# The role of polycystic ovary syndrome in preclinical left ventricular diastolic dysfunction: an echocardiographic approach: a systematic review and meta-analysis

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***Background*** **Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of childbearing age, causing hormonal imbalances, reproductive issues, and metabolic disturbances. Women with PCOS have an increased risk of cardiovascular disease due to insulin resistance, obesity, and hyperandrogenism. Detecting impaired left ventricular (LV) function is important in managing this condition. Echocardiography, a non-invasive imaging technique, can effectively detect LV dysfunction.**

***Aim*** **The goal of this systematic review was to assess whether there are any variations in echocardiographic measures between women with PCOS and those without the condition in order to determine the potential impact of PCOS on LV function.**

***Methods*** **This review followed the PRISMA reporting guidelines. A thorough search of databases including PubMed, Scopus, Web of Science, and Cochrane was conducted. The quality of the selected studies was assessed using the Joanna Briggs Institute appraisal instruments. After applying strict eligibility criteria, data were extracted and organized in Microsoft Excel sheets. Review Manager (RevMan) software was used for the analysis.**

***Results*** **Analysis of 29 studies revealed significant differences in echocardiographic measures related to diastolic function between women with PCOS and healthy controls. However, there were no significant differences in measures of systolic function.**

***Conclusion*** **These findings indicate that PCOS may be linked to impaired LV function, thereby increasing the risk of cardiovascular disease. Further research is necessary to better understand this association and its clinical implications. Early detection and management of PCOS could potentially help prevent cardiovascular complications in affected women. *Cardiovasc Endocrinol Metab* 12: 1–21 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.**

**Cardiovascular Endocrinology & Metabolism** 2023, **12**:1–21

**Keywords: echocardiographic approach, meta-analysis, polycystic ovary syndrome, preclinical left ventricular diastolic dysfunction, systematic review**

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**Received** 18 July 2023 **Accepted** 19 September 2023.

## Background

Polycystic ovary syndrome (PCOS) is the most prevalent heterogeneous syndrome that potentially has an impact on multiple aspects of a woman's overall health, particularly during her reproductive years [1,2]. Women with PCOS are identified by chronic anovulation, which occurs along with excess androgen, hyperinsulinemia, insulin resistance (IR), and changes in gonadotropin secretion [3,4]. In addition to the heightened risk of reproductive abnormalities associated with PCOS, most women with this condition also experience metabolic dysfunction [5] and an increased risk of developing cardiovascular risk factors, including marked IR [6], type 2 diabetes mellitus [7], coronary artery disease (CAD) [8], atherogenic dyslipidemia [9], cerebrovascular morbidity [10]. There is a significant positive correlation between peripheral insulin levels and ovarian androgens [11]. In simpler terms, PCOS has been identified as a type of metabolic syndrome [12], and as a result, researchers are now focusing more on understanding the metabolic mechanisms that contribute to the condition's clinical symptoms [13,14]. Echocardiography, including both conventional and tissue Doppler techniques, is frequently used to evaluate left ventricular (LV) systolic and diastolic function. Studies have demonstrated that diastolic dysfunction, which can be identified through echocardiography, can serve as an early predictor of CAD [15]. Subclinical LV diastolic dysfunction is a prevalent problem in the community [16]. It is considered an important predictor of heart disease [17], and associated with long-term mortality [18]. The

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latest guidelines on heart failure emphasize the importance of identifying asymptomatic LV dysfunction and its primary risk factors as early as possible [19]. The echocardiographic assessment of PCOS has yielded conflicting results. While some studies have observed notable alterations indicative of diastolic dysfunction in individuals with PCOS, other studies have found no significant differences when compared to control groups.

### Objectives

The primary objective of this systematic review and meta-analysis was to compare echocardiographic measures of LV systolic and diastolic function between women with PCOS and healthy women serving as a control group. The aim was to determine whether there is evidence of impaired LV function in women with PCOS, independent of other known cardiovascular risk factors.

## Material and methods

This systematic review and meta-analysis adheres to the PRISMA guidelines and includes the PRISMA checklist (Document S1, Supplemental digital content 1, *http://links.lww.com/CAEN/A46*) in the supporting information. The research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) and assigned the identifier CRD42022340972.

### Eligibility criteria

To be considered for inclusion, published studies had to meet the following criteria: (1) report original data using a cross-sectional, cohort, or case-control study design, (2) identify PCOS cases using any of the diagnostic criteria for PCOS, including the Rotterdam, National Institutes of Health (NIH), and Androgen Excess PCOS (AEPCOS) criteria, (3) report at least one echocardiographic parameter measuring LV systolic and/or diastolic function, (4) present data as means and standard deviations, (5) include appropriately matched control participants and evaluate the relevant parameters in both the PCOS cases and controls, (6) include women of reproductive age with or without PCOS, and (7) exclude individuals with known cardiovascular disease, thyroid disease, neoplasms, pregnancy or lactation, smoking, chronic alcohol consumption, diabetes mellitus, hypertension, and renal impairment.

The meta-analysis had the following general exclusion criteria: (1) studies reported as abstracts, case reports, case series, reviews, editorials, or practice guidelines, (2) studies that included women in menopausal or postmenopausal stages, both with and without PCOS, (3) studies that evaluated left heart function using any other cardiac imaging technique other than echocardiography.

### Information sources

A thorough search was conducted in the PubMed, Scopus, Web of Science, and Cochrane databases to locate relevant studies published until August 2022. Additionally, a manual search of the reference lists of the identified articles was carried out.

### Search strategy

The search strategy of Scopus was conducted as follows: ((ALL ('echocardiograph*' OR 'tissue doppler imaging' OR 'tissue doppler echocardiograph*' OR 'tde' OR 'tdi')) OR (TITLE-ABS-KEY (('left ventric*' OR 'left cardiac*' OR 'left heart*' OR atri* OR myocardi* OR diastol* OR systol*) PRE/ 1 (diastol* OR systol* OR dysfunction OR function OR remodeling OR hypertroph* OR active* OR volume OR mass* OR dimension* OR diameter OR thickness OR index* OR 'ejection time' OR 'ejection fraction'))) OR (ALL ('lvef' OR 'lved' OR 'lvdd' OR 'lvsd' OR 'lvedd' OR 'lvesd' OR 'lvd' OR 'lavi' OR 'e/em ratio' OR 'e/a ratio' OR 'lvmi' OR 'lvm'))) AND (TITLE-ABS-KEY ('polycystic ovar* syndrome' OR 'polycystic ovar* disease' OR 'stein leventhal syndrome' OR 'pcos' OR 'sclerocystic ovar*')).

The search strategy employed for PubMed, Web of Science, and the Cochrane Library was similar to that used for Scopus (refer to S1 Table, Supplemental digital content 2, *http://links.lww.com/CAEN/A47*). Furthermore, two researchers independently reviewed the reference lists of systematic reviews and selected studies to ensure that all pertinent articles were included in the analysis.

### Study selection

Six reviewers independently assessed each title and abstract, and if the articles fulfilled the inclusion criteria, the full text was reviewed. Three reviewers evaluated the full texts of the selected articles to verify their eligibility for inclusion. Any discrepancies were resolved through discussion with a fourth reviewer. The study selection process was summarized using the PRISMA flow diagram.

### Data extraction

Three reviewers extracted data, which was collected using Microsoft Excel spreadsheets. The following data were collected: study characteristics (study design, year of publication, and first author), type of PCOS diagnostic criteria, number of individuals in each study population (PCOS cases and matched controls), baseline characteristics (age, BMI, impaired glucose tests, and androgen profile). If the laboratory units of parameters differed, online laboratory unit converters were used to standardize the units for analysis. Echocardiographic parameters were extracted and divided into two groups based on conventional echocardiographic and tissue Doppler echocardiographic values. A fourth investigator independently reviewed the data to ensure accuracy.

### Outcome definition

The objective of this meta-analysis was to determine the difference in the mean change in echocardiographic parameters between the PCOS cases and control group. The echocardiographic parameters that were included are as follows:

### Conventional echocardiography

#### *LVM and LVMI*

The measurement of LV mass (LVM) typically involves calculating the difference between the volume of the epicardium and the volume of the LV chamber, which is then multiplied by an estimate of myocardial density [20]. LV mass index (LVMI) is the short term for the LV mass indexed to body surface area [21]. Both LVM and LVMI are considered independent indicators of LV hypertrophy and are recognized as risk factors for predicting cardiac morbidity and mortality [22,23].

#### *Interventricular septal thickness and posterior wall thickness*

Interventricular septal thickness (IVST) at end-diastole and posterior end-diastolic wall thickness (PWT) are both used to identify LV hypertrophy, with a normal range of 6–11 mm for each parameter [24,25]. These measurements are typically obtained as the distance between the endocardial and epicardial surfaces during the end-diastolic phase [26].

#### *Left ventricular ejection fraction*

LV ejection fraction (LVEF) is a fundamental measure of LV function during the systolic phase. It represents the proportion of the chamber volume that is expelled during systole relative to the volume of blood in the ventricle at the end of diastole [27].

#### *Isovolumic relaxation time and isovolumic contraction time*

The isovolumic relaxation time (IVRT) is the duration between the closure of the aortic valve and the subsequent opening of the mitral valve [28]. The isovolumic contraction time (IVCT) is defined as the time interval between the closure of the mitral valve and the opening of the aortic valve [29].

#### *Peak E and A wave, and E/A ratio*

The E wave represents the maximum velocity of blood flow resulting from LV relaxation during early diastole, while the A wave represents the peak velocity of flow in late diastole due to atrial contraction. The E/A ratio is a meaningful marker of LV function [30].

#### *Deceleration time*

Deceleration time (DT) refers to the duration between the onset of the peak E-wave and its projected baseline. The DT reflects the time required for the pressure difference between the left atrium and the left ventricle to be equalized [31].

#### *Left ventricular end-diastolic diameter and left ventricular end-systolic diameter*

LV end-diastolic diameter (LVEDD) represents the end-diastolic dimension of the left ventricle, while LV end-systolic diameter (LVESD) indicates the end-systolic dimension of the left ventricle. For women, the cutoff values for LVEDD and LVESD are 52.5 mm and 46.5 mm, respectively [32].

#### *Left atrial diameter*

Left atrial diameter (LAD) is independently associated with all-cause mortality in both men and women, as well as with ischemic stroke in women. A normal LAD is less than 3.9 cm in women [33].

### Tissue Doppler echocardiography

#### *Mitral annular peak diastolic velocities*

Early diastolic mitral annular velocity (E') is an echocardiographic measure that reflects myocardial relaxation in the long-axis direction. It can be measured at either the interventricular-septal annulus (septal E'), lateral annulus (lateral E'), or as the mean value of both (septal-lateral E') [34].

#### *Mitral annular peak systolic velocities*

The mitral annular peak systolic velocity (S') is an echocardiographic measure that reflects longitudinal LV systolic function. It can be measured at either the interventricular-septal annulus (septal S'), lateral annulus (lateral S'), or as the mean value of both (septal-lateral S') [35].

### Quality assessment

Before being included in the review, eligible studies were subject to quality appraisal by three independent reviewers using appraisal instruments from the Joanna Briggs Institute (JBI) for cross-sectional and case-control studies, as well as other comparative studies (S2 Document, Supplemental digital content 3, *http://links.lww.com/CAEN/A48*).

