Review / Derleme

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Risk of cardiovascular and cerebrovascular events in polycystic ovarian syndrome women: An updated meta-analysis of cohort studies

Polikistik over sendromlu kadınlarda kardiyovasküler ve serebrovasküler olay riski: Kohort çalışmalarının güncellenmiş meta-analizi

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Abstract

Polycystic ovary syndrome (PCOS), affecting 5-10% of reproductive-aged women, is linked to metabolic disturbances such as insulin resistance, obesity, and lipid imbalance, which may elevate cardiovascular disease (CVD) risk. The relationship between PCOS and clinical cardiovascular events remains unclear. This meta-analysis evaluates the association between PCOS and cardiovascular and cerebrovascular events, including myocardial infarction (MI), stroke, ischemic heart disease (IHD), and overall CVD. We conducted a systematic review and meta-analysis of observational cohort studies published up to August 2024. Studies investigating the association between PCOS and cardiovascular or cerebrovascular events were included. Hazard ratios (HR) were used to assess mortality risk, while odds ratios (OR) evaluated CVD incidence. Statistical analyses were performed using STATA software, with publication bias assessed via funnel plots. Nineteen cohort studies, involving 1,222,912 participants, were analyzed. Women with PCOS had a significantly higher risk of stroke [OR: 1.89, 95% confidence interval (CI): 1.22-2.55]. However, no significant associations were found between PCOS and overall CVD (HR: 1.80, 95% CI: 5.43-9.04), MI (HR: 2.68, 95% CI: 0.69-4.82), or IHD (HR: 2.68, 95% CI: 0.69-4.67). Additionally, there was no significant increase in cardiovascular or all-cause mortality. This meta-analysis highlights that women with PCOS are at an increased risk of stroke, but no conclusive evidence links PCOS to other cardiovascular outcomes or mortality. Clinicians should prioritize stroke prevention in this population. Further large-scale, long-term studies are needed to clarify the cardiovascular risks associated with PCOS.

Keywords: Polycystic ovary syndrome, cardiovascular diseases, cerebrovascular disorders, meta-analysis

Öz

Üreme çağındaki kadınların %5-10'unu etkileyen polikistik over sendromu (PKOS), insülin direnci, obezite ve lipid dengesizliği gibi metabolik bozukluklarla bağlantılıdır ve bu da kardiyovasküler hastalık (KVH) riskini artırabilir. PKOS ile klinik kardiyovasküler olaylar arasındaki ilişki henüz net değildir. Bu meta-analiz, PKOS ile miyokard enfarktüsü (MI), inme, iskemik kalp hastalığı (İKH) ve genel KVH dahil olmak üzere kardiyovasküler ve serebrovasküler olaylar arasındaki ilişkiyi değerlendirmektedir. Ağustos 2024'e kadar yayınlanmış gözlemsel kohort çalışmalarının sistematik bir incelemesini ve meta-analizini gerçekleştirdik. PKOS ile kardiyovasküler veya serebrovasküler olaylar arasındaki ilişkiyi araştıran çalışmalar dahil edildi. Tehlike oranları (HR) ölüm riskini

PRECIS: Women with polycystic ovary syndrome (PCOS) have a significantly higher risk of stroke but no conclusive evidence links PCOS to other cardiovascular events or mortality.

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değerlendirmek için kullanılırken, olasılık oranları (OR) KVH insidansını değerlendirdi. İstatistiksel analizler STATA yazılımı kullanılarak gerçekleştirildi ve yayında taraf tutma huni grafikleri aracılığıyla değerlendirildi. Bu meta-analizde 1.222.912 katılımcıyı içeren on dokuz kohort çalışması analiz edildi. PKOS'lu kadınlarda inme riski önemli ölçüde daha yüksekti [OR: 1,89, %95 güven aralığı (GA): 1,22-2,55]. Ancak PKOS ile genel KVH (HR: 1,80, %95 GA: 5,43-9,04), MI (HR: 2,68, %95 GA: 0,69-4,82) veya İKH (HR: 2,68, %95 GA: 0,69-4,67) arasında önemli bir ilişki bulunamadı. Ek olarak, kardiyovasküler veya tüm nedenlere bağlı ölüm oranında önemli bir artış olmadı. Bu meta-analiz, PKOS'li kadınların inme geçirme riskinin arttığını vurgulamaktadır, ancak PKOS'yi diğer kardiyovasküler sonuçlar veya ölüm oranıyla ilişkilendiren kesin bir kanıt yoktur. Klinisyenler bu popülasyonda inmeyi önlemeyi önceliklendirmelidir. PKOS ile ilişkili kardiyovasküler riskleri açıklığa kavuşturmak için daha fazla büyük ölçekli, uzun vadeli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Polikistik over sendromu, kardiyovasküler hastalıklar, serebrovasküler bozukluklar, meta-analiz

Introduction

An endocrine condition, known as polycystic ovarian syndrome (PCOS), affects 5-10% of women who are of reproductive age and is characterized by common phenotypic and clinical symptoms[1,2]. It is brought on by insulin resistance (IR), follicular dysplasia, and hyperandrogenism, which collectively contribute to manifestations such as obesity, infertility, irregular menstruation, and hyperandrogenemia[3,4]. Metabolic disturbances are common in PCOS patients and are easily associated with other metabolic synthesis disorders, obesity, hypertension, diabetes, and disorders of lipid metabolism[5]. Therefore, there is a considerable rise in the risk of cardiovascular disease (CVD) in PCOS patients due to the increased risk of atherosclerosis, as indicated in citation[6].

Since PCOS frequently exhibits IR, altered glucose regulation, dyslipidemia, high blood pressure (BP), and obesity as early as young adulthood or even childhood, women with PCOS are exposed to conventional cardiovascular risk factors over an extended period. Nevertheless, data regarding the relationship between the presence of numerous CVD risk factors and an increased risk of CVD events in PCOS-affected women are inconsistent[7,8]. These discrepancies may stem from variations in the diagnostic criteria for PCOS, differences in metabolic profiles, definitions of cardiovascular outcomes, or methodological limitations such as small sample sizes and study design differences. Notably, individuals meeting the National Institutes of Health (NIH) criteria for PCOS tend to exhibit more severe metabolic disturbances and may carry a greater cardiovascular risk than those diagnosed under the broader Rotterdam criteria. We also are not certain if women who have phenotypes C and D, which are non-NIH PCOS phenotypes, are more likely to experience CVD events[9].

