liver to release glucose to the circulatory system [1–3]. However, it may also be secreted by the skin, the pancreas, and the submandibular and parotid salivary glands [2, 4]. It is a centrally orexigenic hormone that crosses the blood barrier and activates specific orexigenic neurons [5]. Asprosin blood levels are increased in children and adults with insulin resistance, type 2 diabetes mellitus (T2DM), and obesity [3, 6].

Maylem et al. [7] have described a possible role of asprosin in ovarian follicular function. They demonstrated that asprosin increases luteinizing hormone (LH) induced theca cell androstenedione production, and reduces insulin growth factor 1 (IGF-1) induced theca cell proliferation, suggesting that the new hormone may regulate ovarian follicle function [8]. Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder during female reproductive years, including a high prevalence of impaired glucose tolerance, hyperandrogenism, and T2DM among those PCOS women with overweight or obesity [9, 10]. Both mice and humans with obesity or insulin resistance display increased asprosin levels [2]. However, asprosin results have been inconsistent in studies of PCOS women. Therefore, the purpose of this systematic review and

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meta-analysis was to study circulating asprosin levels in women with and without PCOS and to evaluate related metabolic and endocrine outcomes.

Methods

This systematic review and meta-analysis of observational studies focused on the evaluation of circulating asprosin levels in women with and without PCOS. We followed the principles of the PRISMA guidelines [11]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021299279). A formal institutional review board approval was not required, since this analysis consisted of the pooling of published studies.

Search strategy and eligibility criteria

A literature search of electronic databases was performed on PubMed, Web of Science, Scielo, and Chinese National Knowledge Infrastructure to study women with and without PCOS (Figure 1). We searched for free terms 'polycystic ovary syndrome' OR 'PCOS' AND 'asprosin.' The search strategy using Boolean operators AND or OR is shown in Table S1. The search included articles in any language published from 2016 until May 20, 2022, based on internationally established criteria, either the Androgen Excess and PCOS Society Recommendation [12], the Rotterdam Criteria of the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus [13], or other validated protocols.

Titles and abstracts of retrieved publications were screened for potentially eligible studies. Eligible for inclusion were relevant studies that: (i) assessed adolescents or women with and without PCOS; (ii) studies reporting information on circulating asprosin levels; and (iii) were in any language irrespective of age, race, and date of publication. References from selected articles were also screened, seeking additional potential publications not captured by the electronic database searches. Articles were excluded if they were narrative reviews, abstracts, conference proceedings, lacked results with validated methods or were non-human studies. All disagreements regarding inclusion/exclusion were discussed and solved by consensus with all authors. Meta-analyses were planned for circulating asprosin levels comparing women with and without PCOS. In addition, other clinical, endocrine, or metabolic parameters traditionally related to PCOS were studied as secondary outcomes if reported in at least three different publications.

Data extraction and risk of bias assessment

The general characteristics of selected articles were screened by study design and asprosin measurement methods. Discrepancies and controversies of extracted data were discussed to reach a consensus. When required the authors of the articles were contacted to obtain any additional clarification. A plot digitizer program was used to obtain numeric results from figures [14] in articles not reporting exact numeric data. Appropriate calculations were also performed to obtain means and standard deviations that served the meta-analysis [15]. Separate meta-analyses were planned for studies assessing endocrine and metabolic outcomes related to PCOS.

Two authors assessed the risk of bias in included studies following the Newcastle-Ottawa Scale (NOS) [16]. Disagreements were solved by discussion between both sides and a third author. This tool evaluates 8 items of selection of exposure and non-exposure comparison, and an additional star can be assigned for comparability based on the analysis. Therefore, the evaluation may reach a maximum number of 9 stars. A total of 7 or more stars suggests that the study has a low risk of bias.

Statistical analysis

Forest plots were planned for outcomes reported in at least three studies using any validated test to assess clinical or laboratory results. Associations among dichotomous outcomes were planned to be expressed as odds ratios and for continuous outcomes mean differences (MDs) or standardized mean differences (SMDs), with their corresponding 95% confidence interval (CI). Because studies might have potential differences in phenotypes, baseline characteristics, lifestyle, and recruitment procedures, we followed the DerSimonian and Laird random-effects model [17] and the inverse variance method. The Hedges' *g* method was used to measure effect sizes, interpreting the magnitude of SMDs as small (0.20), moderate (0.50), or large (0.80) [18, 19].

We evaluated statistical heterogeneity using the Chi^2, the I^2 statistic, and the between-study variance using the Tau^2 [14, 15]. I^2 values of 30–65% indicate a moderate level of heterogeneity.

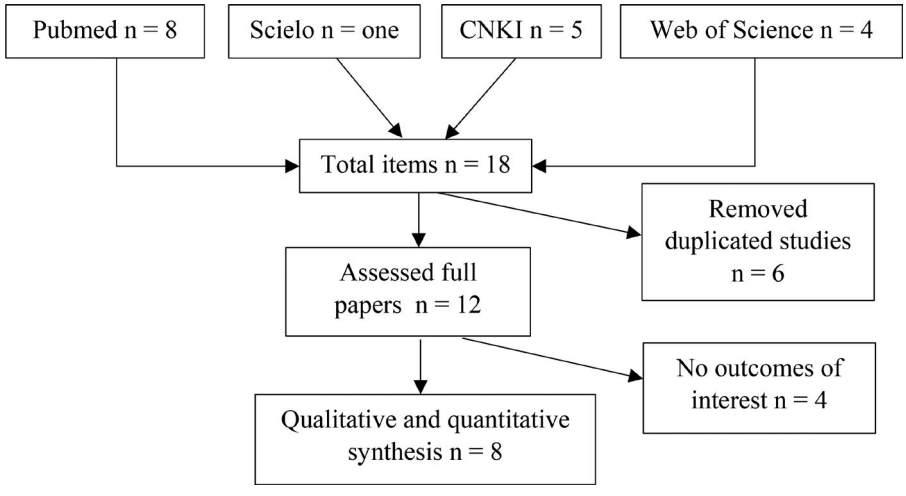

Figure 1. Flowchart of study selection.

