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ORIGINAL ARTICLE
Special populations

Cardiovascular disease risk in women with hyperandrogenism, oligomenorrhea/ menstrual irregularity or polycystic ovaries (components of polycystic ovary syndrome): a systematic review and meta-analysis

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Aims

Prior meta-analyses indicate polycystic ovary syndrome (PCOS) is associated with cardiovascular diseases (CVDs), but have high statistical heterogeneity, likely because PCOS is a heterogenous syndrome diagnosed by having any two of the three components: hyperandrogenism, oligomenorrhea/menstrual irregularity or polycystic ovaries. Several studies report higher risk of CVDs from individual PCOS components, but a comprehensive assessment of how each component contributes to CVD risk is lacking. This study aims to assess CVD risk for women with one of the PCOS components.

Methods and results

A systematic review and meta-analysis of observational studies was conducted. PubMed, Scopus, and Web of Science were searched without restrictions in July 2022. Studies meeting inclusion criteria examined the association between PCOS components and risk of a CVD. Two reviewers independently assessed abstracts and full-text articles, and extracted data from eligible studies. Where appropriate, relative risk (RR) and 95% confidence interval (CI) were estimated by random-effects meta-analysis. Statistical heterogeneity was assessed using the I^2 statistic. Twenty-three studies, including 346 486 women, were identified. Oligo-amenorrhea/menstrual irregularity was associated with overall CVD (RR = 1.29, 95%CI = 1.09–1.53), coronary heart disease (CHD) (RR = 1.22, 95%CI = 1.06–1.41), and myocardial infarction (MI) (RR = 1.37, 95%CI = 1.01–1.88) but not cerebrovascular disease. These results were broadly consistent even after further adjustment for obesity. There was mixed evidence for the role of hyperandrogenism in CVDs. No studies examined polycystic ovaries as an independent exposure for CVD risk.

Conclusion

Oligo-amenorrhea/menstrual irregularity is associated with greater risk of overall CVD, CHD, and MI. More research is needed to assess the risks associated with hyperandrogenism or polycystic ovaries.

Lay Summary

Polycystic ovary syndrome (PCOS) is associated with a higher risk of cardiovascular disease (CVD). It is unclear how risk of CVD varies with the different components of PCOS and whether risk occurs independently of obesity. In this systematic review of 346 486 women, we found that irregular, infrequent or absent periods were associated with a higher risk of CVD, coronary heart disease, and myocardial infarction, with this association occurring independently of obesity. There was mixed evidence of a higher risk of CVDs with hyperandrogenism and no studies evaluated polycystic ovaries as a lone risk factor. The clear association between irregular, infrequent or absent periods and certain CVDs could inform how cardiometabolic screening and risk management may be tailored to specific PCOS phenotypes. Future research could focus on the influence of polycystic ovaries and different manifestations of hyperandrogenism on CVD risk.

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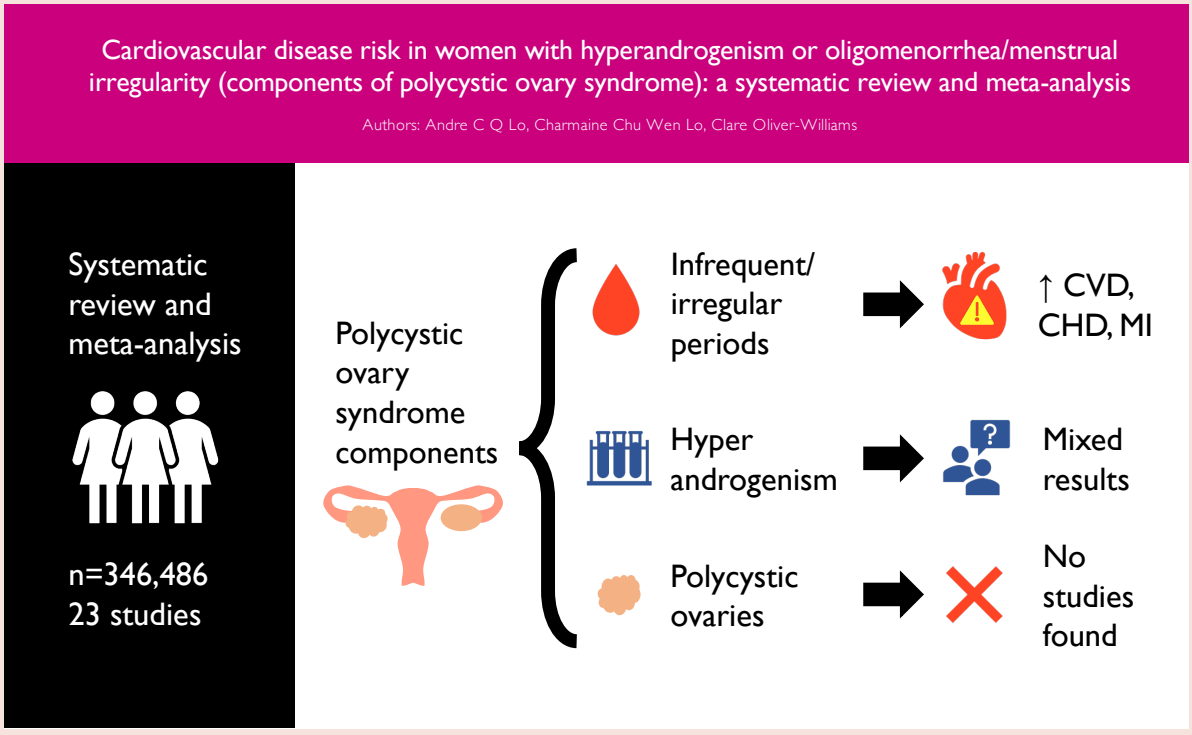
Graphical Abstract



Keywords Polycystic ovary syndrome • cardiovascular disease • oligomenorrhea • hyperandrogenism polycystic ovaries • systematic review • meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age women with a prevalence estimated at 3–10%, although up to 75% of cases are thought to remain undiagnosed.[1] Despite mounting evidence that PCOS is an independent cardiovascular disease (CVD) risk factor, findings from previous meta-analyses examining this relationship have been hampered by substantial between-study heterogeneity.[2,3] This limits the interpretation and clinical use of these results as the pooled estimate may not represent the CVD risk of any PCOS population.

