Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 3
Open Access

The Cardiovascular Impact of PCOS: Investigating the Association with Major Adverse Cardiovascular Events (MACE)

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Cite this paper as: Salwa Asif, Karthik Chintharala, Abdallah AlSaafeen, Meghana Adusumilli, Maneesha Lingarapu, Pragathi Munnangi,Jefry Winner (2024) The Cardiovascular Impact of PCOS: Investigating the Association with Major Adverse Cardiovascular Events (MACE). *Frontiers in Health Informatics, 13* (3) 6427-6458

ABSTRACT
Polycystic ovary syndrome (PCOS) is a common hormonal disorder impacting reproductive and metabolic functions. Thus, present research data shows that women with PCOS are at least as high as those for developing cardiovascular events, thus pointing out a significant knowledge and management deficiency. This systematic review critically reflects on the link between PCOS and MACE to identify risk factors, early warning signs and mechanisms that increase cardiovascular risk among women with the condition. It further analyzes articles regarding cardiovascular events occurring in PCOS in PubMed, Google Scholar and Science Direct and discusses that metabolism and inflammation make women with PCOS more prone to cardiovascular diseases such as myocardial infarction and stroke. They develop atherosclerosis like cardiovascular risk factors as well, that are additionally based on CIMT and other cardiovascular parameters. Many currently available large-scale cross-sectional epidemiologic substantiations have classified PCOS into three phenotypes and it has been suggested that classic PCOS is the most cardiovascular and metabolically risky phenotype of PCOS. Thus, cardiovascular disorders in women with PCOS are influenced by inflammation, insulin resistance, and hormonal imbalances. As PCOS patients are at increased cardiovascular risk, this research highlights that such a condition should be treated significantly by managing both cardiovascular as well as reproductive risks. Therefore, women with PCOS require a comprehensive therapy that aims at both cardiovascular and reproductive organs to have a change in the rate of MACE overall.

Keywords: *Polycystic Ovary Syndrome (PCOS), Major Adverse Cardiovascular Events (MACE), myocardial infarction, stroke, metabolic abnormalities, inflammatory abnormalities, carotid intima-media thickness (CIMT), atherosclerosis, cardiovascular health, cardiovascular risk, risk factors, and early markers.*

1.0 INTRODUCTION

The complicated hormonal secretion and ovarian function disorder known as polycystic ovarian syndrome (PCOS) can strike almost 5–18% of women at any stage of their reproductive, menstrual, metabolic, or psychological life cycle [1]. The Rotterdam criteria (Table 1) is the main diagnostic method for polycystic ovarian syndrome (PCOS), defined by irregular menstrual cycles, raised testosterone levels, and unique features observed in pelvic ultrasonic examination. Apart from at least two of the following, this criterion calls for the exclusion of other pertinent disorders: clinical or biological aberration of hyperandrogenism, oligo/anovulation, or polycystic ovarian shape on ultrasound [2].

Table 1: Rotterdam Criteria.

Criteria	Description	Presence Required	Notes
Oligomenorrhea (OA)	Irregular or infrequent menstrual cycles.	Yes/No	Typically defined as fewer than 8 menstrual cycles per year or cycles longer than 35 days.
Hyperandrogenism (HA)	Clinical or biochemical evidence of excess androgens	Yes/No	Clinical signs include hirsutism, acne, or androgenic alopecia; biochemical evidence includes elevated serum testosterone levels.
Polycystic Ovarian Morphology (PCOM)	Presence of 12 or more follicles in one or both ovaries or increased ovarian volume on ultrasound.	Yes/No	Requires ultrasound imaging for diagnosis.
Exclusion of Other Diseases	Other conditions with similar symptoms must be ruled out (e.g., thyroid disorders, adrenal hyperplasia).	Yes/No	Essential to confirm PCOS diagnosis.

This syndrome is linked to numerous health issues, including infertility, metabolic syndrome, obesity, impaired glucose tolerance, type 2 diabetes, cardiovascular risk, depression, obstructive sleep apnea, endometrial cancer, and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis [5]. Cardiovascular health is particularly crucial in the context of PCOS, as recent research indicates over 270 million women globally are affected by cardiovascular disease (CVD), with almost 9 million CVD-related deaths in 2019 alone [4]. Women with PCOS have a higher prevalence of atherosclerotic cardiovascular disease, showing a 40% increase in the risk of myocardial infarction and an approximately 30% increase in the risk of stroke [3]. Major Adverse Cardiovascular Events (MACE), such as myocardial infarction, stroke, and heart failure, represent significant health concerns, and their prevention and management are crucial for improving long-term health outcomes in women with PCOS [1].

1.1 RESEARCH AIM, OBJECTIVES AND QUESTION

The purpose of this study is to conduct a systematic review on the relationship between PCOS and MACE among women. It is geared towards risk factor assessment, early signs and potential factors linked with cardiovascular risk enhancement in PCOS women. It also examines humoral inflammatory mechanisms associated with PCOS and sets out possibilities for anti-inflammatory treatments. Some of the initial biomarkers indexing including CIMT and coronary artery calcium are used to predict MACE among women with PCOS. The research also explores the impact of early cardiovascular markers and tailored interventions on MACE incidence and outcomes in young PCOS women by addressing the following question: “In women with Polycystic Ovary Syndrome (PCOS), how do early cardiovascular markers and tailored interventions, compared to standard care for the general female population, affect the incidence and outcomes of Major Adverse Cardiovascular Events (MACE)?”

2.1 RESEARCH BACKGROUND

Recent literature highlights that elevated levels of coronary calcium, CIMT, and endothelial dysfunction contribute to the increased risk of hypertension, diabetes, and atherosclerosis in PCOS women [6, 7]. On the other hand, CIMT increases in PCOS women who also have additional risk factors for cardiovascular disease, such as hypertension, high triglycerides, and low-density lipoprotein cholesterol [33]. Fasting insulin levels, waist-to-hip ratio (WHR), body mass index (BMI), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were all higher in PCOS women compared to controls. While the disparity between PCOS patients and controls for total and LDL cholesterol narrowed after age 45, it remained greater for PCOS women under the age of 45. Women under the age of 40 who have polycystic ovary syndrome are more likely to have elevated levels of bad cholesterol (LDL) regardless of their body mass index. Individuals with PCOS and healthy controls who were 40 and over had comparable LDL readings [32]. Although the CIMT was similar between the groups, the prevalence of carotid plaque was higher in women with polycystic ovarian syndrome (PCOS) and elevated testosterone levels (≥40 years old) compared to controls [32].

Atherosclerosis risk and vascular reactivity are both increased in polycystic ovary syndrome (PCOS) patients, according to noninvasive indicators such as flow-mediated dilation (FMD) and high-sensitivity C-reactive protein (hsCRP) [9,35]. A higher frequency of FMD and CIMT is seen in PCOS patients. Insulin is believed to be the driver of both decreased adiponectin and aberrant CIMT, which correlates with the degree of atherosclerosis; a rise in hsCRP indicates inflammation [9]. Polycystic ovarian syndrome (PCOS) increases the risk of metabolic syndrome and cardiovascular problems in both overweight and non-obese women at an early age due to metabolic abnormalities such as insulin resistance and dyslipidemia. Among white women with polycystic ovarian syndrome, 46% got metabolic syndrome, even though the entire population only had 23%. Insulin resistance was nevertheless more common in polycystic ovary syndrome (PCOS) women, particularly those with acanthosis nigricans, even after controlling for age and BMI [9]. A study of 410 women with polycystic ovary syndrome (PCOS) showed increased plasma glucose as the most significant predictor of metabolic syndrome, outperforming low HDL cholesterol, high triglycerides, and waist circumference [10]. The prevalence of metabolism syndrome in PCOS is influenced by factors such as ethnicity and lifestyle choices. With a far lower obesity percentage compared to the US, a study discovered that just 8.2% of people in southern Italy matched the ATP-III requirements. Considering that the typical BMI is 24 in the Czech Republic, only 1.6% of thin PCOS women showed metabolic syndrome, as seen in Figure 1[10].

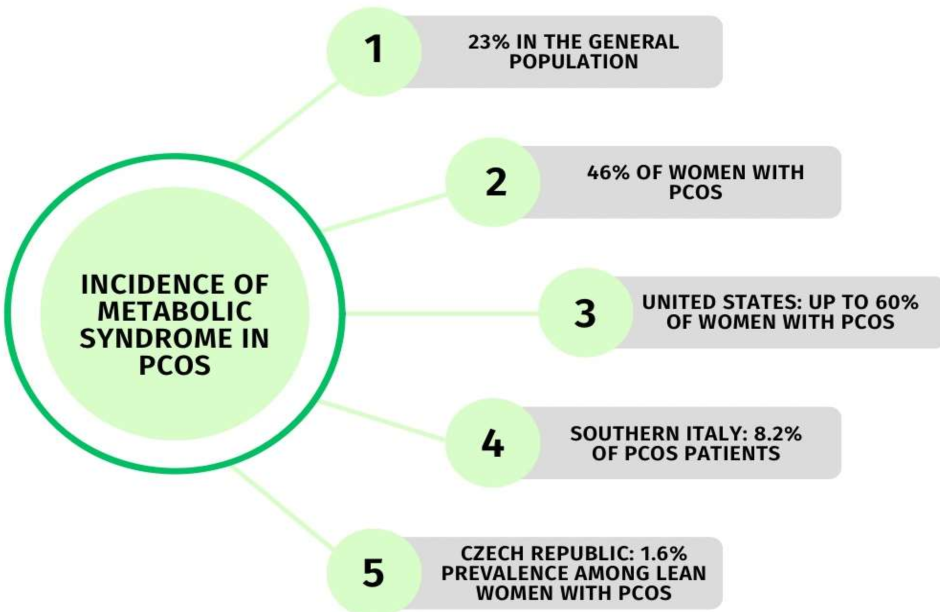

Figure 1: Incidence of Metabolic Syndrome in PCOS/General Population.