### Synthesis methods

For data analysis, the RevMan software (version 5.3) was used with the random effects model. When data were reported as median and interquartile range, they were converted to mean and SD using the Hozo formula [36] so that they could be included in the meta-analysis. Mean differences were pooled for the data, with 95% confidence intervals (CIs) also calculated. The level of statistical heterogeneity for each pooled estimate was calculated using Cochran's chi-squared test and presented with the $I^2$ statistic. $I^2$ values of 25%, 50%, and 75% were considered to represent low, moderate, and high levels of heterogeneity, respectively. To assess the possibility of small study effects, comparison-adjusted funnel plots were visually examined for each outcome. Funnel plots were created for all comparisons of the differences in echocardiographic changes between PCOS cases and controls. Additionally, Begg's test was performed using Comprehensive Meta-analysis (version 3) software to further evaluate the presence of small-study effects. To conduct subgroup analysis,

the data were re-analyzed based on study designs, which included cross-sectional and case-control methodologies. The results of the subgroup analysis were documented in separate tables and included in the supporting information section for reference. To conduct sensitivity analysis, a second analysis was performed excluding cases with obesity, and the results were labeled with a '2' next to each outcome name (e.g. LVMI-2). The main results were labeled with a '1' (e.g. LVMI-1). This approach allowed for the assessment of the impact of obesity on the overall findings and helped determine the robustness of the results.

## Main results

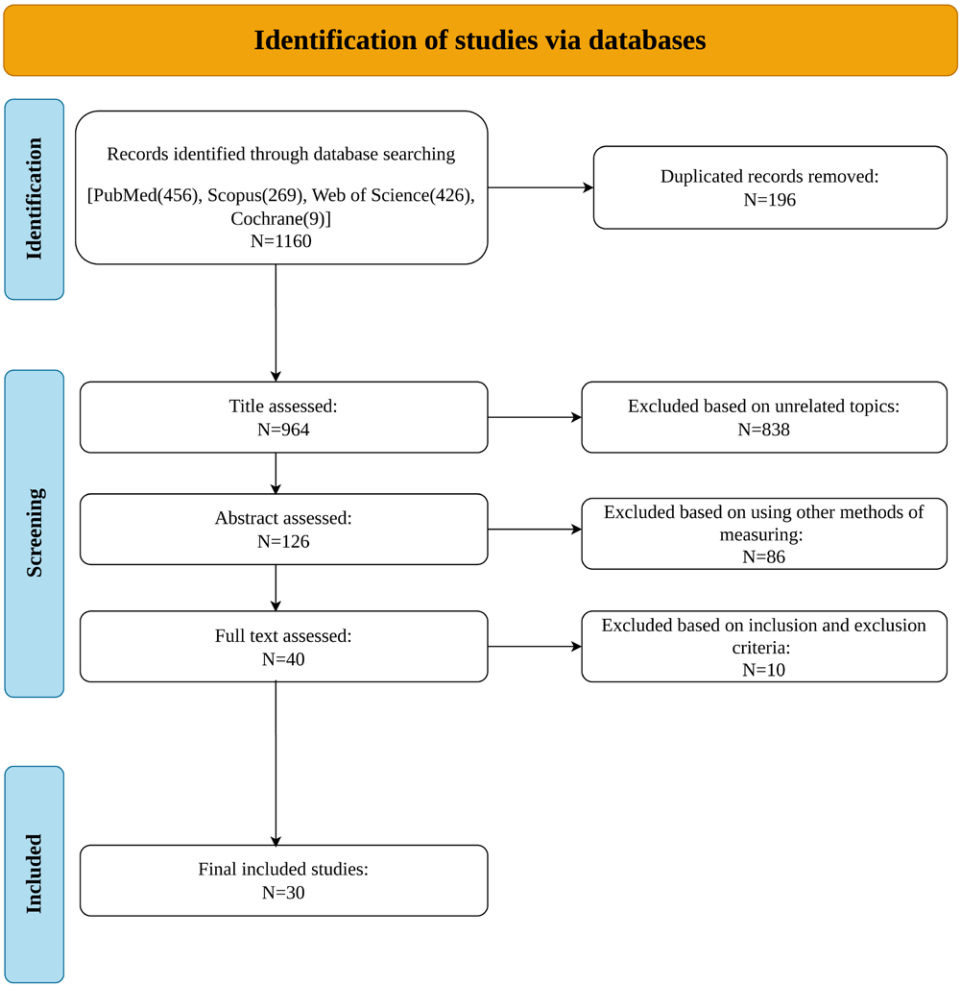
### Study selection

The flowchart of the study is presented in Fig. 1, which indicates that our search strategy identified a total of 1160 studies. After deleting duplicate records, 964 studies underwent title review. Out of these, 126 studies met the requirements for abstract review. Following the abstract review, 40 studies were selected for full-text evaluation. Eventually, 30 studies were deemed eligible for inclusion in this systematic review and meta-analysis, while 10 studies did not meet the criteria for inclusion. The specific reasons for their exclusion are provided in Table S2, Supplemental digital content 4, *http://links.lww.com/CAEN/A49*. Due to an unclear definition of the PCOS population in a study conducted by Prelevic *et al.* [37](1995), it was deemed inappropriate to completely exclude it. Consequently, we have chosen to include it for thorough methodological appraisal.

### Study characteristics

Table 1 displays the characteristics of the 29 studies included in the analysis. The search yielded 29 studies, of which 17 had a cross-sectional study design, 11 had a case-control design, and 1 had a cohort study design. Most of the studies used the Rotterdam criteria for the

**Fig. 1**




The PRISMA flow diagram illustrates the process employed for identifying relevant studies.

**Table 1 Study characteristics**

| First author and year of publication | Study design | Country | No. PCOS | No. Controls | Age (mean ± SD) | BMI (mean ± SD) | PCOS diagnosis criteria | Conventional echocardiography | TDIEchocardiography | Baseline characteristics | Major findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zachurzok-Buczynska *et al* [38] | Cross-sectional | Poland | 34 | 17 | *P* = 16 ± 1.3<br>C = 16.2 ± 1.3 | *P* = 24.6 ± 2.3<br>C = 23.4 ± 2.3 | AEPCOS | LVEDD, LVESD, LVEF, E wave, A wave, E/A, IVRT, IVST, PWT, LVM, LVMI | _ | Age, BMI, Testosterone, Androstenedione, DHEAS, FAI, HOMA-IR | 1) Increased LVEDD, LVESD in PCOS cases, 2) significant correlations between BMI z-score and LVM, LVEDD, LVESD, and IVST. |
| Çetin *et al* [39] | Cross-sectional | Turkey | 30 | 30 | *P* = 15.98 ± 0.27<br>C = 15.46 ± 0.24 | *P* = 22.07 ± 0.09<br>C = 20.46 ± 0.61 | Rotterdam | LVEDD, LVESD, E wave, A wave, E/A, IVRT, IVCT, DT, PWT, IVST | Lateral E', Lateral A', Lateral S, Lateral E/E' | Age, BMI, Testosterone, Androstenedione, DHEAS, HOMA-IR | Presence of diastolic dysfunction in PCOS. |
| Patel *et al* [40] | Case-control | USA | 36 | 17 | *P* = 14.81 ± 1.56<br>C = 13.94 ± 1.75 | *P* = 35.60 ± 3.66<br>C = 32.16 ± 2.57 | NIH | LVMI | _ | Age, BMI, Testosterone, FAI, FBS, F-insulin | 1) No significant echocardiographic changes between two groups of PCOS and controls 2) increased carotidintima–media thickness, higher carotid artery beta stiffness index and lower carotid artery compliance. |
| De Jong *et al* [41] | cross-sectional | Australia and Germany | 24 | 29 | *P* = 39.35 ± 2.06<br>C = 38.43 ± 1.34 | *P* = 35.56 ± 1.52<br>C = 36.23 ± 1.78 | Rotterdam | LVEDD, LVESD, IVST, PWT, LVEF, E wave, A wave, E/A, LVM, LVMI, LAD, DT | E/E' and E' (The analysis did not incorporate these measurements because it remains unclear from which side of the mitral annuli they were obtained) | Age, BMI, FBS | 1) Increased LVM, 2) concentric hypertrophy in PCOS cases, that was not accompanied by the presence of diastolic dysfunction. |
| Tasolar et al[(1)] [42] | Case-control | Turkey | 25 obese PCOS | 25 | *P* = 29.7 ± 3.5<br>C = 29.3 ± 4.1 | *P* = 21.7 ± 1.4<br>C = 22.5 ± 1.6 | Rotterdam | LVED, LVSD, LVEF, PWT, IVST, DT, LAD, A wave, E wave, E/A, IVRT | E', A', S, E/E' (The analysis did not include these values, which were reported as the combined values of the lateral mitral annuli, septal mitral annuli, and tricuspid annuli) | Age, BMI, FBS, F-insulin, HOMA-IR, Testosterone | 1) LV diastolic parameters were impaired in PCOS, 2) increased atrial electromechanical delay in PCOS. |
| Tasolar et al[(2)] [42] | Case-control | Turkey | 25 lean PCOS | 25 | *P* = 29.7 ± 2.6<br>C = 29.3 ± 4.1 | *P* = 32.7 ± 2.0<br>C = 22.5 ± 1.6 | Rotterdam | LVEDD, LVESD, LVEF, PWT, IVST, DT, LAD, A wave, E wave, E/A, IVRT | E', A', S, E/E' (The analysis did not include these values, which were reported as the combined values of the lateral mitral annuli, septal mitral annuli, and tricuspid annuli) | Age, BMI, FBS, F-insulin, HOMA-IR, Testosterone | 1) LV diastolic parameters were impaired in PCOS, 2) increased atrial electromechanical delay in PCOS. |
| Rees *et al* [43] | Cross-sectional | UK (69 Caucasian, 7 Asian, 4 Afro-Caribbean, 2 mixed races, 2 Arab) | 84 | 95 | *P* = 29.8 ± 6.7<br>C = 32.6 ± 7.9 | *P* = 33.3 ± 7.8<br>C = 27.6 ± 6.3 | Rotterdam | LVEDD, IVST, PWT, LVEF | Septal-Lateral E', Septal-Lateral S | Age, BMI, HOMA-IR, Testosterone | No significant differences in central arterial stiffness and diastolic dysfunction between young women with PCOS and controls, after adjustment for age and BMI, whereas they are associated with insulin resistance and abdominal obesity. |

(*Continued*)