The correlation between PCOS and a higher long-term risk of CVD events is still up for debate, despite mounting data linking PCOS to CVD risk factors. It is unclear if established risk factors mitigate the relationship between PCOS and CVD, or if PCOS is a separate risk factor[10]. Notably, many participants in earlier studies were overweight or obese, highlighting the substantial impact of excess weight on conventional cardiovascular risk markers[11]. Some previous meta-analyses have suggested an increased incidence of cardiovascular outcomes-such as coronary artery disease and cerebrovascular conditions-among women with PCOS[12]. Women from East Asian populations with PCOS tend to have a lower average body mass index (BMI) and milder signs of androgen excess than their Western counterparts[13]. It is unclear how East Asian women with PCOS, particularly those who are not obese, would fare in terms of long-term CVD risk. However, this meta-analysis aimed to assess the relationship between PCOS and the risks of CVD in women.

Materials and Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42024625702.

Search Strategy

We followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA-P). We extracted eligible studies from PubMed, Scopus, and Google Scholar databases published in English up to August 2024. The searched keywords included "polycystic ovary syndrome," "PCOS," "sclerocystic ovarian degeneration," "Stein-Leventhal syndrome," "cardiovascular diseases," "myocardial infarction," "coronary heart disease," "cardiovascular stroke," "myocardial infarct," "heart attack," "ischemic heart disease," "myocardial ischemia," "stroke," "cerebrovascular accident," and "apoplexy." Our search strategy is summarized in Table 1.

Inclusion and Exclusion Criteria

Observational studies investigating the association between PCOS and cardiovascular and cerebrovascular diseases were included. Editorials, conference abstracts, reviews, commentaries, and interventional studies were excluded. Animal studies, as well as non-English articles, were also excluded. Cardiovascular outcomes assessed encompassed both clinical and subclinical disease measures, including incidence, prevalence, and mortality. Cardiovascular-related deaths were defined as those caused by sudden cardiac arrest, acute myocardial infarction, advanced heart failure, peripheral arterial disease, or stroke (Table 2).

Data Collection and Quality Assessment

Two independent reviewers extracted the data using a consistent and standardized approach. Any disagreements were settled through discussion with a third reviewer. Extracted data included information such as the first author's name, year of publication, study location, average participant age, sample size, follow-up period, type of study, diagnostic criteria for PCOS, and any confounding variables adjusted for.

Table 1. Search strategy of PubMed and Scopus databases

Database	Search strategy	Search date	Results
Scopus	(TITLE-ABS-KEY (polycystic AND ovary AND syndrome) OR TITLE-ABS-KEY (pcos) OR TITLE-ABS-KEY (stein-leventhal AND syndrome) OR TITLE-ABS-KEY (sclerocystic AND ovarian AND degeneration)) AND (TITLE-ABS-KEY (mortality) OR TITLE-ABS-KEY (cardiovascular AND death) OR TITLE-ABS-KEY (cardiovascular AND diseases) OR TITLE-ABS-KEY (cvd) OR TITLE-ABS-KEY (coronary AND heart AND disease) OR TITLE-ABS-KEY (myocardial AND infarction) OR TITLE-ABS-KEY (myocardial AND infarct) OR TITLE-ABS-KEY (cardiovascular AND stroke) OR TITLE-ABS-KEY (heart AND attack) OR TITLE-ABS-KEY (myocardial AND ischemia) OR TITLE-ABS-KEY (stroke) OR TITLE-ABS-KEY (cerebrovascular) OR TITLE-ABS-KEY (apoplexy)) AND (LIMIT-TO (LANGUAGE , "English"))	8 August	3908
Pubmed	("cerebrovascular"[Title/Abstracts] OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[Title/Abstracts] AND "system"[Title/Abstracts]) OR "cardiovascular system"[Title/Abstracts] OR "cardiovascular"[Title/Abstracts] OR "cardiovasculars"[Title/Abstracts])) AND ("polycystic ovary syndrome"[MeSH Terms] OR ("polycystic"[Title/Abstracts] AND "ovary"[Title/Abstracts] AND "syndrome"[Title/Abstracts]) OR "polycystic ovary syndrome"[Title/Abstracts])	8 August	1850

We also recorded outcomes such as cardiovascular and all-cause mortality, overall cardiovascular disease, ischemic heart disease, myocardial infarction, and stroke. The methodological quality of included studies was evaluated using the Joanna Briggs Institute critical appraisal checklist (available at https://jbi.global/critical-appraisal-tools), as summarized in Table 3.

Data Analysis

Hazard ratios (HR) with 95% confidence intervals (CI) were used to assess mortality risk, while odds ratios (OR) with 95% CI were applied to cardiovascular and cerebrovascular event rates, respectively. Heterogeneity across studies was evaluated using the I^2 statistic derived from chi-squared tests. Publication bias was visually assessed using funnel plots. All statistical analyses were conducted using STATA software, version 14.

Results

Study Selection

A total of 5,708 studies were found through PubMed and Scopus. After removing 3,433 duplicates, an additional 2,224 were excluded based on their titles and abstracts for not meeting the criteria. This left 51 studies for full-text review, and finally, 19 cohort studies with 1,222,912 participants were included (Figure 1).

Included Studies

Table 2 summarizes the characteristics of the included studies. The majority were conducted in in the United Kingdom (n=4)[7,14,15], with additional studies from Sweden (n=3)[16-18], USA (n=3)[19-21], Denmark (n=2)[22,23], and single studies from Australia[24], Norway[25], the Netherlands[26], Taiwan[27], Iran[28], Finland[29], and Korea[30]. Most studies followed a cohort design, including 12 prospective and 7 retrospective cohort studies. Assessment of study quality is detailed in Table 2. PCOS diagnosis varied, with the Rotterdam criteria (n=6)[9,17-19,22,28] and International Classification of Diseases (ICD) codes (n=6)[7,22-24,27,29] being the most frequently used methods. Other diagnostic approaches included the NIH criteria (n=2)[9,21], histopathological evaluation, laparoscopic criteria, self-reported characteristics, and androgen excess (n=2)[20,26].

Follow-up durations ranged from 3.83 years to 32 years, and the mean or median age at follow-up spanned from 25 to 81 years. Outcomes assessed included myocardial infarction (MI), cerebrovascular events (stroke or transient ischemic attack), composite CVD outcomes, ischemic heart disease, large-vessel disease, and major adverse cardiovascular events. Data collection methods included questionnaires, medical records, health insurance databases, clinical examinations, and registry records. Most studies adjusted for factors such as age, BMI, and metabolic conditions like diabetes and hypertension.