A $p < 0.1$ for the Chi^2 defined the presence of heterogeneity; and a $Tau^2 > 1$ defined the presence of substantial statistical heterogeneity. One-study leave-out sensitivity analysis was performed to test the robustness of the overall asprosin result [19]. We planned to estimate the publication bias if at least ten studies reported the same outcome [20]. The Review Manager program (RevMan, version 5.3, Oxford, UK; The Cochrane Collaboration) was used for statistical analyses.

Results

Study characteristics and risk of bias assessment

Our searches yielded 18 potentially eligible articles (Figure 1). After screening abstracts and deleting duplicates, twelve were assessed as full-text, and eight studies [21–28] were included in the final qualitative and quantitative synthesis. Seven studies [21–24, 26–28] followed the ESHRE/ASRM 2003 Rotterdam criteria [13] and one study [25] followed the Chinese Medical Association of Obstetrics and Gynecology Recommendations for PCOS diagnosis [29].

Meta-analyzed studies were performed: four in China [25–28], two in Turkey [21, 24], one in Iraq [22], and another in Taiwan [23]. Sample size ranged from 30 [24] to 444 PCOS patients [23], and from 30 [24] to 233 women [28] without the syndrome. Six articles were published in English [21–24, 26, 27] and two in the Chinese language [25, 28]. Seven studies diagnosed PCOS using the Rotterdam Criteria [21–24, 26–28] and one study [25] followed the Guideline of PCOS from the Expert Group of Obstetrics and Gynecology of the Chinese Medical Association [29]. Age ranges and other clinical characteristics are displayed in Table 1. All studies measured circulating asprosin levels by chemiluminescence assays.

Using the NOS scale, six studies were identified as high-quality [21, 24–28], and the other two of moderate quality [22, 23] (Table S2). All publications identified the study population, patients were representative of average PCOS cases, and controls were derived from the same population as cases. In all studies, secure patient records were used for the ascertainment of PCOS and assessment of outcomes.

Meta-analyses, sensitivity analyses, and publication bias

Detailed meta-analysis results of eight studies are displayed in Figures 2–4, and Table 2. Women with PCOS were younger as compared to controls (MD = −2.40 years, 95% CI −2.46 to −2.33. Table 2; Figure 2A) and had higher body mass index (BMI; MD = 1.41, 95% CI −0.07 to 2.89. Table 2; Figure 2B). They had increased circulating levels of asprosin (SMD = 2.57, 95% CI 1.64–3.50. Table 2; Figure 2C), and insulin (SMD = 2.73, 95% CI 1.18–4.28. Table 2; Figure 2D). Women with PCOS also displayed higher homeostatic model assessment of insulin resistance (HOMA-IR) values (Table 2; Figure 2E). Circulating glucose levels did not differ between women with and without PCOS (Table 2; Figure 2F). Cross-sectional studies did not display significant differences in insulin (Figure 2D), HOMA-IR (Figure 2E), and glucose (Figure 2F) levels in women with and without PCOS as compared to case-control studies. Women with PCOS had significantly higher circulating levels of LH (Table 2; Figure 3A), total testosterone (Table 2; Figure 3B), and DHEA-S (Table 2; Figure 3C), and significantly lower circulating sex hormone-binding globulin (SHBG, Table 2; Figure 3D) than those without the syndrome. There were no significant differences in circulating follicle-stimulating hormone (FSH, Table 2; Figure 3E) and estradiol (Table 2; Figure 3F).

Women with PCOS also had significantly lower circulating levels of HDL-C (Table 2; Figure 4A), whereas there were no significant differences in total cholesterol (Table 2; Figure 4B) and LDL-C between the two groups of women (Table 2; Figure 4C). Finally, women with PCOS had significantly higher triglyceride levels as compared to controls (Table 2; Figure 4D). Table 2 shows that there was high heterogeneity of effects on all compared outcomes across studies ($I^2 > 90\%$).

Subgroup analyses were performed for asprosin and insulin comparing studies from China [25–28] and Taiwan [23] to those from Turkey [21, 24] and Iraq [22]. There were similarly increased levels of asprosin (Figure S1) and insulin (Figure S2). No other sub-analyses were possible due to the few available studies.

Sensitivity analyses were performed for both asprosin and insulin, including the removal of studies one by one (Table S3). The asprosin SMD ranged from 1.95 [CI 95%, 1.05 to 2.84] by deleting the publication by Deniz et al. [24], and 2.91 [CI 95%, 2.08–3.74] when deleting the Jiang et al. results [26] (Table S3). The insulin SMD ranged from 1.12 [CI 95%, 0.58–1.66] when omitting the paper by Chang et al. [23], and 3.04 [CI 95%, 1.32 to 4.76] when deleting the Deniz et al. results [24] (Table S3). Therefore, the increased asprosin and insulin levels in women with PCOS are robust findings. The I^2 values were very high (> 90%) for both hormones (Table S3).

Since there were only eight studies, there was no option to assess the publication bias risk using funnel plots and Egger tests.

Discussion

This systematic review and meta-analyses included studies reporting women with PCOS, without duplicated populations, assessing circulating asprosin levels as the primary outcome and insulin and HOMA-IR index values as secondary outcomes. Participants with PCOS were younger with higher BMI in comparison to those without the syndrome. They had increased circulating values of asprosin, insulin, HOMA-IR, LH, total testosterone, DHEA-S, and triglycerides; with lower SHBG and HDL-C levels as compared to controls. There were no significant differences in circulating FSH, estradiol, total cholesterol, and LDL-C levels. Many of the hormonal and metabolic findings reported here fit well with what one can expect when comparing young women with and without PCOS.

PCOS is not an exclusive ovarian dysfunction, but a total endocrine and metabolic disorder related to insulin resistance. The meta-analyzed data of PCOS patients displayed increased insulin, glucose, HOMA-IR, triglyceride, and asprosin levels, and reduced HDL-C values. Asprosin regulates lipid and carbohydrate metabolism [2], stimulates the production of reactive oxygen species and inflammation-associated cytokines, and decreases insulin secretion [30, 31]. In obese children and adult subjects asprosin secretion is increased, and related to increased waist circumference and triglyceride levels [6, 32]. Increased asprosin levels have also been reported in patients with insulin resistance and T2DM [2, 32]. Some experimental studies postulate the use of antibodies against asprosin as a way to neutralize metabolic syndrome [33].