**Table 1**
(*Continued*)

| First author and year of publication | Study design | Country | No. PCOS | No. Controls | Age (mean ± SD) | BMI (mean ± SD) | PCOS diagnosis criteria | Conventional echocardiography | TDIEchocardiography | Baseline characteristics | Major findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zehir *et al* [44] | Case-control | Turkey | 51 | 48 | *P* = 30.2 ± 3.4<br>C = 31.0 ± 3.2 | *P* = 31.8 ± 2.4<br>C = 31.2 ± 2.5 | Rotterdam | LVEDD, LVESD, LVEF, PWT, IVST, DT, LAD, A wave, E wave, E/A | _ | Age, BMI, Testosterone, DHEAS, FBS, HOMA-IR, | 1) Significantly increased A wave, and DT in PCOS compared to controls, 2) Increased atrial electromechanical conduction delay in PCOS. |
| Zimmermann *et al* [45] | Case-control | Canada (Caucasian or Caribbean) | 14 | 18 | *P* = 30 ± 1<br>C = 31 ± 1 | *P* = 31 ± 2<br>C = 30 ± 2 | NIH | LVM | _ | Age, BMI, Testosterone, Androstenedione, DHEAS, FBS, F-insulin | No significant difference in LVM and arterial pressure between PCOS and controls. |
| Yildirim et al[(1)] [46] | Cross-sectional | Turkey | 41 | 52 | *P* = 23.9 ± 3.6<br>C = 27.2 ± 6.1 | *P* = 25.6 ± 4.1<br>C = 23.5 ± 3.1 | Rotterdam | LVEDD, IVST, PWT, LVEF, E wave, A wave, E/A, LVM, LVMI, LAD | Lateral E', Lateral E/E' | Age, BMI, FBS, F-insulin, HOMA-IR, Testosterone, Androstenedione, DHEAS, FAI | 1) Decreased E/A ratio, 2) increased LVMI, 3) significant difference in LVEF with controls and other phenotypes. |
| Yıldırım et al[(2)] [46] | Cross-sectional | Turkey | 20 | 52 | *P* = 24.9 ± 4.4<br>C = 27.2 ± 6.1 | *P* = 24.2 ± 2.7<br>C = 23.5 ± 3.1 | Rotterdam | LVEDD, IVST, PWT, LVEF, E wave, A wave, E/A, LVM, LVMI, LAD | Lateral E', Lateral E/E' | Age, BMI, FBS, F-insulin, HOMA-IR, Testosterone, Androstenedione, DHEAS, FAI | 1) Decreased E/A ratio, 2) increased LVMI. |
| Yıldırım et al[(3)] [46] | Cross-sectional | Turkey | 25 | 52 | *P* = 22.5 ± 2.6<br>C = 27.2 ± 6.1 | *P* = 25.7 ± 4.3<br>C = 23.5 ± 3.1 | Rotterdam | LVEDD, IVST, PWT, LVEF, E wave, A wave, E/A, LVM, LVMI, LAD | Lateral E', Lateral E/E' | Age, BMI, FBS, F-insulin, HOMA-IR, Testosterone, Androstenedione, DHEAS, FAI | Decreased E/A ratio. |
| Yıldırım et al[(4)] [46] | Cross sectional | Turkey | 27 | 52 | *P* = 24.7 ± 4.3<br>C = 27.2 ± 6.1 | *P* = 23.8 ± 3.3<br>C = 23.5 ± 3.1 | Rotterdam | LVEDD, IVST, PWT, LVEF, E wave, A wave, E/A, LVM, LVMI, LAD | Lateral E', Lateral E/E' | Age, BMI, FBS, F- insulin, HOMA-IR, Testosterone, Androstenedione, DHEAS, FAI | Decreased E/A ratio. |

(*Continued*)

**Table 1**
(*Continued*)

| First author and year of publication | Study design | Country | No. PCOS | No. Controls | Age (mean ± SD) | BMI (mean ± SD) | PCOS diagnosis criteria | Conventional echocardiography | TDIEchocardiography | Baseline characteristics | Major findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gazi *et al* [47] | Cross-sectional | Turkey | 48 | 38 | *P* = 24 ± 4<br>C = 30 ± 7 | *P* = 25.4 ± 5.4<br>C = 22.5 ± 3.4 | AEPCOS | LVEDD, LVESD, LVEF, DT, LAD, A wave, E wave, E/A, IVRT, IVCT (due to inappropriate reporting of this value, we did not include it in the meta-analysis) | E', E/E' (The analysis did not include these values, which were reported as the combined values of the lateral mitral annuli, septal mitral annuli, and tricuspid annuli) | Age, BMI, Testosterone, FBS, HOMA-IR, F-insulin | 1) Significantly decreased E/A in PCOS, 2) increased inter- and intra-atrial conduction delays, decreased LA passive Empting volume and fraction. |
| Rashid *et al* [48] | Cross-sectional | India | 260 | 250 | *P* = 28.08 ± 4.18<br>C = 29.44 ± 6.74 | *P* = 24.43 ± 4.15<br>C = 23.93 ± 4.21 | Rotterdam | LVMI, LVM, LVEDD, IVST, PWT | _ | Age, BMI, F-Insulin, HOMA-IR, FBS, Testosterone | 1) Significantly increased IVST, PWT, LVDD, LVM, and LVMI in women with PCOS compared to controls, 2) positive correlation between LVMI with IR and markers of inflammation but not with hyperandrogenism. |
| Demirelli *et al* [49] | Cross-sectional | Turkey | 31 | 32 | *P* = 24.6 ± 4.8<br>C = 22.5 ± 3.6 | *P* = 23.3 ± 4.8<br>C = 22.3 ± 3.0 | Rotterdam | LVEF, E wave, A wave, E/A, DT, IVRT, LAD, IVSD | Septal E', Septal S | Age, BMI, FBS, F-insulin, HOMA-IR | 1) Significantly higher A wave, DT, IVRT and significantly lower E' and E/A ratio in PCOS cases, 2) strong negative correlations between GLS (Global longitudinal strain), and both the fasting insulin and DT, significant, moderate correlation between GLS and HOMA-IR, significant weak, negative correlation between GLS and IVRT. |
| Özkan *et al* [50] | cross-sectional | Turkey | 60 | 60 | *P* = 26.4 ± 7.1<br>C = 30.5 ± 6.6 | *P* = 25.84 ± 5.4<br>C = 24.02 ± 3.3 | Rotterdam | LVEDD, LVESD, LVEF, PWT, IVST, LAD | _ | Age, BMI, DHEAS, HOMA-IR | No significant difference in cardiac chamber dimensions between PCOS cases and controls. |
| Aldrighi et al[(1)] [51] | Cross-sectional | Brazil | 18 | 11 | *P* = 25 ± 8<br>C = 28 ± 6 | *P* = 29 ± 4<br>C = 23 ± 2 | Rotterdam | LVEDD, IVST, PWT, LVEF, LAD | _ | Age, BMI, FBS, F-insulin, Testosterone, Androstenedione, DHEAS | No significant difference in cardiac chamber dimensions between PCOS cases and controls. |
| Aldrighi et al[(2)] [51] | Cross-sectional | Brazil | 26 | 11 | *P* = 29 ± 6<br>C = 28 ± 6 | *P* = 24 ± 3<br>C = 23 ± 2 | Rotterdam | LVEDD, IVST, PWT, LVEF, LAD | _ | Age, BMI, FBS, F-insulin, Testosterone, Androstenedione, DHEAS, | No significant difference in cardiac chamber dimensions between PCOS cases and controls. |

(*Continued*)

**Table 1**
(*Continued*)

| First author and year of publication | Study design | Country | No. PCOS | No. Controls | Age (mean ± SD) | BMI (mean ± SD) | PCOS diagnosis criteria | Conventional echocardiography | TDIEchocardiography | Baseline characteristics | Major findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Deveer *et al* [52] | Cross-sectional | Turkey | 25 | 25 | *P* = 27.24 ± 5.34<br>C = 31.8 ± 8.11 | *P* = 25.86 ± 4.61<br>C = 25.44 ± 5.10 | Rotterdam | LVMI | Lateral-Septal E/E' | Age, BMI, Testosterone, FBS, HOMA-IR, F- insulin | No significant difference in echocardiographic indices and carotid intima–media thickness between PCOS and controls. |
| Erdogan *et al* [53] | Cross-sectional | Turkey | 40 | 46 | *P* = 25.45 ± 6.72<br>C = 26.76 ± 6.04 | *P* = 28.1 ± 7.8<br>C = 26.8 ± 4.5 | Rotterdam | LVEDD, LVESD, LVEF, DT, LAD, A wave, E wave, E/A, IVRT, IVCT | _ | Age, BMI, FBS, F- insulin, HOMA-IR | 1) Increased IVRT and DT in PCOS, 2) P wave dispersion was significantly correlated with WHR, DT, E/A ratio and DBP. |
| Celik *et al* [54] | Cross-sectional | Turkey | 30 | 30 | *P* = 22 ± 3.48<br>C = 24.75 ± 3.76 | *P* = 24.6 ± 6.5<br>C = 20.15 ± 1.5 | Rotterdam | LVEF, LVM, PWT, IVST, IVRT, DT, LAD | _ | Age, BMI, Testosterone, DHEAS, FBS, F-insulin, HOMA-IR | 1) Increased PWT and LVM in PCOS, 2) a positive correlation between LVM and HOMA-IR, 3) a positive correlation between PWT and fasting insulin, HOMA-IR. |
| Kosmala *et al* [55] | Cross-sectional | Australia | 52 | 54 | *P* = 30.0 ± 6.2<br>C = 32.1 ± 5.2 | *P* = 38.1 ± 9.5<br>C = 36.1 ± 5.5 | Rotterdam | LVEDD, IVST, PWT, LVMI, LVEF, LAD, E/A, DT | Septal E/E' | Age, BMI, Testosterone, DHEA-S, FBS, F-insulin, HOMA-IR | Impaired LV systolic and diastolic function in PCOS cases with IR, as compared with women with normal insulin sensitivity. |
| Erdoğan *et al* [56] | Cross-sectional | Turkey | 30 | 30 | *P* = 25.9 ± 6.5<br>C = 26.1 ± 4.5 | *P* = 29.4 ± 8.5<br>C = 28.2 ± 4.1 | Rotterdam | LVEDD, LVESD, IVST, PWT, LAD, LVEF, LVM, LVMI, E wave, A wave, E/A ratio, DT, IVRT, IVCT | Septal E'<br>Septal E/E' | Age, BMI, FBS, F-insulin, HOMA-IR | Prolonged DT and IVRT, lower E' and higher E/E' ratio in PCOS cases. |
| Akdag *et al* [57] | Cross-sectional | Turkey | 82 | 74 | *P* = 25.9 ± 5.7<br>C = 26.4 ± 6.8 | *P* = 26.4 ± 4.1<br>C = 25.9 ± 5.9 | Rotterdam | LVEDD, LVESD, LVEF, DT, LAD, A wave, E wave, E/A, IVRT | _ | Age, BMI, Testosterone, FBS | 1) No significant changes in echocardiographic measures between PCOS and control groups, 2) increased atrial conduction time in PCOS. |
| Bayir *et al* [58] | Cross-sectional | Turkey | 40 | 20 | *P* = 27.6 ± 7.2<br>C = 26.3 ± 6.1 | *P* = 26.6 ± 5.7<br>C = 25.1 ± 4.7 | Rotterdam | LVEDD, LVESD, LVEF, PWT, IVST, DT, LAD, A wave, E wave, E/A, IVRT | _ | Age, BMI, FBS | 1) Significantly decreased E wave, E/A, and increased IVRT and LAD in PCOS compared to controls, 2) Increased Inter- and intra-atrial conduction times in PCOS |
| Tekin *et al* [59] | Case-Control | Turkey | 26 | 24 | *P* = 25.5 ± 3.9<br>C = 26.0 ± 3.8 | *P* = 25.2 ± 4.3<br>C = 25.3 ± 4.7 | Rotterdam (type 1, classic PCOS phenotype) | LVESD, LVEDD, IVST, PWT, LVEF, E wave, A wave, E/A, IVRT, DT, LAD | Septal E', Lateral E', Septal S, Lateral S, Lateral-Septal E', Septal-Lateral E/E' | Age, BMI, F-insulin, HOMA-IR, FBS, Testosterone, DHEAS | 1) No significant differences in LVEF, E/A ratio, DT, IVRT between PCOS cases and controls, 2) the TDI parameters of patients with PCOS and controls were not significantly different. |
| Aslan *et al* [60] | Case-control | Turkey | 26 | 23 | *P* = 25.9 ± 5.8<br>C = 25.7 ± 2.8 | *P* = 28 ± 5.1<br>C = 22 ± 2.9 | Rotterdam | IVST, PWT, LVEDD, LVESD, LVEF, LVMI, A wave, E wave, E/A | Lateral E', Septal E', Lateral S, Septal S, Lateral E/E', Septal E/E' | Age, BMI, DHEAS, FBS, HOMA-IR, F-insulin, | No differences were detected between the PCOS and control groups' conventional echocardiographic measurements. |