A key source of this heterogeneity may be the presentation of PCOS. PCOS is primarily defined using the Rotterdam criteria, where at least two of the following three components are required for diagnosis: (i) oligo-anovulation (infrequent or absent ovulation) with oligo-amenorrhea (infrequent or absent menses) and menstrual irregularity often used as a proxy, (ii) clinical or biochemical signs of hyperandrogenism, and (iii) ultrasound diagnosis of polycystic ovaries.[4] Therefore, women diagnosed with PCOS will have one of four different phenotypes: (A) having all three components, (B) only hyperandrogenism and oligo-amenorrhea, (C) only hyperandrogenism and polycystic ovaries, and (D) only oligo-amenorrhea and polycystic ovaries.[5] Another source of heterogeneity may be the presence of common co-morbidities, such as obesity, which may also impact the magnitude of CVD risk.

Therefore, to understand how each PCOS component affects CVD risk and thus which women with PCOS may be at highest risk, we performed a systematic review and meta-analysis examining CVD risk in women with hyperandrogenism, oligomenorrhea or polycystic ovaries. To our knowledge, no review has previously addressed this. To further our understanding of how obesity impacts CVD risk in women with PCOS, we also examined if risk of CVD may be entirely explained or mediated by obesity in patients with oligo-anovulation/menstrual irregularity, hyperandrogenism or polycystic ovaries.

Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA and MOOSE guidelines.[6,7] The protocol for this review is registered on PROSPERO (Registration: CRD42020212326).[8]

Selection criteria

To be included in the review, articles had to compare the risk of any CVD (or composite CVD) for women older than 15 years with a component of PCOS compared to control women without this component of PCOS, respectively. The PCOS components considered as exposures were: (i) oligomenorrhea, amenorrhea or menstrual irregularity; (ii) hyperandrogenism which includes hirsutism, acne, androgenic alopecia and elevated free androgen index (FAI) levels, the recommended biochemical test for hyperandrogenism by NICE;[9] and (iii) polycystic ovaries. Included study designs were limited to cohort studies, case-control studies and cross-sectional studies. Exclusion criteria were: (i) studies on animals, men or children; (ii) studies that only examined subclinical cardiovascular outcomes or cardiometabolic risk factors;

and (iii) studies that did not evaluate a PCOS component as its own independent exposure. Detailed inclusion and exclusion criteria are presented according to the PICO framework in Supplementary material online, *Table SI*.

Search strategy

To identify studies according to the inclusion criteria, we searched PubMed, Scopus, and Web of Science in July 2022. The PubMed search terms based on the aforementioned PICO framework are provided in Supplementary material online, *Table SV*. No restrictions were applied to the language or publication period of the articles. Both medical search headings and open text fields were used to identify articles. The PubMed search was restricted to articles relating to humans. We performed forward and backwards citation searches of relevant articles and reviews found during our search to identify additional studies that fit our inclusion criteria.

Selection of studies

All abstracts found with our search strategy were screened by two authors (ACQL, CCWL) using the software Abstrackr,[10] with any discrepancies adjudicated by a third author (COW). For relevant abstracts, full texts were accessed to determine their eligibility for the review.

Data extraction

The following data was abstracted and independently verified by a second author: follow-up period; study design; population characteristics; sample size; exposure and outcome; methods of ascertaining PCOS components and cardiovascular events; and controlled variables. Measures of exposure-outcome association and 95% confidence intervals (CIs) were also extracted and verified, with any differences discussed and resolved by a third author.

Risk of bias assessment

Study quality was assessed using the Newcastle-Ottawa Scale.[11] This is a semi-quantitative scale for assessing the quality of non-randomized studies and allocates a maximum of nine stars to a study, across three categories. The categories are the quality of studies on the participant selection criteria, comparability of cases and controls, and exposure assessment (for case-control studies) or outcome assessment (for cohort studies). Based on their scores, studies were then classified as being good, fair, or low quality as per the Agency for Healthcare Research and Quality standards.[12]

The certainty of the evidence for significant exposure-outcome associations found in meta-analyses was assessed using the GRADE approach.[13] This approach assesses study limitations to provide an overall rating of the confidence in each result. As all data came from observational studies, the quality was initially graded as low. Quality was downgraded by one level for serious risk of bias, indirectness of evidence, serious inconsistency (heterogeneity), imprecision of effect estimates, or potential publication bias.

Statistical analysis

A minimum of two studies evaluating a particular exposure-outcome association were required to conduct a meta-analysis. Therefore, separate meta-analyses were conducted for the associations between oligo-amenorrhea/menstrual irregularity and the following outcomes: CVD, fatal CVD, coronary heart disease (CHD), fatal CHD, cerebrovascular disease/stroke (pooled together since stroke is the most common form of cerebrovascular disease), and myocardial infarction (MI). A meta-analysis was also conducted for normoandrogenic oligo-amenorrhea/menstrual irregularity and CHD.

For studies with missing information, the corresponding author was contacted, but none replied. If studies only provided the number of cases and non-cases or incidence rates amongst exposed and non-exposed women, the crude relative risk (RR) or rate ratio (for cohort studies) and odds ratio (OR) (for case-control or cross-sectional studies) was calculated using an online statistical calculator.[14] Studies with zero cases in one comparison group were recalculated with the Haldane–Anscombe correction to allow inclusion in meta-analyses.[15] To examine if risk may be explained or mediated by obesity, meta-analyses were conducted separately for results which adjusted for obesity or a proxy of obesity [e.g. body mass index (BMI), waist–hip ratio (WHR), weight, waist circumference] and those without such adjustment.