Our results show that asprosin secretion is altered in women with PCOS during reproductive years as compared to women without the syndrome. It remains to be determined which are the roles of this new hormone in the development and progress of PCOS. New studies are needed in adolescents and very young

Table 1. Studies comparing circulating asprosin in women with and without polycystic ovary syndrome (PCOS): Authors, study location and period of study, aims of studies, number of participants, age, study design and exclusion criteria, and main findings.

Authors [reference]	Location and period of study. Aims.	Sample size. Age.	Study design and exlusion criteria	Main findings
1. Alan et al. [21]	Location: Izmir, Turkey; June 2017 to January 2018. Aim: To compare asprosin levels in women with and without PCOS, and if there is a link between asprosin and metabolic parameters in PCOS.	Sample size: PCOS = 78; control women n = 78. Age: 18–45 year-old women.	Age and BMI matched case-control study of women. Exclusion criteria: irregular menstrual cycles related to the excess of androgens or other adrenal or thyroid disorders, galactorrhea, breastfeeding, hypertension, impaired glucose tolerance or diabetes mellitus, hyperlipidemia, congestive heart failure or coronary artery disease, liver/renal disorders, malignancy or acute infection, chronic inflammatory and autoimmune diseases, hormonal contraception, or anti-androgen therapy. The consumption of medications for hypertension, dyslipidemia, hyperglycemia, insulin resistance, or obesity were also an exclusion criterion.	Asprosin levels are higher in PCOS patients than in the control group. Women with PCOS had higher insulin, HOMA-IR, triglycerides, LH, total testosterone, free androgen index, and DHEA-S. There were also lower HDL-cholesterol and sex hormone-binding globulin.
2. Ameen et al. [22]	Location: Duhok, Iraq. June 20, 2020, to January 11, 2021. Aim: To study asprosin, metabolic outcomes, and insulin resistance in women with PCOS.	Sample size: PCOS = 75; control women n = 96. Age: 17–44 years.	Cross-sectional study. The control group included women with regular menstrual cycles and without endocrine anomalies. Exclusion criteria: women with hypothyroidism, renal or liver diseases, androgen-secreting tumor, Cushing's syndrome, congenital adrenal hyperplasia, congestive heart diseases, or use of medications for decreasing hypertension, dyslipidemia, hyperglycemia, or obesity.	Serum asprosin was higher in women with PCOS than in the control group and was positively correlated with BMI, waist circumference, fasting insulin and glucose, HOMA-IR, total cholesterol, and triglycerides.
3. Chang et al. [23]	Location: Kweishan, Taoyuan, Taiwan; 2010–2016. Aim: To study irisin and asprosin levels and metabolic and endocrine characteristics in women with and without PCOS.	Sample size: PCOS = 444, control group = 156. Age: PCOS: 25 ± 0.22 years; control group: 27.42 ± 0.37 years.	A cross sectional study of women with and without PCOS assessing insulin, lipids, irisin, asprosin, steroid hormones, lipids, and clinical endpoints as well as HOMA-IR, and Matsuda index stratified by BMI or the presence of the metabolic syndrome.	The regulation of irisin is altered in PCOS patients, while asprosin is not affected by metabolic changes. Asprosin level was significantly correlated with follicle-stimulating hormone, free testosterone, and total testosterone levels.
4. Deniz et al. [24]	Location: Several centers in Turkey; period of study: no stated. Aim: To investigate the relationship between PCOS and asprosin.	Sample size: PCOS = 30, control group = 30. Age: PCOS = 27.14 ± 3.21; control group = 28.22 ± 2.6 years.	Case-control study matched by age and BMI. Exclusion criteria: lactating women, those receiving hormonal treatment for any disease for at least six months, patients with liver or pancreatic diseases, hyperprolactinemia, Cushing's syndrome, adrenal hyperplasia, thyroid diseases, impaired glucose tolerance, type 1 or T2DM, or those with chronic medical illness. Furthermore, those using alcohol, tobacco, and its products and women using antiandrogen, antidiabetics, insulin sensitizers, lipid-lowering drugs, glucocorticoids, or other hormonal drugs were also excluded from the study.	There were significant relationships between high LH, androgen, and dyslipidemia, increased asprosin in patients with PCOS. The effect on metabolic parameters was probably due to the action of asprosin on appetite.
5. Guo et al. [25]	Location: Huadong, Qingdao, China; January 2017 to December 2018. Aim: to study asprosin levels and androgens, and correlations with other metabolic indexes.	Sample size: PCOS = 80, controls = 82. Age: PCOS = 34.8 ± 6.3, control group = 35. 9 ± 3.2.	Case-control study matched by age, BMI, and waist circumference. Exclusion criteria: patients with irregular menstrual function, diabetes mellitus, hypertension, coronary heart disease, hyperlipidemia, severe liver and kidney disease, primary hypothyroidism, Cushing syndrome, autoimmunity diseases, chronic infections, psychiatric diseases, or malignant tumors.	In PCOS patients, asprosin levels correlated with BMI, waist circumference, HOMA-IR, and free androgen index. The asprosin level in obese patients is nearly two times higher than in no-obese.
6. Jiang et al. [26]	Location: Jinan, China. Period of study: no stated. Aim: to investigate the relationship between serum asprosin levels and PCOS subtypes.	Sample size: PCOS = 93, controls = 77. Age: total sample 28.48 ± 3.47.	An age-matched case-control study. Exclusion criteria: women with androgen-secreting tumors, thyroid disease, hyperprolactinemia, 21-hydroxylase deficiency, Cushing's syndrome, congenital adrenal hyperplasia, and abnormal intrauterine cavity. A history of recurrent spontaneous abortion, intake of antidiabetic drugs, antiandrogens, oral contraceptives, insulin sensitizers, glucocorticoids, and ovulation induction agents were also excluded.	Asprosin levels were no significant difference between the PCOS and control group. In the PCOS group, asprosin was negatively correlated with BMI, LH, testosterone, basal antral follicles, insulin, HOMA-IR, and triglycerides. Correlations were not significant after adjusting for BMI.
7. Li et al. [27]	Location: Chongqing, China; February 2017 to December 2018. Aim: To investigate the association of asprosin with metabolic profiles, sex-related hormones, or inflammation in PCOS, T2DM and healthy women.	Sample size: PCOS = 41, controls 66 healthy women. Age: PCOS 22.68 ± 5.66: control group 37.02 ± 8.16 years.	Cross-sectional study. Exclusion criteria: patients with androgen-secreting tumors, hyperprolactinemia, 21-hydroxylase deficiency, Cushing's syndrome, congenital adrenal hyperplasia, thyroid disease, abnormal intrauterine cavity, a history of recurrent spontaneous abortion, or unilateral oophorectomy.	Asprosin was higher in PCOS patients than in healthy women but lower than in T2DM patients, and it was positively correlated with glucose, glycated hemoglobin, HOMA-IR, and testosterone. The BMI-categorized subgroups of PCOS women showed correlations of asprosin with metabolic profiles and sex-related hormones.
8. Liu et al. [28]	Location: Hangzhou, China; December 2018 to December 2019. Aim: To investigate the association between serum asprosin level and insulin resistance in women with PCOS.	Sample size: PCOS = 213, control group 213. Age: PCOS: 25.58 ± 4.82, control group: 25.35 ± 4.50.	Age and BMI matched case-control study. Exclusion criteria: Women with menstrual disorders related to hyperandrogenism, thyroid disease, pregnancy or breastfeeding, hypertension, glucose intolerance or diabetes mellitus, coronary heart failure, liver or kidney diseases, acute infections, chronic inflammation, and autoimmune diseases, malignant diseases, oral contraceptives and/or antiandrogen treatments.	Serum asprosin, glucose, insulin, triglycerides, LH, total testosterone, and DHEA-S in the PCOS group were significantly higher than in the control group. Asprosin levels correlated with BMI, fasting glucose and insulin levels, insulin resistance index, and C-reactive protein in PCOS patients.