(*Continued*)

**Table 1**
(*Continued*)

| First author and year of publication | Study design | Country | No. PCOS | No. Controls | Age (mean ± SD) | BMI (mean ± SD) | PCOS diagnosis criteria | Conventional echocardiography | TDIEchocardiography | Baseline characteristics | Major findings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Topcu *et al* [61] | Case-control | Turkey | 28 | 26 | *P* = 27.1 ± 4.5<br>C = 28.8 ± 4.4 | *P* = 26.6 ± 5.7<br>C = 24.7 ± 3.7 | Rotterdam | LVEDD, LVESD, LVEF, LAD, PWT, IVST, A wave, E wave, E/A, LVMI | _ | Age, BMI, Testosterone, Andreostenedione, DHEAS, FBS, F- insulin, HOMA-IR, | No significant findings. |
| Tiras *et al* [62] | Case-control | Turkey | 35 | 35 | *P* = 24.5 ± 6.0<br>C = 23.6 ± 3.9 | *P* = 22.9 ± 4.2<br>C = 22.0 ± 1.8 | Rotterdam | LVEF, DT, A wave, E wave, E/A, IVRT | _ | Age, BMI, DHEAS, Androstenedione, FBS, F- insulin | Presence of diastolic dysfunction in PCOS. |
| Orio *et al* [63] | Case-Control | Italy | 30 | 30 | *P* = 24.3 ± 5.6<br>C = 24.8 ± 4.2 | *P* = 28.7 ± 6.7<br>C = 27.3 ± 5.0 | Rotterdam | LVMI, LVESD, LVEDD, IVST, PWT, LVEF, E/A, LAD | _ | Age, BMI, Androstendione, FAI, Testosterone, DHEAS, | 1) Significantly higher IVST, PWT, LVMI in PCOS cases, 2) significantly lower LVEF and E/A ratio in PCOS cases, 3) positive correlation between LVMI and HOMA-IR in PCOS cases. |
| Selcoki *et al* [64] | Case-control | Turkey | 48 | 21 | *P* = 24.4 ± 5.4<br>C = 26.3 ± 3.9 | *P* = 26 ± 3.5<br>C = 25 ± 1.8 | NIH | LVEDD, LVESD, LAD, IVST, PWT, LVEF, E wave, A wave, E/A, DT, IVRT | Septal E', Lateral E', Septal-Lateral E' Septal S, Lateral S, | Age, BMI, FBS, Testosterone, DHEAS, F-Insulin, HOMA-IR | No significant difference in echocardiographic measures between PCOS cases and controls. |
| Yarali *et al* [65] | Case -Control | Turkey | 30 | 30 | *P* = 27.9 ± 6.1<br>C = 31.4 ± 6.5 | *P* = 27.3 ± 6.0<br>C = 25.0 ± 3.3 | NIH | LVEF, E wave, A wave, E/A, IVRT, DT | _ | Age, BMI, Testosterone, DHEAS | 1) Significantly lower E wave and E/A ratio and longer IVRT in PCOS cases comparing to controls, 2) significantly higher mean serum homocysteine concentration in patients with PCOS compared with the controls. |
| Abacioglu *et al* [66] | Retrospective cohort | Turkey | 44 | 60 | *P* = 22 ± 5<br>C = 24 ± 5 | *P* = 24.86 ± 2.74<br>C = 24.26 ± 2.25 | NIH | LVEF, IVST, PWT | _ | Age, BMI, FBS, HOMA-IR | 1) No significant difference in LVEF, PWT, IVST between PCOS and controls, 2) increased pulmonary artery stiffness. |

A wave, late diastolic mitral flow peak velocity; DHEAS, dehydroepiandrosterone sulfate; DT, deceleration time; E wave, early diastolic mitral flow peak velocity; E/A, E wave to A wave ratio; FAI, free androgen index; FBS, fasting blood glucose; F-insulin, fasting serum insulin; HOMA-IR, homeostatic model for insulin resistance; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; IVST, inter-ventricular septal thickness; LAD, left atrium diameter; Lateral E', early diastolic myocardial velocity obtained from mitral lateral annulus; Lateral S', mitral lateral annular peak systolic velocity. BMI, BMI; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; PWT, posterior wall thickness; Septal E', early diastolic myocardial velocity obtained from mitral septal annulus; Septal S', mitral septal annular peak systolic velocity; septal-lateral E', mean value of lateral E' and septal E'.

diagnosis of PCOS, while some employed the NIH or AEPCOS diagnostic criteria. One study diagnosed PCOS based on all three diagnostic criteria, including hyperandrogenism, polycystic ovarian morphology, and oligo-anovulation (classic phenotype). The majority of the studies included PCOS cases who were over 18 years old, while 3 studies focused on adolescent cases (Zachurzok-Buczynska *et al*. [38], Çetin *et al*. [39], Patel *et al*. [40]). Six studies included obese PCOS cases with a BMI above 30 (De Jong *et al* [41], Patel *et al*. [40], Tasolar *et al*. [42], Rees *et al*. [43], Zehir *et al*. [44] and Zimmermann *et al*. [45]). One study (Yildirim *et al*. [46]) divided PCOS cases into four groups based on four PCOS phenotypes. To ensure consistency with the other included studies, we separated this study into four distinct studies, each with a common healthy control group. Another study (Tasolar *et al*. [42]) evaluated lean and obese PCOS cases, which we also divided into two separate groups marked as Tasolar *et al*. [1] for obese PCOS and Tasolar *et al*. [2] for lean cases. All studies reported at least one conventional echocardiographic value, while only 13 studies used TDI in combination with conventional echocardiography. Among these 13 studies, three (De Jong *et al* [41], Gazi *et al* [47] and Tasolar *et al* [42]) excluded TDI analysis, and one (De Jong *et al* [41]) did not specify which side of the mitral annulus was used for TDI assessment. Two studies (Gazi *et al* [47] and Tasolar *et al* [42]) reported their TDI parameters as the average of the lateral mitral, septal, and anterior mitral annuli. The main findings of each study, along with the echocardiographic results, are presented in Table 2.

## Risk of bias in studies

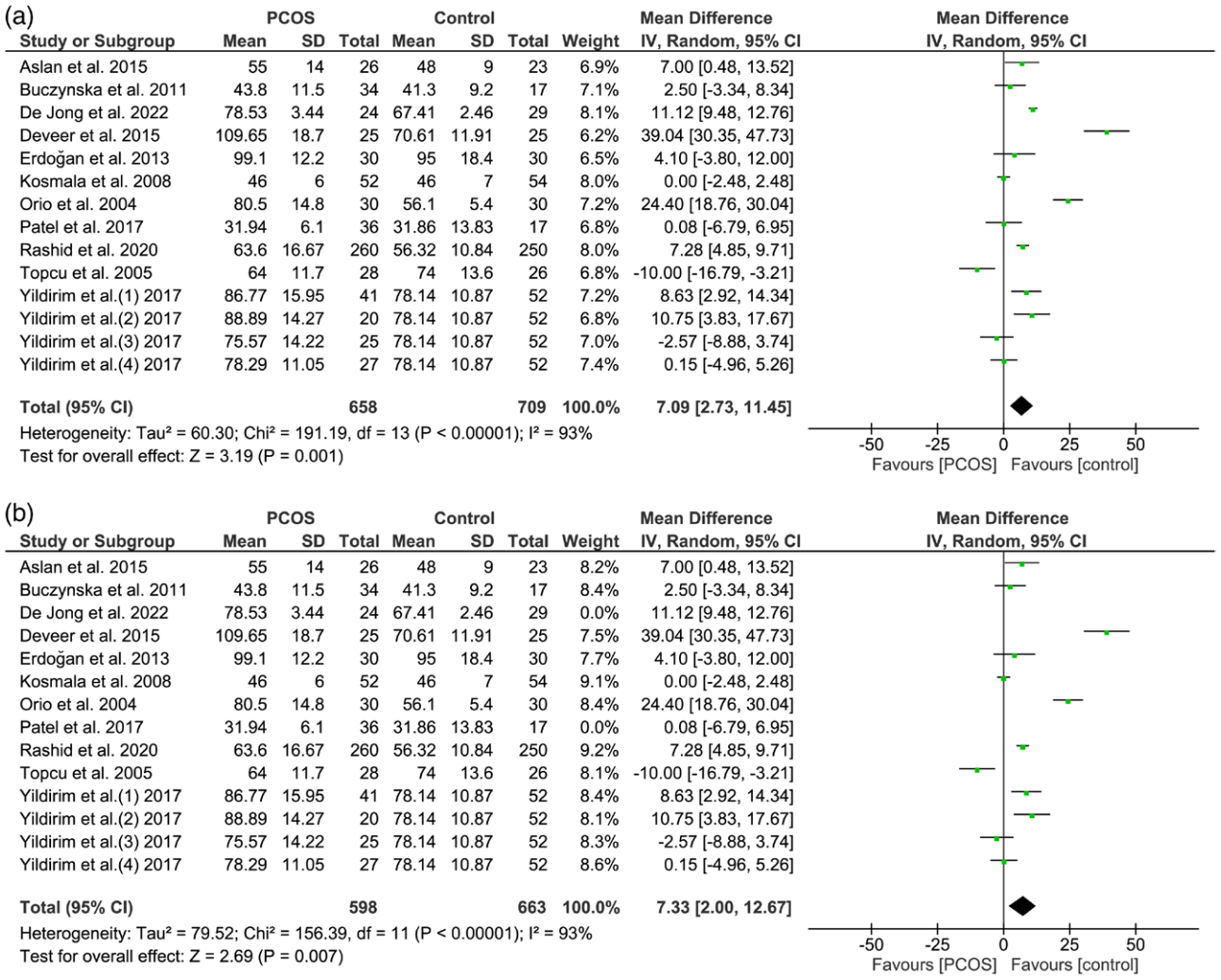
The S3 document, Supplemental digital content 5, *http://links.lww.com/CAEN/A50* provides risk of bias tables for the included studies. Out of the 17 studies that employed a cross-sectional study design, 10 studies (Rashid *et al*. [48], Rees *et al*. [43], Demirli *et al*. [49], Özkan *et al*.

