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REVIEW

Are women with polycystic ovary syndrome at increased cardiovascular disease risk later in life?

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ABSTRACT

To date, the world's leading cause of death amongst women is cardiovascular disease. Polycystic ovary syndrome (PCOS) is associated with an unfavorable cardiometabolic profile in early life. Apart from dyslipidemia, obesity and onset of type 2 diabetes mellitus, androgens are thought to influence cardiovascular health. The question rises whether women with PCOS are truly at risk for cardiovascular disease in later life. In this review paper, we aim to reflect on this assumed relation based on studies in different stages of life in women with PCOS. Cardiovascular risk factors (type 2 diabetes mellitus, obesity and metabolic syndrome), surrogate outcomes (flow-mediated dilation, carotid intima-media thickness and coronary artery calcium) and clinical long-term outcomes (cardiovascular disease and mortality) will be summarized. Data on cardiovascular disease and mortality in peri- and postmenopausal women with PCOS appear to be controversial. Whether androgens have a protective or unfavorable influence on the manifestation of cardiovascular disease remains uncertain. The need for large, prospective, well-phenotyped cohort studies of women with PCOS is high. Only then will we be able to answer this research question.

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Introduction

Polycystic ovary syndrome (PCOS) represents the most common endocrine disorder in women of reproductive age, with a reported prevalence of 6–15%, depending on the criteria used for defining this heterogeneous condition[1–3]. According to the Rotterdam criteria, at least two out of the three following features must be present: ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology[1] (Table 1). Other possible underlying pathologies must be excluded. Familial clustering of this heterogeneous condition has clearly been shown, although the etiology as well as the genetic determinants of PCOS remain uncertain[4–6].

An association between PCOS and cardiometabolic dysfunction (such as hyperinsulinemia, dyslipidemia, hypertension and obesity) is common. Numerous studies have convincingly demonstrated in recent years that – not surprisingly – even singleton pregnancies in women with PCOS are more often complicated by gestational diabetes, pregnancy-induced hypertension and pre-eclampsia. As women age, an increased incidence of type 2 diabetes mellitus emerges[7,8]. Considering the presence of metabolic risk factors already present in many women with PCOS at a young age, it is generally believed that the chances for developing cardiovascular disease in later life are significantly increased. Evidence generated so far, however, remains inconclusive. A large heterogeneity exists in women with PCOS, and therefore cardiovascular risk profiles may vary with PCOS phenotype, age, ethnicity and body mass index (BMI).

Metabolic dysfunction per stage of life

During adolescence, the most common complaints of women with PCOS consist of acne/hirsutism and irregular menstrual bleedings[8,9]. However, as the time from menarche passes, irregular bleedings may normalize (Figure 1). In addition, many women with PCOS use steroid contraception at a young age and these women are therefore unaware of their spontaneous bleeding patterns. During later reproductive years, the most common reason for referral is anovulatory infertility.

Features such as hyperandrogenism and obesity in women with PCOS are clearly associated with metabolic syndrome and insulin resistance[10–12]. Metabolic features of women with PCOS compared to healthy controls were assessed in a meta-analysis in which 35 studies were included. Women with PCOS had a less favorable metabolic profile in comparison to healthy controls, even when patients and controls were matched for body weight. The latter suggests that BMI in itself does not solely explain the observed metabolic abnormalities in women with PCOS (Table 2)[13].

A large proportion of women with PCOS will undergo infertility treatment to establish a pregnancy[14]. Several pregnancy complications are more common in women with PCOS[15,16], such as gestational diabetes mellitus (GDM) (reported odds ratios (OR) 2.94; 95% confidence interval (CI) 1.70–5.08), pre-eclampsia (OR 3.47; 95% CI 1.95–6.17) and preterm birth (OR 1.75; 95% CI 1.16–2.62)[15,17,18]. Some preliminary studies even suggest that PCOS offspring have an

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Table 1. Possible phenotypes of polycystic ovarian syndrome according to different combinations of diagnostic criteria.

	Phenotype			
	A	*B*	*C*	*D*
Diagnostic criteria	Oligo- or anovulation; polycystic ovaries; hyperandrogenism	Oligo- or anovulation; polycystic ovaries	Oligo- or anovulation; hyperandrogenism	Polycystic ovaries; hyperandrogenism
Original NIH, 1990[42]			x	
ESHRE/ASRM, 2003[1]	x	x	x	x
Androgen Excess and PCOS Society criteria, 2006[43]	x		x	x

