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## Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis

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### ABSTRACT

This study aimed to evaluate the prevalence (P)/hazard ratio (HR) of cardiovascular (CV) events among reproductive age and menopausal age women with polycystic ovary syndrome (PCOS) in comparison with healthy controls. PubMed, Scopus, ScienceDirect, Web of science, and Google scholar were searched for retrieving observational studies published up to April 2018 investigating CV events in patients with PCOS. The primary outcomes were a composite outcome of CV events [including coronary arterial disease (CAD), cardiovascular disease (CVD), myocardial infarction (MI), angina, heart failure, and ischemic heart disease] and mortality due to CV events; secondary outcomes were specific CVD events, including cerebrovascular disease, CAD, CVD, MI, angina, heart failure, ischemic heart disease, and stroke. In this meta-analysis, both fixed and random effect models were used. Potential sources of heterogeneity were explored by meta-regression and subgroup analyses. Sixteen studies including 12 population-based were analyzed for the meta-analysis. Results showed that the pooled HRs of CV events in PCOS patients of reproductive age and in menopausal/aging women were higher than healthy controls (pooled HR: 1.38, 95% CI: 1.12–1.71) and (pooled HR: 1.53, 95% CI: 1.15, 2.04), respectively. Compared to healthy controls, analysis of population-based studies revealed that the HR of CV events increased only in reproductive age PCOS patients (1.43-fold, 95% CI: 1.27, 1.61), whereas the difference was not statistically significant when comparing menopausal/aging PCOS patients to healthy controls (1.03-fold, 95% CI: 0.41, 2.59). Sufficient data were not available for comparing the HRs of mortality due to CV events between the two PCOS age groups. Mainly based on population-based study, we found a greater risk of CV events in reproductive aged but not in menopausal/aging PCOS women, suggesting that having a history of PCOS during reproductive ages may not be an important risk factor for developing events in later life. This is a preliminary assumption and needs to be reevaluated by further comprehensive cohort studies of longer duration, initiated in the reproductive period, considering all known CVD risk factors.

### ARTICLE HISTORY

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### KEYWORDS

Cardiovascular disease; meta-analysis; polycystic ovary syndrome (PCOS); hazard ratio

### Introduction

There is much controversy regarding whether cardiovascular (CV) events are increased in women with polycystic ovary syndrome (PCOS) [1,2]. While it is clear that women with PCOS have increased prevalence of risk factors for cardiovascular disease (CVD) [3–12], data on CV events are inconclusive [13,14], suggesting that in these patients the expected relationship between CV risk and CV events does not exist [1,2,14].

In the general population, there is a good correlation between CV risk and CVDs and drugs that reduce CV risk have proven very beneficial in increasing mean life expectancy [15]. On the contrary, in women with PCOS, it is still unclear whether increased CV risk translates into a proportionally higher number of CV events. In fact, some studies show that the risk of CV events in PCOS patients ameliorates by aging [1,2,16] and, because of this, the actual number of CV events in women with PCOS may be lower than that expected based on simple risk calculation [1,14,15].

While more studies are needed, one of the classic ways to obtain more information about a controversial phenomenon is to perform a meta-analysis of data available. Two meta-analyses recently reported increased prevalence of CV events in women with PCOS [12,13]. However, some of the papers utilized in previous meta-analyses have been withdrawn [16,17] and the meta-analyses have been criticized because they reported the pooled prevalence of young and aging women with PCOS including several young patients and only a few old women with PCOS [2]. It must be kept in mind that CV events are greatly influenced by age and occur mainly in older aged women [18]. In addition, prevalence of CV events varies according to the studied populations [19] and analysis of population based data is needed to perform a precise analysis of evidence available.

We hence decided to perform a new meta-analysis for investigating whether CV events are really increased in women with PCOS and the possible difference between CV events in reproductive age PCOS women, compared to menopausal/aging women, who had PCOS during their younger ages.

To avoid the above-mentioned criticisms, withdrawn studies were excluded and studies of PCOS patients during their reproductive age and postmenopausal patients with a previous diagnosis of PCOS were separately analyzed. In our main meta-analysis, only population-based studies were included. However, for comparison, a meta-analysis, including nonpopulation-based studies was also conducted.

## Methods

This systematic review and meta-analysis was designed according to the guidelines for the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [20] (Supplementary File 1) and the Cochrane Handbook for Systematic Review of Interventions [21] to achieve the following objectives:

1. Study the pooled prevalence (P)/HR of CV events and its effect on mortality rates in reproductive and menopausal/aging PCOS groups, compared to healthy women
2. Study the pooled P/HR of CV events and its effect on mortality rates in reproductive and menopausal/aging PCOS groups compared to healthy women in population-based studies
3. Compare the pooled P/HR of CV events and its effect on mortality rates between reproductive age PCOS women and menopausal/aging group
4. Compare the pooled P/HR of CV events and its effect on mortality rates between reproductive age PCOS women and those in menopausal/aging group in population-based studies

## Search strategy

To conduct this meta-analysis, PubMed, Scopus, ScienceDirect, web of science, and Google scholar were searched for retrieving observational studies published up to April 2018 investigating CV events in patients with PCOS.

At initiation of the study, we implemented the search strategy with the assistance of a professional healthcare librarian. Two reviewers (M.A and E.C) performed searches separately. At first, the search in PubMed was performed, based on MESH terms using the following key words: ('polycystic Ovary Syndrome' OR 'PCOS') AND ('cardiovascular' OR 'cardiovascular disease' OR 'myocardial infarction' OR 'stroke' OR 'heart failure' OR 'heart disease' OR 'coronary arterial disease' OR 'aortic' OR 'artery' OR 'cerebrovascular' OR 'angina' OR 'event').

We also searched PubMed and other databases using free-text terms. Search limitations were humans, and English language publications. Search strategies were almost similar for all databases, being conducted based on the 'all fields' in the PubMed and 'titles, abstracts and keywords' in other databases. A 'pearl growing' strategy was employed, whereby, after obtaining the full text articles, the reference lists of all included studies were reviewed for any additional publications that could be used in this review.

## Eligibility criteria

All types of analytic observational studies including cross-sectional, case-control, and cohort designs assessing CV events in women with PCOS were eligible to be included in the meta-analysis. In addition, studies needed to report number of events, relative risk (RR), and hazard ratio had to provide sufficient

information to allow calculations, e.g. either number of events, or their incidence in PCOS and control groups. Moreover, studies needed to diagnose PCOS based on the Rotterdam, National Institute of Health (NIH), Androgen Excess Society (AES), International Classification of Diseases (ICD) or histologic criteria.