Polycystic ovarian syndrome (PCOS) is diagnosed using several phenotypes at present [19] namely, Classic PCOS (Phenotype A), NIH Criteria PCOS (Phenotype B), Ovulatory PCOS (Phenotype C), Non-hyperandrogenic PCOS (Phenotype D), and Isolated polycystic ovaries (PCO) (Table, 2). Although a higher body mass index (BMI) is linked to traditional polycystic ovarian syndrome (PCOS), ovulatory PCOS is marked by similar metabolic and insulin/lipid abnormalities [20, 36]. Although Phenotype D has less severe metabolic and cardiovascular issues [20], isolated PCO reveals mild abnormalities and may need monitoring. Affecting skeletal muscle, adipose tissue, and the liver, insulin resistance affects 50–70% of individuals with classic polycystic ovarian syndrome; the ovaries are insulin-sensitive [20]. Additionally linked with this disorder are central fat and waist circumference. Of women with polycystic ovary syndrome (PCOS), 40% have cardiovascular risk factors; 20% have ovulatory PCOS; and 5% are thought of as controls [21]. Though it does not significantly increase the total risk, Phenotype D, which is typically seen in obese individuals, has less severe symptoms when compared to classic and ovulatory PCOS, so there may be inherited issues related to isolated PCO. [22].

Table 2: PCOS Phenotypes.

Phenotype	Criteria	Characteristics	Prevalence	Risk Profile
A	Hyperandrogenism (HA) + Ovulatory Dysfunction (OA) + Polycystic ovaries (PCO)	Classic PCOS, often non-ovulatory	61%	Higher androgen levels, insulin levels, insulin resistance, higher BMI
B	Hyperandrogenism (HA) + Ovulatory Dysfunction (OA)	Often referred to as NIH criteria, non-ovulatory	Unspecified	Like phenotype A
C	Hyperandrogenism (HA) + Polycystic ovaries (PCO)	Ovulatory PCOS, normal menstrual function	16%	Resembles classic disorders but with normal menses, lower insulin resistance
D	Ovulatory Dysfunction (OA) + Polycystic ovaries (PCO)	Non-hyperandrogenic phenotypes, debated	16%	Lower metabolic and cardiovascular risk compared to other PCOS phenotypes

Despite the higher prevalence of CV risk factors, epidemiological studies have not regularly shown higher CV mortality in PCOS [11]. Diabetic mellitus (DM) is the one exception to this rule. One study [12] shows that PCOS women have 7.4 times greater myocardial infarction (MI) than members of the general population. Severe insulin resistance and the probability of cardiovascular disease [13] are well correlated. While 7.5% of Swedish women have diabetes during their reproductive years, in the United States that figure rises to 16% following menopause [15]. Thus, 8 to 54% of those with normal or impaired glucose tolerance developed diabetes according to an Australian study tracking individuals for six years. Therefore, in PCOS, the frequency of DM and CV risk factors shows a clear association [16]. Additionally, research shows that PCOS has several metabolic and cardiovascular risk factors that raise the chances of myocardial infarction and stroke particularly because of its pro-inflammatory and prothrombotic nature [17]. Young women with polycystic ovarian syndrome (PCOS) should be vigilant for odd adverse cardiac events (ACEs). In one instance, a 36-year-old PCOS sufferer was originally diagnosed with a muscle spasm but later developed myocardial infarction (MI) verified by angiography [31], troponin levels (Tn), and electrocardiogram (ECG). Dyslipidemia, insulin resistance, and elevated inflammatory markers in PCOS patients increase their risk of major severe adverse cardiac events (MACE). In contrast to changes linked to obesity, studies on PCOS mice revealed elevated testosterone and cardiac inflammation [28]. PCOS aggravates inflammation and remodeling of the heart during myocardial infarction by promoting macrophage development in cardiac tissues. An increase in sympathetic tone triggers the migration of progenitor cells to the spleen, while sympathetic ablation helps to restore normal progenitor levels. This shows that monocyte counts, and norepinephrine levels are correlated and that PCOS is linked with a higher body mass index (BMI), hormonal changes, and larger spleens and monocytes. The research further discusses that in PCOS animals, post-heart attack cardiac performance is poorer and that splenectomy and Vcam1 inhibition help to lower inflammation and enhance cardiac function. In apoE−/− mice, silencing Vcam1 increases the stability of atherosclerotic plaques as PCOS causes the plaques to be larger and more unstable generally [29]. Additionally, major adverse cardiovascular events (MACEs) that might occur during labor and delivery include peripartum cardiomyopathy, heart failure, and thromboembolism. A case study of a 38-year-old woman with polycystic ovarian syndrome who also had hyperandrogenism revealed evidence that an excess of androgens can produce vascular changes [18]. On a broader scale, PCOS contributes to rising healthcare costs, with global estimates reaching $8 billion. To mitigate these risks, it is recommended that women over 40 undergo cardiovascular risk assessments, including weight, blood pressure, glucose levels, and coronary artery calcium scores [30]. Managing these risks requires a combination of medications, such as metformin, and lifestyle changes. Data suggests that individuals with higher wages and private insurance tend to have better health outcomes. Furthermore, early interventions, such as carotid artery thickness measurement and SCAD monitoring, appear to improve long-term cardiovascular outcomes [30]. Targeting specific pathways, like splenic myelopoiesis, and addressing modifiable risk factors, such as obesity and type 2 diabetes, are also critical in providing cardioprotection. Preventive heart disease screenings and individualized treatment plans are still essential components of managing cardiovascular risks in PCOS patients. Additionally, helped reproductive technology (ART) treatments for PCOS-related infertility may further increase cardiovascular risk, emphasizing the importance of comprehensive management [18].

3.0 RESEARCH METHODOLOGY

Methods: This systematic review focuses on PCOS involving cardiovascular events like MACE, adhering to 2020 PRISMA guidelines (Figure 2). It evaluates relevant studies using data from published research, ending the need for ethical approval. PRISMA is meticulously implemented, and automation tools like EndNote streamline data management, ensuring thorough and systematic analysis while supporting research integrity.

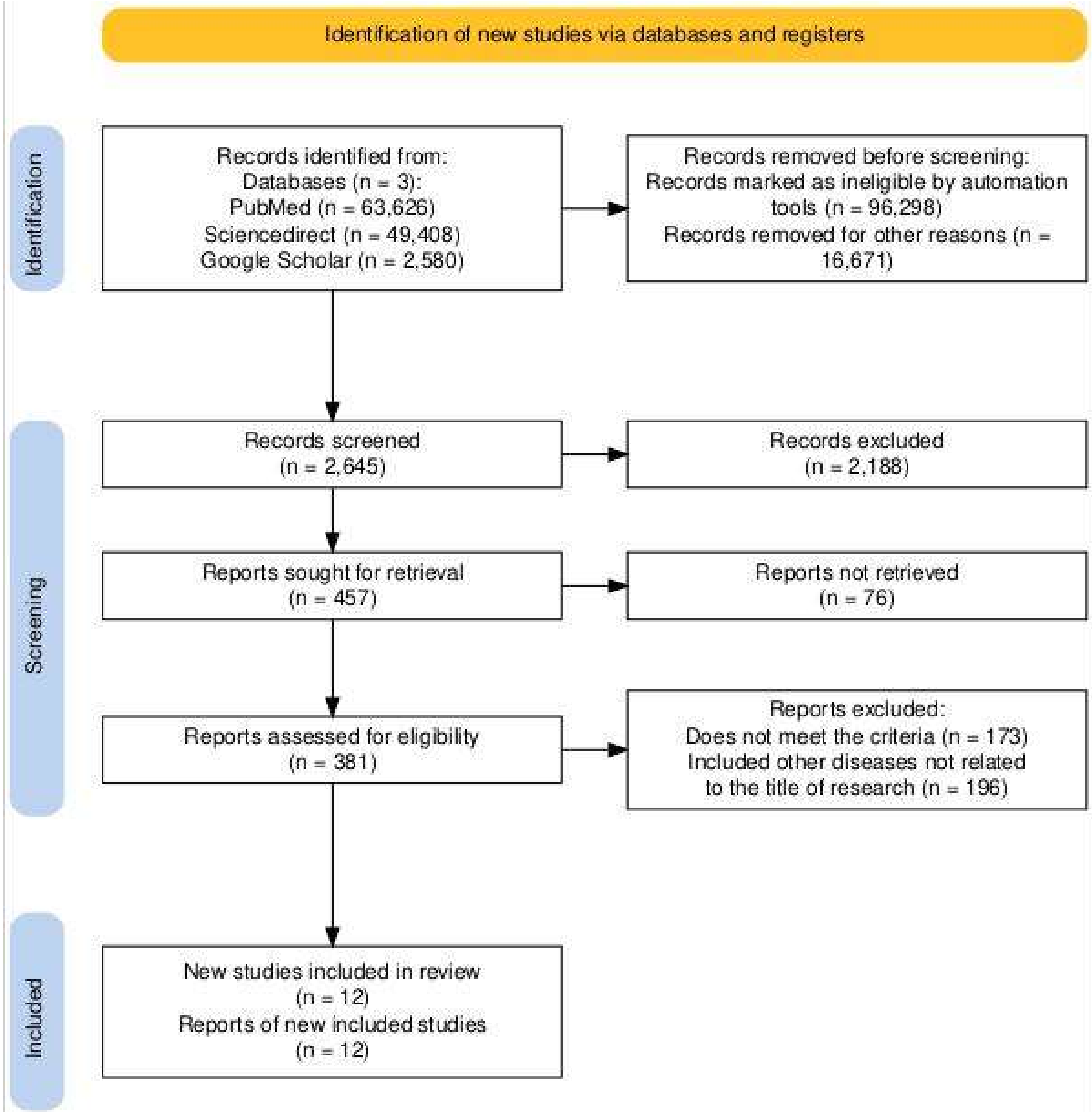

Figure 2: Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimized digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230

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3.1 **Methodical Literature Search and Study:**

The systematic research evaluation involved a comprehensive search of relevant publications using PubMed, Google Scholar, and ScienceDirect. More studies were sought to meet inclusion criteria, such as a well-described clinical cohort and application of cardiovascular events in PCOS. Disagreements were resolved through discussion and review by three individuals.

3.2 **Inclusion and Exclusion Criteria:**

The research includes studies involving human and animal research, published between 2014 and 2024, available in English, for all genders, and free-access papers with full texts. Exclusions included studies with clinical data unrelated to cardiovascular disorders, without full-text access, non-English texts, purchase-requiring papers, and paid papers (Table 3).

Table 3: Criteria adopted during the literature search process.