**Table 2 Echocardiography results**

| Conventional Echocardiography | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Heterogeneity | |
| Characteristics of study | Number of studies | Number of PCOS | Number of controls | Mean difference (95% CI) | *P* value | $I^2$ | *P* value |
| LVEDD-1 | 26 | 1200 | 1195 | 0.41 [–0.27 to 1.09] | 0.23 | 88% | < 0.00001 |
| LVEDD-2 | 22 | 1016 | 998 | 0.65 [–0.12 to 1.41] | 0.10 | 86% | < 0.00001 |
| LVESD-1 | 17 | 647 | 566 | 0.26 [–0.30 to 0.83] | 0.36 | 73% | < 0.00001 |
| LVESD-2 | 14 | 547 | 464 | 0.50 [–0.07 to 1.08] | 0.09 | 67% | < 0.00001 |
| LVEF-1 | 29 | 1080 | 1102 | –0.25 [–0.72 to 0.22] | 0.29 | 53% | 0.0004 |
| LVEF-2 | 25 | 896 | 905 | –0.39 [–0.89 to 0.12] | 0.13 | 47% | 0.0005 |
| IVST-1 | 26 | 1135 | 1159 | **0.29 [0.02 to 0.57]** | **0.04** | 91% | <0.00001 |
| IVST-2 | 22 | 951 | 962 | **0.27 [0.01 to 0.53]** | **0.04** | 85% | <0.00001 |
| PWT-1 | 23 | 1060 | 1105 | **0.33 [0.11 to 0.54]** | **0.003** | 84% | <0.00001 |
| PWT-2 | 19 | 876 | 908 | **0.36 [0.12 to 0.59]** | **0.003** | 79% | <0.00001 |
| LVM-1 | 10 | 505 | 582 | **10.52 [4.60 to 16.43]** | **0.0005** | 80% | < 0.00001 |
| LVM-2 | 8 | 467 | 535 | **10.41 [3.83 to 16.98]** | **0.004** | 74% | |
| LVMI-1 | 14 | 658 | 709 | **7.09 [2.73 to 11.45]** | **0.001** | 93% | < 0.00001 |
| LVMI-2 | 12 | 598 | 663 | **7.33 [2.00 to 12.67]** | **0.007** | 93% | < 0.00001 |
| IVRT-1 | 15 | 554 | 477 | **5.71 [2.77 to 8.66]** | **0.0001** | 97% | < 0.00001 |
| IVRT-2 | 14 | 529 | 452 | **4.80 [2.06 to 7.54]** | **0.0006** | 96% | < 0.00001 |
| IVCT | 3 | 100 | 106 | **3.22 [0.72 to 5.73]** | **0.01** | 86% | 0.0008 |
| DT-1 | 17 | 647 | 591 | **5.11 [1.90 to 8.31]** | **0.002** | 84% | <0.00001 |
| DT-2 | 14 | 547 | 489 | **4.38 [1.41 to 7.35]** | **0.004** | 78% | <0.00001 |
| Peak E wave-1 | 22 | 766 | 781 | **–0.02 [–0.04 to –0.00]** | **0.03** | 72% | <0.00001 |
| Peak E wave-2 | 19 | 666 | 679 | **–0.02 [–0.05 to –0.00]** | **0.04** | 72% | <0.00001 |
| Peak A wave-1 | 22 | 766 | 781 | **0.03 [0.00 to 0.06]** | **0.03** | 94% | <0.00001 |
| Peak A wave-2 | 19 | 666 | 679 | **0.02 [0.01 to 0.04]** | **0.01** | 75% | <0.00001 |
| E/A ratio-1 | 24 | 848 | 865 | **–0.13 [–0.18 to –0.07]** | **<0.00001** | 93% | <0.00001 |
| E/A ratio-2 | 21 | 748 | 763 | **–0.12 [–0.18 to –0.07]** | **<0.00001** | 91% | <0.00001 |
| LAD-1 | 21 | 752 | 765 | **1.20 [0.46 to 1.93]** | **0.002** | 82% | < 0.00001 |
| LAD-2 | 20 | 727 | 740 | **0.84 [0.34 to 1.34]** | **0.0010** | 58% | 0.0006 |
| Tissue Doppler echocardiography | | | | | | | |
| Septal E' | 5 | 161 | 130 | –0.97 [–1.96 to 0.01] | 0.05 | 76% | 0.002 |
| Lateral E' | 8 | 243 | 306 | –0.28 [–0.89 to 0.33] | 0.37 | 57% | 0.02 |
| Septal-lateral E'-1 | 4 | 154 | 163 | –0.11 [–0.59 to 0.37] | 0.66 | 26% | 0.25 |
| Septal-lateral E'-2 | 3 | 100 | 68 | –0.25 [–1.05 to 0.54] | 0.54 | 45% | 0.16 |
| Septal S' | 4 | 131 | 100 | –0.37 [–0.74 to –0.00] | 0.05 | 0% | 0.51 |
| Lateral S' | 4 | 130 | 98 | 0.14 [–0.06 to 0.35] | 0.17 | 0% | 0.43 |
| Septal-lateral S'-1 | 4 | 184 | 163 | –0.28 [–0.60 to 0.04] | 0.19 | 40% | 0.17 |
| Septal-lateral S'-2 | 3 | 100 | 68 | **–0.47 [–0.88 to –0.06]** | **0.02** | 31% | 0.23 |
| Septal E/E' | 3 | 108 | 107 | 0.38 [–0.32 to 1.09] | 0.29 | 44% | 0.17 |
| Lateral E/E' | 6 | 169 | 261 | –0.08 [–0.40 to 0.24] | 0.62 | 60% | 0.03 |
| Septal-lateral E/E' | 3 | 135 | 143 | –0.18 [–0.59 to 0.23] | 0.39 | 0% | 0.94 |

*P*-value < 0.05 is considered significant.
Bold values indicate statistically significant results.

**Fig. 2**




Forest plot graphs for the comparison of LVMI between women with polycystic ovarian syndrome and women in the control group. Panel (a) indicates analysis of LVMI including all studies that reported this value (LVMI-1) and Panel (b) shows analysis of LVMI after excluding studies that reported this value in obese women (LVMI-2). The studies by De Jong *et al.* (2022) and Patel *et al.* (2017) only included obese women with and without PCOS in their surveys. A random-effects model was used in this meta-analysis, and mean differences (MD) were used to measure the effect size. A positive effect indicates higher values in women with PCOS than women in control group and vice versa. CI, confidence interval; LVMI, Left Ventricular Mass Index; PCOS, polycystic ovarian syndrome.

[50], Aldrighi *et al.* [51], Buczynska *et al.* [38], Deveer *et al.* [52], Erdogan *et al.* [53], Celik *et al.* [54], Çetin *et al.* [39]) scored 8 'yes' answers out of 8 methodological questions, two studies (Kosmala *et al.* [55], Erdoğan *et al.* [56]) scored 7/8, and the remaining five studies (De Jong *et al.* [41], Yildirim *et al.* [46], Zimmermann *et al.* [45], Akdag *et al.* [57], Bayir *et al.* [58]) scored 6/8 using the JBI scoring method to evaluate the methodological quality of cross-sectional studies. Among the 11 studies that utilized a case-control study design, 6 studies (Tekin A *et al.* [59], Patel *et al.* [40], Aslan *et al.* [60], Zehir *et al.* [44], Topcu *et al.* [61], Tiras *et al.* [62]) scored 9 'yes' answers out of 10 methodological questions, three studies (Orio *et al.* [63], Gazi *et al.* [47], Tasolar *et al* [42]) scored 8/10, and the remaining two studies (Selcoki *et al.* [64] and Yarali *et al.* [65]) scored 7/10 and 6/10, respectively, using the JBI scoring method to measure the methodological quality of case controls. One study (Abacioglu *et al.* [66]) reported the results of a retrospective cohort study design and scored 10/11 using the JBI scoring method for measuring the methodological qualities of cohorts.

The study conducted by Prelevic *et al* [37] scored less than 50% (3/8). Furthermore, the case and control group of this study were not properly screened for other medical conditions aside from PCOS. Due to weak approval for inclusion/exclusion criteria and the low JBI score, we made the decision to exclude it from this review in order to prevent potential bias in the analysis.

## Results of syntheses

### *Conventional echocardiography*

Table 1 provides information on the analysis conducted, where results labeled with the number 1 represent the analysis including all studies reporting the relevant parameter, regardless of participants' BMI. Conversely, results labeled with the number 2 represent the analysis after excluding studies reporting the relevant parameter in obese participants.

#### *LVMI-1*

The meta-analysis of 14 studies showed that LVMI was significantly higher in PCOS cases (n = 658) compared to controls (n = 709), with an effect size of 7.09 (95% CI [2.73, 11.45], $P = 0.001$). The analysis also revealed high heterogeneity ($I^2 = 93\%$; $P < 0.00001$), indicating variability among the studies (Fig. 2).

#### *LVMI-2*

The meta-analysis of 12 studies showed that LV mass index (LVMI) was significantly higher in PCOS cases (n = 598) compared to controls (n = 663), with an effect size of 7.33 (95% CI [2.00, 12.67], $P = 0.007$). The analysis also revealed high heterogeneity ($I^2 = 93\%$; $P < 0.00001$), indicating variability among the studies (Fig. 2).

#### *LVM-1*

The meta-analysis of 10 studies found that LVM was significantly higher in PCOS cases (n = 505) compared to controls (n = 582), with an effect size of 10.52 (95% CI [4.60, 16.43] $P = 0.0005$). The analysis also revealed moderate heterogeneity ($I^2 = 80\%$; $P < 0.00001$), indicating some variability among the studies.

#### *LVM-2*

The meta-analysis of 8 studies found that LVM was significantly higher in PCOS cases (n = 467) compared to controls (n = 535), with an effect size of 10.41 (95% CI [3.83, 16.98], $P = 0.002$). The analysis also revealed moderate heterogeneity ($I^2 = 73\%$; $P = 0.0005$), indicating some variability among the studies.

#### *LVESD-1*

The meta-analysis of 17 studies found no statistically significant difference in LVESD between PCOS cases (n = 647) and controls (n = 566), with an effect size of 0.26 (95% CI [–0.30, 0.83], $P = 0.36$).

#### *LVESD-2*

The meta-analysis of 14 studies found no statistically significant difference in LVESD between PCOS cases (n = 547) and controls (n = 464), with an effect size of 0.50 (95% CI [–0.07, 1.08], $P = 0.09$).

#### *LVEDD-1*

The meta-analysis of 26 studies found no statistically significant difference in LVEDD between PCOS cases (n = 1200) and controls (n = 1195), with an effect size of 0.41 (95% CI [–0.27, 1.09], $P = 0.23$).

#### *LVEDD-2*

The meta-analysis of LVEDD results of 22 studies revealed no statistically significant difference between PCOS cases (n = 1016) and controls (n = 998). The effect size was 0.65 (95% CI [–0.12, 1.41], $P = 0.10$).

#### *IVST-1*

The meta-analysis of 26 studies found that IVST was significantly higher in PCOS patients (n = 1135) compared to controls (n = 1159), with an effect size of 0.29 (95% CI [0.02, 0.57], $P = 0.04$). However, the analysis also revealed high heterogeneity ($I^2 = 91\%$; $P < 0.00001$), indicating substantial variability among the studies.