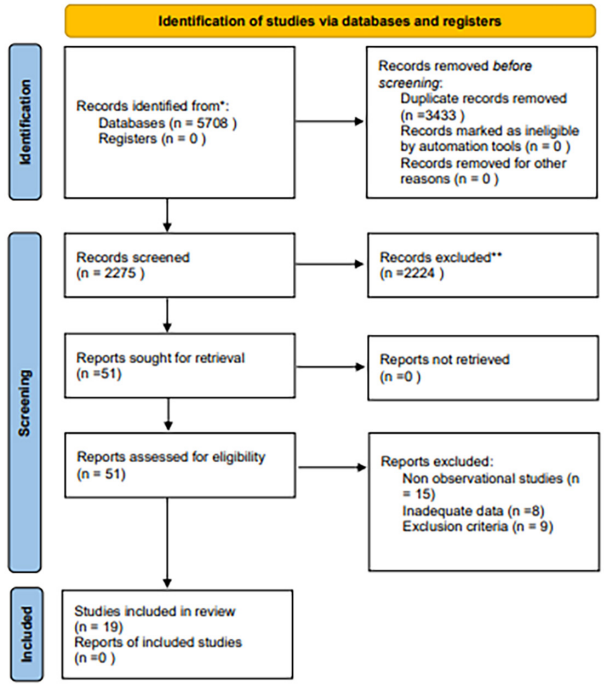

Figure 1. Preferred reporting items for systematic review and meta-analysis flow diagram for current systematic review

Table 2. Overview of included studies

Study	Study type	Population source (country)	Sample size (PCOS/control)	Follow-up duration	Mean age at follow-up	Exposure (definition)	Outcome (definition)	Method of data collection	Covariates controlled for
Dahlgren et al.[16] 1992	Prospective cohort	Sweden	33/132	12 y	PCOS; 45.9 (40-61), age matched controls	Histopathological characteristics	Myocardial infarction	Questionnaire, venous blood sampling	NR
Wild et al.[14] 2000	Prospective cohort	UK	319/106	31 (15-47) y since diagnosis of PCOS	56.7 (38-98) y, control; 56.7 (38-98) y	Laparoscopic criteria	Cardiovascular endpoints were grouped as composite CVD events, encompassing MI, angina, revascularization procedures, and abnormal treadmill test findings. Cerebrovascular disease outcomes included stroke and TIA)	ICD, patient-reported	Controlled for BMI
Lunde and Tanbo[25] 2007	Prospective cohort	Norway	131/723	15-20 y	NR	Ultrasound examination, with histological examination and two or more of the symptoms	Myocardial infarction, stroke	Patient-reported and checked with the reports from the hospitals	NR
Schmidt et al.[18] 2011	Prospective cohort	Sweden	25/68	21 y	PCOS; 70.4±5.0 y, control; 70.7±5.6 y	Rotterdam	Stroke, MI, cardiovascular disease (including MI and stroke), mortality due to MI	ICD	NR
Iftikhar et al.[19] 2012	Retrospective cohort	USA	309/343	23.7±13.7	PCOS; 46.7	Rotterdam	MI, angina, stroke, CABG, composite CVD (MI, angina, stroke, CABG), CVD deaths	Patient-reported or official mortality records	Controlled for age at final assessment, BMI, use of fertility treatments, prior diagnosis of hypertension, postmenopausal hormone therapy exposure, and relevant familial medical history

Table 2. Continued

Study	Study type	Population source (country)	Sample size (PCOS/control)	Follow-up duration	Mean age at follow-up	Exposure (definition)	Outcome (definition)	Method of data collection	Covariates controlled for
Morgan et al.[15] 2012	Retrospective cohort	UK	21,734/ 86,936	PCOS; 4.7y (median) Controls; 5.8y (median)	27.1±7.1 both PCOS and control	Medical records	Large-vessel pathology: initial occurrence of myocardial infarction, stroke, angina, or any form of central or peripheral revascularization	Medical records	Controlled for age frequency of general practitioner visits, BMI, and the year of condition diagnosis.
Mani et al.[8] 2013	Prospective cohort	UK	2301/ local and national population	5.2±5.1	36.3±10.0	AEPCOS	Cerebrovascular accident cardiovascular death, MI, angina, heart failure, composite CVD outcome	Hospital records	Controlled for BMI, age, hypertension, and diabetes
Calderon-Margalit et al.[20] 2014	Prospective cohort	USA	55/668	20 y	45.4±3.44; 45.4±3.57	Oligomenorrhea (self-report), hyperandrogenism (self-reported hirsutism, 95th percentile testosterone levels)	Ischemic heart disease (self-report)	Questionnaire, stored serum samples	controlled for age, racial background, level of formal education, tobacco use, menopausal stage, BMI, systolic blood pressure, log-transformed triglyceride levels, and insulin resistance as measured by HOMA-IR
Glintborg et al.[22] 2015	Prospective cohort	Denmark	19,199/57,483	17 y	OUH: PCOS; 29.3±8.5, Denmark: PCOS; 30.6±9.6, control; 30.6±9.6	Rotterdam Criteria/ ICD-10	Cardiovascular disease, Myocardial infarction, Stroke	Medical history, clinical examination, transvaginal ultrasound, and fasting blood samples	NR
Hart and Doherty[24] 2015	Retrospective cohort	Australia	2566/25,660	22 y	35.8 years (range: 16.6-47.0 y) for both groups	ICD-10 or ICD-9	Cerebrovascular conditions, ischemic heart disease.	ICD-10	Controlled for age, BMI
Merz et al.[21] 2016	Prospective cohort	USA	25/27	10 y	62.6±11.6, control; 64.8±9.6	NIH	CAD, Composite CVD (including MI, stroke, and cardiovascular death), CVD death (including sudden cardiac deaths, CHF, MI, PAD, and stroke)	Angiogram results, official mortality records, family-provided data, and clinical documentation	Controlled for DM, waist circumference, hypertension, and angiographic CAD