Exclusion criteria included: (1) Studies that did not differentiate between women and men, (2) studies assessing only CV risk factors such as hypertension, dyslipidemia and diabetes mellitus, as well as those evaluating the composite CVD including CV risk factors and CV events, (3) studies without control groups, and (4) Studies with unreliable and incomplete results.

## Study selection

We included all relevant studies assessing CV events in women with PCOS. At least one of the following events had to be reported: CVD, myocardial infarction (MI), stroke, cerebrovascular disease, heart failure, coronary arterial disease (CAD), angina, or death. We excluded studies assessing CV risk factors from our meta-analysis.

Search results were screened based on predefined eligibility criteria. All references were entered to EndNote software. Initial selection was performed based on their titles, followed by a second selection performed by one reviewer (M.A), who deleted duplicates and reviewed the abstracts of all remaining records. Any disagreement in the selection of abstracts was resolved by consensus or by other reviewers (F.R.T and E.C). Full text articles for review and data processing were obtained for all selected abstracts.

## Data extraction

Two reviewers (M.A and S.B.G), in close consultation with senior reviewers (F.R.T and E.C), extracted data from full text articles, and double checked all data extracted to minimize errors. For each study, the following information was extracted: Authors, year of publication, title, study design, characteristics of study population, number of events, unadjusted or adjusted risk ratios provided (OR, RR, or HR) by each outcome. To prevent extraction errors, all reviewers performed a quality control check between the final data used in the meta-analysis and the original publications.

## Quality assessment

All studies included for the meta-analysis were appraised for the quality of their methodological and result presentation. Two reviewers (M.A and S.B.G), blinded to study authors, institution, and journal name, assessed the quality of the studies separately. Disagreement was resolved and adjusted by the senior reviewer (F.R.T). All observational studies including cross-sectional, case-control, and cohort were appraised according to the Newcastle-Ottawa scale [22]. In this respect, three domains were scored for selection and comparability of study cohorts, and to determine the outcome of interest (Supplementary File 2). If a study obtained  $\geq 70\%$  of the highest level of the Newcastle-Ottawa scale, it was considered as high quality, those with 40–70% as moderate, and those with 20–40% as low and those with  $< 20\%$  as very low quality.

### Risk of bias assessment

We assessed risk of bias in each study, using the Cochrane Collaboration's tools, tools designed for various methodological studies including both cross-sectional and case-control, and cohorts (Supplementary File 3). Review authors' judgments were categorized as 'low risk', 'high risk', and 'unclear risk' of bias (either low or high risk of bias) [21].

### Outcome measures

Primary outcomes of interest were: (i) CV events, as composite outcome, i.e. specific events including CAD, CVD, MI, angina, heart failure and ischemic heart disease, and (ii) mortality due to CV events; secondary outcomes were separate events, including cerebrovascular disease, CAD, CVD, MI, angina, heart failure and ischemic heart disease, and stroke.

### Statistical analysis

Meta-analysis was performed to evaluate the pooled P/HRs of our outcomes of interest. Heterogeneity was evaluated using the  $I^2$  statistics; values above 50% were interpreted as heterogeneity. Both the random and fixed effect models

were used for heterogeneous and non-heterogeneous results, respectively. Publication bias was assessed using the Begg's test [23] and the funnel plot [24]; bias was found to be significant for  $p$  values  $<.05$ , and also for asymmetry in funnel plot [23,24]. For significant results or an asymmetric funnel plot, the trim and fill method was used for adjusting publication bias [24].

Pooled P and pooled HR (Pooled HR) were used for reporting results of the meta-analysis. The meta-prop method was applied for the pooled estimation of the prevalence of CV events, which used binomial distribution to overcome the negative confidence intervals in outlier values of prevalence (zero and one) [25]; pooled HR was also estimated by the 'Metan' method, using normal distribution to estimate confidence intervals. Mantel-Haenszel method was used to pooled data [26]. Some studies included reported the odds ratio (OR) and RR for measuring the outcomes. It should be noted that since CV events are considered as rare outcomes, the HR, OR, and RR values are approximately equal (28). Yates' correction was applied for studies that contained a zero in the number of events of interest [27].

We assessed the pooled P/HR of CV events, based on age groups (reproductive vs. menopausal/aging). We also conducted an additional subgroup analysis based on study design (population- versus non-population-based studies). Furthermore, the

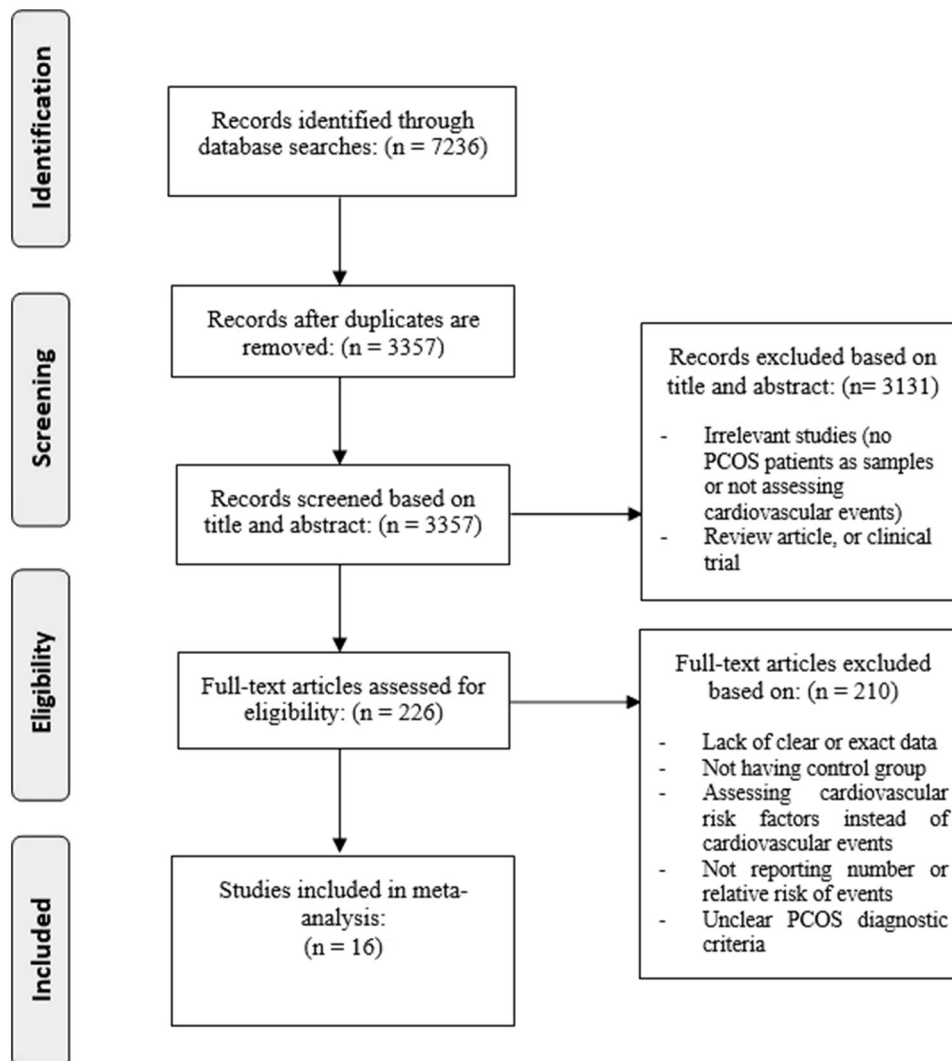


Figure 1. PRISMA flow diagram of study.