Seven studies [21–24, 26–28] followed the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Criteria [21–24, 26–28], and one study [25] followed the Recommendations from the Endocrinology Expert Group of the Obstetric and Gynecology Branch of the Chinese Medical Association.

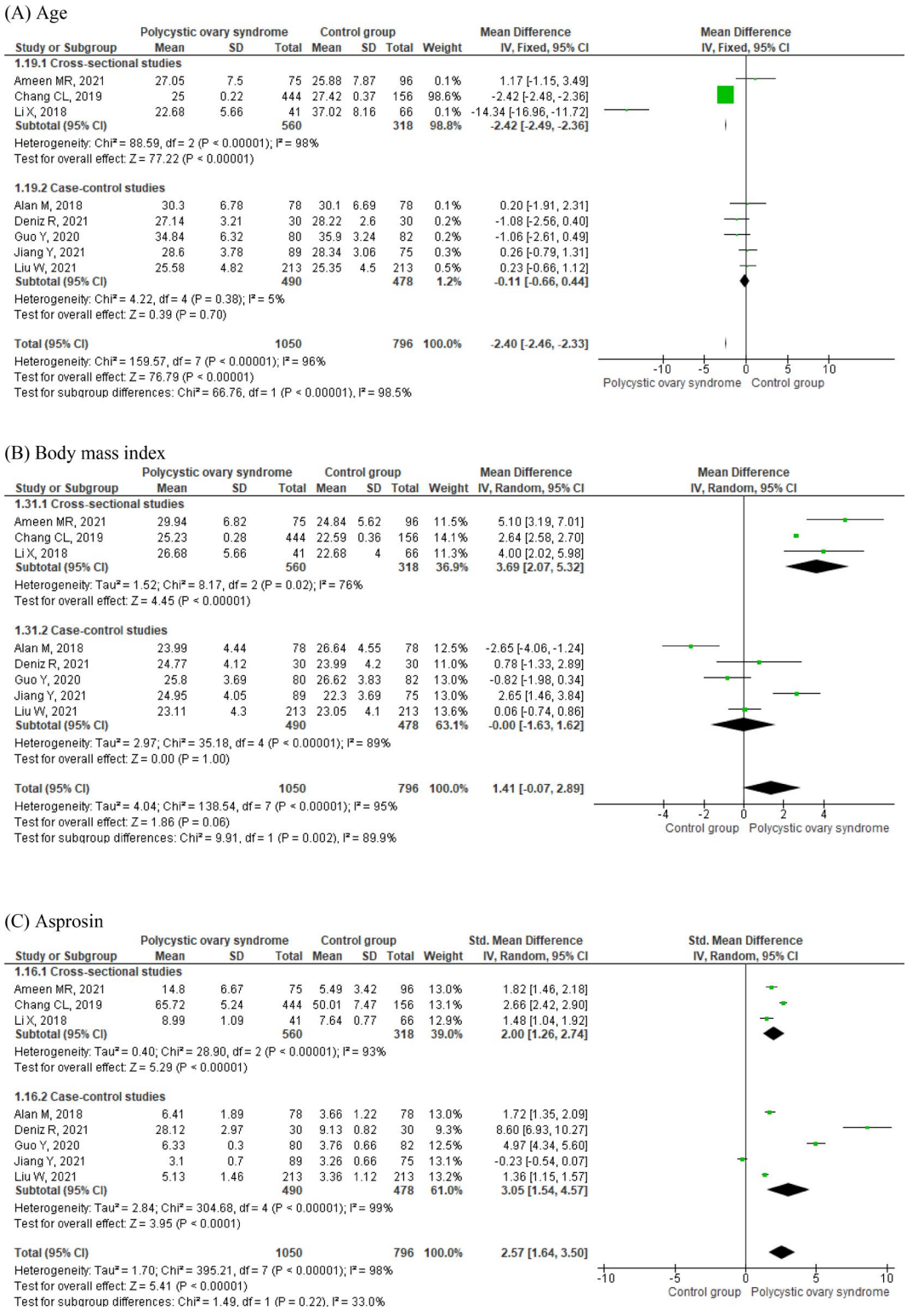

Figure 2. Age, body mass index, circulating asprosin and insulin, HOMA-IR and glycemia in women with and without polycystic ovary syndrome.