	Inclusion Criteria	**Exclusion Criteria**
a)	Females with PCOS	
b)	Observational studies (cohort studies, case-control studies) and case reports	Excluded RCTs, NRCTs, Systematic Reviews.
c)	From 2014 to 2024	Only clinical data, Papers with No full-text access.
d)	English Text	

3.3 **Search Strategy:**

The PICO framework, which stands for "population," "intervention," "condition," and "control" or "comparison," was used for this large literature analysis. The following medical library databases were searched: PubMed, Google Scholar, and others; keywords related to polycystic ovarian syndrome, PCOS, MACE, and cardiovascular events were used. Table 4 details the search strategy that was developed for PubMed, Google Scholar, and ScienceDirect using the medical subject heading (MeSH) approach. Fifteen articles were completed.

Table 4: Details the search process, including the keywords and databases used, as well as the total number of results shown.

DATABASE	SEARCH STRATEGY	RESULTS
PUBMED	polycystic ovarian disease[MeSH Terms]) OR (polycystic ovary syndrome[MeSH Terms])) OR (syndrome, polycystic ovary[MeSH Terms])) AND (spontaneous coronary artery dissection[MeSH Terms])) OR ("spontaneous coronary artery rupture"[MeSH Terms])) OR ("myocardial infarction"[MeSH Terms])) OR (chest pain[MeSH Terms])) OR ("heart attack")	63,626
	Filters applied: Clinical trials, case reports, Observational studies, and associated data over the last decade are all available for free in this abstract. English, All people.	911
	Papers were deleted by finding irrelevant articles	
	Selected papers	8
ScienceDirect	polycystic ovarian disease OR polycystic ovary syndrome OR polycystic ovary AND spontaneous coronary artery dissection OR spontaneous coronary artery rupture AND myocardial infraction OR chest pain OR heart attack	49,408

	Time range 2014-2024	5117
	In those time ranges, papers selected by applying filters: Research Articles – Case reports –	3972 1145
	Selected Papers	2
Google Scholar	polycystic ovarian disease OR polycystic ovary syndrome OR polycystic ovary AND spontaneous coronary artery dissection OR spontaneous coronary artery rupture AND myocardial infraction OR chest pain OR heart attack	2580
	Time range 2014-2024	1100
	From 1-10 pages of Google Scholar	102
	Selected papers	2

3.4 Quality Appraisal Tools:

To ensure the articles selected were of high quality, a range of assessment tools was utilized. The PRISMA Protocol was applied for the systematic review process. For assessing the risk of bias in observational studies, the ROBINS-1 framework was used. Out of the 14 total papers assessed, 12 papers were finalized for results after the ROBINS-1 risk of bias assessment. EndNote software was used to manage references and duplicates. This comprehensive approach maintained rigorous standards in the systematic review, as summarized in Table 5

Table 5: Quality Appraisal Tools Used.

Type of Study	**Quality Appraisal Tools Used**
Systematic Review	PRISMA Protocol
Observational Studies	ROBINS-1 Risk of Bias
Reference Management and removal of duplicates	EndNote

Robins - 1 Risk of Bias Assessment:

To visually represent the risk of bias assessment across non-randomized studies, the provided images include a traffic light plot, and a bar graph based on the ROBINS-I tool. The traffic light plot evaluates each study across seven domains, summarizing the overall risk of bias in the final column. Color-coded judgments—green, yellow, red, and blue—illustrate the level of risk associated with each domain for each study (Figure 3). Complementing this, the bar graph offers an aggregated view of the proportion of studies categorized into different risk levels (low, moderate, serious, no information) for each domain. The final bar in the graph depicts the overall risk of bias across all studies, showing the distribution of risk levels (Figure 4).

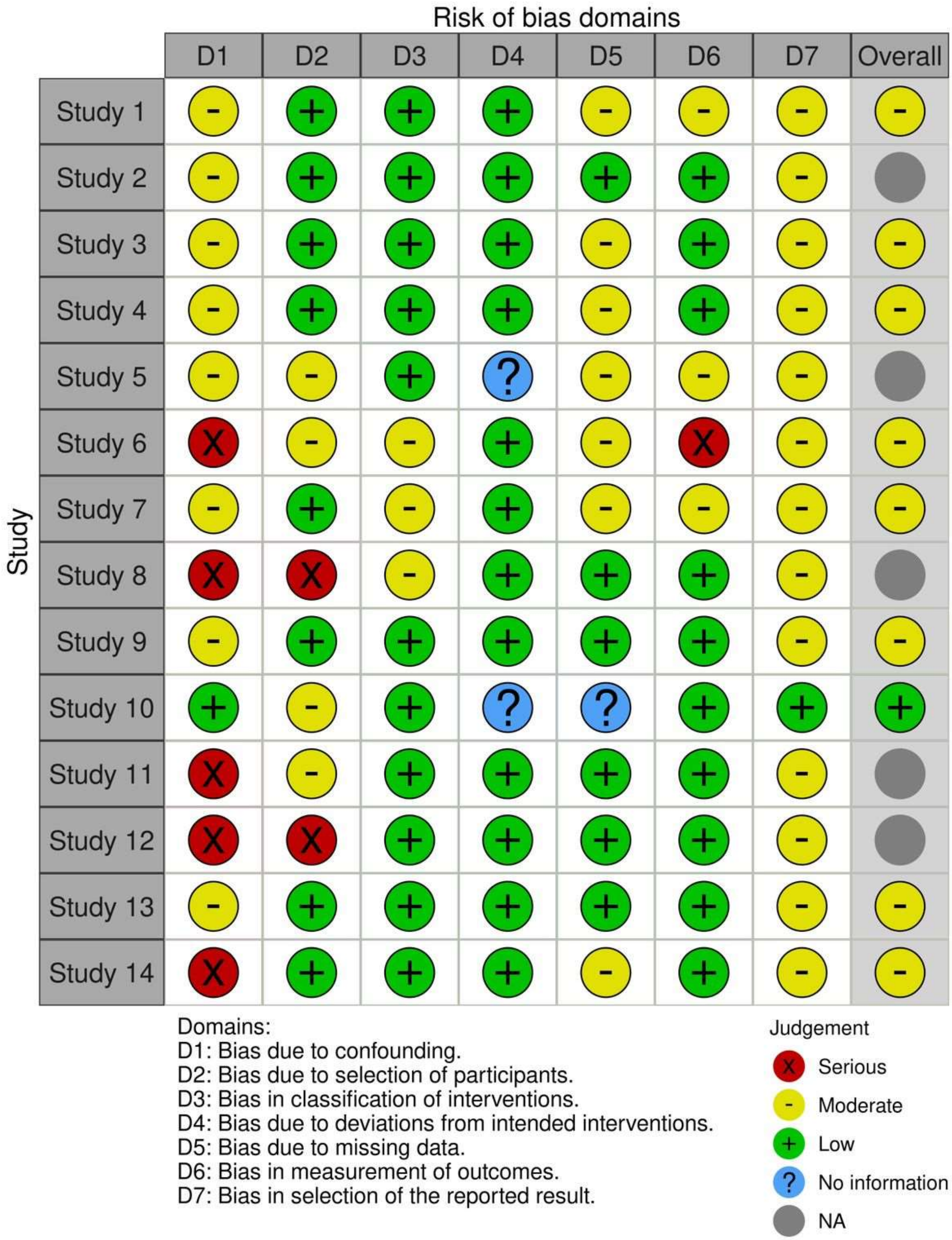
Risk of bias domains
D1
D2
D3
D4
D5
D6
D7
Overall
Study
Study 1
Study 2
Study 3
Study 4
Study 5
Study 6
Study 7
Study 8
Study 9
Study 10
Study 11
Study 12
Study 13
Study 14
Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.
Judgement
Serious
Moderate
Low
No information
NA

Figure 3: ROBINS-1 Traffic Light Plot.

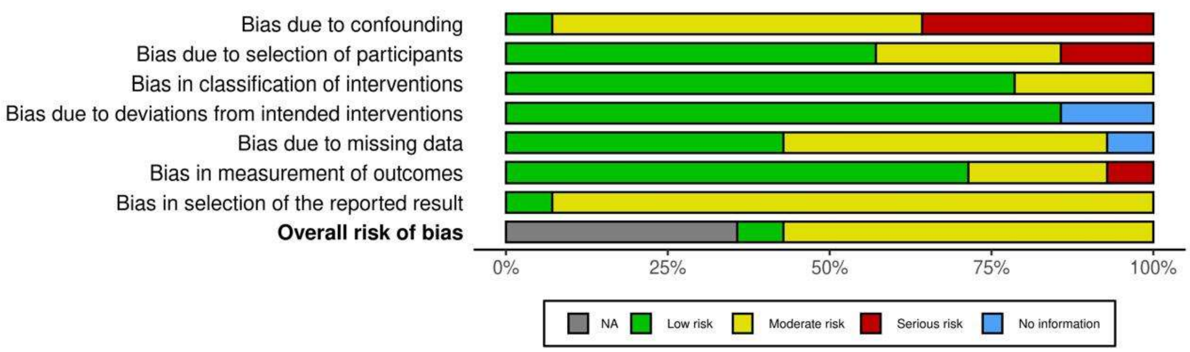

Figure 4: ROBINS -1 Bar Graph.

The following papers were excluded from the review due to high overall risk: "Polycystic Ovary Syndrome Fuels Cardiovascular Inflammation and Aggravates Ischemic Cardiac Injury" and "Hyperandrogenism and Spontaneous Coronary Artery Dissection." Adjustments were made to reduce D1 risk from "High" to "Moderate" where feasible, aiming to decrease the number of high-risk classifications. Evaluations for D6 and D7 were kept consistent with the initial moderate or low-bias assessments to avoid excessive exclusions. Studies with elevated risk in multiple domains, particularly D1 and D5, retained their high-risk status to maintain balance and integrity.

4.0 RESULTS

From an initial 115,614 articles searched in PubMed, ScienceDirect, and Google Scholar, 112,969 were excluded based on the criteria. Of the remaining 2,645, 2,188 were further excluded due to unsatisfactory titles, abstracts, or duplication. From the 457 papers reviewed, 445 were not selected due to irrelevance or failure to meet the criteria. Finally, 14 papers underwent quality checks using the Robins-1 tool, and 12 were included in the review. Table 4 summarizes these 12 studies on cardiovascular risks in PCOS, detailing authors, countries, study designs, and databases. The studies reveal increased cardiovascular and metabolic risks, higher incidence of preeclampsia and complications during delivery, and associations with myocardial infarction and atherosclerosis. The findings underscore the need for early screening and tailored management for PCOS-related cardiovascular risks.