When pooling results, the inverse variance weighted method was used to combine ORs, RR, and hazard ratios (HRs) to produce a pooled RR, under the rare outcome assumption. Random effects models were used to allow for between-study heterogeneity. Heterogeneity was assessed using the I^2 statistic with the restricted maximum likelihood estimator for between-study variance. Some studies reported risk estimates for multiple outcomes (e.g. angina and MI) or multiple exposures (e.g. irregular menses and very irregular menses). To deal with these dependent risk estimates, we used a correlated and hierarchal effects model which combines a three-level meta-analysis model and robust variance estimation (with small-sample corrections), where the within-study correlation parameter was set at 0.5.[16]

For studies that reported separate risk estimates for independent subgroups (e.g. by age group), we first used inverse variance weighted fixed effects meta-analysis to generate overall study-level risk estimates before meta-analysing. For studies which reported results stratified by obesity but used a non-obese cohort as control in all strata, a ratio of the risk estimates for exposed obese women compared to unexposed obese women was calculated so that the results could be included in the meta-analysis adjusted for obesity.[17] Individual RR estimates and pooled estimates were displayed graphically with forest plots.

Small study effects and publication bias were evaluated if the meta-analyses included 10 or more studies, the minimum number recommended for tests of funnel plot asymmetry to have adequate power to distinguish chance and real asymmetry.[18] Funnel plots were produced, and Egger's test was conducted using a robust variance estimation variant for correlated and hierarchal meta-analysis models.[19]

Sensitivity analyses

Sensitivity analyses were performed to assess the consistency of the results. Correlated and hierarchal effects models were rerun varying the intra-study correlation parameter to 0 and 1 (which, respectively, assumes complete independence or dependence of the outcomes within a study), and the basic random-effects models were rerun as fixed-effects models. We also performed a sensitivity analysis excluding case-control studies (no cross-sectional studies were included in meta-analyses because they did not examine the same exposure-outcome associations as other studies and thus were only included in the systematic literature review) or low-quality studies to examine the effect of study design and risk of bias on results, especially to ensure exposure-outcome temporality. Finally, because Solomon *et al.*[20] and Wang *et al.*[21] are 'companion' cohort studies with similarities in study design, location and patient profiles, the inclusion of both in a single meta-analysis could bias results. In meta-analyses where both could be included, each study was individually excluded to assess the robustness of results.

All tests were two-tailed and P values of <0.05 were considered statistically significant. The meta, metafor, robumeta, clubsandwich, and dmetar packages in R version 4.0.5 were used for statistical analyses and plots.[22–27]

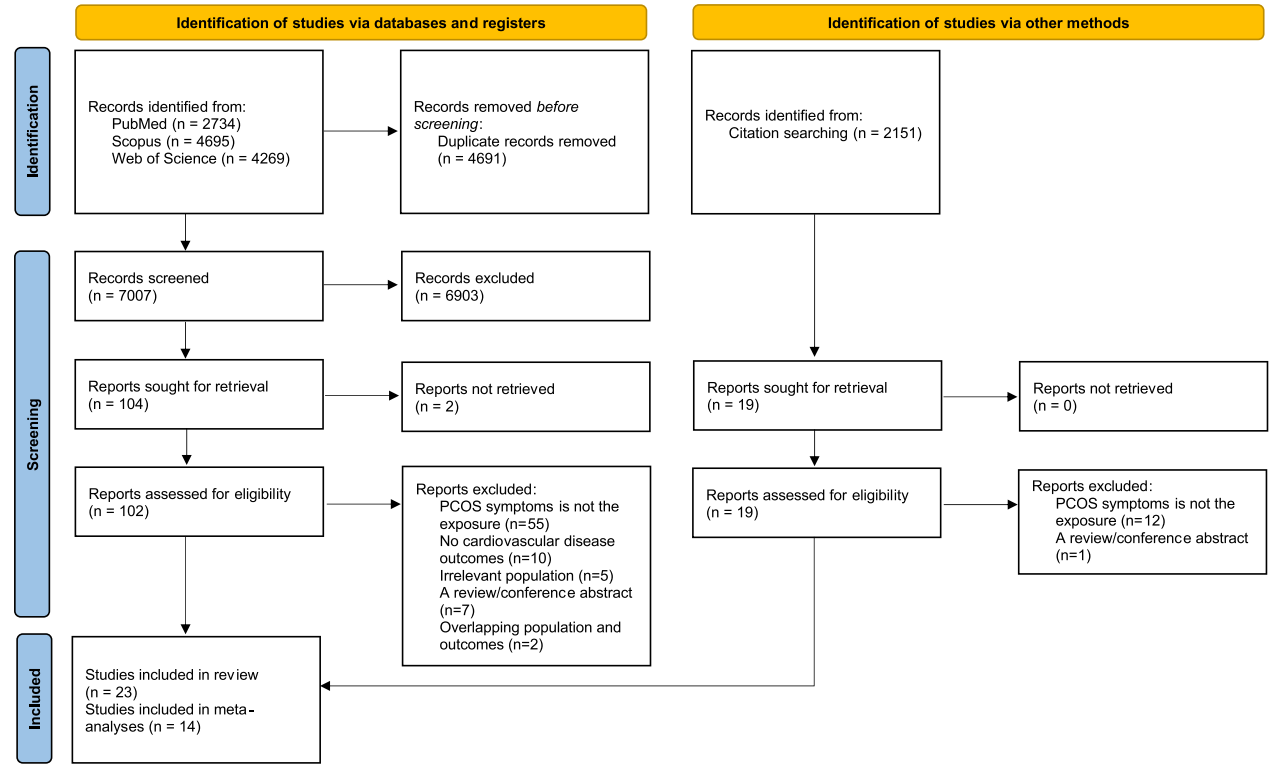


Figure 1 Flow diagram of studies included in the current review.