women combining the traditional hormonal and metabolic outcomes along with the recently discovered ones which might open a new approach to the PCOS since the early clinical manifestations. Preliminary experimental studies suggest that aerobic exercise may reduce asprosin levels and cardiometabolic risks in rats [34]. In young women with low physical activity and visceral obesity, an 8-week program of exercise improves BMI, insulin resistance, and asprosin levels [35]. The pharmacological inhibition of asprosin to manage excessive body weight and insulin resistance might open a new therapeutic avenue since anti-asprosin antibodies may reduce appetite, body weight, and circulating glucose levels [36]. Previous studies demonstrate the benefits of metformin treatment on PCOS symptoms [37], and future research should identify the effect of metformin on asprosin levels in PCOS patients with different degrees of obesity and insulin resistance.

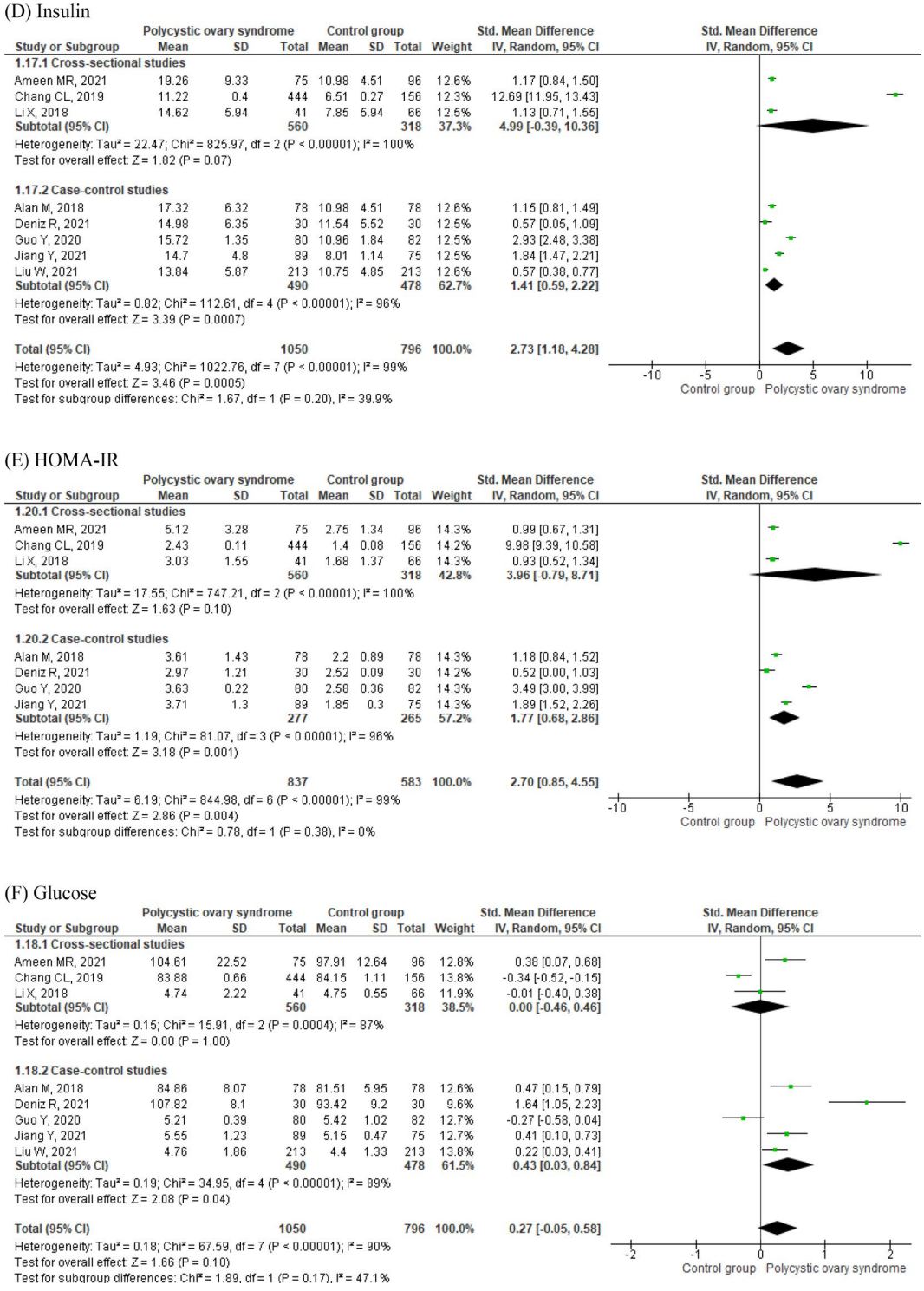

Figure 2. Continued.

Strengths and limitations

This meta-analysis has the strength that PCOS patients were diagnosed according to standardized international scientific recommendations, including 1,050 cases without possible duplicated populations. Our meta-analysis provides new information that asprosin is significantly increased in women with PCOS as compared to those without the syndrome in a similar social and healthcare scenario. Our results fill some gaps and controversies from individual studies concerning endocrine and metabolic PCOS knowledge concerning asprosin and its relationships with pituitary and ovarian hormones, androgens, and insulin secretion. Finally, our meta-analysis included a proportion of Chinese women, with their particular cultural peculiarities and lifestyle which are not usually considered in Western scientific literature.