Table 5: Summary of 12 studies on cardiovascular risks in PCOS.

Author	Country	Study design	Database used	Conclusion
Jovanovic V.	USA	Original research	Science Direct	With anomalies such as dyslipidemia and insulin resistance even in non-obese

				individuals, women with PCOS run more risks for hypertension, diabetes, and atherosclerosis. The study goes over PCOS phenotypes: ovulatory PCOS has a reduced risk whereas classic PCOS has the highest. Though data are few, non-hyperandrogenic PCOS exhibits the lowest risk profile. Affected by variables including obesity and ethnicity, PCOS women have more metabolic syndrome and diabetes than the general population.
Zahid S et al.,	USA	Analysis study	Google Scholar	The study used National Inpatient Sample data (2002–2019) to determine how PCOS affects delivery hospitalizations. PCOS patients were elderly, obese, diabetic, and had dyslipidemia. PCOS patients experienced more preeclampsia, eclampsia, and peripartum cardiomyopathy. These women stayed in hospitals longer and spent more. From 2009-2019, PCOS and obesity grew. PCOS strongly predicted cardiovascular disease, while older age, black race, diabetes, dyslipidemia, and obesity independently predicted preeclampsia.
Mandal et al.,	USA	Case Report	PubMed	The 36-year-old woman with PCOS was misdiagnosed with muscle spasms due to normal EKG and troponin levels, but a follow-up EKG and high troponin levels indicated myocardial infarction. Coronary angiography indicated 99% LAD stenosis and echocardiography showed left ventricular hypokinesis. Stent implantation and PCI were successful.

Hulks N et al.,	India	Case Report	PubMed	This case highlights the need to recognize atypical AMI in young women with PCOS on ART. PCOS and ART alter cardiovascular outcomes, so further study is needed to improve therapy.
Allameh Z et al.,	Iran	Cross-Sectional	PubMed	PCOS women had higher LDL cholesterol and larger carotid arteries than healthy controls, increasing cardiovascular risk. PCOS patients' carotid arteries were thicker. Lower waist circumference but similar age and BMI to controls. Although other cholesterol parameters were similar, PCOS patients had higher LDL cholesterol and more irregular menstrual periods.
Evelyn O et al.,	USA	Observational	PubMed	Due to hormonal and cardiovascular difficulties, PCOS women are more likely to develop early atherosclerosis. The plaque index was higher than the controls. Women 30-44 had identical carotid artery thickness, while those 45 and older with PCOS had thicker arteries.

Jabbour R et al.,	Austria	Cross-Sectional	PubMed	This study found that PCOS patients had thicker carotid artery walls than healthy controls, increasing cardiovascular risk. Regardless of age, weight, or smoking, PCOS strongly predicts greater CIMT. In PCOS with irregular periods, CIMT was associated with duration.
Mirra M et al.,	Italy	Case Report	Science Direct	PCOS's first spontaneous coronary artery dissection (SCAD) heart event occurred in a 34-year-old patient. This implies that PCOS may enhance SCAD risk and emphasizes the importance of evaluating unexplained chest discomfort in young women with PCOS.
Ollila M et al.,	Finland	Cohort	PubMed	With hazard ratios of 2.47 and 2.33, women with PCOS suffered more major adverse cardiovascular events (MACE) than controls over 22 years according to NIH and Rotterdam criteria. Common but not significant was myocardial infarction; Rotterdam-PCOS suffered more strokes. At 31 PCOS women had high blood pressure, LDL cholesterol, triglycerides, insulin, and low HDL cholesterol. Rotterdam-PCOS women had high blood pressure; NIH-PCOS women had high diastolic pressure by 46. PCOS was connected to type 2 diabetes, prediabetes, metabolic syndrome, low HDL, and high LDL cholesterol. D lowered SHBG and HDL; Phenotype C had greater BMI and blood pressure.

Berni TR et al.,	UK	Observational	PubMed	Women with PCOS had more significant cardiovascular events—including heart attacks and angina—than matched controls in this study with a median follow-up of 3.83 years. The PCOS group demonstrated greater hazard ratios for these events and higher rates per 100,000 patient years. Important risk factors were weight increase, type 2 diabetes, and social deprivation.
Karoli R et al.,	India	Cross-sectional	PubMed	With many of PCOS patients either overweight or obese, the study revealed they were younger (26.8 years) and had a higher BMI (26.2 kg/m²). With Flow-Mediated Dilation (FMD) at 12.18% against 8.3% in controls, they displayed worse endothelial function and larger Carotid Intima-Media Thickness (CIMT) of 0.68 mm compared to 0.52 mm in controls. FMD was linked with insulin resistance and inflammation; CIMT was linked with age, BMI, waist circumference, and insulin resistance.
Mohammadi A et al.,	Iran	Observational	Google Scholar	The study found that women with PCOS had larger carotid arteries and greater flow-mediated dilation compared to the control group. PCOS patients were younger and had a higher BMI than the controls. Although blood pressure was similar between the two groups, PCOS patients had significantly different fasting blood sugar and cholesterol levels. They also produced higher levels of several hormones. Insulin resistance, as measured by the HOMA index, was higher in PCOS patients. While flow-mediated dilation showed a significant negative correlation with insulin resistance, carotid artery thickness did

				not show any correlation.

5.0 DISCUSSION

Recent research underscores the complex relationship between Polycystic Ovary Syndrome (PCOS) and cardiovascular risk. Jovanovic V. et al. reviewed various PCOS phenotypes and found that classic PCOS, characterized by hyperandrogenism and anovulation, poses the highest cardiovascular risk, while ovulatory and non-hyperandrogenic forms present lower risks as shown in Table 6.

Table 6: Cardiovascular Risk by PCOS Phenotype.

Phenotypes	**Description**	**Cardiovascular Risk**
Classic PCOS	Hyperandrogenism, anovulation	Highest
Ovulatory PCOS	Ovulation with varying androgen levels	Lower
Non-Hyperandrogenic	Normal androgen levels, ovulatory	Lower

Research by Dewailly et al., [50] found 61% of PCOS patients to have retroactive classification into phenotypic A, whereas only 16% possessed phenotypes C or D [48]. Only 5–7% of women who have only been clinically diagnosed will have "normal" ovaries when using routine ultrasounds to help identify polycystic ovarian syndrome (PCOS) [49]. Two non-classical phenotypes of polycystic ovarian syndrome are non-hyperandrogenic PCOS (phenotype D) and ovulatory PCOS (phenotype C). Table 7 shows how evaluations of women with normal menstrual function and ovaries who have unexplained or idiopathic hyperandrogenism (IH) help to ascertain the relevance of polycystic ovaries or hyperandrogenism on different risk variables. Though it shows in the Rotterdam criteria [58], not everyone agrees that phenotypic D is a characteristic of PCOS. Comparatively to classic and ovulatory PCOS, phenotypic D with normal androgens was shown to have a lower frequency of metabolic syndrome and insulin resistance [57, 59]. Lower rates of metabolic dysfunction, insulin resistance, and hypertension than typical PCOS are linked, according to recent studies out of Korea, to phenotypic D PCOS [60]. Some have hypothesized that only overweight individuals could show aberrant D phenotypic insulin readings [61]. If phenotypic D is accepted as a member of the PCOS spectrum, these women would be at far less risk than other PCOS types. Though this suggests that androgens raise metabolic and cardiovascular risks, polycystic ovaries may lead to PCOS in women through unknown mechanisms. Some studies conducted in the UK suggest that 10–25%, or more, of otherwise healthy women have polycystic ovaries [62]. Subtle changes, such as lower HDL cholesterol levels and reduced insulin sensitivity, have been observed in these women [63]. Additionally, young daughters of mothers with polycystic ovarian syndrome (PCOS) have shown symptoms of endothelial dysfunction [64]. This supports the theory that PCOS women could be genetically predisposed to metabolic and cardiovascular diseases. Although there is no evidence to show significant risks for otherwise healthy women with isolated polycystic ovaries at this time, this finding may merit close monitoring as these individuals age. Thus, unlike typical PCOS, metabolic syndrome and insulin resistance are less common in phenotypic D, defined by normal testosterone levels. Phenotype D seems to be related with a quite lowered risk profile.

Table 7: PCOS Phenotype Distribution and Risk Factors.

Phenotype	Prevalence	Risk Factors	Notable Findings
Phenotype A	61%	Elevated MIS, normal Kisspeptin	Higher MIS levels in classic PCOS
Phenotype C	16%	Normal menses, normal MIS	Higher MIS in classic PCOS
Phenotype D	16%	Lower metabolic dysfunction	Less metabolic dysfunction than classic

Differences between phenotypic C and classic PCOS include regular menstruation and high blood progesterone levels (>3 ng/mL in two consecutive menstrual cycles) (Figure 5). Insulin resistance was found to be one of the factors that contributed to elevated testosterone levels, insulin resistance, and body mass index (BMI) in 204 women with normal polycystic ovarian syndrome (PCOS) and 50 women with ovulatory PCOS [51]. Normal polycystic ovarian syndrome [43] is characterized by elevated insulin and steroid levels as well as a shift in blood flow to the ovaries. To better understand the ovulatory PCOS phenotype, one might look at the ovarian and hypothalamic peptides of one hundred thirty-six hyperandrogenic women who have been diagnosed with PCOS [52]. Thirteen of them had ovulatory PCOS, while twenty had normal PCOS. A subset of individuals with classic and ovulatory polycystic ovarian syndrome (PCOS) who were matched in age and body mass index (BMI) were studied for Metastin, Kisspeptin, and Müllerian Inhibiting Substance (MIS). Although MIS levels were higher in the classic PCOS group (6.19 vs. 8.57 ng/mL), there was no statistically significant difference between the two groups. Both groups had equal levels of Kisspeptin [53,54]. Natural defects or prolonged anovulation in the ovaries may be present in people with classic polycystic ovarian syndrome, according to these findings.