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

First author, year	Country	Study design	PCOS criteria	PCOS group characteristics	Control group characteristics	Number of events (Prevalence <sup>a</sup> or Incidence <sup>b</sup> %) in PCOS group	Number of events (Prevalence <sup>a</sup> or Incidence <sup>b</sup> %) in control group	Unadjusted RR (95% CI)	Quality assessment
Caldernon-Margalit et al. [28]	USA	Population-based prospective cohort	NIH	N = 55 Age = 45.4 (3.44) BMI: 29.3 (6.5)	N = 668 Age = 45.40 (3.57) BMI: 29.90 (4.73)	Ischemic heart disease: 0 (0) <sup>a</sup>	Ischemic heart failure: 7 (1.2) <sup>a</sup>	Ischemic heart disease: 0	High
Ding et al. [29]	Taiwan	Population-based prospective cohort	ICD	N = 8048 Age = 28.11 (6.89) BMI = not reported	N = 32192 Age = 28.11 (6.90) BMI = not reported	CAD: 107 (2.25) <sup>b</sup>	CAD: 259 (1.38) <sup>b</sup>	CAD: 1.65 (1.33, 2.05)	High
Glimborg et al. [30]	Denmark	Population-based prospective cohort	Rotterdam	N = 20416 Age = 29.3 (8.5) BMI = not reported	N = 57483 Age = 30.6 (9.6) BMI = not reported	Cerebrovascular disease: 27 (0.13) <sup>a</sup> CVD: 74 (0.36) <sup>a</sup> MI: 41 (0.20) <sup>a</sup> Stroke: 51 (0.25) <sup>a</sup>	Cerebrovascular disease: 52 (0.09) <sup>a</sup> CVD: 177 (0.31) <sup>a</sup> MI: 121 (0.21) <sup>a</sup> Stroke: 82 (0.14) <sup>a</sup>	Cerebrovascular: 1.46 (0.91, 2.34) CVD: 1.18 (0.90, 1.55) MI: 0.95 (0.67, 1.35) Stroke: 1.75 (1.23, 2.49)	Moderate
Haakova et al. [38]	Czech Republic	Case-control	NIH	N = 66 Age = 29.9 (2.97) BMI = 23.7 (4.27)	N = 66 Age = 29.8 (4.94) BMI = 23.2 (3.89)	Ischemic heart disease: 0 (0)	Ischemic heart disease: 0 (0)	Ischemic heart disease: 0	Moderate
Hart et al. [31]	Australia	Population-based retrospective cohort	ICD	N = 2560 Age = 27.9 (23.6–32) <sup>c</sup> BMI = not reported	N = 25660 Age = 15–45 <sup>d</sup> BMI = not reported	Cerebrovascular disease: 15 (0.6) <sup>a</sup>	Cerebrovascular disease: 51 (0.2) <sup>a</sup>	Cerebrovascular disease: 2.95 (1.67, 5.21)	High
Iftikhar et al. [39]	USA	Retrospective cohort	Rotterdam	N = 309 Age = 25.0 (5.3) BMI = 29.4 (7.77)	N = 343 Age = 18–40 <sup>d</sup> BMI = 28.3 (7.47)	Ischemic heart disease: 21 (0.8) <sup>a</sup> CVD: 26 (8.40) <sup>b</sup> MI: 15 (4.9) <sup>b</sup> Angina: 10 (3.2) <sup>b</sup> Stroke: 6 (1.9) <sup>b</sup> Death due to CVD: 4 (1.3) <sup>b</sup>	Ischemic heart disease: 50 (0.2) <sup>a</sup> CVD: 28 (8.2) MI: 16 (4.7) <sup>b</sup> Angina: 6 (1.8) <sup>b</sup> Stroke: 7 (2.0) <sup>b</sup> Death due to CVD: 2 (0.6) <sup>b</sup>	Ischemic heart disease: 4.21 (2.53, 7.01) CVD: 1.03 (0.62, 1.71) MI: 1.04 (0.52, 2.07) Angina: 1.85 (0.68, 5.03) Stroke: 0.95 (0.32, 2.79) Death due to CVD: 2.22 (0.41, 11.98)	High
Lo et al. [32]	USA	Population-based cross-sectional	ICD	N = 11,035 Age = 30.7 (7.2) BMI = not reported	N = 55,175 Age = 30.8 (7.5) BMI = not reported	CAD: 24 (0.22) <sup>a</sup> Cerebrovascular disease: 27 (0.24) <sup>a</sup>	CAD: 134 (0.24) <sup>a</sup> Cerebrovascular disease: 104 (0.19) <sup>a</sup>	CAD: 0.90 (0.58, 1.39) Cerebrovascular disease: 1.30 (0.84, 2.001)	High
Lunde et al. [40]	Norway	Prospective cohort	Laparoscopic PCOS criteria	N = 131 Age = mean 24.7 <sup>d</sup> BMI = not reported	N = 723 Age = not reported BMI = not reported	MI: 2 (1.53) <sup>b</sup> Stroke: 0 (0) <sup>b</sup>	MI: 4 (0.55) <sup>b</sup> Stroke: 0 (0) <sup>b</sup>	MI: 2.08 (0.10, 71) Stroke: 0.0 (0.0, 11)	Moderate
Mani et al. [33]	UK	Population-based retrospective cohort	AES	Group 1: N = 1855 Age = 15–44 <sup>e</sup> BMI = not reported Group 2: N = 83 Age = 55–64 <sup>e</sup> BMI = not reported Group 3: N = 11 Age ≥ 65 <sup>e</sup> BMI = not reported	Group 1: N = 1855 Age = 15–44 <sup>e</sup> BMI = not reported Group 2: N = 83 Age = 55–64 <sup>e</sup> BMI = not reported Group 3: N = 11 Age = > 65 <sup>e</sup> BMI = not reported	Group 1: CVD: not reported MI: 2 (0.1) <sup>a</sup> Angina: 6 (0.3) <sup>a</sup> Heart failure: 2 (0.1) <sup>a</sup>	Group 1: CVD: 2.04 (1.05, 3.96) MI: 1.23 (0.90, 15.51) Angina: 1.85 (0.53, 6.41) Heart failure: not reported	High	

(continued)

Table 1. Continued.