The heterogeneity of studies was very high (I^2 > 95%) and represents a limitation, and by the sensitivity analyses, I^2 values remained high. This finding may be explained by the

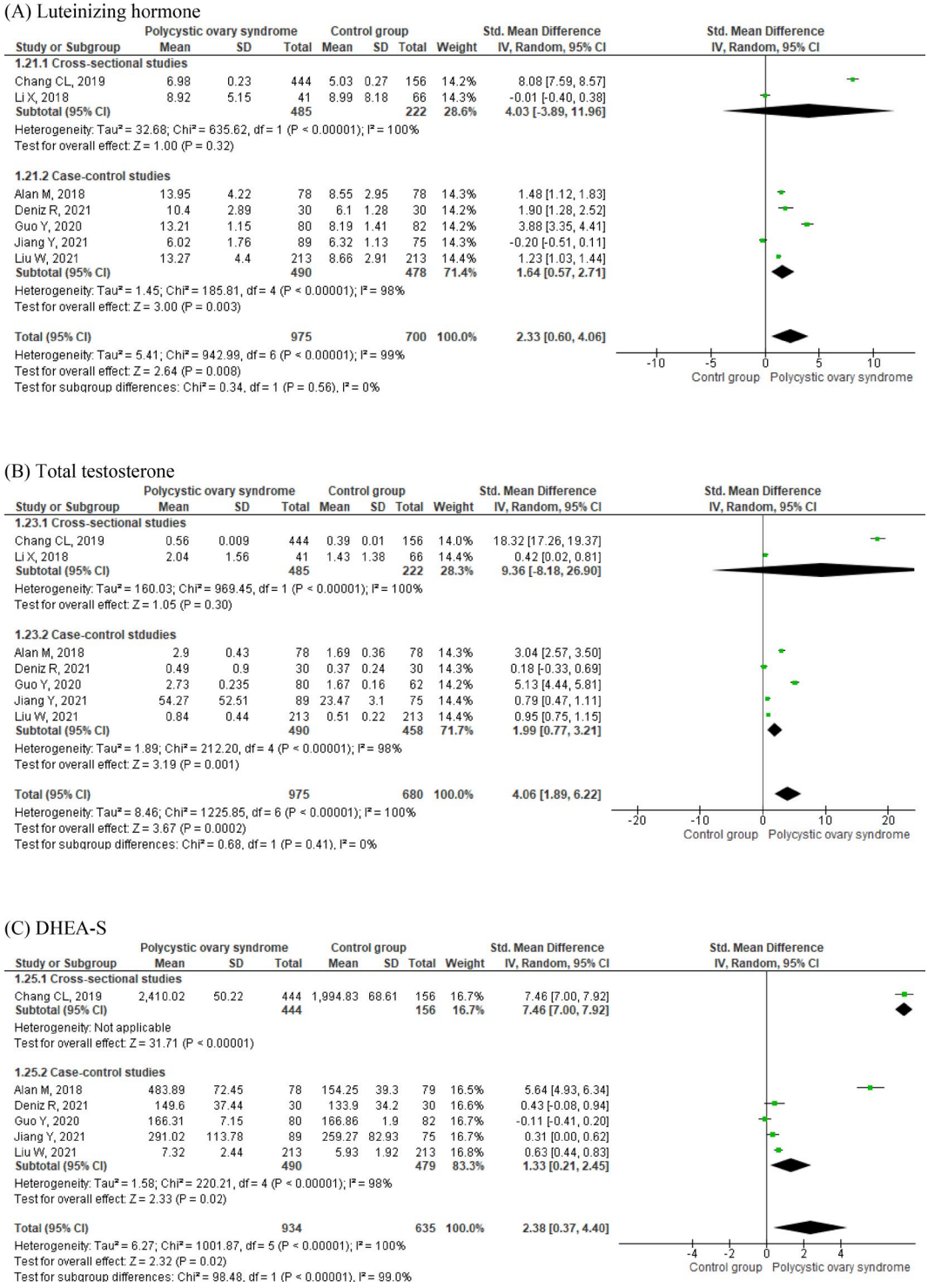

Figure 3. Luteinizing hormone (A), total testosterone (B), DHEA-S (C), sex hormone-binding globulin (D), follicle-stimulating hormone (E), and estradiol (F) in women with and without polycystic ovary syndrome.

polymorphic characteristics of the syndrome which may be related to the wide variability of expression in clinical symptoms, the severity of metabolic and endocrine alterations, BMI, the severity of insulin resistance and hyperandrogenism, inflammatory presence, and lifestyle factors. The inclusion criteria, study designs, and primary publication objectives were quite variable, despite all primary sources being based on validated diagnosis criteria. The heterogeneity of studied PCOS patients, ethnicity, natural history, diet, physical activity, and other lifestyle factors may also contribute to the statistical heterogeneity [35, 38], which we tried to sort out using random effects models. However, there remains a heterogeneous source of uncertainty for estimated endpoints that may be related to the difference in PCOS phenotypes, delay of the publication of negative results, and small sample size variability that can significantly contribute to heterogeneity in continuous but not binary outcomes [39–41].