Table 2. Continued

Study	Study type	Population source (country)	Sample size (PCOS/control)	Follow-up duration	Mean age at follow-up	Exposure (definition)	Outcome (definition)	Method of data collection	Covariates controlled for
Meun et al.[26] 2018	Prospective cohort	Netherlands	106/171	11.36 y (median)	69.57±8.72, control; 69.20±8.60	High FAI (highest quartile vs middle two)	PAD, CHD, stroke, CVD (medical notes)	Interview, examinations, medical notes	Controlled for age, WHR, time passed since menopause, cohort classification, lipid profile (total and HDL cholesterol), smoking behavior, systolic blood pressure, use of antihypertensive therapy, diabetes status, and hormone therapy usage.
Ding et al.[27] 2018	Retrospective cohort	Taiwan	8,048/32,192	5.9 y (median)	28.11 y	ICD-9	Coronary artery disease (ICD-9-CM)	Health insurance database	Controlled for age, obesity status, history of DM, hypertension, lipid disorders, atrial fibrillation, chronic renal impairment, and evidence of arterial plaque formation.
Oliver-Williams et al.[23] 2021	Retrospective cohort	Denmark	6,149/54,426	8.9 y	32.9 (29.7-36.5)	ICD-10	Cardiovascular disease (ICD-10), death	Registry records	Controlled for age, timing of initial ART intervention, parity at study entry, presence of gestational diabetes, marital or relationship status, and educational background.
Berni et al.[7] 2021	Retrospective cohort study	UK	174,660/174,660	PCOS; 3.83 (1.89-7.78)/ control; 3.00 (1.37-6.36)	29 (24.00-34.00)	ICD-10	Time to significant adverse cardiovascular event (MACE), comprising MI, stroke, angina, revascularization procedures, and cardiovascular mortality.	Patient electronic healthcare records (EHR) recovered regularly in primary care	Controlled for age, BMI classification, tobacco and alcohol use, presence of T2DM, overall baseline comorbidity burden as quantified by the Charlson Comorbidity Index, systolic and diastolic blood pressure, and socioeconomic status using the Index of Multiple Deprivation (IMD) quintiles)

Table 2. Continued

Study	Study type	Population source (country)	Sample size (PCOS/control)	Follow-up duration	Mean age at follow-up	Exposure (definition)	Outcome (definition)	Method of data collection	Covariates controlled for
Forslund et al.[17] 2022	Prospective cohort with cross-sectional analysis	Sweden	35/99	32 y	81 y	Rotterdam criteria	All-cause mortality, CVD-related mortality, all CVD, Myocardial infarction, Stroke/TIA	Patients' medical records, registry records	NR
Mahboobifard et al.[28] 2022	Prospective cohort with longitudinal analysis	Iran	356/1235	15.4 y	29.7±6.8 (PCOS) 31.1±7.6 (control)	Rotterdam criteria	Prevalence and incidence: CVD (including stroke, MI, angina, angiographic evidence), silent CVD (indicated by potential and probable ECG changes)	Patient-reported and confirmed by medical interview and documents	Controlled for age, BMI, smoking habit, hypertension, DM, and lipid profile
Ollila et al.[9] 2023	Prospective, population-based cohort study	Northern Finland	NIH-PCOS (144)/Non-NIH (2,051) Rotterdam-PCOS (386)/ non-Rotterdam (1518)	22 y	From 31 to 53	National Institute of Health (NIH) criteria (n=144) or the Rotterdam criteria (n=386)	Major adverse cardiovascular events (MACE), including myocardial infarction (MI), stroke, heart failure and cardiovascular mortality	Comprehensive questionnaires and clinical examinations	Controlled for BMI
Ryu et al.[29] 2024	Retrospective matched cohort study	Korea	137,416/412,118	4.0 y (PCOS) 4.5 y (Control)	30.4±5.5	ICD-10	Ischemic heart disease, cerebrovascular diseases, combined cardiocerebrovascular diseases	Health insurance claims	Controlled for age, BMI, prior diagnoses of diabetes, hypertension, and lipid disorders, as well as lifestyle factors including physical activity, alcohol intake, and smoking status. Blood pressure (systolic/diastolic), total cholesterol, and triglyceride concentrations were also included

Mean (range), Mean ± SD

PCOS: Polycystic ovary syndrome, CVD: Cardiovascular disease, MI: Myocardial infarction, TIA: Transient ischemic attack, MACE: Major adverse cardiovascular event, CAD: Coronary artery disease, CABG: Coronary Artery bypass grafting, FAI: Free androgen index, ICD: International classification of diseases, SBP: Systolic blood pressure, TG: Triglycerides, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WHR: Waist-to-hip ratio, NR: Not reported, BMI: Body mass index, DM: Diabetes mellitus, CHF: Congestive heart failure, OUH: Odense University Hospital, SD: Standard deviation

Table 3. Quality assessment of included studies

Study	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilized?	Was appropriate statistical analysis used?
Dahlgren et al.[16] 1992	✓	✓	✓	×	×	✓	×	✓	✓	NA	✓
Wild et al.[14] 2000	✓	✓	✓	Unclear	×	✓	✓	✓	✓	NA	✓
Lunde and Tanbo[25] 2007	✓	✓	✓	×	×	✓	✓	✓	✓	NA	✓
Schmidt et al.[18] 2011	✓	✓	✓	×	×	✓	✓	✓	✓	NA	✓
Iftikhar et al.[19] 2012	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Morgan et al.[15] 2012	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Mani et al.[8] 2013	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Calderon-Margalit et al.[20] 2014	✓	✓	×	✓	✓	✓	×	✓	✓	NA	✓
Glintborg et al.[23] 2015	✓	✓	✓	×	×	✓	✓	✓	✓	NA	✓
Hart and Doherty[24] 2015	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Merz et al.[21] 2016	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Meun et al.[26] 2018	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Ding et al.[27] 2018	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓

Table 3. Continued

Study	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilized?	Was appropriate statistical analysis used?
Oliver-Williams et al.[23] 2021	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Berni et al.[7] 2021	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Forslund et al.[17] 2022	✓	✓	✓	×	×	✓	✓	✓	✓	NA	✓
Mahboobifard et al.[28] 2022	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Ollila et al.[9] 2023	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓
Ryu et al.[29] 2024	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓

All-Cause Mortality

Seven studies evaluated the risk of all-cause mortality in PCOS versus non-PCOS groups. No significant difference in risk was observed between the two groups (HR: 0.98, 95% CI: 0.80-1.15, I^2=0%) in a random-effects model (Figure 2).

Cardiovascular Death

Five studies assessed the risk of cardiovascular death. Similarly, there was no significant change in risk for the PCOS group compared to the non-PCOS group (HR: 1.75, 95% CI: -2.20-5.71, I^2=38.4%) in a random-effects model (Figure 3).

Any CVD

Nineteen studies evaluated the risk of any CVD. Patients with PCOS did not have a significantly higher risk compared to those without PCOS (HR: 1.80, 95% CI: -5.43-9.04, I^2=0%) in a random-effects model (Figure 4).

Myocardial Infarction

Twelve studies investigated the risk of MI. There was no significant difference between the PCOS and non-PCOS groups (HR: 2.68, 95% CI: 0.69-4.82, p=0.003; I^2=82%, p<0.00001) in a random-effects model (Figure 5).

Ischemic Heart Disease

Seven studies evaluated ischemic heart disease outcomes. The analysis showed no significant increase in risk for patients with PCOS compared to controls (HR: 2.68, 95% CI: 0.69-4.67, I^2=99.8%) in a random-effects model, Figure 6).