#### *IVST-2*

The meta-analysis of 22 studies revealed that IVST was significantly higher in PCOS patients (n = 951) compared to controls (n = 962) with the effect size of 0.27 (95% CI [0.01, 0.53], $P = 0.04$). Heterogeneity was high ($I^2 = 85\%$; $P < 0.00001$).

#### *PWT-1*

The meta-analysis of 23 studies found that PWT was significantly higher in PCOS patients (n = 1060) compared to controls (n = 1105), with an effect size of 0.33 (95% CI [0.11, 0.54], $P = 0.003$). However, the analysis also revealed high heterogeneity ($I^2 = 84\%$; $P < 0.00001$), indicating substantial variability among the studies.

#### *PWT-2*

The meta-analysis of 19 studies found that PWT was significantly higher in PCOS patients (n = 876) compared to controls (n = 908), with an effect size of 0.36 (95% CI [0.12, 0.59], $P = 0.003$). However, the analysis also revealed high heterogeneity ($I^2 = 79\%$; $P < 0.00001$), indicating substantial variability among the studies.

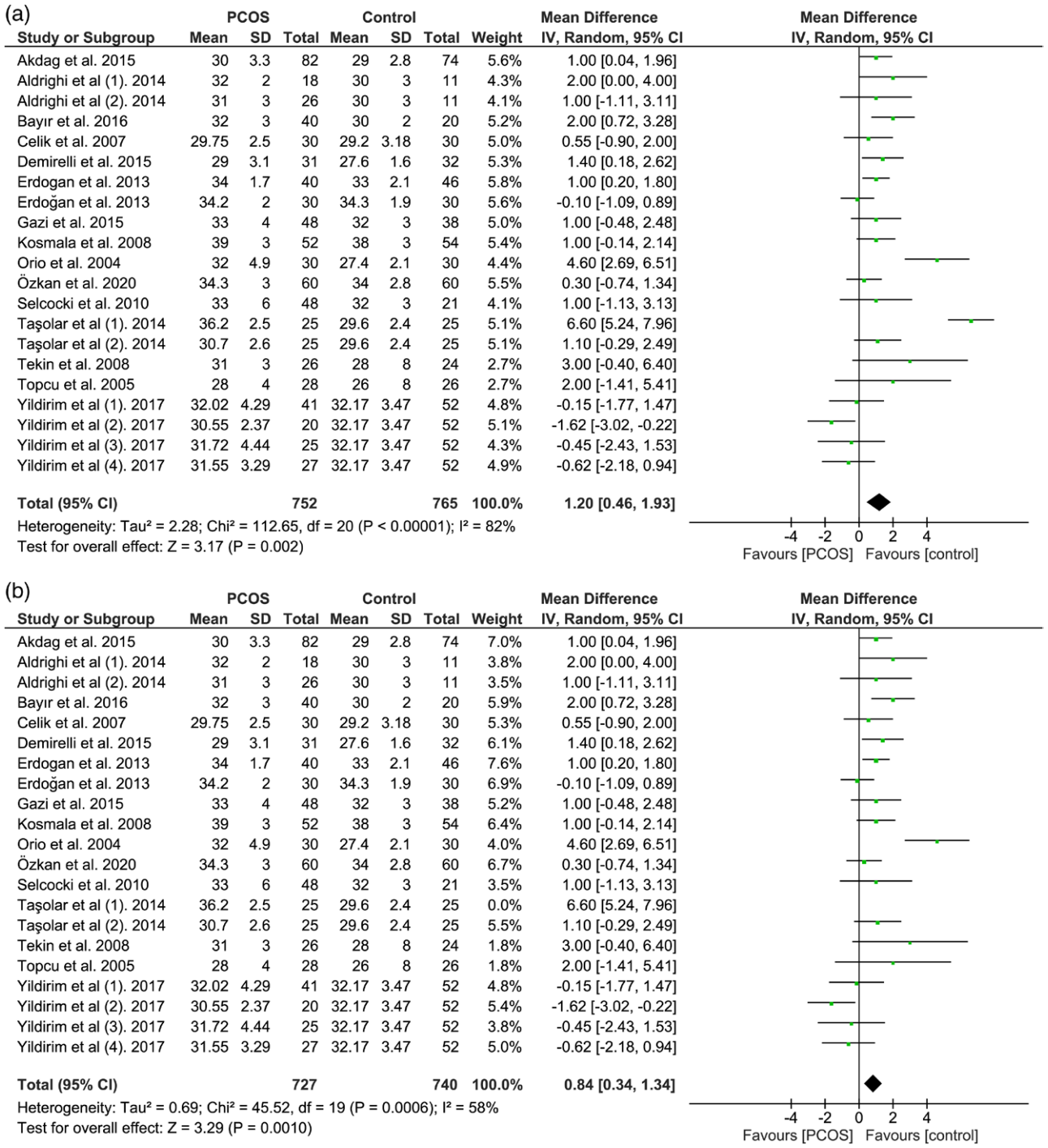
#### *LVEF-1*

The meta-analysis of 29 studies found no significant differences in LVEF between PCOS patients (n = 1080) and controls (n = 1102) in terms of LVEF, with an effect size of –0.25 (95% CI [–0.72, 0.22], $P = 0.29$).

#### *LVEF-2*

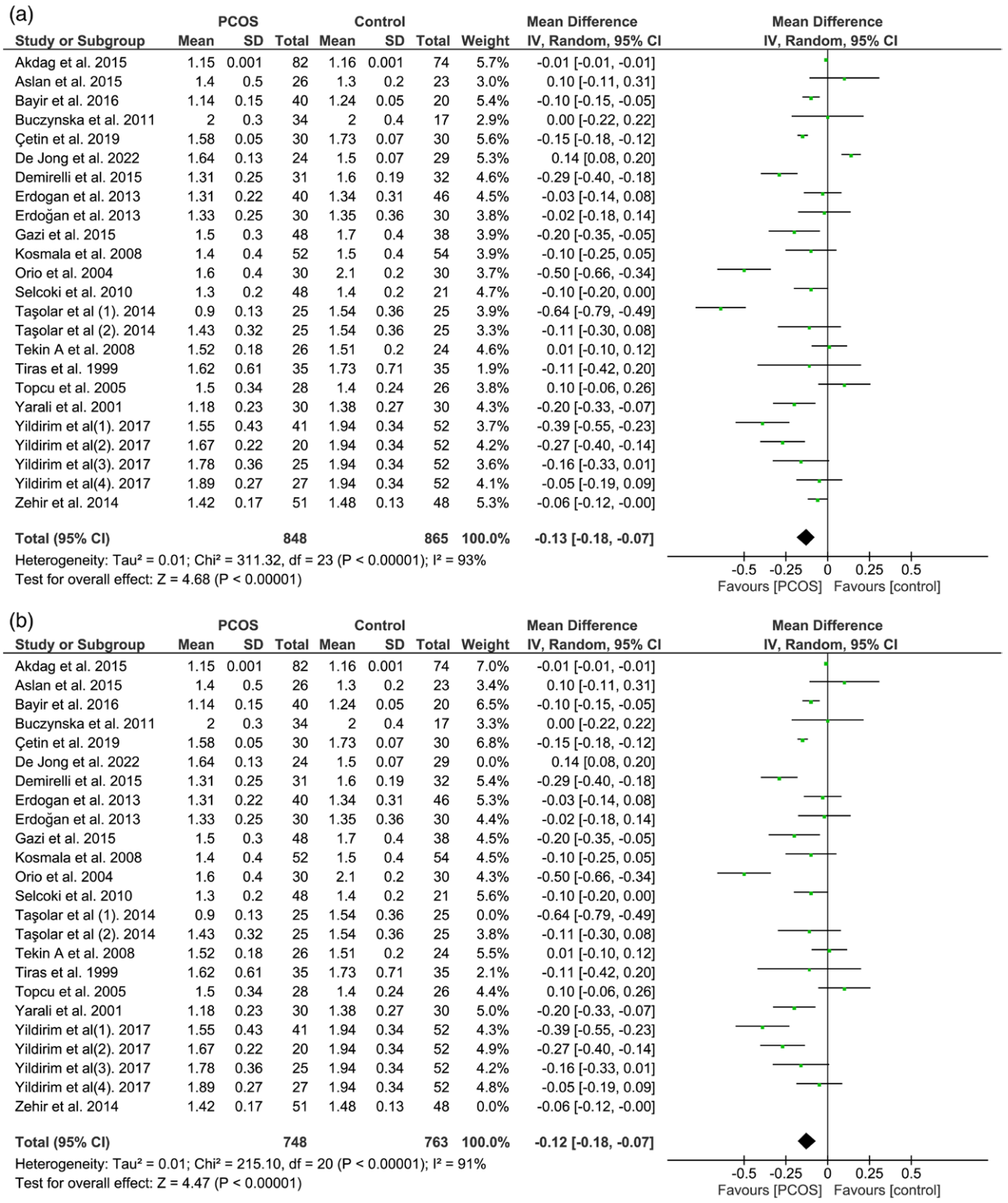
The meta-analysis of 25 studies found no significant differences in LVEF between PCOS patients (n = 896) and controls (n = 905), with an effect size of –0.39 (95% CI [–0.89, 0.12], $P = 0.13$).

**Fig. 3**




Forest plot graphs for the comparison of LAD between women with polycystic ovarian syndrome and women in the control group. Panel (a) indicates analysis of LAD including all studies that reported this value (LAD-1) and Panel (b) shows analysis of LAD after excluding studies that reported this value in obese women (LAD-2). The studies by Tasolar (1) *et al.* (2014) only included obese women with and without PCOS in their surveys. A random-effects model was used in this meta-analysis, and mean differences (MD) was used to measure the effect size. A positive effect indicates higher values in women with PCOS than women in control group and vice versa. CI, confidence interval; LAD, Left Atrium Diameter; PCOS, polycystic ovarian syndrome.

**Fig. 4**




Forest plot graphs for the comparison of E/A ratio between women with polycystic ovarian syndrome and women in the control group. Panel (a) indicates analysis of E/A including all studies that reported this value (E/A-1) and Panel (b) shows analysis of E/A after excluding studies that reported this value in obese women (E/A-2). The studies by De Jong *et al.* (2022), Tasolar (1) *et al.* (2014) and Zehir *et al.* (2014) only included obese women with and without PCOS in their surveys. A random-effects model was used in this meta-analysis, and mean differences (MD) were used to measure the effect size. A positive effect indicates higher values in women with PCOS than women in control group and vice versa. CI, confidence interval; E/A, E wave to A wave ratio; PCOS, polycystic ovarian syndrome.

### *IVRT-1*

The meta-analysis of 15 studies revealed that IVRT was significantly higher in PCOS patients (n = 554) comparing to controls (n = 477) with the effect size of 5.71 (95% CI [2.77, 8.66], $P = 0.0001$). Heterogeneity was high ($I^2 = 97\%$; $P < 0.00001$).

### *IVRT-2*

The meta-analysis of 14 studies revealed that IVRT was significantly higher in PCOS patients (n = 529) comparing to controls (n = 452) with the effect size of 4.80 (95% CI [2.06, 7.54], $P = 0.0006$). Heterogeneity was high ($I^2 = 96\%$; $P < 0.00001$).