First author, year	Country	Study design	PCOS criteria	PCOS group characteristics	Control group characteristics	Number of events (Prevalence <sup>a</sup> or Incidence <sup>b</sup> %) in PCOS group	Number of events (Prevalence <sup>a</sup> or Incidence <sup>b</sup> %) in control group	Unadjusted RR (95% CI)	Quality assessment
Merz et al. [34]	USA	Population-based prospective cohort	NIH	N = 25 Age = 62.6 (11.6) BMI = 28.7 (5.9)	N = 270 Age = 64.8 (9.8) BMI = 64.8 (9.6)	Angina: 5 (6) <sup>a</sup> Heart failure: 1 (1.2) <sup>a</sup>	Group 2: CVD: 3.09 (1.64, 5.84) MI: 3.94 (1.44, 10.77) Angina: 1.93 (0.74, 5.04) Heart failure: not reported	Group 2: CVD: 3.09 (1.64, 5.84) MI: 3.94 (1.44, 10.77) Angina: 1.93 (0.74, 5.04) Heart failure: not reported	High
Meun et. [35]	Netherlands	Population-based prospective cohort	NIH	N = 106 Age = 69.57 (8.72) BMI = 27.92 (4.53)	N = 171 Age = 69.20 (8.60) BMI = 26.84 (3.83)	CAD: not reported CVD: 7 (6.6) <sup>a</sup> Stroke: not reported	CAD: not reported CVD: 11 (6.4) <sup>a</sup> Stroke: not reported	CAD: not reported <sup>f</sup> CVD: 1.03 (0.41, 2.59) Stroke: not reported <sup>f</sup>	High
Okoroh et al. [36]	USA	Population-based cross-sectional	ICD	N = 125,268 Age = mean 33.4 <sup>d</sup> BMI = not reported	N = 250,536 Age = mean 33.4 <sup>d</sup> BMI = not reported	CVD: 68 (0.05) <sup>a</sup> MI: 8 (0.01) <sup>a</sup> Stroke: 35 (0.03) <sup>a</sup>	CVD: 60 (0.02) <sup>a</sup> MI: 15 (0.01) <sup>a</sup> Stroke: 31 (0.01) <sup>a</sup>	not reported <sup>f</sup> CVD: 2.27 (1.59, 3.23) MI: 1.07 (0.45, 2.53) Stroke: 2.26 (1.38, 3.69)	High
Schmidt et al. [41]	Sweden	Prospective cohort	Rotterdam	N = 32 Age = 61–79 <sup>e</sup> BMI = not reported	N = 95 Age = 61–79 <sup>e</sup> BMI = not reported	CVD: 9 (28.1) <sup>b</sup> MI: 3 (9.4) <sup>b</sup> Stroke: 6 (18.8) <sup>b</sup>	CVD: 16 (16.8) <sup>b</sup> MI: 7 (7.4) <sup>b</sup> Stroke: 10 (10.5) <sup>b</sup>	CVD: 1.67 (0.82, 3.38) MI: 1.27 (0.35, 4.63) Stroke: 1.78 (0.71, 4.47)	Moderate
Sirmans et al. [37]	USA	Population-based cross-sectional	ICD	N = 1689 Age = mean 25.24 <sup>e</sup> BMI = not reported	N = 5067 Age = mean 25.23 BMI = not reported	CAD: 21 (1.2) <sup>a</sup> MI: 1 (0.06) <sup>a</sup> Angina: 14 (0.8) <sup>a</sup> Stroke: 8 (0.5) <sup>a</sup> Heart failure: 5 (0.3) <sup>a</sup>	CAD: 45 (0.89) <sup>a</sup> MI: 4 (0.08) <sup>a</sup> Angina: 36 (0.7) <sup>a</sup> Stroke: 14 (0.3) <sup>a</sup> Heart failure: 9 (0.17) <sup>a</sup>	CAD: 1.40 (0.84, 2.33) MI: 0.75 (0.08, 6.74) Angina: 1.17 (0.51, 2.64) Stroke: 1.71 (0.72, 4.05) Heart failure: 1.67 (0.56, 5.005)	Moderate
Wild et al. [18]	UK								High

(continued)

Table 1. Continued.

First author, year	Country	Study design	PCOS criteria	PCOS group characteristics	Control group characteristics	Number of events (Prevalence <sup>a</sup> or Incidence <sup>b</sup> % in PCOS group)	Number of events (Prevalence <sup>a</sup> or Incidence <sup>b</sup> % in control group)	Unadjusted RR (95% CI)	Quality assessment
Pierpoint et al. [19]	UK	Nonpopulation-based retrospective cohort	Laparoscopic criteria	N = 1060 Age = 56.7 (38–98) <sup>c</sup> BMI = mean 25.9 <sup>d</sup>	N = 319 Age = 56.7 (38–98) <sup>c</sup> BMI = mean 26.6	CAD: 15 (4.7) <sup>a</sup> Cerebrovascular disease: 10 (3.1) <sup>a</sup>	CAD: 42 (4) <sup>a</sup> Cerebrovascular disease: 13 (1.2) <sup>a</sup>	CAD: 1.18 (0.67, 2.08) Cerebrovascular disease: 2.55 (1.10, 5.92)	High
		Population-based prospective cohort	Laparoscopic criteria	N = 786 Age = 20–79 BMI = not reported <sup>e</sup>	N = - Age = 20–79 BMI = not reported <sup>e</sup>	Death due to CV events: 15	Death due to CV events: 18.1	Death due to CV events: 0.83 (0.46, 1.37)	High

AES: Androgen Excess Society; BMI: body mass index; CAD: coronary arterial disease; MI: myocardial infarction; NIH: National Institute of Health.

<sup>a</sup>Values represent prevalence.

<sup>b</sup>Values represent incidence.

<sup>c</sup>Values represent median and interquartile.

<sup>d</sup>Values represent mean; standard deviation is not reported.

<sup>e</sup>Values represent range.

<sup>f</sup>Adjusted RR was reported.

random effect meta-regression model was fitted to estimate the association between age group and outcomes of interest in the subgroup of study design. Bubble plots were drawn to illustrate the fitted models for each covariate. Sensitivity analyses were performed to explore the source of heterogeneity with detecting the influence of any single study on the prevalence or HR of outcomes. Statistical analysis was performed using STATA software (version 10; STATA, INC., College Station, TX).