Results

During initial screening, 9158 studies were identified and 121 were selected for full text review (*Figure 1*). After screening, 23 studies involving 346 486 participants from 23 populations were included in the systematic review (see Supplementary material online, *Table SI*).[20,21,28–48] Of the studies, nine were from North America,[20,21,30,32,41–44,48] six were from Europe,[29,35,38,45–47] five were from Asia,[33,34,37,39,40] two were from Brazil,[28,31] and one was from Australia.[36] There were 12 cohort studies,[20,21,28–48] eight case-control studies,[28,29,39,40,43,44,46,47] and three cross-sectional studies.[31,33,37] Average follow-up period ranged from 2.9 to 41 years, and the average age ranged up to 73 years.

Exposures evaluated in the identified studies were oligomenorrhea, amenorrhea, menstrual irregularity, high FAI levels, hirsutism, acne and androgenic alopecia. Outcomes included overall CVD, CHD, cerebrovascular disease, MI, stroke, heart failure, angina, peripheral artery disease (PAD), venous thromboembolism (VTE), cardiomyopathy, and subarachnoid haemorrhage (SAH).

Quality assessment of the literature

The quality assessment of included studies is summarized in Supplementary material online, *Table SII*. Seven studies were judged as good quality, five were fair quality, and eleven were poor quality. The overall certainty of evidence for relevant associations, as judged by the GRADE criteria, is presented in Supplementary material online, *Table SIII*. The evidence was of low certainty for the associations between oligo-amenorrhea/menstrual irregularity and CVD, fatal CVD and CHD, and of very low certainty for the association between oligo-amenorrhea/menstrual irregularity and MI.

Oligo-amenorrhea/menstrual irregularity and risk of CVD outcomes

Fifteen studies including 291 847 participants investigated the relationship between oligo-amenorrhea/menstrual irregularity and risk of CVD outcomes.[20,21,28–30,32,34–36,39–42,44–48] These included 11 cohort studies,[20,21,30,32,34–36,41,42,45–48] and 5 case-control studies.[28,29,39,40,44]

Fourteen studies were included in meta-analyses (see Supplementary material online, *Table SVI*)[20,21,28–30,32,34–36,39,41,42,44,48] and six results from five studies could not be included in meta-analyses (see Supplementary material online, *Table SVII*).[20,28,40,44,48] The outcomes evaluated included CVD and fatal CVD, angina, fatal cerebrovascular disease, CHD and fatal CHD, heart failure, MI, SAH, stroke, and Takotsubo cardiomyopathy.

Oligo-amenorrhea/menstrual irregularity and overall risk of CVD

The meta-analysis of results without adjustment for obesity found that oligo-amenorrhea/menstrual irregularity was associated with higher risk of overall fatal CVD (RR = 1.29, 95%CI = 1.09–1.53, 2 studies[21,48]) with no evidence of between-study heterogeneity ($I^2 = 0.00\%$, $P = 0.379$) (*Figure 2*). With adjustment for obesity, oligo-amenorrhea/menstrual irregularity was still associated with fatal CVD (RR = 1.20, 95%CI = 1.02–1.43, 2 studies[21,48]) again with no between-study heterogeneity ($I^2 = 0.00\%$, $P = 0.478$), as well as with fatal or non-fatal

CVD (RR = 1.25, 95%CI = 1.03–1.52, 3 studies[20,21,48]) which had evidence of moderate statistical heterogeneity ($I^2 = 51.69\%$, $P = 0.040$) entirely attributed to within-study variance instead of between-study variance (*Figure 3*). The age-stratified results from Wang *et al.*[21] also indicated that CVD risk may increase over the reproductive lifespan.

Oligo-amenorrhea/menstrual irregularity and risk of CHD

In meta-analyses, oligo-amenorrhea/menstrual irregularity was associated with CHD in results without adjustment for obesity (RR = 1.22, 95%CI = 1.06–1.41, 10 studies[20,28,30,32,34–36,39,41,48]) (*Figure 2*), Results were broadly similar when risk estimates adjusted for obesity were pooled (RR = 1.25, 95%CI:1.03-1.51, 5 studies[20,28,34,35,48]) (*Figure 3*). There was evidence of moderate statistical heterogeneity in both meta-analyses ($I^2 = 51.06\%$, $P = 0.006$; $I^2 = 36.94\%$, $P = 0.044$) entirely attributed to within-study variance instead of between-study variance.

When restricting results to fatal CHD, meta-analyses were not significant without adjustment for obesity (RR = 1.48, 95%CI = 0.96–2.28, 2 studies[20,48]) (*Figure 2*) or with adjustment for obesity (RR = 1.43, 95%CI = 0.79–2.52, 2 studies[20,48]) (*Figure 3*) and substantial statistical heterogeneity attributed to within-study variance was noted for both (respectively, $I^2 = 73.36$, $P = 0.003$; $I^2 = 79.82$, $P < 0.001$).

When restricting results to normoandrogenic oligo-amenorrhea/menstrual irregularity, there was no significant association with CHD, (RR = 1.02, 95%CI = 0.08–13.32, 2 studies,[30,34]) with little evidence of between study heterogeneity ($I^2 = 18.25$, 95%CI = 0.404) (see Supplementary material online, *Figure S1*).