### *IVCT*

The meta-analysis of 3 studies revealed that IVCT was significantly higher in PCOS patients (n = 100) comparing to controls (n = 106) with the effect size of 3.22 (95% CI [0.72, 5.73], $P = 0.01$). Heterogeneity was high ($I^2 = 86\%$; $P = 0.008$).

### *LAD-1*

The meta-analysis of 21 studies which revealed that LAD was significantly higher in PCOS patients (n = 752) comparing to controls (n = 765) with the effect size of 1.20 (95% CI [0.46, 1.93], $P = 0.002$). Heterogeneity was high ($I^2 = 82\%$; $P < 0.00001$) (Fig. 3).

### *LAD-2*

The meta-analysis of 20 studies revealed that LAD was significantly higher in PCOS patients (n = 727) comparing to controls (n = 740) with the effect size of 0.84 (95% CI [0.34, 1.34], $P = 0.001$). Heterogeneity was moderate ($I^2 = 58\%$; $P = 0.0006$) (Fig. 3).

### *DT-1*

The meta-analysis of 17 studies revealed that DT was significantly higher in PCOS patients (n = 647) compared to controls (n = 591) with the effect size of 5.11 (95% CI [1.90, 8.31], $P$ value = 0.002). Heterogeneity was high ($I^2 = 84\%$, $P < 0.00001$).

### *DT-2*

The meta-analysis of 14 studies revealed that DT was significantly higher in PCOS patients (n = 547) compared to controls (n = 489) with the effect size of 4.38 (95% CI [1.41, 7.35], $P$ value = 0.004). Heterogeneity was high ($I^2 = 78\%$, $P < 0.00001$).

### *E wave-1*

The meta-analysis of 22 studies revealed that E peak rate was significantly lower in PCOS patients (n = 766) compared to controls (n = 781) with the effect size of –0.02 (95% CI [–0.04, –0.00], $P$ value = 0.03). Heterogeneity was moderate ($I^2 = 72\%$, $P < 0.00001$).

### *E-wave-2*

The meta-analysis of 19 studies revealed that E peak rate was significantly lower in PCOS patients (n = 666) compared to controls (n = 679) with the effect size of –0.02 (95% CI [–0.05, –0.00], $P$ value = 0.04). Heterogeneity was moderate ($I^2 = 72\%$, $P < 0.00001$).

### *A wave-1*

The meta-analysis of 22 studies revealed that A peak rate was significantly higher in PCOS patients (n = 766) compared to controls (n = 781) with the effect size of 0.03 (95% CI [0.00, 0.06], $P$ value = 0.03). Heterogeneity was high ($I^2 = 94\%$, $P < 0.00001$).

### *A wave-2*

The meta-analysis of 19 studies revealed that A peak rate was significantly higher in PCOS patients (n = 666) compared to controls (n = 679) with the effect size of 0.02 (95% CI [0.01, 0.04], $P$ value = 0.01). Heterogeneity was high ($I^2 = 75\%$, $P < 0.00001$).

### *E/A ratio-1*

The meta-analysis of 24 studies revealed that this parameter was significantly lower in PCOS patients (n = 848) compared to controls (n = 865) with the effect size of –0.13 (95% CI [–0.18, –0.07], $P$ value <0.00001). Heterogeneity was high ($I^2 = 93\%$, $P < 0.00001$) (Fig. 4).

**Table 3 Baseline characteristics results**

| Characteristics of study | Number of studies | Number of PCOS | Number of controls | Mean difference (95% CI) | *P* value | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | | | | $I^2$ | *P* value |
| Age | 34 | 1445 | 1442 | **–1.13 [–1.69 to –0.56]** | 0.0001 | 82% | < 0.00001 |
| BMI | 34 | 1445 | 1442 | **1.96 [1.21 to 2.71]** | **<0.00001** | 92% | < 0.00001 |
| Androstenedione | 12 | 328 | 386 | **1.02 [0.27 to 1.76]** | **0.007** | 93% | <0.00001 |
| Testosterone | 25 | 1115 | 1107 | **22.70 [18.24 to 27.15]** | **<0.00001** | 92% | <0.00001 |
| DHEAS | 20 | 651 | 676 | **25.42 [3.01 to 47.82]** | **0.03** | 90% | <0.00001 |
| FAI | 7 | 213 | 272 | **3.43 [1.71 to 5.14]** | **<0.00001** | 95% | < 0.00001 |
| FBS | 27 | 1129 | 1159 | **2.61 [1.32 to 3.90]** | **<0.0001** | 81% | <0.00001 |
| Fasting Insulin | 24 | 966 | 979 | **6.08 [4.33 to 7.82]** | **<0.00001** | 97% | < 0.00001 |
| HOMA-IR | 24 | 1089 | 1149 | **1.33 [0.98 to 1.69]** | **<0.00001** | 96% | < 0.00001 |

*P*-value < 0.05 is considered significant.
Bold values indicate statistically significant results.

#### *E/A ratio-2*

The meta-analysis of 21 studies revealed that this parameter was significantly lower in PCOS patients (n = 748) compared to controls (n = 763) with the effect size of –0.12 (95% CI [–0.18, –0.07], *P* value <0.00001). Heterogeneity was high ($I^2$ = 91%, *P* < 0.00001) (Fig. 4).

### Tissue Doppler echocardiography

#### *Septal E'*

The meta-analysis of 5 studies reporting septal E', revealed that there was no significant difference in this value between PCOS cases (n = 161) compared to controls (n = 130) with the effect size of –0.97 (95% CI [–1.96, 0.01], *P* value = 0.05).

#### *Lateral E'*

The meta-analysis of 8 studies reporting lateral E', revealed that there was no significant difference in this value between PCOS cases (n = 243) and controls (n = 306) with the effect size of –0.28(95% CI [–0.89, 0.33], *P* = 0.37).

#### *Septal-lateral E'-1*

The meta-analysis of 4 studies reporting septal-lateral E', revealed that there was no significant difference in this value between PCOS cases (n = 154) and controls (n = 163) with the effect size of –0.13(95% CI [–0.70, 0.44], *P* = 0.66).

#### *Septal-lateral E'-2*

The meta-analysis of 3 studies reporting septal-lateral E', revealed that there was no significant difference in this value between PCOS cases (n = 100) and controls (n = 68) with the effect size of –0.25(95% CI [–1.05, 0.54], *P* = 0.54).

#### *Septal S'*

The meta-analysis of 4 studies reporting septal S', revealed that there was no significant difference in this value between PCOS cases (n = 131) and controls (n = 100) with the effect size of –0.37(95% CI [–0.74, –0.00], *P* = 0.05).

#### *Lateral S'*

The meta-analysis of 4 studies reporting lateral S', revealed that there was no significant difference in this value between PCOS cases (n = 130) and controls (n = 98) with the effect size of 0.14(95% CI [–0.06, 0.35], *P* = 0.17).

#### *Septal-lateral S'-1*

The meta-analysis of 4 studies reporting septal-lateral S', revealed that there was no significant difference in this value between PCOS cases (n = 184) and controls (n = 163) with the effect size of –0.28(95% CI [–0.60, 0.04], *P* = 0.99).

#### *Septal-lateral S'-2*

The meta-analysis of 3 studies that reported septal-lateral S' found no significant difference in this value between PCOS cases (n = 100) and controls (n = 68), with an effect size of –0.47(95% CI [–0.88, –0.06], *P* = 0.97).

#### *Septal E/E'*

The meta-analysis of 3 studies reporting septal E/E', revealed that there was no significant in this value between PCOS cases (n = 108) and controls (n = 107) with the effect size of 0.38(95% CI [–0.32, 1.09], *P* = 0.29).

#### *Lateral E/E'*

The meta-analysis of 6 studies reporting lateral E/E', revealed that there was no significant in this value between PCOS cases (n = 169) and controls (n = 261) with the effect size of –0.08(95% CI [–0.40, 0.24], *P* = 0.62).

#### *Septal-lateral E/E*

The meta-analysis of 3 studies reporting septal-lateral E/E', revealed that there was no significant in this value between PCOS cases (n = 135) and controls (n = 143) with the effect size of –0.18(95% CI [–0.59, 0.23], *P* = 0.39).

### Baseline characteristics

Based on the meta-analysis results, PCOS participants had higher BMI compared to controls, with effect sizes of 1.96 (95% CI [1.21, 2.71], *P* < 0.00001). Androgen profile, including serum testosterone, androstenedione, DHEAS, and FAI, were significantly increased in PCOS comparing to controls, with effect sizes of 22.70 (95% CI [18.24, 27.15], *P* < 0.00001), 1.02 (95% CI [0.27, 1.76], *P* = 0.007), 25.42 (95% CI [3.01, 47.82], *P* = 0.03), and 3.43 (95% CI [1.71, 5.14], *P* < 0.00001), respectively. HOMA-IR, FBS, and serum fasting insulin levels were revealed to be significantly higher in PCOS cases than in controls, with effect sizes of 1.33 (95% CI [0.98, 1.69], *P* < 0.00001), 2.61 (95% CI [1.32, 3.90], *P* < 0.0001), and 6.08 (95% CI [4.33, 7.82], *P* < 0.00001), respectively. The detailed results of baseline characteristics are shown in Table 3.

### Subgroup synthesis

The analysis of both echocardiographic and baseline parameters revealed significant heterogeneity among the parameters, which we attributed to differences in study design (case-control, cross-sectional, or cohort). To address this issue, we conducted a subgroup analysis based on study methodology, with separate analyses for studies with a cross-sectional design and studies with a case-control design. However, the majority of the results from these subgroup analyses were not significantly different from the overall analysis, as shown in Tables S3, Supplemental digital content 6, *http://links.lww.com/CAEN/A51* and S4, Supplemental digital content 7, *http://links.lww.com/CAEN/A52*.

### Publication bias

The results of Begg's test for small-study effects indicated that, except for LAD, there was no significant

evidence of small-study effects for the outcomes of interest (p-value= 0.04). Funnel plots for all outcomes were visually inspected and are available in the supporting information section (S5 Document, Supplemental digital content 8, *http://links.lww.com/CAEN/A53*).

## Discussion

### Conventional echocardiography

This systematic review and meta-analysis revealed that individuals with PCOS showed notable changes in their LV diastolic function as assessed through traditional echocardiography, in comparison to healthy individuals. Nevertheless, the question of whether PCOS can independently affect diastolic function remains a topic of debate.

In terms of measurements of mitral inflow velocities, individuals with PCOS showed a decline in the E wave, the E/A ratio, and an elongation in the DT. Additionally, there was an elevation in the IVRT and the A wave. During the early stages of diastolic dysfunction, there is an impairment in the relaxation of the LV, which results in an increase in mitral flow velocity as a compensatory mechanism. This leads to a higher peak E wave and a lower peak A wave, causing a decrease in the E/A ratio and lengthening of DT. As the disease progresses, the pressure in the LA rises, and the mitral inflow may appear normal. However, a restrictive filling pattern emerges, characterized by a shortened DT and IVRT [67,68]. These factors not only indicate the stage and condition of diastolic dysfunction but also play a significant role in predicting the prognosis [68]. Beyond the aforementioned parameters, modifications in LV geometric indices, such as increased IVST and PWT during diastole, as well as LAD, hold promise as potential indicators of diastolic dysfunction [69]. The current meta-analysis of cardiac dimensions revealed that individuals with PCOS exhibited higher IVST, PWT, and LAD compared to the control group. However, both groups displayed similar LVEDD and LVESD.