## Results

### Search results, study selection, study characteristics, and quality assessment

Figure 1 illustrates the flow diagram of the search strategy and study selection. Of 7236 records retrieved through searching databases, 16 studies including 12 population-based [18,19,28–37] and 4 non-population-based studies [38–41] were selected for the final analyses. Three studies were cross-sectional [32,36,37], 12 cohort [18,19,28–31,33–35,39–41] and 1 study was a case-control [38]. Eleven studies were classified as high [18,19,28,29,31–36,39], and five as moderate [30,37,38,40,41]; no study had low quality; details of quality assessment are presented as Supplementary File 2. Four studies diagnosed PCOS using the Rotterdam criteria [30,35,39,41], three the NIH [28,34,38], one the AES [33], five the ICD [29,31,32,36,37], and three studies used laparoscopic criteria [18,19,40] (Table 1). Eleven studies assessed a population of reproductive age patients with PCOS [19,28–32,36–40], four studies—menopausal/aging women [34,35,41], and one study both age groups of patients (reproductive and menopausal/aging women) [33]. Five studies reported CAD [18,29,32,35,37], four cerebrovascular disease [18,30–32], six CVD [30,33,35,36,39,41], seven MI [30,33,36,37,39–41], three angina [33,37,39], five stroke [30,36,37,39,41], one heart failure [37], one ischemic heart disease [31], and three mortalities due to CV events [19,34,39].

### Meta-analysis and meta-regression of outcomes

Table 2 shows the pooled prevalence of CV events among reproductive age PCOS patients and in menopausal/aging women compared to healthy women. This study reveals that the pooled prevalence of CV events in PCOS patients of reproductive age and in menopausal/aging women was higher than healthy controls (Pooled  $p = .003$ , 95% CI: 0.003, 0.004 versus pooled  $p = .002$ , 95% CI: 0.002, 0.003) and (Pooled  $p = .097$ , 95% CI: 0.041, 0.153) versus pooled  $p = .098$ , 95% CI: 0.045, 0.152). Subgroup analysis of population-based studies showed an increased pooled prevalence of CV events in PCOS patients of reproductive age and in menopausal/aging women, compared to their healthy counterparts (Pooled  $p = .003$ , 95% CI: 0.002–0.004 versus pooled  $p = .002$ , 95% CI: 0.002–0.003) and (pooled  $p = .066$ , 95% CI: 0.019–0.113 versus pooled  $p = .064$ , 95% CI: 0.028–0.101), respectively.

Figure 2 illustrates the forest plot of pooled HRs of CV events in patients with PCOS, compared to healthy women. The pooled HR of CV events in patients with PCOS compared to healthy controls is presented in Table 3. We found that the pooled HRs of CV events in PCOS patients of reproductive age and in menopausal/aging women were higher than in healthy controls (Pooled HR: 1.38, 95% CI: 1.12–1.71) and (Pooled HR: 1.53, 95% CI: 1.15, 2.04), respectively (Figure 2). Subgroup analysis of population-based studies revealed that the HR of CV events in

**Table 2.** Meta-analysis of studies conducted on the prevalence of cardiovascular events and its mortalities.

Events	Number of study groups	$I^2$ %	Publication bias <sup>a</sup>	Pooled Prevalence (95% CI)
<b>Cardiovascular events<sup>b</sup></b>				
<b>All studies</b>				
Reproductive age	32	96	0.422	0.002 (0.002, 0.003)
PCOS	16	95	0.520	0.003 (0.003, 0.004)
Control	16	85	0.840	0.002 (0.002, 0.003)
Nonreproductive age	10	79	0.222	0.095 (0.062, 0.128)
PCOS	5	68	0.452	0.097 (0.041, 0.153)
Control	5	82	0.445	0.098 (0.045, 0.152)
<b>Population-based studies</b>				
Reproductive age	22	96	0.771	0.002 (0.002, 0.002)
PCOS	11	98	0.820	0.003 (0.002, 0.004)
Control	11	98	0.891	0.002 (0.002, 0.003)
Nonreproductive age	2	79	0.317	0.065 (0.036, 0.094)
PCOS	1	—	—	0.066 (0.019, 0.113)
Control	1	—	—	0.064 (0.028, 0.101)
<b>Mortality due to cardiovascular events</b>				
<b>All studies<sup>c</sup></b>				
Reproductive age	2	0	0.317	0.008 (0.001, 0.015)
PCOS	1	—	—	0.013 (0.000, 0.026)
Control	1	—	—	0.006 (0.000, 0.014)
Nonreproductive age	2	0	0.317	0.173 (0.129, 0.216)
PCOS	1	—	—	0.200 (0.043, 0.357)
Control	1	—	—	0.170 (0.126, 0.215)

<sup>b</sup> $I^2$ : I-squared.<sup>a</sup>Assessed by Begg's test.<sup>b</sup>Cardiovascular events, as composite outcome, which consisted of events of CAD, CVD, MI, angina, heart failure, and ischemic heart disease.<sup>c</sup>All studies were nonpopulation-based.

reproductive age PCOS patients was 1.43-fold (95% CI: 1.27–1.61) higher than those of healthy counterparts, a difference not statistically significant among menopausal/aging PCOS patients compared to healthy controls (1.03-fold, 95% CI: 0.41, 2.59) (Table 3; Figure 3). The results of nonpopulation-based studies are presented as Supplementary Appendices S4 and S5. Meta-regression of population-based studies showed that the HRs of CV events in reproductive age PCOS patients was 1.34-fold (95% CI: 0.32–5.50) higher than those of CV events in menopausal/aging PCOS patients (Figure 5). Meta-regression results of all studies and non-population-based studies are presented as Supplementary Appendix S5.

Figure 4 illustrates the forest plot of pooled HR of mortality due to CV events in patients with PCOS compared to healthy women. This study showed a higher pooled prevalence of mortality due to CV events in reproductive and menopausal PCOS groups, compared to their healthy counterparts (Table 2). In addition, the HRs of mortality due to CV events in reproductive age and menopause/aging PCOS groups had no statistically significant differences, compared to those of healthy counterparts (Table 3). Insufficient data were available for comparing the HRs of mortality due to CV events in population based studies.

Supplementary files S4 and S5 present the pooled prevalence/HR of specific CV events, including CAD, CVD, MI, angina, stroke, heart failure, and ischemic heart disease for all studies and subgroup analyses based on the age groups and study design. Insufficient population-based studies were available for assessing these specific CV events in menopausal/aging groups.

Results of sensitivity analysis are presented in Supplementary Files 4 and 5, indicating that no particular study heavily influenced the results of the study for HR (Supplementary File 4). For prevalence, we found and presented influential studies in the forest plots; the pooled effect sizes after their exclusion were reported as well (Supplementary File 5).

### Publication bias and risk of bias

The Begg's test showed substantial publication bias for CV event in menopause/aging group and some secondary outcomes including CAD and MI, which were adjusted by the trim and fill method (Table 2 and Supplementary File 5).