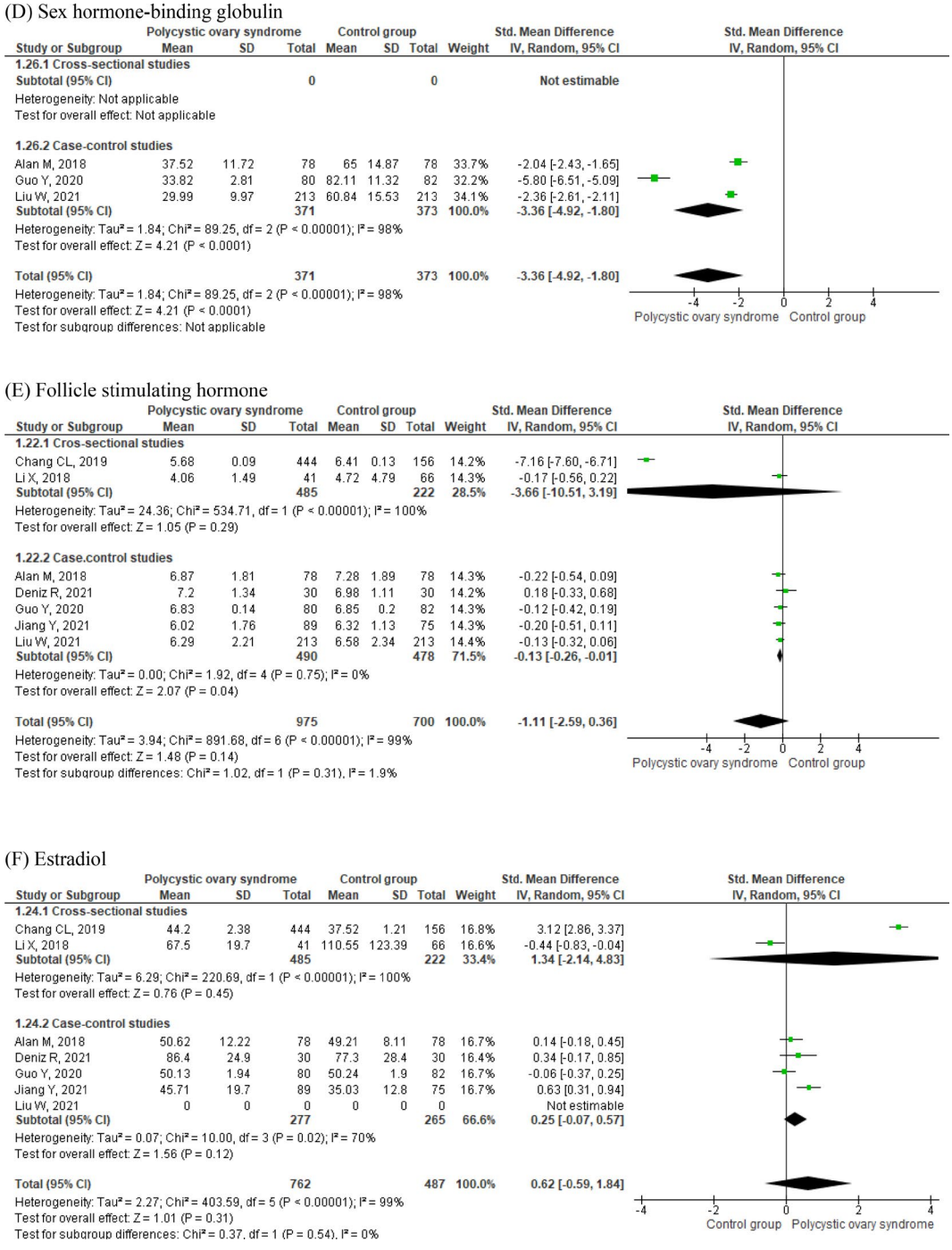

Figure 3. Continued.

Future studies should overcome these limitations to better define the endocrine and metabolic role of asprosin in PCOS patients considering their different phenotypes. To overcome the presence of heterogeneity between studies, we used random effects method that produces wider confidence intervals that reflects the heterogeneity between sample estimates.

Conclusion

We demonstrated that asprosin is significantly increased in women of reproductive age with PCOS compared to those without the syndrome. The studied women with PCOS displayed the usual concomitant endocrine and metabolic alterations for this particular syndrome. Altered asprosin secretion indicates that white fat tissue may have a role in the PCOS origin and maintenance of the typical metabolic alterations and dysfunctional secretion of insulin and steroid hormones. Interventions to reduce asprosin levels, including diet and physical activity or the anti-diabetic drug metformin [42], should be studied along with other metabolites and hormones.

Acknowledgments

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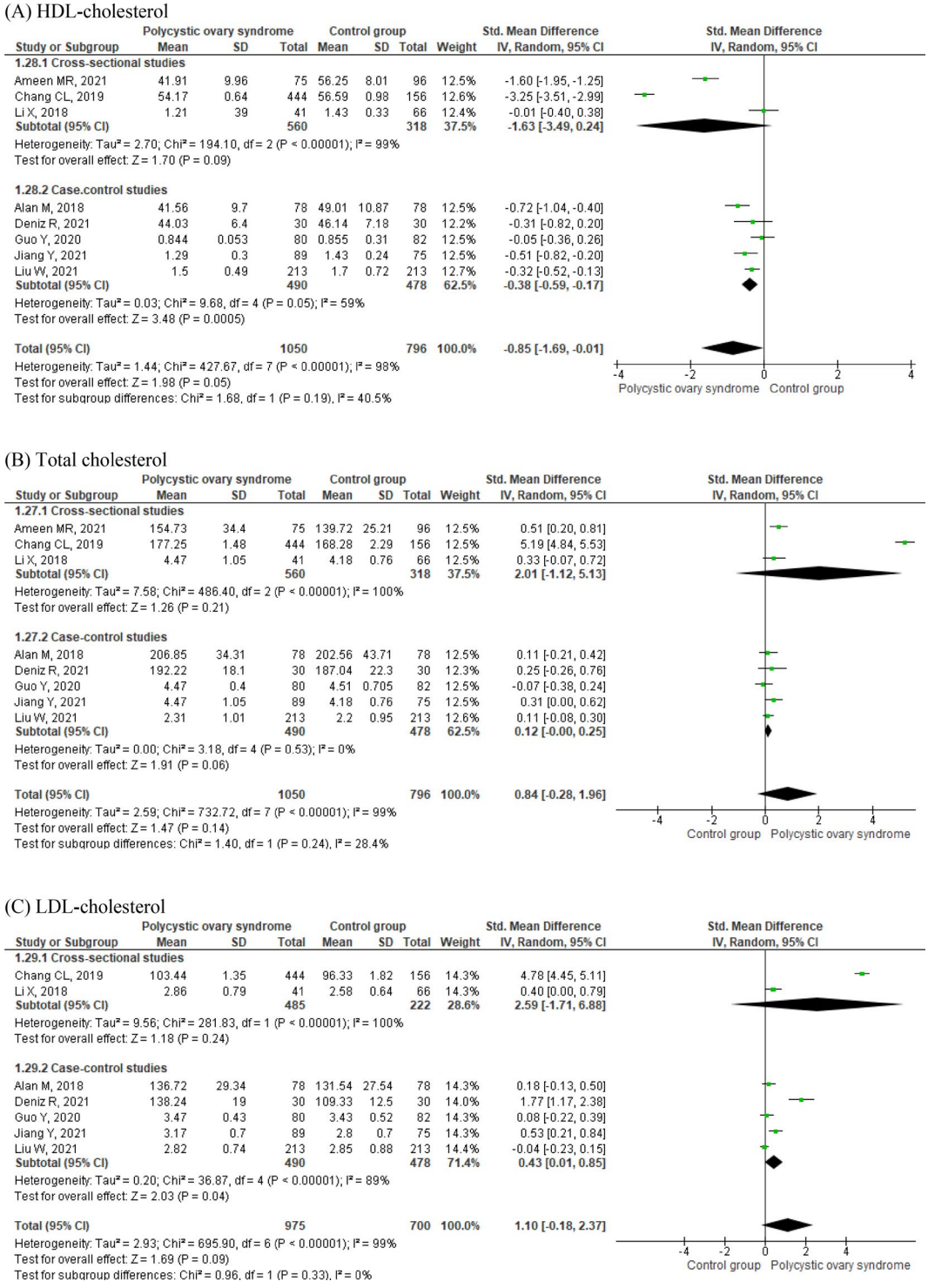