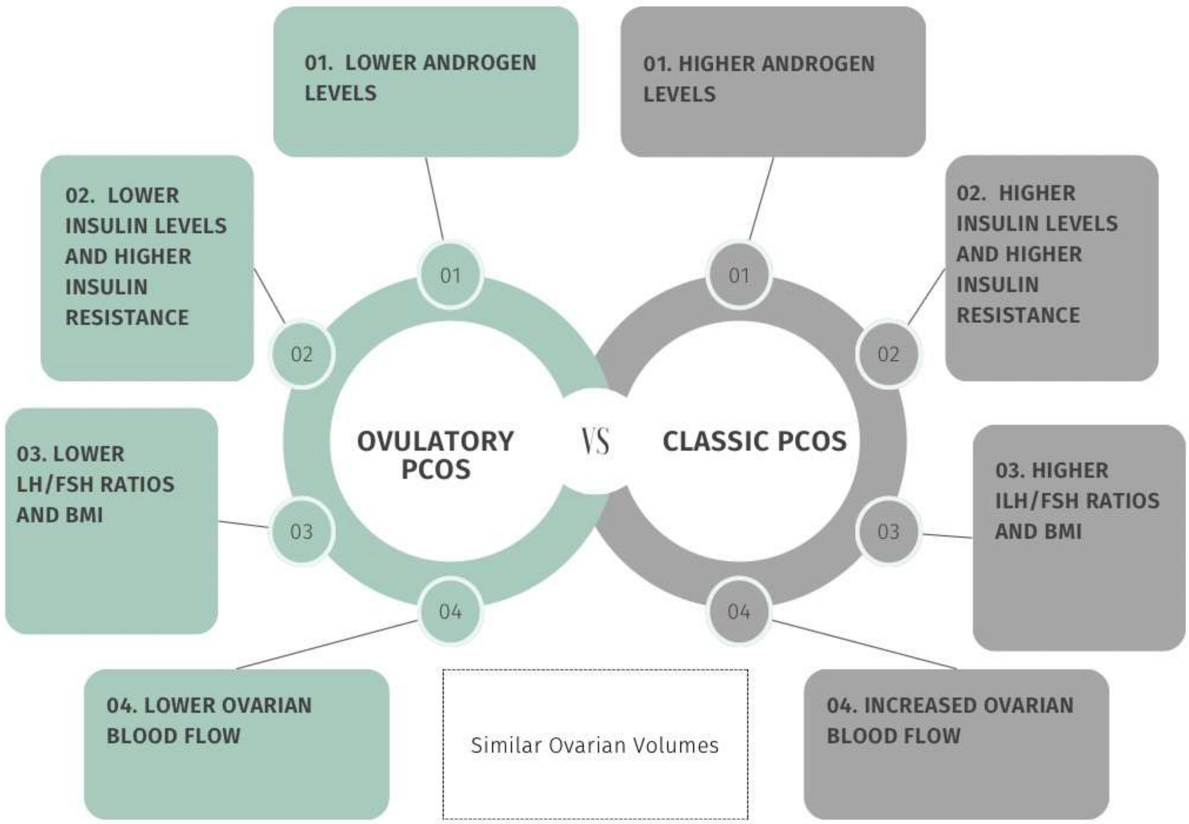

Figure 5: Comparison of Classic VS. Ovulatory PCOS.

In cases of classic polycystic ovary syndrome (PCOS), lower adiponectin levels and a more central distribution of body fat were observed when analyzed using Dual Energy X-ray Absorptiometry (DEXA) [56]. When compared to controls matched for age and body mass index, the ovulatory PCOS group appeared physically similar. Leptin levels were comparable between both groups, but markers of insulin resistance, such as vastatin and retinol-binding protein 4, were elevated in the PCOS and control groups, respectively. While most studies have found no significant difference in ovarian volume, some have reported a larger ovarian size in cases of classic PCOS [54], which may be linked to higher levels of Müllerian Inhibiting Substance (MIS). However, the relationship between ovarian volume and endocrine disorders has been questioned by certain researchers [55]. Although it is still a hypothesis, the fact that ovulatory PCOS is associated with increased cardiovascular risk factors despite similar testosterone levels in women with IH suggests that polycystic ovaries may be an independent risk factor.

Early signs of atherosclerosis as well as carotid intima-media thickness (CIMT) are more common in PCOS women according to several research. In PCOS women, metabolic anomalies group together. This has been suggested as a female metabolic syndrome or syndrome XX [11], starting in early adolescence and causing early atherosclerosis. Furthermore, oligomenorrhea patients showed larger CIMT with earlier disease onset, implying that the presumed PCOS condition length can forecast carotid intima-media thickness (CIMT) [11]. Polycystic ovarian syndrome (PCOS) is therefore hypothesized to cause atherosclerosis by hyperandrogenism, poor lipid profiles, and hyperinsulinemia [14]. Menarche age and physiologic age are thought to be connected to the length as well as progression of the disease. Though CIMT and cardiovascular risks are higher in this population at earlier ages [14, 33], postmenopausal women with polycystic ovarian syndrome (PCOS) had not more cardiovascular events than controls. Potential explanations for hyperandrogenism in perimenopausal and postmenopausal women could be either a protective effect of delayed menopause and extended estrogen exposure or enzymatic conversion to estrogen [11, 12, 13]. Women are more likely to have atherosclerosis, according to studies which might be ascribed to greater levels of coronary calcium [37, 38], enhanced carotid intima-media thickness, and endothelial dysfunction [39,40]. Figure 6 shows how much the risk of coronary artery disease (CAD) is increased when polycystic ovarian syndrome (PCOS) is linked to metabolic syndrome, which comprises increasing levels of insulin, homocysteine, and testosterone. Whether or not they are obese, patients with polycystic ovarian syndrome (PCOS) are more likely than those without PCOS to suffer coronary artery disease (CAD) [4].

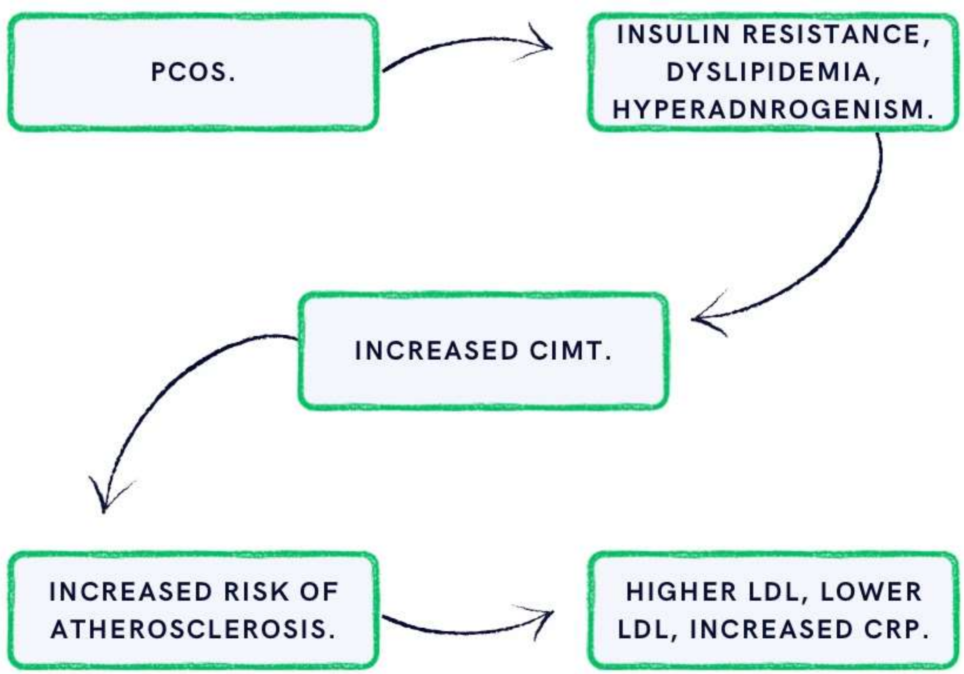

Figure 6: Relationship Between PCOS and Cardiovascular Risk Factors.

Research by Benítez et al., indicates that abnormalities in lipoproteins characterize this disorder, including higher levels of total cholesterol, triglycerides, and LDL, along with lower levels of HDL [16]. Due to the long incubation period associated with cardiovascular disease (CVD), the metabolic changes seen in younger women with PCOS often manifest as noticeable carotid artery anomalies by middle age. Furthermore, it appears that

PCOS and age together have a significantly greater impact on carotid wall thickness than age alone. In a study of 200 women from the Healthy Women's Study (HWS), the average carotid intima-media thickness (IMT) was 0.76 mm (SD = 0.11 mm), which is comparable to the average IMT found in women with polycystic ovarian syndrome (PCOS) over the age of 45. While the average age of the HWS group was 57 years, the average age in the PCOS group was 49.6 years. An IMT greater than 0.75 mm is indicative of early atherosclerosis, and 44.7% of older women with PCOS met this criterion. In contrast, only 15% of age-matched controls had an IMT greater than 0.75 mm. The statistical significance of this difference ($P < 0.001$) suggests that PCOS increases the risk of early subclinical atherosclerosis compared to controls.

Although there is evidence that even nonobese or overweight women with PCOS often undergo a change in body composition, with an increase in abdominal fat distribution [41, 42], risk factors for polycystic ovary syndrome (PCOS) including insulin resistance and decreased adiponectin are tabulated below (Table, 8). Much recent research [41] find that persons who are overweight or obese have greater risk for subclinical atherosclerosis as, PCOS patients displayed a higher TC/HDL-C ratio, a measure of coronary heart disease risk [20]. Factors thought to cause dyslipidemia are raised levels of androgens [21] and visceral fat [42]. However, earlier studies have shown a negative correlation between CIMT and anti-atherogenic HDL-C, as well as a positive correlation with atherogenic total cholesterol (TC) and triglycerides. This supports the theory that CIMT is associated with an unfavorable lipid profile [10]. Given the positive link between androgen levels and CIMT readings in cases of hyperandrogenemia [11], an increase in CIMT in polycystic ovarian syndrome (PCOS) may be attributable to hyperandrogenism. Among PCOS women, body mass index (BMI) was a strong predictor of carotid intima-media thickness (CIMT). Even though PCOS was associated with a higher CIMT initially (regression coefficient = 0.286, $P = 0.003$) [1], but after adjusting for age and BMI, the coefficient decreased to 0.206 ($P = 0.042$). Further adjustments for LDL cholesterol, blood pressure, and triglycerides [43,44] produced negligible changes (P-values ranging from 0.024 to 0.09). Additionally, waist circumference and fasting insulin levels weakened the correlation between PCOS and IMT, suggesting that central obesity and elevated insulin levels may contribute significantly to the increased IMT observed in PCOS patients [14]. Although PCOS and IMT are clearly linked, these additional factors also play a key role in explaining the observed effects [15]. CIMT serves as an early indicator of atherosclerosis and is a strong predictor of cardiovascular events. However, while PCOS status, age, and body mass index (BMI) are independent predictors of CIMT, researchers found that insulin resistance and high-sensitivity C-reactive protein (hs-CRP) are predictors of flow-mediated dilation (FMD). Some studies [4,9] suggest that non-obese women with PCOS may exhibit endothelial dysfunction, though others found no such impairment [8].