Supplementary File 3 shows risk of bias of the studies included. Most cross-sectional and case-control studies had a low risk of bias in the assessment of exposure, development of outcome of interest in cases and controls, selection of cases, and selection of controls, and a high risk of bias in control of prognostic variable.

In addition, cohort studies had a low risk of bias for selection of exposed and non-exposed cohorts, assessment of exposure, presence of outcome of interest at initiation of study, outcome assessment, and adequate follow-up of cohorts; however there was a high risk of bias in control of prognostic variables and assessment of the presence or absence of prognostic factors.

### Discussion

Despite not having sufficient population-based study for a precise comparison of CV events in PCOS women in particular in postmenopausal ones, the present meta-analysis revealed that CV events increased mainly in young PCOS women; those who had PCOS during their reproductive life, may not always suffer from significant increase in CV events with ageing.

Previous meta-analyses have reported an increase of CV events in women with PCOS; however, these meta-analyses did not differentiate between reproductive age and postmenopausal patients [12,13]. This is an important bias because CV events are not equally distributed throughout the life of women but increase considerably after menopause and at older ages [42–44]. Hence, a large increase in those CV events % during younger ages may signify only few CV events, while lower percentage of

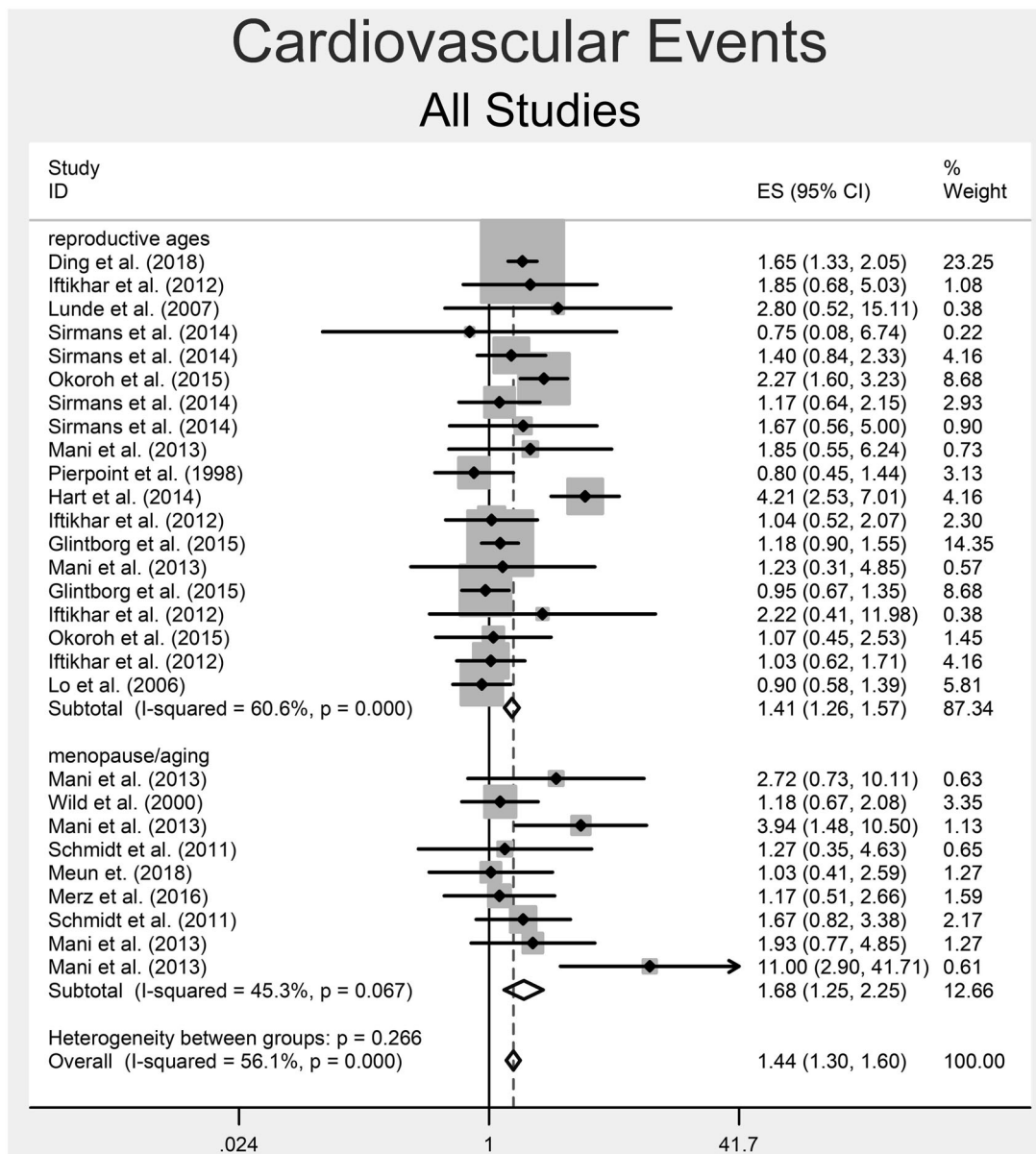


Figure 2. Forest plot of pooled hazard ratio of cardiovascular events for all included studies.

changes in postmenopausal women may identify a higher number of important CV events, representing a relevant social issue.

An additional bias depend on the fact that most data have been collected in young women with PCOS while only three studies evaluated the HR of CV events in postmenopausal women who had PCOS [34,35,41]. In fact, when we compared the reported number of CV events in women with PCOS, independently of age, with the total number of CV events in a general population, we found that the number of events in PCOS was increased.

Finally, in all analyses, including pooled, young and aging women with PCOS, mortality rates due to CV events did not significantly differ between PCOS patients and healthy controls.

Our conclusions are somewhat surprising, considering the increased risk of CV events in young women with PCOS. It is well known that many young patients with PCOS, particularly those with phenotypes A and B, have central obesity, insulin resistance, and alterations of glucose metabolism and of lipid pattern [45,46]. All these factors as well as androgen excess,

which is prevalent in PCOS patients, represent an important risk for developing CV events.