LA enlargement may be an early indication of CVD such as congestive heart failure, atrial fibrillation, and stroke [70]. The function of the LA is closely linked to the function of the LV, and any changes in LV volume or pressure are reflected in the LA [71]. LA remodeling is also considered an independent marker of LV hemodynamic burden in CVD [72]. When LV diastolic dysfunction occurs, LA enlargement often follows and progressively worsens as CVD advances. Diastolic dysfunction is known to be an early sign of CAD. Whether it is due to increased LV rigidity leading to higher diastolic pressure or reduced early filling caused by LV hypertrophy (LVH), constant LA enlargement can occur in chronic heart diseases [73,74].

Moreover, the meta-analysis revealed that individuals with PCOS displayed a significant increase in both LVM and LVMI in comparison to non-PCOS controls. It is worth noting that LVH is a significant independent predictor of CVD survival [75]. The Framingham study demonstrated that in women, a 50 g/m increase in LVM corresponds to a 1.57 relative risk of developing cardiovascular disease [22]. An elevation in LVMI is often an early indication of diastolic dysfunction, which refers to the heart's inability to properly relax and fill during the diastolic phase. This increase in LVMI can be attributed to common stressors like hypertension or increased wall stress within the LV cavity [76].

The complex and multifactorial nature of PCOS makes it challenging to determine the precise mechanisms involved in the development of LV remodeling and hypertrophy in PCOS [77]. The pathophysiological mechanisms of IR causing LVH and diastolic dysfunction have been extensively studied [78,79]. IR increases the production of insulin and insulin-like growth factor-1, both of which can promote cardiac hypertrophy, fibrosis, and progressive increases in fatty acid turnover in cardiomyocytes [80]. Moreover, PCOS has been associated with chronic low-grade inflammation. Inflammation in PCOS is primarily driven by increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6 [81]. This chronic inflammation may contribute to the development and progression of LV remodeling. These cytokines promote the release of other inflammatory mediators, stimulate the production of reactive oxygen species, and activate various signaling pathways that can directly affect cardiac cells and induce structural changes in the heart [82].

Also, excessive levels of androgen can activate cardiac insulin signaling, leading to the activation of PI3K/AKT/mTORC1 and indirectly causing cardiac hypertrophy [83]. Additionally, there is another potential mechanism involving the cooperation of androgen and $Ca2+$-dependent signaling [84]. Another study suggests that testosterone is involved in the activation of calcineurin/nuclear factor of activated T cells and the inhibition of GSK-3β, both of which contribute to the development of cardiac myocyte hypertrophy [85]. It is important to note that the above mechanisms (IR, hyperandrogenism and chronic low-grade inflammation) are interconnected and can influence each other.

### Tissue Doppler echocardiography

The present systematic review and meta-analysis revealed no statistically significant disparities in specific tissue Doppler echocardiography (TDE) parameters, namely myocardial velocities, between individuals with PCOS and their respective controls. TDE is a specialized modality of Doppler flow imaging that is distinct from conventional methods. This particular technique enables the quantification of the Doppler shift that occurs within

the range of tissue motion in the myocardium [86]. Some previous studies showed significant changes of TDE in PCOS cases compared to controls [39,42,49,56]. Erdoğan *et al*. and Demirelli *et al*. discovered that individuals with PCOS had a reduced E' and an increased E/E' ratio in comparison to healthy individuals [49,56]. Tasholar *et al*. also found that obese PCOS cases had a significantly higher E/E' ratio when compared to lean PCOS cases and the control group. However, there was no notable difference in the E/E' ratio between lean PCOS cases and the healthy control group [42]. E' is considered to be relatively unaffected by preload, indicating that changes in the amount of blood filling the LV do not have a significant impact on E'. Therefore, E' is a reliable indicator of LV relaxation [87]. The E/E' ratio provides information about the LV filling pressure, making it a valuable measure for assessing diastolic function. Higher E/E' values suggest increased LV filling pressure, indicating impaired relaxation or heightened LV stiffness [88].

Additionally, Çetin *et al*. noted that individuals with PCOS had a higher A' (late diastolic myocardial velocity) and a lower E'/A' ratio compared to the control group. The authors stated that, based on their study, 50% of PCOS patients exhibited IR, which is believed to contribute to the early onset of LV diastolic dysfunction in PCOS [39]. Tasholar *et al*. discovered that obese individuals with PCOS had a noticeably elevated A' compared to lean PCOS cases and the control group. Nevertheless, there was no significant disparity in the A' between lean PCOS cases and the healthy control group [42]. However, certain studies have posited that specific TDE parameters pertaining to myocardial velocities, such as E', E/E', and E'/A', do not exhibit any significant differences in PCOS [41,43,46,47,52,55,59,60,64].

### Conventional echocardiography vs. tissue Doppler echocardiography

In comparison to conventional echocardiography, there have been limited studies evaluating LV function in individuals with PCOS using TDE. Furthermore, there was inconsistency in reporting TDE measurements depending on the specific location of the mitral annuli they were obtained from.

Myocardial velocities are generally considered to be more sensitive than mitral inflow velocities in detecting LV remodeling in echocardiography [89]. Myocardial velocities, provide direct assessment of the movement and velocities of the myocardium, allowing for a more accurate evaluation of regional and global ventricular function [90]. On the other hand, mitral inflow velocities may be affected by factors other than LV remodeling, such as alterations in loading conditions Therefore, while both measurements can provide valuable information, myocardial velocities are often considered to be more sensitive in detecting LV remodeling [91].

It is widely acknowledged that PCOS is being indirectly linked to cardiovascular risk factors. These factors can all contribute to an increased risk of heart-loading conditions [92–94]. In this systematic review and meta-analysis, it seems that cardiovascular risk factors did not have a significant impact on myocardial velocity in PCOS cases. However, further studies are needed to explore the relationship between PCOS and cardiovascular loading conditions, as well as to investigate the potential mechanisms that may explain the lack of impact on myocardial velocity and deformation endpoints. It would also be valuable to examine the connection between PCOS and other cardiovascular risk factors in order to fully understand the potential cardiovascular implications of the loading condition.

This review primarily consisted of studies conducted in Turkey, accounting for two-thirds of the total. The remaining studies were conducted in other countries including the USA, Poland, Italy, Brazil, India, Australia, and the UK. However, it is worth noting that the race of participants was only specified in two of the studies. Numerous studies have highlighted variations in the characteristics of PCOS among different racial and ethnic groups worldwide [95]. Additionally, there are disparities in the prevalence of metabolic issues associated with PCOS across various racial and ethnic groups [96]. Hispanic women diagnosed with PCOS exhibit the most pronounced phenotype, characterized by more severe manifestations of hyperandrogenism and metabolic criteria. On the other hand, non-Hispanic Black women generally display a comparatively milder phenotype of PCOS compared to both Hispanics and, to some extent, non-Hispanic White women [97].

Moreover, a large proportion of participants with PCOS were in their twenties and early thirties. Despite significant differences in echocardiographic indices favoring diastolic dysfunction in PCOS compared to controls, the average values of most of these indices were within the upper or lower limits of the normal range. This may imply that prolonged exposure to IR and excessive androgens in individuals with PCOS could potentially lead to the emergence of clinical LV remodeling and other cardiovascular problems. If left untreated, we anticipate that these indices may eventually fall into the pathological range.

Given these considerations, it is advisable to exercise caution when interpreting the conclusions drawn from this meta-analysis.

Overall, the findings of this review indicate that women with PCOS have a significantly higher risk of developing LV diastolic dysfunction and subsequently cardiovascular diseases. Echocardiography, a non-invasive and readily available imaging technique, can be used to detect diastolic dysfunction and cardiovascular abnormalities at an early stage. This allows for timely intervention and management. The use of echocardiography findings can help healthcare

providers assess the cardiovascular risk in women with PCOS and identify subtle changes in cardiac dysfunction. This information can guide the implementation of appropriate preventive measures and treatment strategies. Understanding the cardiovascular implications of PCOS through echocardiography can also inform public health planning and resource allocation. It enables healthcare systems to recognize the burden of cardiovascular disease associated with PCOS and allocate resources accordingly for screening, early detection, and management. This can contribute to the development of targeted interventions and policies that address the specific needs of this population. Additionally, incorporating echocardiography in the evaluation of PCOS patients raises awareness about the potential cardiovascular risks associated with the condition. It provides an opportunity for healthcare providers to educate patients about the importance of cardiovascular health, promote lifestyle modifications, and encourage regular cardiac evaluations.

## Limitations

The present meta-analysis has several limitations that must be addressed. Firstly, there were a limited number of studies that evaluated PCOS myocardial function using TDE measures. Additionally, most of the studies did not report important indices, such as E/E' ratio, left atrial volume index, and tricuspid annular velocity, which are crucial indicators of LV diastolic function based on new diagnostic guidelines. Another significant limitation is that not all studies classified their included PCOS cases into subgroups based on phenotypes and hormonal patterns, which may have contributed to the high heterogeneity in data and analysis. Despite the significant findings, it is important to highlight the need for comprehensive studies with larger sample sizes and different subgroups with varying PCOS phenotypes to confirm and validate the results presented here. In the studies that included both obese and non-obese participants, the presence of obesity could potentially confound the relationship between PCOS and cardiovascular parameters. Therefore, further studies require to exclude obese participants to minimize the influence of obesity on the results and provide a clearer understanding of the association between PCOS and cardiovascular parameters in non-obese individuals.

## Acknowledgements

We want to acknowledge all the healthcare providers of the Cardiology Department of Tabriz University of Medical Sciences for all the guides during the study. We express our gratitude to Dr. Kamran Mohammadi, a highly esteemed Cardiologist, for his invaluable assistance in enhancing our comprehension of echocardiographic indices and diastolic function. Additionally, we would like to express our gratitude to the Student Research Committee of Tabriz University of Medical Sciences for their approval and support in conducting this research (proposal number: 72903).

ST-M: Review conceptualization, protocol registration, independent reviewer, risk of bias assessment, data collection, statistical data analysis, data interpretation, and writing of initial draft/revision of the final manuscript. PP: Independent reviewer, data collection, risk of bias assessment, statistical data analysis, data interpretation, and writing of initial draft/revision of final manuscript. HZ: Independent reviewer, data collection, risk of bias assessment, statistical data analysis, data interpretation, and writing of initial draft/revision of final manuscript. MZ: Data collection, statistical data analysis, data interpretation, and writing of initial draft/revision of final manuscript. NF: Data collection, statistical data analysis, data interpretation, and revision of final manuscript. MD: Data collection, statistical data analysis, data interpretation, and revision of final manuscript. PS: Data curation, statistical data analysis, data interpretation, revision of final manuscript. All authors read and approved the final version of the manuscript.

The protocol for this work was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (identifier: CRD42022340972). The Ethics Committee of Tabriz University of Medical Sciences approved this study. All study steps were conducted under the supervision of this committee, and the principles of the Declaration of Helsinki were followed in the present study.

The datasets used or analyzed during the present study are available from the corresponding author on reasonable request and as the supplementary material appendix.

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