Oligo-amenorrhea/menstrual irregularity and risk of MI

The meta-analysis of results without adjustment for obesity found that oligo-amenorrhea/menstrual irregularity was associated with MI (RR = 1.37, 95%CI = 1.01–1.88, 4 studies.[20,28,29,44]) (*Figure 2*). The significance of this relationship was maintained in the pooled results that adjusted for obesity with little difference in the point estimate (RR = 1.31, 95%CI = 1.11–1.55, 4 studies[20,28,29,42]) (*Figure 3*). There was little evidence for between-study heterogeneity in either meta-analysis ($I^2 = 6.47\%$, $P = 0.602$; $I^2 = 0.00\%$, $P = 0.567$).

Oligo-amenorrhea/menstrual irregularity and risk of cerebrovascular disease/stroke

In results not adjusted for BMI, Wang *et al.*[48] found that oligo-amenorrhea/menstrual irregularity was not associated with cerebrovascular disease (HR = 0.85, 95%CI = 0.49–1.47). Consistent with this, the meta-analysis of results adjusted for obesity similarly found no association between oligo-amenorrhea/menstrual irregularity and cerebrovascular disease/stroke (RR = 1.09, 95%CI:0.50–2.34, 3 studies[20,42,48]) and there was evidence of moderate statistical heterogeneity ($I^2 = 32.22\%$, $P = 0.102$) attributed to within-study variance (*Figure 3*).

Oligo-amenorrhea/menstrual irregularity and risk of other CVDs

No association between menstrual irregularity and angina was found by Azevedo *et al.*[28] (OR = 0.94, 95%CI:0.37–2.41). Okamoto *et al.*[40] did not find oligomenorrhea to be associated with SAH (OR = 0.84, 95% CI: 0.48–1.48). Although formal statistics were not performed, Salmoirago-Blotcher *et al.*[44] described an increased incidence of Takotsubo cardiomyopathy in women with menstrual irregularity (21% vs. 0%) or amenorrhea (3% vs. 0%).

Hyperandrogenism and risk of CVD outcomes

Nine studies including 13 532 participants explored the association between hyperandrogenism and risk of cardiovascular outcomes (see Supplementary material online, *Table SVIII*).[30,31,33,37,38,43,45–47] These included three cohort,[30,38,45] three case-control,[43,45–47] and three cross-sectional studies.[31,33,37] Due to the different means of assessing hyperandrogenism it was not possible to conduct meta-analyses. Outcomes evaluated included CVD, CHD, heart failure, MI, PAD, stroke, and VTE.

Hyperandrogenism and overall risk of CVD

Three studies[38,43,45] reported no elevated risk of CVD for women in the highest tertile or quartile of FAI levels. Nevertheless, Rexrode *et al.*[43] noted significantly higher risk of CVD across increasing quartiles of FAI ($P = 0.03$), a finding not reproduced by Schaffrath *et al.*[45] across increasing FAI tertiles ($P = 0.16$), and results were not significant in either study after adjusting for BMI/waist circumference ($P = 0.69$, $P = 0.24$, respectively).

Hyperandrogenism and risk of CHD

Five studies[30,31,33,37,38] examining CHD risk reported mixed results. Mansouri *et al.*[37] found androgenic alopecia was associated with CHD (RR = 1.26, 95%CI not given, $P = 0.01$). Comim *et al.*[31] found higher risk of CHD only in women with hirsutism and/or oligomenorrhea (OR = 1.9, 95%CI = 1.2–2.9) and not in women with eumenorrheic hirsutism (OR = 1.5, 95%CI = 0.9–2.4). Calderon-Margalit *et al.*[30] and Meun *et al.*[38] did not find higher risk of CHD in women with hyperandrogenism (Case: 0/211, Control: 7/665) or in women in the highest vs. middle FAI quartiles (OR = 1.04, 95%CI = 0.67–1.60), respectively. In results adjusted for obesity, Meun *et al.*[38] again found no association between being in the highest vs. middle quartiles of FAI and CHD (OR = 0.84, 95%CI = 0.54–1.32) even though Das *et al.*[33] reported women with CHD had higher FAI levels ($P < 0.01$).

Hyperandrogenism and risk of stroke

Two studies[31,38] examining hyperandrogenism and stroke found mixed results. Comim *et al.*[31] found increased stroke risk in women with hirsutism and/or oligomenorrhea (OR = 1.8, 95%CI = 1.04–3.0) but not in women with eumenorrheic hirsutism (OR = 1.3, 95%CI = 0.7–2.5). Meun *et al.*[38] found that women in the highest quartile of FAI were not at higher risk of stroke compared to women in the middle two quartiles, in analyses not adjusted for WHR (OR = 0.82, 95%CI = 0.57–1.17) and in analyses adjusted for WHR (OR = 0.75, 95%CI = 0.52–1.10).

Hyperandrogenism and risk of other CVDs

For other CVD outcomes, Mansouri *et al.*[37] found that androgenic alopecia was associated with MI (RR = 1.42, $P = 0.02$). Comim *et al.*[31] found a higher risk of heart failure in women with hirsutism and/or oligomenorrhea (OR = 2.2, 95%CI = 1.3–3.9) or eumenorrheic hirsutism (OR = 2.2, 95%CI:1.3–3.9), likely indicating that hirsutism in general is associated with heart failure. Meun *et al.*[38] did not find women in the highest quartile of FAI were at higher risk of PAD compared to women in the middle two quartiles in results with or without adjustment for WHR (without adjustment: OR = 0.99, 95%CI = 0.72–1.35; with adjustment: OR = 0.87, 95%CI:0.62–1.21). Seaman *et al.*[47] did not find acne associated with altered risk of VTE (RR = 0.95, 95%CI:0.72–1.24); similarly Scheres *et al.*[46] found that women in the highest quartile of FAI had no altered risk of VTE compared to women in the lowest FAI quartile in results without adjustment for BMI (OR = 0.9, 95%CI = 0.6-1.4), though a lower risk of VTE was observed in results adjusted for BMI (OR = 0.5, 95%CI:0.3–0.8).