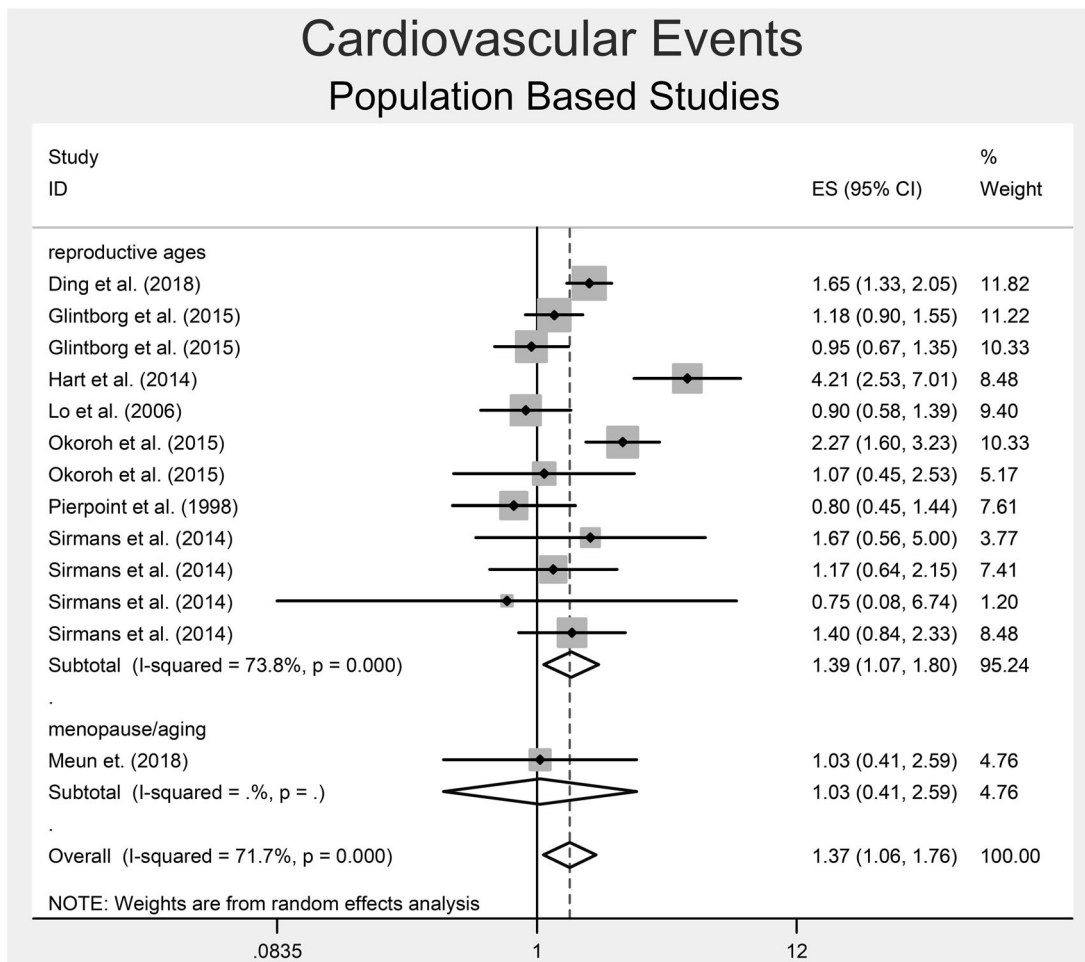
Most probably, the risk for CV diseases in women with PCOS progressively normalizes with aging. In fact, it has been reported that the progressive reduction of androgen secretion in the decade preceding menopause reduces certain risk factors. In most patients, the severity of PCOS symptoms decreases with aging and in some patients this syndrome may even disappear [47,48]. A follow-up study showed that approximately 50% of PCOS patients improve during later reproductive ages due to ovarian and adrenal aging that results in decreasing androgen levels; these changes over time can be associated with a progressive decrease in some CV risk factors such as low-density lipoprotein-cholesterol levels [48]. Another decade long follow-up study showed a reduction in lipid profiles and insulin resistance with aging [49]. Similar longitudinal data suggest that although diabetes mellitus is prevalent in young women with PCOS, there is no increased risk in their late reproductive age [50].

**Table 3.** Meta-analysis of studies conducted on the hazard ratio of cardiovascular events and its mortalities.

Events	Number of study groups	$I^2\%$	Publication bias <sup>a</sup>	Pooled HR (95% CI)
<b>Cardiovascular events<sup>b</sup></b>				
All studies				
Reproductive	19	60	0.255	<b>1.38 (1.12, 1.71)</b>
Menopause/aging	9 + 1 <sup>c</sup>	45	0.028 <sup>d</sup>	<b>1.53 (1.15, 2.04)<sup>e</sup></b>
Total	28	60	0.157	<b>1.44 (1.30, 1.60)</b>
Population-based studies				
Reproductive	12	73	0.783	<b>1.43 (1.27, 1.61)</b>
Menopause/aging	1	—	—	1.03 (0.41, 2.59)
Total	13	71	0.806	<b>1.42 (1.26, 1.60)</b>
<b>Mortality due to CV events</b>				
All studies				
Reproductive	2	19	0.317	0.90 (0.51, 1.56)
Menopause/aging	1	—	—	1.17 (0.51, 2.67)
Total	3	0	0.117	0.97 (0.62, 1.54)
Population-based studies				
Reproductive	1	—	—	0.80 (0.45, 1.45)
Menopause/aging	0	—	—	—
Total	1	—	—	0.80 (0.45, 1.45)

<sup>f</sup> $I^2$ : I-squared.<sup>a</sup>Assessed by Begg's test.<sup>b</sup>Cardiovascular events, as composite outcome, which consisted of events of CAD, CVD, MI, angina, heart failure, and ischemic heart disease.<sup>c</sup>Observation + fill study to adjust publication bias.<sup>d</sup>Significant results were shown as bolded values.<sup>e</sup>Obtained from trim and fill analysis to adjust publication bias.

Bold values are considered as significant results.