Stroke

Eleven studies assessed the risk of stroke. Unlike other outcomes, PCOS was associated with a significantly increased risk of stroke (OR: 1.89, 95% CI: 1.22-2.55, I^2=97.7%) in a random-effects model (Figure 7).

Publication Bias

Publication bias for CVD death risk was assessed using Egger's regression test, Begg's test, and funnel plot analysis. While Begg's test indicated no bias (p=1.00), Egger's regression test and the funnel plot (Figure 8) revealed evidence of publication bias (p=0.01).

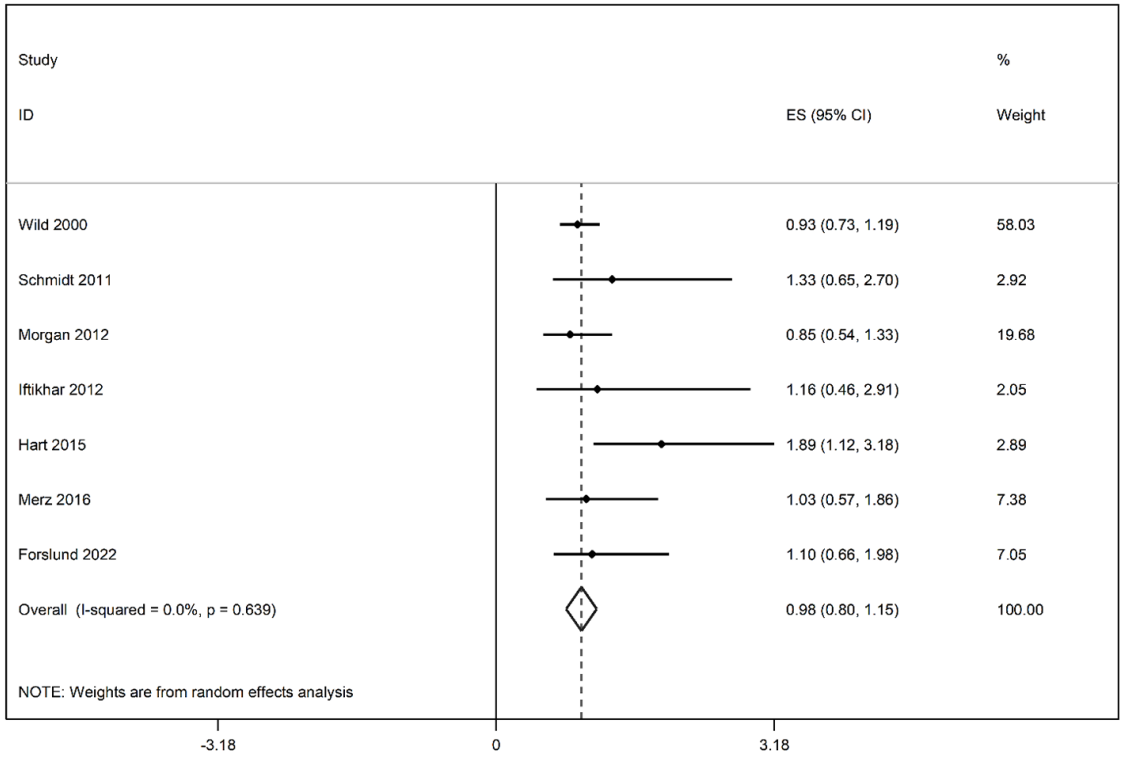

Figure 2. Forest plot for all-cause mortality