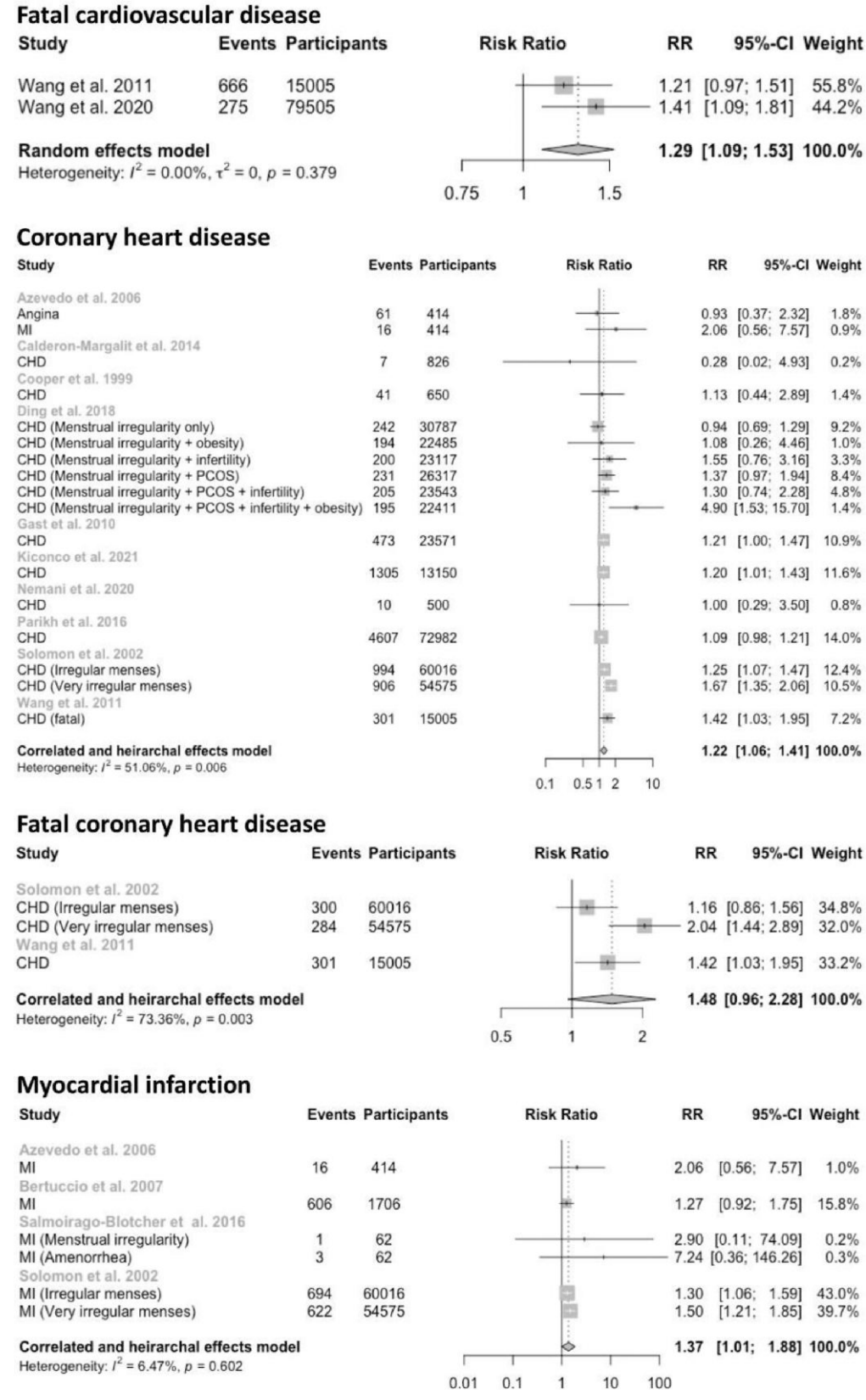


Figure 2 Forest plots showing the results for studies investigating the association between oligomenorrhea and cardiovascular outcomes/menstrual irregularity without adjustment for obesity.