**Figure 3.** Forest plot of pooled hazard ratio of cardiovascular events for population based studies.

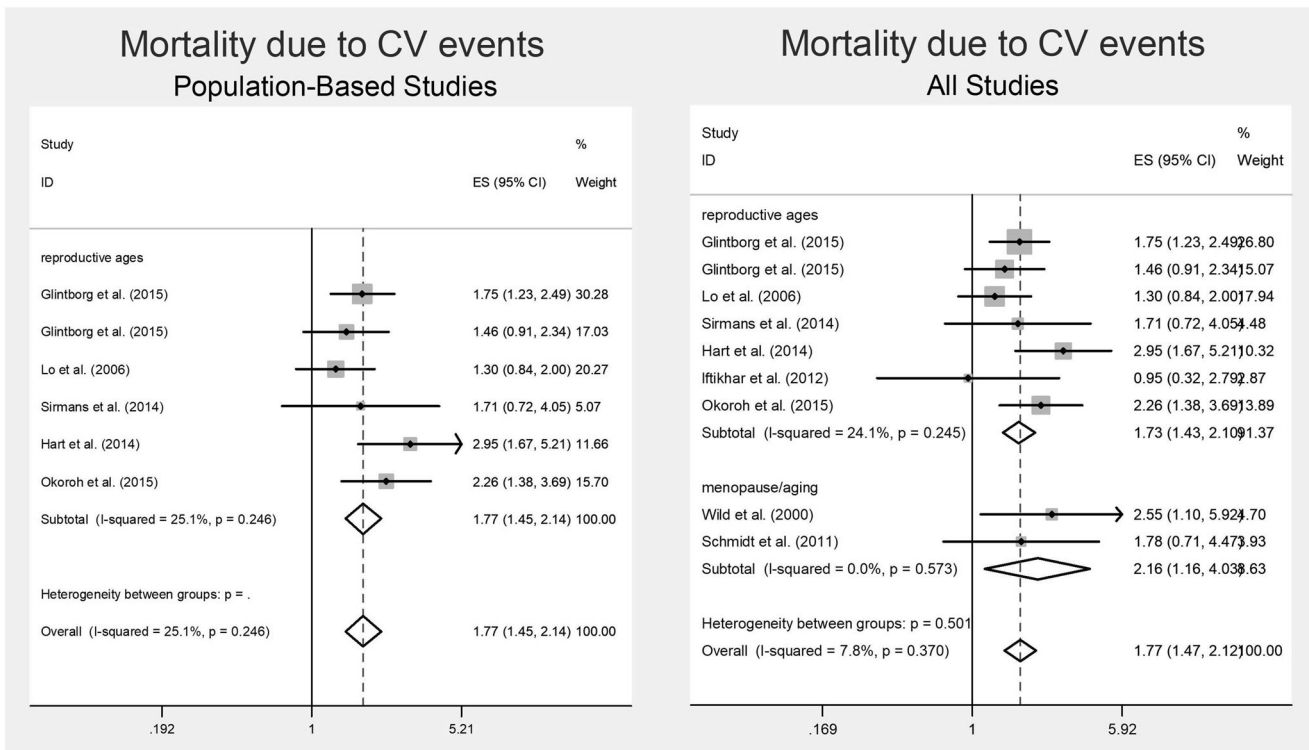


Figure 4. Forest plot of pooled hazard ratio of mortality due to cardiovascular events.

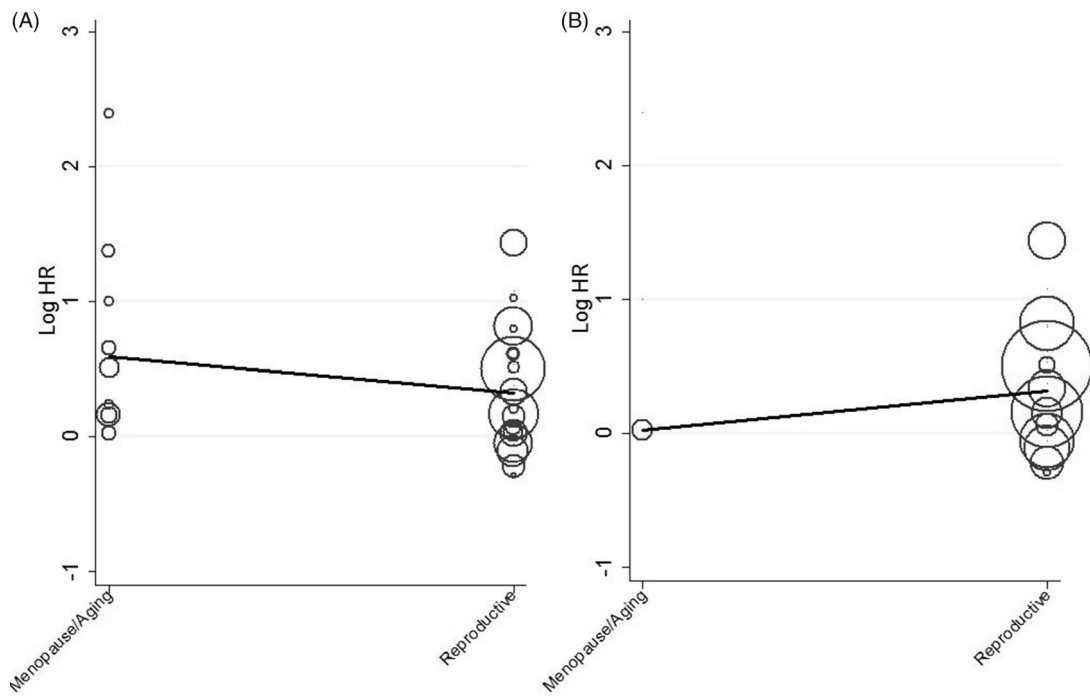


Figure 5. Bubble plot of association between hazard ratio of cardiovascular events and age group (A: total studies, B: population-based studies).

Other factors, still unclear, may contribute to normalize the HR for CV events in postmenopausal women. Studying women who had PCOS during their last decade of reproductive life may help us to understand better the mechanisms that regulate the evolution of CV events HR with age in general populations.

Interestingly, there is growing evidence that, also in general populations, CV risk estimation at younger age may not accurately predict later CV events. Some of the errors in risk

estimation arise from unpredictable changes that occur in risk factors over time, such as blood pressure and insulin resistance, which may increase relatively quickly with age [51]. At 50 years of age, however, the absence of traditional risk factors is associated with extremely low lifetime risk and significantly greater longevity [52,53].

The main limitation of this study is the small number of publications assessing CV events in aging PCOS patients.

Cardiovascular disease in this group is associated with various CV risk factors, which were not accounted for in this meta-analysis due to the lack of sufficient data and small sample size of the studies; significance of publication bias was also limited the reliability of the interpretation of our findings in ageing group. Additionally, there were inadequate number of studies for running the subgroup analysis according to the PCOS criteria.

The report of our findings in menopausal/ageing PCOS women may be used as a preliminary assumption that needs to be reevaluated in well-designed comprehensive cohort studies initiated in reproductive period (considering all those known CVD risk factors), and continued till older ages. Until such data are available, conclusions on CV morbidity and mortality in ageing PCOS women should be interpreted with caution.

## Conclusions

In conclusion, this meta-analysis demonstrated an increased number of CV events in reproductive age patients with PCOS. After menopause, having a history of PCOS features may not be a risk factor for the development of CV events, an issue that needs to be further elucidated and confirmed by comprehensive well-designed population-based studies.

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## Authors' contributions

F.R.T was involved in study design, quality assessment, data analysis, manuscript drafting, revising manuscript, and critical discussion. M.A was involved in study design, search in databases, quality assessment, study selection, data extraction, data analysis, manuscript drafting, and critical discussion. S.B.G contributes in quality assessment, data extraction, manuscript drafting and critical discussion. R.B.Y contributed in statistical analysis, interpreting data, and manuscript drafting. E.C was involved made substantial contributions to conception and design, search in databases, data analysis, the manuscript revision, and critical discussion. All authors have read and approved the final manuscript.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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