CI: Confidence interval

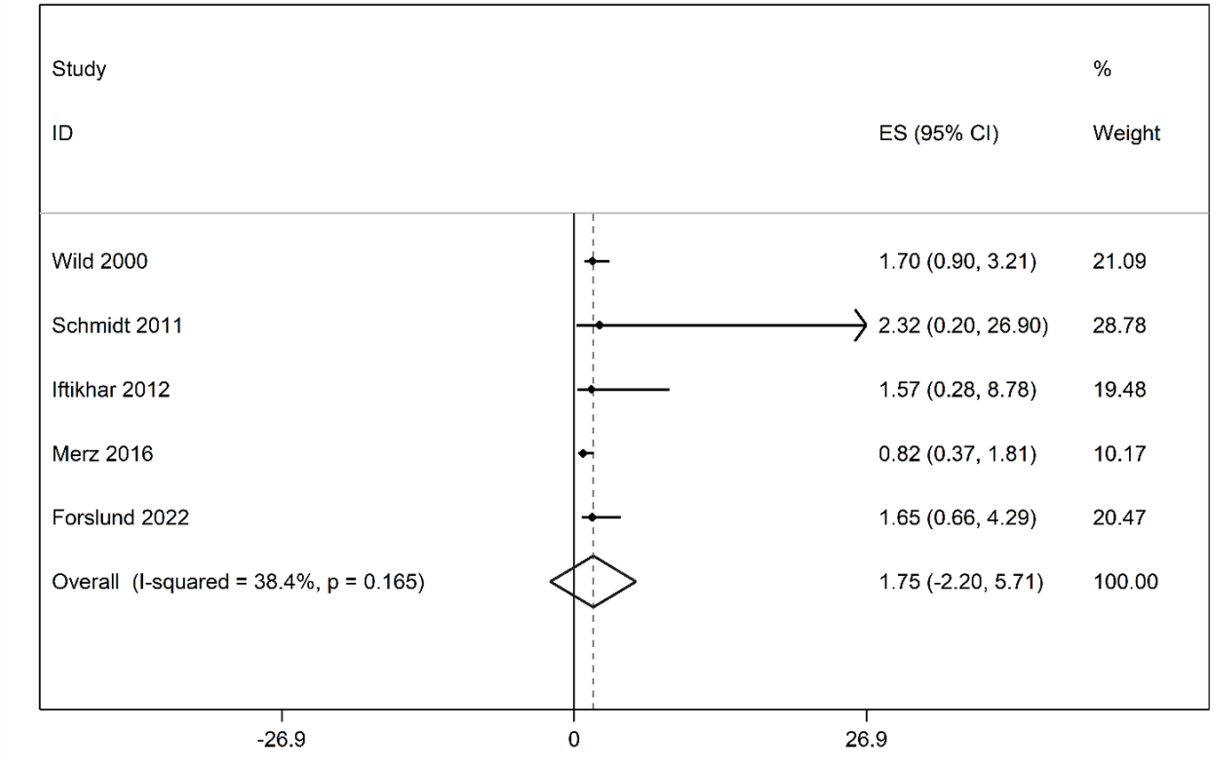

Figure 3. Forest plot for CVD death

CVD: Cardiovascular disease, CI: Confidence interval

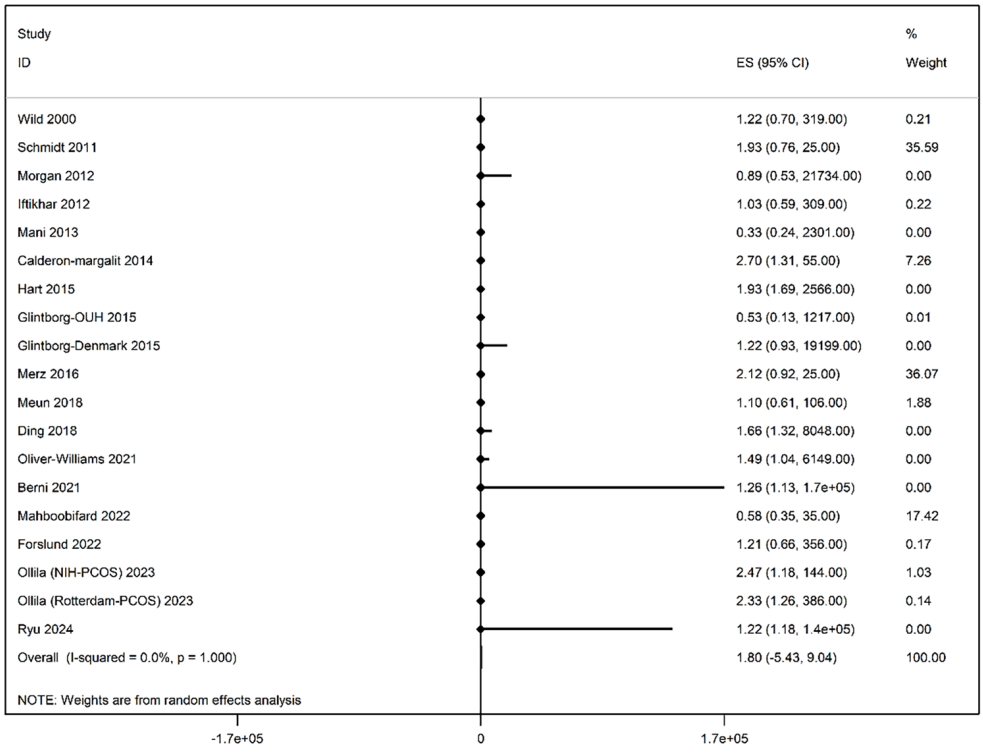

Figure 4. Forest plot for any CVD

CVD: Cardiovascular disease, CI: Confidence interval

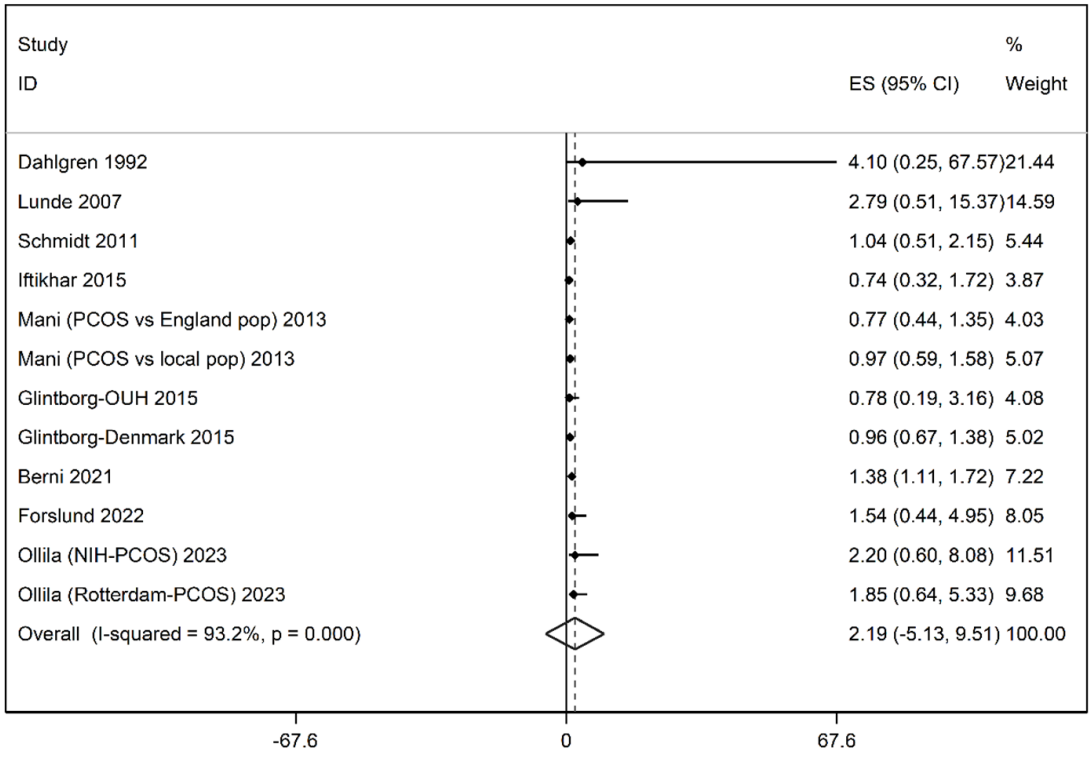

Figure 5. Forest plot for MI

MI: Myocardial infarction, CI: Confidence interval

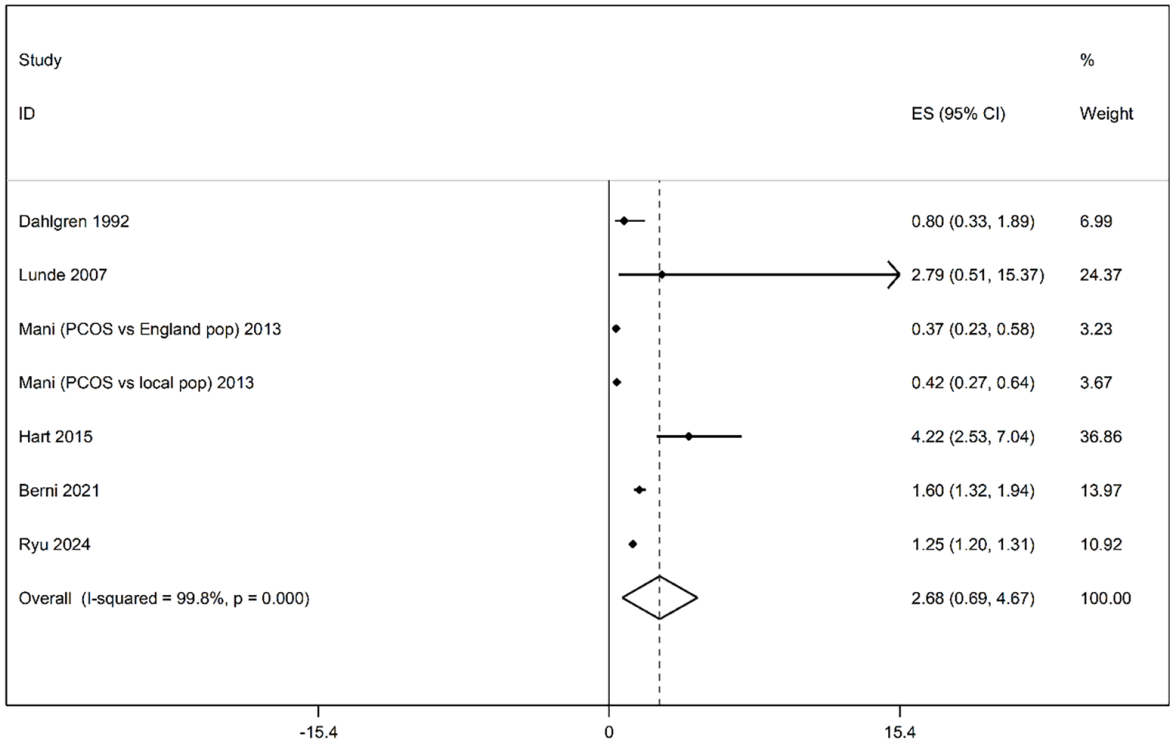

Figure 6. Forest plot for IHD

IHD: Ischemic heart disease, CI: Confidence interval

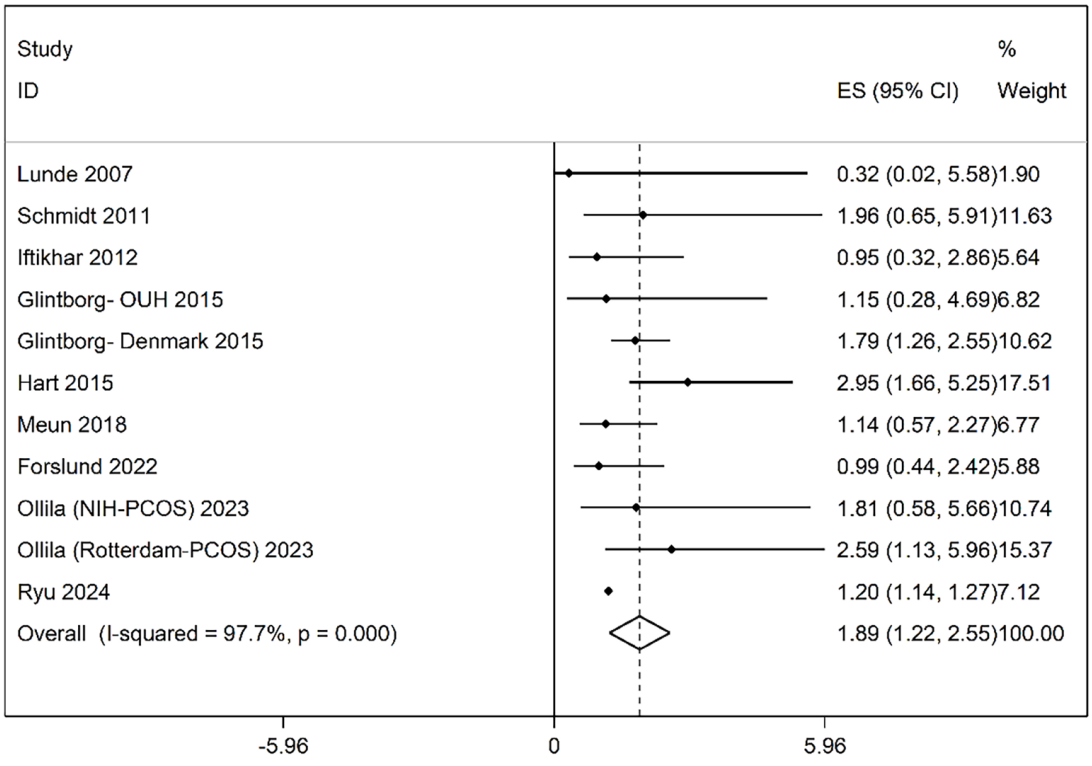