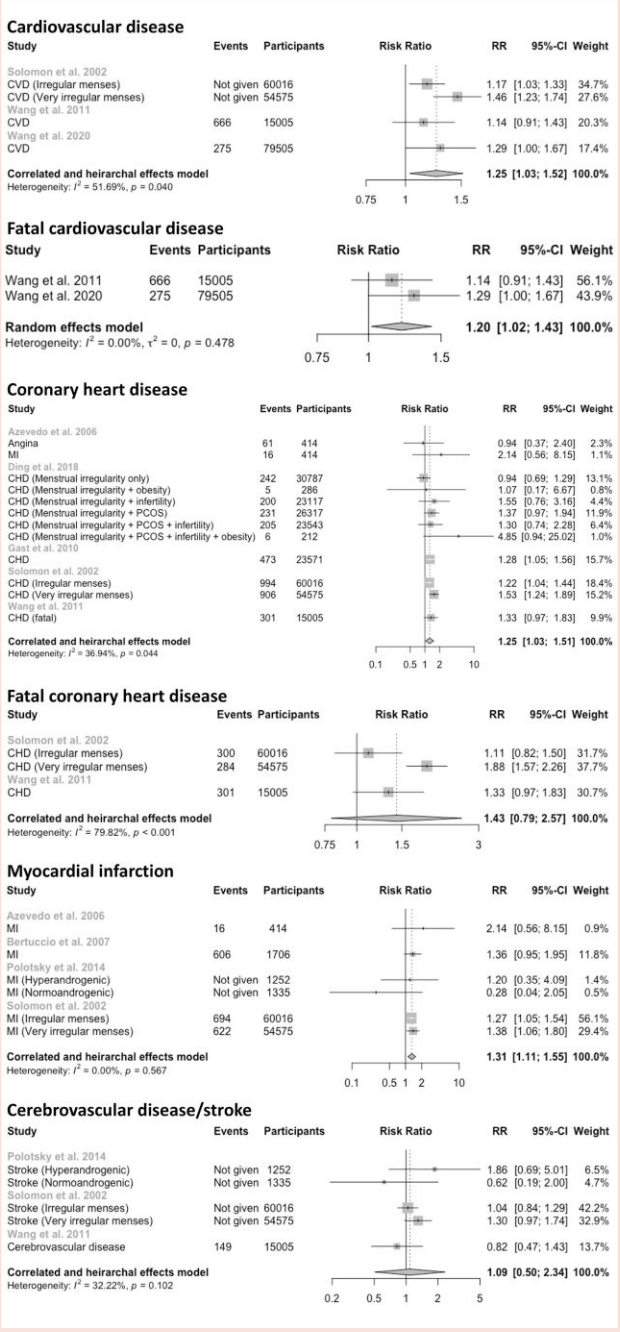


Figure 3 Forest plots showing the results for studies investigating the association between oligo-amenorrhea/menstrual irregularity and cardiovascular outcomes with adjustment for obesity.

Polycystic ovaries and risk of CVD outcomes

No studies were identified that looked at the association between polycystic ovaries and the risk of any CVD outcome.

Sensitivity analyses

To assess the consistency of the findings arising from statistical assumptions, sensitivity analyses were conducted.

Sensitivity analyses varying the within-study correlation parameter for correlated and hierarchal models were largely consistent with the exception of the meta-analysis for oligo-amenorrhea and MI without adjustment for obesity when the within-study correlation parameter approached 1 (see Supplementary material online, *Table SIX*). Meta-analyses rerun with the fixed-effects model instead of the basic random-effects model were broadly consistent (see Supplementary material online, *Table SIX*).

Most results were consistent when poor quality or case-control studies were excluded (see Supplementary material online, *Table SX*). Exceptions to this were the meta-analyses for oligo-amenorrhea/menstrual irregularity and MI where the pooled results were no longer significant after excluding poor quality studies. Examining the impact of including both Solomon *et al.*[20] and Wang *et al.*[21] ('companion' cohort studies) in the same meta-analysis, exclusion of Solomon *et al.*[20] from the obesity-adjusted CVD and oligomenorrhea/menstrual irregularity meta-analysis did not materially alter the results (RR = 1.20, 95% CI:1.02–1.43; $I^2 = 0.0\%$, $P = 0.478$). However, although exclusion of Wang *et al.*[21] did not alter the point estimate, results were no longer significant (RR = 1.25, 95%CI:0.59–2.64) with substantial statistical heterogeneity ($I^2 = 63.9\%$, $P = 0.018$) attributed to within-study variance of the results from Solomon *et al.*[20]

Small study effects/publication bias

The funnel plot for risk of CHD with oligo-amenorrhea/menstrual irregularity without adjustment for obesity was suggestive of possible asymmetry, however this was not confirmed by random variance estimation Egger test ($P = 0.353$). (see Supplementary material online, *Figure S2*).

Discussion

This systematic review found that women with oligo-amenorrhea/menstrual irregularity had a higher risk of CVD, CHD, and MI. The results for hyperandrogenism were mixed. To our knowledge, this is the first review to examine the contribution of individual PCOS components to risk of CVD, and it highlights how few studies have evaluated these components independently. This limited the conclusions that could be drawn, with no studies examining the CVD risk of having polycystic ovaries. This study also separately pooled risk estimates that adjusted for obesity and did not adjust for obesity separately to examine whether higher risk of CVD could be attributed to or mediated by obesity associated with PCOS and its components. The broadly consistent results regardless of whether obesity was adjusted for indicates that oligo-amenorrhea/menstrual irregularity confers increased risk of CVD, CHD, and MI independently of obesity.

The cardiometabolic risk associated with a PCOS diagnosis is understood to vary depending on the presence of different components and this has potentially important implications for long-term cardiovascular management of women with PCOS. PCOS has been classified into four phenotypes: (A) oligo-anovulation, hyperandrogenism and polycystic ovaries; (B) oligo-anovulation and hyperandrogenism (C); hyperandrogenism and polycystic ovaries; and (D) oligo-anovulation and polycystic ovaries.[5] Although all phenotypes appear to predispose elevated risk of CVD, phenotype C and especially phenotype D are thought to entail a milder cardiometabolic risk profile.[49]

It has previously been reported that hyperandrogenism may be a key risk factor for cardiometabolic dysfunction in PCOS.[50,51] Our review indicates that not all manifestations or measures of hyperandrogenism may be associated with CVD. On the other hand, oligo-amenorrhea/menstrual irregularity was associated with CVD, especially CHD development. The underlying mechanism driving this correlation likely relates in part to the association between oligo-amenorrhea/menstrual irregularity and hyperinsulinemia.[52]

Hyperinsulinemia and corresponding insulin resistance leads to poor cardiometabolic health including obesity, glucose intolerance, hypertension and hypertriglyceridemia, all risk factors of atherosclerosis and CVD.[52–54]

Critically, oligo-amenorrhea and hyperinsulinemia are also linked to hyperandrogenism.[52,55] This means that many women with oligo-anovulation symptoms have PCOS.[53] Individuals with PCOS, under the combined actions of hyperinsulinemia and hyperandrogenism, have an adverse cardiometabolic profile, including dyslipidaemia and metabolic syndrome which contributes to their risk of CVD.[2] Therefore, although not all manifestations of hyperandrogenism may be associated with CVD, symptoms of oligo-anovulation may be a specific indicator that hyperandrogenemia has reached a level where CVD risk is substantially increased. This is supported by our meta-analysis which found that that normoandrogenic oligo-amenorrhea is not associated with higher risk of CHD, as well as other literature that indicate phenotype C (ovulatory) PCOS involves less severe subclinical markers of CVD.[56]