Figura 4. Standardized mean differences of circulating (A) HDL-cholesterol, (B) total cholesterol, (C) LDL-cholesterol, and (D) triglycerides in women with and without polycystic ovary syndrome.

Disclosure statement

The authors report no conflicts of interest and are alone responsible for the content and the writing of the article.

Author contributions

Conceptualization of the study and PROSPERO protocol design, data curation, and risk of bias assessment: MTLB, PC, PGA, and FRPL. Meta-analyses and related methodology were performed by SRV, GPR, and FRPL. The initial manuscript was drafted by FRPL, and all authors contributed with critical intellectual input, reviewing and approving the final manuscript.

Data statement

The present meta-analysis was based on published articles. All summary data generated during this study are included in this published article. Raw data used for the analyses are available presented in the original reviewed articles.

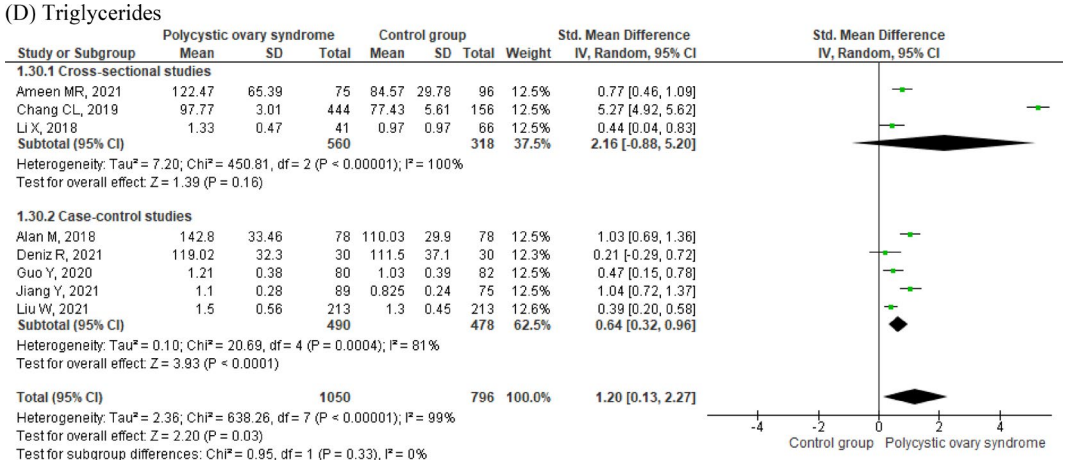

Figura 4. Continued.

Table 2. Pooled effects reported as mean differences (MDs) or standardized MDs (SMDs) and 95% confidence interval (CI), Z score and *p*-values, and heterogenity (I^2) in women with and without polycystic ovary syndrome.

Outcomes (Figures)	Included studies	Participants (PCOS / Control)	MD or SMD [95% CI]	Z score (*p* value)	I^2 (%)
Age (Figure 2A)	8	1050 / 796	MD −2.40 [−2.46 to −2.33]	76.79 (< 0.0001)	98
Body mass index (Figure 2B)	8	1050 / 796	MD 1.41 [−0.07 to 2.89]	1.86 (0.06)	95
Asprosin (Figure 2C)	8	1050 / 796	SMD 2.57 [1.64 to 3.50]	5.41 (< 0.0001)	98
Insulin (Figure 2D)	8	1050 / 796	SMD 2.73 [1.18 to 4.28]	3.46 (0.0005)	99
HOMA-IR (Figure 2E)	7	837 / 583	SMD 2.70 [0.85 to 4.55]	2.86 (0.004)	99
Glucose (Figure 2F)	8	1050 / 796	SMD 0.27 [−0.05 to 0.58]	1.66 (0.10)	90
Luteinizing hormone (Figure 3A)	7	975 / 700	SMD = 2.33 [0.60 to 4.06]	2.64 (0.008)	99
Total testosterone (Figure3B)	7	975 / 680	SMD = 4.06 [1.89 to 6.22]	3.67 (0.0002)	100
Dehydroepiandrosterone sulfate (Figure 3C)	6	934 / 635	SMD = 2.38 [0.37 to 4.40]	2.32 (0.02)	100
Sex hormone-binding globulin (Figure 3D)	3	371 / 373	SMD = −3.36 [−4.92 to −1.80]	4.21 (0.0001)	98
Follicle-stimulating hormone (Figure 3 E)	7	975 / 700	SMD = −1.11 [−259 to 0.36]	1.48 (0.14)	99
Estradiol (Figure 3F)	7	762 / 487	SMD = 0.62 [−0.59 to 1.84]	1.01 (0.31)	99
HDL-cholesterol (Figure 4A)	8	1050 / 796	SMD = −0.85 [−1.69 to −0.01]	1.98 (0.05)	98
Total cholesterol (Figure 4B)	8	1050 / 796	SMD = 0.84 [−0.28 to 1.96]	1.47 (0.14)	99
LDL-cholesterol (Figure 4C)	7	975 / 700	SMD = 1.10 [−0.18 to 2.37]	1.69 (0.09)	99
Triglycerides (Figure 4D)	8	1050 / 796	SMD = 1.20 [0.13 to 2.27]	2.20 (0.03)	99

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