Figure 7. Forest plot for stroke

CI: Confidence interval

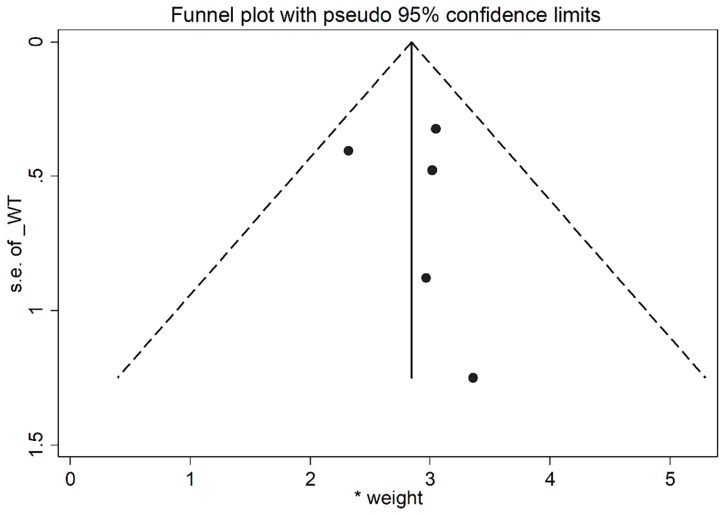

Figure 8. Funnel plot for IHD
IHD: Ischemic heart disease

Discussion

This meta-analysis investigated the relationship between PCOS and cardiovascular outcomes, including all-cause mortality, cardiovascular mortality, MI, IHD, stroke, and overall CVD. Our findings indicate that while women with PCOS are at an increased risk for stroke, no significant association was observed for other cardiovascular outcomes, underscoring the need for further investigation into the specific pathways underlying these risks.