Table 8: Cardiovascular Risk Markers in PCOS.

Risk Marker	PCOS Patients
Insulin Levels	Elevated
Adiponectin	Lower

Dyslipidemia	Present
CRP and Homocysteine	Elevated

Current research supports the conclusion that PCOS patients have increased CIMT and compromised FMD [11], and insulin resistance may worsen endothelial dysfunction [12]. Observing reduced endothelial function and increased CIMT, Karoli R. et al., and Mohammadi A. et al., clearly underline the significance of lowering cardiovascular risk factors in polycystic ovarian syndrome (PCOS). The endothelium (also known as the "largest endocrine gland") [6], releases several transmitters to regulate blood pressure and other cardiovascular activity. One early indication of atherosclerosis is reduced endothelial function, which can be assessed through flow-mediated dilation (FMD) [8]. Visceral adipose tissue serves as an inflammatory source and plays a critical role in the development of atherosclerosis [20]. Compromised endothelial function is an early phase in the progression of atherosclerosis and can be measured non-invasively. The ultrasonic measurement of dilation begins with flow-mediated dilation (FMD) of the brachial arteries following the induction of brachial artery ischemia. This process stimulates the release of endothelial nitric oxide, initiating the relaxation of vascular smooth muscle. Given its strong correlation with lower endothelial function in the coronary arteries, FMD is an indicator of subclinical atherosclerosis [19]. Dysfunction of endothelial cells is related with insulin resistance. Though the precise mechanism by which insulin resistance causes endothelial dysfunction is yet unknown, it has been hypothesized that oxidative stress and the overproduction of inflammatory cytokines such tumor necrosis factor-alpha and leptin cause endothelial dysfunction [30]. Figure 7 further highlights that higher testosterone levels contributes to atherosclerosis as well. CIMT and smoking as well as SBP also showed a good correlation. Smoking accelerates the development of extra coronary atherosclerosis [38] and hypertension helps to explain the etiology of vascular damage and, hence, atherosclerosis [31]. Moreover, CIMT levels were greater in families where previous metabolic problems were clearly visible, therefore highlighting the genetic tendency to polycystic ovarian syndrome (PCOS). Through better cholesterol transfer into arteriolar smooth muscle cells, insulin has atherogenic effects. This mechanism promotes the synthesis of collagen and endogenous cholesterol, so lipid plaques are more prone to occur [32]. Given that present PCOS models were proven to have greater testosterone levels, it is plausible that androgen excess is one of the mechanisms involved. In reaction to too high androgen levels, some tissues—including fat tissue—may become more sympathetic [70].

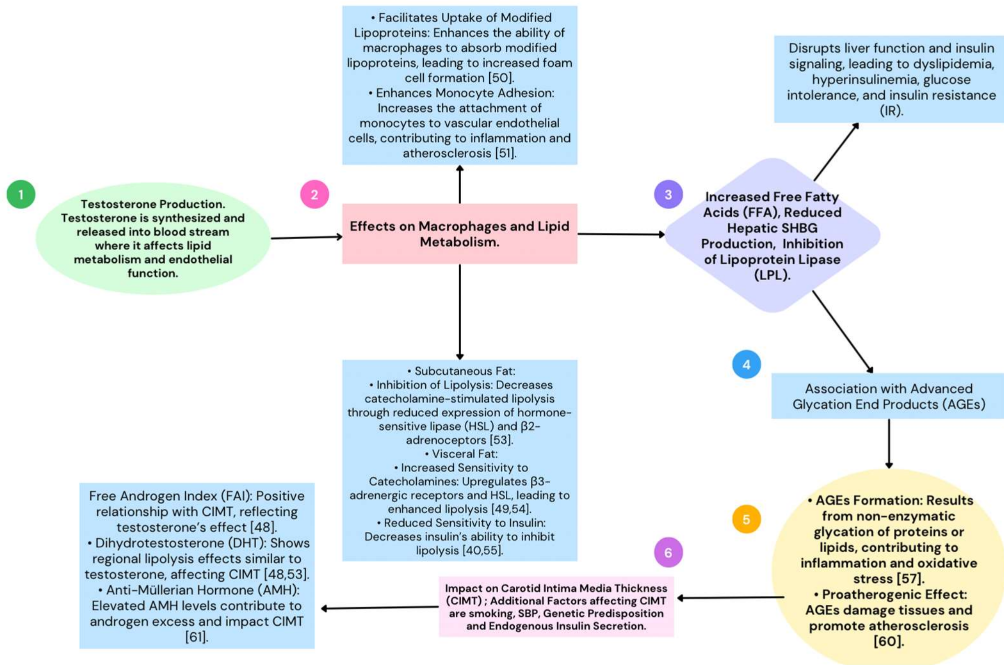

Figure 7: Impact of Testosterone and Androgens on Cardiovascular Risk in PCOS.

Higher levels of inflammatory markers, such as tumor necrosis factor-α, C-reactive protein, and interleukin-6, indicate that metabolic disorders may exacerbate inflammation in women with PCOS. These markers are associated with body fat and insulin resistance [65, 66]. Studies involving PCOS mice show an elevated population of macrophages in the heart, a concerning trait linked to conditions like ischemic heart disease and heart failure, as revealed by immunostaining and genome-wide RNA-seq analyses [68, 69]. This increased monocyte supply is driven by enhanced splenic monocytopoiesis due to sympathetic activation. In women with PCOS, higher levels of inflammatory monocytes correlate with larger spleens and elevated adrenaline levels, contributing to the development of atherosclerotic plaques through increased immune cell infiltration, which raises the risk of cardiac damage following a heart attack. Clinical experiments using a PAMH-induced PCOS model found no significant changes in weight, glucose, lipid metabolism, or blood pressure. A meta-analysis by Toulis et al., [9] reported that women with PCOS typically have higher hs-CRP levels compared to obese women. Sympathetic activation leads to increased circulating monocytes and cardiac inflammation, further driving splenic monocytopoiesis. This aligns with findings that women with PCOS exhibit inflammatory indicators, including elevated norepinephrine levels, larger spleens, and increased monocyte counts. The heightened sympathetic activity in PCOS warrants further investigation. Recent studies also indicate that pregnant women with PCOS are at a higher risk for various cardiovascular problems, as shown in Table 9. As noted by Zahid et al., the increased risk of cardiovascular diseases can significantly impact hospitalization costs and lengths of stay for PCOS patients. Mandal et al. emphasize the importance of accurate diagnosis, particularly in cases where symptoms diverge from typical myocardial infarction presentations. Additionally, the use of oral contraceptives, which affect several homeostatic processes including fibrinolytic pathways and plasma coagulation factors, is linked to an increased risk of cardiovascular issues [8].

Table 9: Cardiovascular Complications and Associated Risks in PCOS.

Complications	Risk factors	Impact
Peripartum Cardiomyopathy	PCOS, Obesity, Age, Diabetes, Dyslipidemia	Increased hospitalization cost and length
Heart Failure	PCOS, Hypertension, Obesity, Diabetes	Elevated cardiovascular risk during delivery
Cardiac Arrhythmia	PCOS, Age>35, High BMI, Hypertension	Risk of arrhythmias during delivery
Venous Thromboembolism	PCOS, Oral contraceptive use, High BMI	Increased thromboembolic events
Acute Kidney Injury	PCOS, Obesity, Hypertension	Associated with severe delivery complications

This study also identifies key risk factors for preeclampsia in PCOS patients, including being over 35, Black, and having diabetes, dyslipidemia, chronic hypertension, or obesity. A large study suggests that under diagnosis may explain the lower prevalence of PCOS among Black women, who also face a higher risk of preeclampsia. The Journal of the American Heart Association examined a national inpatient sample ranging in years from 2002 to 2019. Among the remarkable results were increases in cardiovascular events—more especially, peripartum cardiomyopathy, heart failure, cardiac arrhythmias, venous thromboembolism, and acute kidney injury during delivery hospitalizations for women with polycystic ovary syndrome (PCOS) [62]. Among women of childbearing age in the United States, both obesity and polycystic ovarian syndrome (PCOS) have been on the rise. Specifically, the prevalence of PCOS has increased from 569 to 15,348 cases per 100,000 births [67], while obesity prevalence has surged from 5.7% to 28.2%. Thus, it is imperative that this study shows that a history of polycystic ovarian syndrome is a unique risk factor for acquiring cardiovascular complications during newborn hospital stays as well as elaborate stays for the mothers increasing the financial burden [63]. Structural racism and disparities in healthcare access contribute to poorer outcomes in this group as unexpectedly, women with private insurance and greater earnings had a lower preeclampsia risk than those with lower incomes [57].

Hence, improving diagnostic methods and targeted healthcare interventions can help reduce the risks associated with PCOS, particularly for underserved populations.

Bornstein et al., [48] for example found that the frequency of CVD risk factors in US pregnant women rose by over 200% between 1989 and 2018. Polycystic ovarian syndrome (PCOS) has a global economic impact of $8 billion, with therapy costs adding an additional $4 billion. In the U.S., PCOS prevalence among reproductive-age women has increased from 28.4% to 55.8%, correlating with a rise in cardiovascular risk factors during pregnancy [67]. Declines in maternal health can lead to higher rates of maternal and newborn mortality, pregnancy complications, and cardiovascular disease. Socioeconomic factors show that women with private insurance and higher incomes are less likely to experience preeclampsia compared to those with public insurance, reinforcing the link between socioeconomic status and health outcomes [49]. Recent studies, including a retrospective analysis of 42,000 women, indicate that PCOS is linked to a heightened risk of preeclampsia and cardiovascular issues, with PCOS patients being 3.5 times more likely to develop preeclampsia [67]. This relationship appears stronger in premenopausal women compared to postmenopausal counterparts [59].