Nevertheless, cardiovascular morbidity likely varies not only between different PCOS phenotypes, but also by age and between different types of CVD. In terms of changes to CVD risk across the lifespan, the adverse cardiometabolic profile caused by PCOS is thought to ameliorate after menopause.[57] Although the results of Wang *et al.*[21] indicate higher risk of fatal CVD with increased age, they examined only pre-menopausal women. Regarding varying risk by CVD subtype, Okoroh *et al.*[58] reported that although all phenotypes of PCOS were associated with higher risk of VTE, prevalence was lowest in phenotype B, which contrasts to the general perception for CVDs more generally that phenotype C is the least severe phenotype.[56]

It is important to also address that although PCOS is reported to be associated with cerebrovascular disease,[2] this was not observed for oligo-anovulation/menstrual irregularity in our review. Although it is not entirely clear why this discrepancy exists, there are several potential explanations. Firstly, PCOS involves additional components to oligo-anovulation and these components may drive the increased risk of stroke. Oligomenorrhea in particular can be associated with lower levels of oestrogen secretion, since oestrogen is mainly produced by the developing ovarian follicle.[59] Mixed evidence from randomised controlled trials of recently postmenopausal women indicate that oestrogen therapy could increase risk of stroke and be protective of CHD.[60,61] There may also be design differences in the studies which examine PCOS and the studies that examine oligo-anovulation/menstrual irregularity, with PCOS being a more severe condition more likely to be recalled in retrospective studies.

Strengths and weaknesses of the study

This study has multiple strengths including the large range of cardiovascular outcomes assessed, enabling a comprehensive picture of the relationship between different PCOS components and cardiovascular health. Compared to previous reviews,[2] the between-study heterogeneity in meta-analyses was also lower. There was also enough follow-up in a reasonable proportion of the studies (10 studies had more than 10 years of follow-up), which allowed the medium-term risk of CVD to be adequately assessed.

Nevertheless, our study has limitations. It is possible that relevant studies were not identified despite searching multiple databases without time or language restrictions and searching reference lists of previous reviews. Second, no studies were identified that assessed CVD risk associated with polycystic ovaries specifically. Third, due to the design of the included studies, it is possible some of the subjects with PCOS components will have diagnoses of other endocrine disorders. Outcome definitions may also have varied between studies because of the different methods by which they were assessed. Similarly, the different methods by which hyperandrogenism was investigated precluded the quantitative synthesis of these results and made it difficult to draw firm conclusions. On the other hand, similarities in the design and population profiles of the 'companion' cohort studies, Solomon *et al.*[20] and Wang *et al.*[21], could have biased the obesity-adjusted result for risk of CVD in individuals with oligo-amenorrhea/menstrual irregularity since both studies were included in this meta-analysis. However, the results were still significant despite the exclusion of Solomon *et al.*[20] which indicates the results are robust; the non-significance of the results after the exclusion of Wang *et al.*[21] is likely a reflection of the high within-study variance of the results from Solomon *et al.*[20] which analysed irregular and very irregular menses separately. Finally, sixteen studies were judged to be of poor quality, although removal of poor-quality studies had little impact on the findings, and the quality of evidence as assessed by the GRADE criteria was low to very low.

Implications for clinical practice

Given the links between PCOS and CVD, guidelines from the International PCOS Network, endorsed by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, recommend screening for cardiometabolic risk factors including obesity and hypertension in women with PCOS.[5] It is however still unclear if it would be more effective for screening to be tailored to specific PCOS phenotypes based on their differing CVD risk profiles and how this might be approached. Nevertheless, before changes to existing guidelines can be recommended, dedicated studies are needed to assess the utility of altered screening practices, especially since reproductive factors associated with increased risk of CVD may not provide meaningful improvements to prediction of CVD later in life beyond that of conventional CVD predictors.[62]

Furthermore, for screening to be effective, it is important for there to be effective interventions to reduce CVD risk. Although the combined oral contraceptive pill is often used as a first-line treatment for PCOS, it may not deliver the desired improvements in cardiometabolic profile.[5,63] One potential route is to utilise interventions that specifically decrease cardiometabolic risk factors, such metformin and lifestyle modifications.[5,63] However additional approaches, such as exploring the use of androgen antagonists,[63] may also be worthwhile for hyperandrogenic PCOS phenotypes considering our meta-analyses show that CVD risk in oligo-amenorrhea/menstrual irregularity appears to be independent of some of the traditional CVD risk factors such as obesity.

Unanswered questions and future research

Future studies should explore the contribution of polycystic ovaries to CVD risk in women with and without PCOS. More clarification is also warranted for how different manifestations of hyperandrogenism may be linked to cardiometabolic risk, including whether there may be a threshold of biochemical hyperandrogenemia that represents higher risk of CVD.

In conclusion, our review found that women with oligo-amenorrhea or irregular menses are at higher risk of CVD, CHD, and MI, independent of obesity. Women with oligo-amenorrhea or irregular menses should be investigated for PCOS and made aware of these higher risks. They may also benefit from counselling to provide strategies to reduce their CVD risk.

Lead author biography

Andre Lo is a medical student at the University of Cambridge. He has a passion for public health and epidemiology, and is pursuing a Masters in Biostatistics at the University of Sydney. Currently his research centres around the wider comorbidities of reproductive health.

Data availability

The data used in this article can be found in the *supplementary material*.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Authors' contribution

All authors participated in the design of the study as well as literature searching and screening. ACQL and CCWL extracted the data. ACQL analysed the data. ACQL and COW interpreted the results. All authors wrote, revised and approved the final version of the manuscript.

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