The current body of evidence on the impact of PCOS on CVD risk remains inconsistent. Although multiple studies have linked PCOS with various cardiometabolic abnormalities such as diabetes[30], dyslipidemia[31,32], hypertension[31], and metabolic syndrome[30], the direct connection to clinical cardiovascular events is not yet clear. IR and hyperinsulinemia, both of which are common in PCOS, contribute to oxidative stress, vascular dysfunction, and reduced vascular compliance, all of which increase the risk of CVD[33]. Furthermore, PCOS leads to dysregulation of lipid metabolism, resulting in elevated levels of low-density lipoprotein and triglycerides and reduced high-density lipoprotein, which exacerbate the risk of atherosclerosis and dyslipidemia[34]. The presence of excess adipose tissue in women with PCOS also raises levels of inflammatory cytokines and leptin, further worsening IR and promoting hypertension[35]. Previous systematic reviews have presented mixed findings regarding the association between PCOS and cardiovascular outcomes. For instance, De Groot et al.[36] reported that women with PCOS had approximately twice the risk of developing coronary heart disease and experiencing strokes. A review by Millán-de-Meer et al.[32] showed the prevalence of cardiovascular outcomes in both premenopausal and postmenopausal women, displaying a notable increase in OR for MI and stroke, though no remarkable increase was observed for overall CVD or coronary artery disease. A 2020 meta-analysis by Ramezani Tehrani et al.[37] found that reproductive-aged women with PCOS had a significantly higher HR for clinical cardiovascular events. More recently, studies by Tay et al.[38] and Zhang et al.[39] have indicated an elevated risk of myocardial infarction, ischemic heart disease, and stroke in women with polycystic ovary syndrome. Despite these findings, neither study reported a significant association between PCOS and either all-cause or cardiovascular-specific mortality, highlighting the complexity of this relationship.

Several methodological limitations must be considered when interpreting these findings. Many of the studies included in this analysis had small sample sizes, short follow-up periods, and primarily focused on younger women, which may limit the generalizability of the results. Additionally, there was inconsistency in the diagnostic criteria for PCOS across studies, and the inclusion of different PCOS phenotypes introduced heterogeneity. Importantly, the cardiovascular impact of different PCOS phenotypes is not uniform. Women with oligo-amenorrhea or menstrual irregularities appear to be at a higher risk for CVD, likely due to the effects of hyperinsulinemia and IR. On the other hand, the evidence linking hyperandrogenism to cardiovascular outcomes remains mixed[40].

Age also appears to be an important factor influencing cardiovascular risk in women with PCOS[37]. Younger women tend to have higher cardiovascular risk due to factors such as central obesity, IR, and unfavorable lipid profiles[41,42]. However, these risks often decrease with age[43], as androgen excess and metabolic abnormalities tend to improve over time[44,45]. The wide age range of participants in many cohort studies could have obscured significant associations between PCOS and cardiovascular outcomes, especially among older women.

Geographic and socioeconomic disparities should also be considered when interpreting these findings. Recent evidence suggests that cardiovascular risks associated with PCOS may be more pronounced in East Asian and African populations, particularly in lower-income countries[46]. Variations in healthcare access, lifestyle, and socioeconomic conditions likely contribute to these differences[14].

Despite the high prevalence of metabolic abnormalities in women with PCOS, the risk of cardiovascular events is not uniformly elevated across all individuals. Several protective factors may contribute to a more favorable cardiovascular profile in some women with PCOS. For example, women with PCOS tend to experience delayed menopause, and earlier menarche, which may lead to an extended exposure to the cardio-protective effects of estrogen. Additionally, due to heightened awareness of PCOS, proactive management of cardiovascular risk factors may mitigate some of the cardiovascular risks[47,48].

Although the exact impact of PCOS on cardiovascular health remains unclear, existing guidelines recommend preventive measures due to the high prevalence of cardiometabolic issues among affected individuals. These guidelines suggest that weight should be tracked in a non-stigmatizing and supportive manner, and lipid profiles should be first assessed at diagnosis, and thereafter, periodically based on overall cardiovascular risk. BP should be measured once a year, and an oral glucose tolerance test should be conducted at the time of diagnosis, with follow-up tests up to three times per year or more frequently if there are elevated diabetes risk factors or if pregnancy is being planned or achieved[49,50].

In conclusion, while PCOS is associated with significant metabolic and vascular abnormalities, the clinical translation to cardiovascular events is complex and influenced by factors such as age, phenotype, geography, and proactive risk management. Future research should focus on phenotype-specific risks, long-term outcomes, and diverse populations to better clarify the cardiovascular implications of PCOS.

Strengths and Limitations

This meta-analysis has several strengths. It includes a large sample size of over one million women and examines a broad range of cardiovascular outcomes, providing a comprehensive view of the relationship between PCOS and cardiovascular health. The inclusion of longitudinal studies, many of which had follow-up periods of 10 years or more, adds reliability to the findings. However, several limitations need to be acknowledged. Despite searching multiple databases and reviewing reference lists of prior studies, some relevant studies may have been missed. There was significant variability in how cardiovascular outcomes and study designs were defined across the included studies. Many studies relied on ICD codes to classify cardiovascular events. While widely used, these codes can be inaccurate. Additionally, some studies used questionnaires or self-reported data to collect information, which may introduce bias. Another challenge was the inconsistency in diagnostic criteria for PCOS. Different studies used varying definitions, such as the Rotterdam criteria, and others, which capture a range of PCOS phenotypes. This lack of standardization makes it difficult to differentiate cardiovascular risks associated with different PCOS subtypes. Moreover, most studies focused on premenopausal women, providing limited insights into how cardiovascular risks may change in aging women with PCOS. Therefore, further research is needed to address these limitations and provide more definitive answers regarding the long-term cardiovascular risks associated with PCOS.

Implications for Practice

This meta-analysis highlights the need for proactive management of cardiovascular risks in women with PCOS, particularly given the increased risk of stroke. Regular monitoring of blood pressure, glucose, and lipid levels, along with lifestyle modification, should be promoted. Care should be personalized based on age and PCOS phenotype, with younger women requiring a focus on metabolic health and older women on long-term vascular risk reduction. Addressing geographic and socioeconomic disparities is also essential to improve access to preventive care. Educating patients about their risks and promoting healthy lifestyles can further reduce complications.

Conclusion

This meta-analysis demonstrates an elevated risk of stroke among women with PCOS, but the evidence linking PCOS to other cardiovascular outcomes, for instance, MI and overall cardiovascular mortality, remains unclear. Although PCOS is frequently linked to metabolic disturbances like IR, abnormal lipid profiles, and high blood pressure, the impact of these factors on clinical cardiovascular events is complex and influenced by age, phenotype, geography, and preventive management. Future research should focus on phenotype-specific risks and larger, long-term studies to better understand the cardiovascular implications of PCOS.

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Footnotes

Authorship Contributions

Concept: S.T.M., P.B.A., Design: S.T.M., P.B.A., Data Collection or Processing: A.A., H.P., R.K., Analysis or Interpretation: S.T.M., P.B.A., Literature Search: A.A., H.P., R.K., Y.J., Writing: S.T.M., A.A., R.K., Y.J.

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