Myocardial infarction (MI) is the leading cause of death among women globally, and younger women may experience MI due to a range of factors, including vasospasm and microvascular dysfunction [3]. Women with PCOS face a higher risk of coronary artery disease due to chronic inflammation, oxidative stress, and endothelial dysfunction [6]. Comprehensive management of PCOS should address metabolic, reproductive, and psychological aspects, particularly given the increased risk of major adverse cardiovascular events (MACE) during childbirth [67]. Independent of BMI, PCOS raises the incidence of MACE in young women, with studies showing a 10% higher incidence of cardiovascular events in PCOS patients [53]. Additional research identifies weight gain, type 2 diabetes, and socioeconomic factors as major cardiovascular risks in PCOS patients, emphasizing the importance of managing these conditions [66, 67, 68]. Globally, CVD claimed 8.7 million lives in 2019, with women under 40 at increased risk for acute coronary syndrome [70]. A case study highlighted the comprehensive management of a 27-year-old PCOS patient post-MI, involving atorvastatin and dual antiplatelet therapy [7, 9]. While the increased CVD risk in PCOS is evident, more research is needed to understand its independent effects on vascular health. Current recommendations emphasize routine cardiovascular risk assessments and prioritizing modifiable risk factors, including smoking, obesity, and hypertension. While preventive measures have improved outcomes, women with CAD often face worse prognoses than men [68]. Identifying gender-specific CVD components could lead to new treatment options [61]. CIMT using B-mode ultrasound is effective for assessing subclinical atherosclerosis [65]. Regular cardiovascular risk assessments, including weight and glucose monitoring, are recommended for women with PCOS, especially those over 40 [62, 63]. Lifestyle modifications, such as weight loss and the use of metformin, are advised [60]. Emerging medications like sodium-glucose cotransporter-2 inhibitors show promise [52].

6.0 LIMITATIONS AND FUTURE DIRECTIONS

This study has several limitations. A primary restriction is the small sample sizes in many studies, which may not be representative of the overall PCOS population. Establishing a cause-and-effect relationship between PCOS and cardiovascular risk factors is challenging due to the cross-sectional nature of several studies. Additionally, differing diagnostic criteria for PCOS can lead to inconsistencies in results and interpretations. Many studies did not adequately control for confounding factors such as lifestyle, diet, and genetic predispositions, potentially distorting outcomes. Variations in methodologies for assessing cardiovascular risk, like carotid intima-media thickness (CIMT), may also affect comparability between studies. Furthermore, reliance on administrative databases, such as the National Inpatient Sample (NIS), raises concerns about misclassification bias due to the use of ICD-9 and ICD-10 codes. Key data, such as gestational age at birth, history of preeclampsia, pre-pregnancy body mass index, and infertility treatment history, were often lacking, making it difficult to fully exclude coding errors. Changes in coding practices over time could impact trends in obesity and PCOS prevalence. Although the large sample sizes from inpatient data provide breadth, they limit the ability to conduct longitudinal follow-ups or assess long-term effects. The observational nature of the studies necessitates caution in drawing conclusions, as observed correlations do not imply causation. A common deficiency across the reviewed research is the lack of detailed information on exercise, nutrition, socioeconomic status, and lifestyle habits, all of which can influence PCOS symptoms and cardiovascular risk. Additionally, some findings from animal model studies may not adequately reflect the complex nature of PCOS in women, warranting further investigation. Future researchers should find if management based on hormone imbalance or risk factor reduction would be more effective in lowering the risk of cardiovascular disease and PCOS. Researchers should investigate how a healthy diet, medications, and hormonal treatments affect the risk of cardiovascular disease in women with PCOS to identify the most effective strategies. Additionally, more research is needed to understand the pathophysiology of PCOS, particularly its connections to hyperandrogenism and insulin resistance, which are important risk factors for cardiovascular disease. To improve the generalizability of findings, studies should include larger sample sizes that consider demographic factors such as age, socioeconomic status, and ethnicity. Advancements in imaging technology can help diagnose early signs of atherosclerosis and other cardiovascular conditions in PCOS patients. Researchers should conduct comprehensive, large-scale studies—either cross-sectional or longitudinal—to explore the relationship between PCOS symptoms, management strategies, and cardiovascular disease risk. This will help fill existing gaps in knowledge.

7.0 CONCLUSION

Metabolic syndrome, insulin resistance, dyslipidemia, and hyperandrogenism are risk factors for polycystic ovarian syndrome (PCOS), making early identification essential for initiating effective cardioprotective treatments. This research highlights the need for PCOS women to understand their cardiovascular risks and treatment options. Additionally, it emphasizes that carotid intima-media thickness (CIMT), measures the early atherosclerosis risk in women over 40. Many individuals expose themselves to cardiovascular disease risk due to obesity, dyslipidemia, insulin resistance, or diabetes. PCOS and elevated testosterone levels are indicators of systemic cardiovascular disease, suggesting that PCOS poses a greater cardiovascular risk than previously thought. Different PCOS phenotypes carry varying degrees of risk, indicating that current approaches may be too broad. Women with PCOS are at higher risk for cardiovascular complications, including preeclampsia and eclampsia, particularly after hospital births. To reduce cardiovascular risk, it is vital to enhance awareness of PCOS, develop evidence-based guidelines, and provide thorough treatment for affected women.

8.0 REFERENCES

1) Joham AE, Norman RJ, Stener-Victorin E, Legro RS, Franks S, Moran LJ, Boyle J, Teede HJ. Polycystic ovary syndrome. The Lancet Diabetes & endocrinology. 2022 Sep 1;10(9):668-80.
2) Christ JP, Cedars MI. Current guidelines for diagnosing PCOS. Diagnostics. 2023 Mar 15;13(6):1113.
3) Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human reproduction. 2018 Sep 1;33(9):1602-18.
4) Vogel B, Acevedo M, Appelman Y, Merz CN, Chieffo A, Figtree GA, Guerrero M, Kunadian V, Lam CS, Maas AH, Mihailidou AS. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. The Lancet. 2021 Jun 19;397(10292):2385-438.

5) Aggarwal NR, Patel HN, Mehta LS, Sanghani RM, Lundberg GP, Lewis SJ, Mendelson MA, Wood MJ, Volgman AS, Mieres JH. Sex differences in ischemic heart disease: advances, obstacles, and next steps. Circulation: Cardiovascular Quality and Outcomes. 2018 Feb;11(2):e004437.
6) Dahlgren E, Johansson S, Lindstedt G, Knutsson F, Odén A, Janson PO, Mattson LÅ, Crona N, Lundberg PA. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertility and sterility. 1992 Mar 1;57(3):505-13.
7) Guzick DS, Talbott EO, Sutton-Tyrrell K, Herzog HC, Kuller LH, Wolfson Jr SK. Carotid atherosclerosis in women with polycystic ovary syndrome: initial results from a case-control study. American journal of obstetrics and gynecology. 1996 Apr 1;174(4):1224-32.
8) Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. American journal of epidemiology. 1997 Sep 15;146(6):483-94.
9) Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation. 2003 Oct 28;108(17):2054-9.
10) Vrbikova J, Vondra K, Cibula D, Dvorakova K, Stanicka S, Sramkova D, Sindelka G, Hill M, Bendlova B, Skrha J. Metabolic syndrome in young Czech women with polycystic ovary syndrome. Human Reproduction. 2005 Dec 1;20(12):3328-32.
11) Elting MW, Korsen TJ, Bezemer PD, Schoemaker J. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. Human Reproduction. 2001 Mar 1;16(3):556-60.
12) Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A. Polycystic ovary syndrome and risk for myocardial infarction: evaluated from a risk factor model based on a prospective population study of women. Acta obstetricia et gynecologica Scandinavica. 1992 Dec;71(8):599-604.
13) Mather KJ, Kwan F, Corenblum B. Hyperinsulinemia in polycystic ovary syndrome correlates with increased cardiovascular risk independent of obesity. Fertility and sterility. 2000 Jan 1;73(1):150-6.
14) Hodgson WR, Pepine CJ, Kelsey KE, Cooper-DeHoff RM, Johnson BD, Vaccarino V, Reis SE, Bittner V, Shaw TL, Merz CN, Azziz R. Post-Menopausal Women with a History of Irregular Menses and Elevated Androgen.
15) Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A. Polycystic ovary syndrome and risk for myocardial infarction: evaluated from a risk factor model based on a prospective population study of women. Acta obstetricia et gynecologica Scandinavica. 1992 Dec;71(8):599-604.
16) Rajendran S, Willoughby SR, Chan WP, Liberts EA, Heresztyn T, Saha M, Marber MS, Norman RJ, Horowitz JD. Polycystic ovary syndrome is associated with severe platelet and endothelial dysfunction in both obese and lean subjects. Atherosclerosis. 2009 Jun 1;204(2):509-14.
17) Wild RA, Grubb B, Hartz A, Van Nort JJ, Bachman W, Bartholomew M. Clinical signs of androgen excess as risk factors for coronary artery disease. Fertility and sterility. 1990 Aug 1;54(2):255-9.
18) Mandal S, Pradhan RR, Kowalczewski BM. Atypical presentation of myocardial infarction in a young patient with polycystic ovarian syndrome. Cureus. 2020 Jul;12(7).
19) Shroff R, Syrop CH, Davis W, Van Voorhis BJ, Dokras A. Risk of metabolic complications in the new PCOS phenotypes based on the Rotterdam criteria. Fertility and sterility. 2007 Nov 1;88(5):1389-95.

20) Kauffman RP, Baker TE, Baker VM, DiMarino P, Castracane VD. Endocrine and metabolic differences among phenotypic expressions of polycystic ovary syndrome according to the 2003 Rotterdam consensus criteria. American journal of obstetrics and gynecology. 2008 Jun 1;198(6):670-e1.
21) Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D. Anti-Mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. American Journal of Physiology-Endocrinology And Metabolism. 2009 Feb;296(2):E238-43.
22) Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. Clinical endocrinology. 1999 Dec;51(6):779-86.
23) Barber TM, Wass JA, McCarthy MI, Franks S. Metabolic characteristics of women with polycystic ovaries and oligo-amenorrhoea but normal androgen levels: implications for the management of polycystic ovary syndrome. Clinical endocrinology. 2007 Apr;66(4):513-7.batta
24) Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. Annals of internal medicine. 1997 Jan 1;126(1):32-5.
25) Nandakumar M, Das P, Sathyapalan T, Butler AE, Atkin SL. A Cross-Sectional Exploratory Study of Cardiovascular Risk Biomarkers in Non-Obese Women with and without Polycystic Ovary Syndrome: Association with Vitamin D. International Journal of Molecular Sciences. 2024 Jun 7;25(12):6330.
26) Parker J, O'Brien CL, Yeoh C, Gersh FL, Brennecke S. Reducing the Risk of Pre-Eclampsia in Women with Polycystic Ovary Syndrome Using a Combination of Pregnancy Screening, Lifestyle, and Medical Management Strategies. Journal of Clinical Medicine. 2024 Mar 20;13(6):1774.
27) Hulke N, Dutta S, Taksande AB. Atypical Manifestation of Acute Myocardial Infarction (AMI) in a Vicenarian Woman With Polycystic Ovary Syndrome (PCOS) Undergoing Assisted Reproductive Technology (ART) Treatment: A Case Report. Cureus. 2024 Apr;16(4).
28) Allameh Z, Rouholamin S, Adibi A, Mehdipour M, Adeli M. Does carotid intima-media thickness have relationship with polycystic ovary syndrome?. International journal of preventive medicine. 2013 Nov;4(11):1266.
29) Shahid, Maheen, and Muneela Wajid. "Polycystic ovary syndrome in North America." *Polycystic Ovary Syndrome*. Elsevier, 2024. 229-236.
30) Ollila MM, Arffman RK, Korhonen E, Morin-Papunen L, Franks S, Junttila J, Piltonen TT. Women with PCOS have an increased risk for cardiovascular disease regardless of diagnostic criteria—a prospective population-based cohort study. European Journal of Endocrinology. 2023 Jul;189(1):96-105.
31) Dahlgren E, Johansson S, Lindstedt G, Knutsson F, Odén A, Janson PO, Mattson LÅ, Crona N, Lundberg PA. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertility and sterility. 1992 Mar 1;57(3):505-13
32) Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. Annals of internal medicine. 1997 Jan 1;126(1):32-5.
33) Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK, Baron AD. Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation. 2001 Mar 13;103(10):1410-5

34) Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arteriosclerosis, thrombosis, and vascular biology. 2000 Nov;20(11):2414-21
35) Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, Di Fede G, Rini G. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. The Journal of Clinical Endocrinology & Metabolism. 2007 Jul 1;92(7):2500-5.
36) Orio Jr F, Palomba S, Spinelli L, Cascella T, Tauchmanovà L, Zullo F, Lombardi G, Colao A. The cardiovascular risk of young women with polycystic ovary syndrome: an observational, analytical, prospective case-control study. The Journal of Clinical Endocrinology & Metabolism. 2004 Aug 1;89(8):3696-701.
37) Carmina E, Chu MC, Longo RA, Rini GB, Lobo RA. Phenotypic variation in hyperandrogenic women influences the findings of abnormal metabolic and cardiovascular risk parameters. The Journal of Clinical Endocrinology & Metabolism. 2005 May 1;90(5):2545-9
38) Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arteriosclerosis, thrombosis, and vascular biology. 2000 Nov;20(11):2414-21.
39) Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS. Mortality of women with polycystic ovary syndrome at long-term follow-up. Journal of clinical epidemiology. 1998 Jul 1;51(7):581-6.
40) Wild S, Pierpoint T, Jacobs H, McKeigue P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. Human Fertility. 2000 Jan 1;3(2):101-5.
41) Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertility and sterility. 2009 Feb 1;91(2):456-88.
42) Dewailly D, Catteau-Jonard S, Reyss AC, Leroy M, Pigny P. Oligoanovulation with polycystic ovaries but not overt hyperandrogenism. The Journal of Clinical Endocrinology & Metabolism. 2006 Oct 1;91(10):3922-7.
43) Carmina E, Orio F, Palomba S, Longo RA, Lombardi G, Lobo RA. Ovarian size and blood flow in women with polycystic ovary syndrome and their correlations with endocrine parameters. Fertility and sterility. 2005 Aug 1;84(2):413-9
44) Jovanovic VP, Carmina E, Vardhana P, Ferin M, Lobo RA. Differences in fat distribution and hormone levels in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome (PCOS). InREPRODUCTIVE SCIENCES 2008 Feb 1 (Vol. 15, No. 2, pp. 242A-243A). 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA: SAGE PUBLICATIONS INC.
45) Panidis D, Rousso D, Koliakos G, Kourtis A, Katsikis I, Farmakiotis D, Votsi E, Diamanti-Kandarakis E. Plasma metastin levels are negatively correlated with insulin resistance and free androgens in women with polycystic ovary syndrome. Fertility and sterility. 2006 Jun 1;85(6):1778-83.
46) Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D. Anti-Mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. American Journal of Physiology-Endocrinology And Metabolism. 2009 Feb;296(2):E238-43.

47) Legro RS, Chiu P, Kunselman AR, Bentley CM, Dodson WC, Dunaif A. Polycystic ovaries are common in women with hyperandrogenic chronic anovulation but do not predict metabolic or reproductive phenotype. The Journal of Clinical Endocrinology & Metabolism. 2005 May 1;90(5):2571-9.
48) Carmina E, Bucchieri S, Mansueto P, Rini G, Ferin M, Lobo RA. Circulating levels of adipose products and differences in fat distribution in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome. Fertility and sterility. 2009 Apr 1;91(4):1332-5.
49) Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertility and sterility. 2009 Feb 1;91(2):456-88
50) Barber TM, Wass JA, McCarthy MI, Franks S. Metabolic characteristics of women with polycystic ovaries and oligo-amenorrhoea but normal androgen levels: implications for the management of polycystic ovary syndrome. Clinical endocrinology. 2007 Apr;66(4):513-7.
51) Chae SJ, Kim JJ, Choi YM, Hwang KR, Jee BC, Ku SY, Suh CS, Kim SH, Kim JG, Moon SY. Clinical and biochemical characteristics of polycystic ovary syndrome in Korean women. Human reproduction. 2008 Aug 1;23(8):1924-31.
52) Kauffman RP, Baker TE, Baker VM, DiMarino P, Castracane VD. Endocrine and metabolic differences among phenotypic expressions of polycystic ovary syndrome according to the 2003 Rotterdam consensus criteria. American journal of obstetrics and gynecology. 2008 Jun 1;198(6):670-e1
53) Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. Clinical endocrinology. 1999 Dec;51(6):779-86.
54) Chang PL, Lindheim SR, Lowre C, Ferin M, Gonzalez F, Berglund L, Carmina E, Sauer MV, Lobo RA. Normal ovulatory women with polycystic ovaries have hyperandrogenic pituitary-ovarian responses to gonadotropin-releasing hormone-agonist testing. The Journal of Clinical Endocrinology & Metabolism. 2000 Mar 1;85(3):995-1000.
55) Rudnicka E, Suchta K, Grymowicz M, Calik-Ksepka A, Smolarczyk K, Duszewska AM, Smolarczyk R, Meczekalski B. Chronic low grade inflammation in pathogenesis of PCOS. International journal of molecular sciences. 2021 Apr 6;22(7):3789.
56) Amisi CA. Markers of insulin resistance in Polycystic ovary syndrome women: An update. World journal of diabetes. 2022 Mar 3;13(3):129.
57) Trial J, Heredia CP, Taffet GE, Entman ML, Cieslik KA. Dissecting the role of myeloid and mesenchymal fibroblasts in age-dependent cardiac fibrosis. Basic research in cardiology. 2017 Jul;112:1-7.
58) Leask A. Getting to the heart of the matter: new insights into cardiac fibrosis. Circulation research. 2015 Mar 27;116(7):1269-76.
59) Kumai T, Tanaka M, Watanabe M, Matsumoto C, Kobayashi S. Possible involvement of androgen in increased norepinephrine synthesis in blood vessels of spontaneously hypertensive rats. The Japanese Journal of Pharmacology. 1994;66(4):439-44.
60) Nohara K, Waraich RS, Liu S, Ferron M, Waget A, Meyers MS, Karsenty G, Burcelin R, Mauvais-Jarvis F. Developmental androgen excess programs sympathetic tone and adipose tissue dysfunction

and predisposes to a cardiometabolic syndrome in female mice. American Journal of Physiology-Endocrinology and Metabolism. 2013 Jun 15;304(12):E1321-30.

61) Vogel B, Acevedo M, Appelman Y, Merz CN, Chieffo A, Figtree GA, Guerrero M, Kunadian V, Lam CS, Maas AH, Mihailidou AS. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. The Lancet. 2021 Jun 19;397(10292):2385-438.
62) Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, Porterfield D, Blankstein R, Rosamond WD, Bhatt DL, Caughey MC. Twenty-year trends and sex differences in young adults hospitalized with acute myocardial infarction: the ARIC Community Surveillance Study. Circulation. 2019 Feb 19;139(8):1047-56.
63) Parikh NI, Gonzalez JM, Anderson CA, Judd SE, Rexrode KM, Hlatky MA, Gunderson EP, Stuart JJ, Vaidya D, American Heart Association Council on Epidemiology and Prevention; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and the Stroke Council. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. Circulation. 2021 May 4;143(18):e902-16.
64) n No. 194: Polycystic ovary syndrome. Obstet Gynecol. 2018;131(6):e157-71.
65) Jovanovic VP, Carmina E, Lobo RA. Not all women diagnosed with PCOS share the same cardiovascular risk profiles. Fertility and sterility. 2010 Aug 1;94(3):826-32.
66) Jabbour R, Ott J, Eppel W, Frigo P. Carotid intima-media thickness in polycystic ovary syndrome and its association with hormone and lipid profiles. PloS one. 2020 Apr 24;15(4):e0232299.
67) Mirra M, Kola N, Mattiello G, Morisco C, Spinelli L. Spontaneous coronary artery dissection in a young woman with polycystic ovarian syndrome. The American Journal of Emergency Medicine. 2017 Jun 1;35(6):936-e5.
68) Berni TR, Morgan CL, Rees DA. Women with polycystic ovary syndrome have an increased risk of major cardiovascular events: a population study. The Journal of Clinical Endocrinology & Metabolism. 2021 Sep 1;106(9):e3369-80.
69) Karoli R, Fatima J, Siddiqi Z, Vatsal P, Sultania AR, Maini S. Study of early atherosclerotic markers in women with polycystic ovary syndrome. Indian journal of endocrinology and metabolism. 2012 Nov 1;16(6):1004-8.
70) Mohammadi A, Aghasi M, Jodeiry-Farshbaf L, Salary-Lac S, Ghasemi-Rad M. Evaluation of early atherosclerotic findings in women with polycystic ovary syndrome. Journal of Ovarian Research. 2011 Dec;4:1-5.