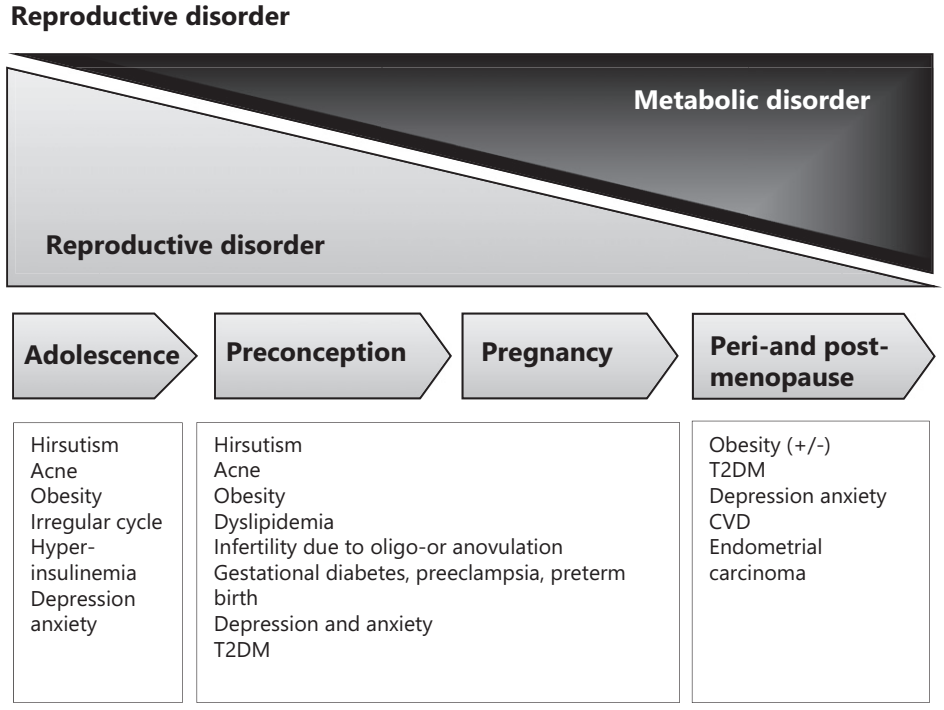

Figure 1. Polycystic ovarian syndrome, a shift in focus during different stages of life. (+/−), unsure; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease.

Table 2. Unfavorable cardiometabolic risk factors in women with polycystic ovarian syndrome (PCOS) compared to controls: a systematic review of 35 studies involving a total of 14 887 PCOS women and 62 865 controls[13].

	Pooled risk estimate	
Metabolic feature	*PCOS vs. non-PCOS controls*	*PCOS vs. BMI-matched non-PCOS controls*
Impaired glucose tolerance	*n* = 835 vs. 568 pOR: 2.48 (95% CI 1.63–3.77)	*n* = 347 vs. 319 pOR: 2.54 (95% CI 1.44–4.47)
Type 2 diabetes mellitus	*n* = 12 105 vs. 56 959 pOR: 4.43 (95% CI 4.06–4.82)	*n* = 441 vs. 1175 pOR: 4.00 (95% CI 1.97–8.10)
Metabolic syndrome	*n* = 2256 vs. 4130 pOR: 2.88 (95% CI 2.40–3.45)	*n* = 273 vs. 276 pOR: 2.20 (95% CI 1.36–3.56)

BMI, body mass index; *n*, number of patients; pOR, pooled odds ratio; CI, confidence interval.

increased risk for unfavorable cardiometabolic features such as increased concentrations of fasting serum glucose, insulin, triglyceride, total cholesterol and low density lipoprotein (LDL) cholesterol[19,20].

Vascular dysfunction

The metabolic dysfunctions described in the different stages of life implicate an increased risk for cardiovascular disease. Endothelial dysfunction is the starting point of progression towards cardiovascular disease. Flow-mediated dilation (FMD) is a technique developed to measure vascular dysfunction. This assessment is used to measure artery dilator response to reactive hyperemia induced by a brief period of artificial limb ischemia. A decreased FMD is a prognostic marker for cardiovascular disease in general, but, more specifically, it independently predicts occult coronary artery disease[21]. FMD in women with PCOS is reported extensively. In a large meta-analysis, 21 studies were included with 908 women with PCOS versus 566 controls. In seven out of 21 studies, cases and controls were matched on BMI. The pooled mean FMD was 3.4% (95% CI 1.9–4.9) lower in PCOS women compared to controls, with substantial heterogeneity between studies. In the subanalysis, the PCOS-mediated reduction in FMD was 4.1% (95% CI 2.7–5.5). Heterogeneity remained substantial ($I^2 = 81\%$). Moreover, the size of the FMD difference was not significantly influenced by BMI or age (Table 3)[22].

Table 3. Surrogate outcomes for cardiovascular disease in women with polycystic ovarian syndrome (PCOS) versus controls.

Surrogate outcomes	*Pooled risk estimate*
Flow-mediated dilation: systematic review[22]	$n = 908$ vs. 566 Pooled mean difference: -3.021 (95% CI 3.315–2.727); $p < 0.0001$
Intima media thickness: systematic review[25]	$n = 1123$ vs. 923 Pooled OR: 0.072 (95% CI 0.040–0.105), $p < 0.0001$
Coronary calcium score: individual study[29]	$n = 61$ vs. 85 Any CAC: 45.9% vs. 30.6%, OR 2.31; 95% CI 1.00–5.33, $p = 0.049$ CAC >10: 19.7% vs. 7.1%, $p < 0.033$
Coronary calcium score: individual study[31]	$n = 24$ vs. 24 Any CAC: 33% vs. 8%, $p < 0.03$; OR 5.5; 95% CI 1.03–29.45
Coronary calcium score: individual study[30]	$n = 149$ vs. 166 Any CAC: 63.1% vs. 41%, $p < 0.05$, adjusted $p = 0.037$ CAC >10: 35.5% vs. 12.2%, $p < 0.05$, adjusted

CAC, coronary artery calcium; *n*, number of patients; OR, odds ratio; CI, confidence interval.

Measuring carotid intima-media thickness (CIMT) is an accepted non-invasive method for diagnosing atherosclerosis[23]. CIMT is a structural change in the vascular system visualized by ultrasonography and a strong predictor of cardiovascular events in both males and females[24]. In a meta-analysis regarding CIMT within the PCOS population, a total of 19 studies were included: 1123 women with PCOS conforming to NIH criteria versus 923 controls. The mean ages of included women ranged from 21 to 39 years and their BMI from 21 to 41 kg/m^2. The summary estimate of the mean difference in CIMT among women with PCOS compared with controls was 0.072 mm (95% CI 0.040–0.105, $p < 0.0001$) for highest-quality studies and 0.084 mm (95% CI 0.042–0.126, $p = 0.0001$) for good-quality studies, with higher CIMTs for women with PCOS[25].

A third parameter which is a non-invasive method for the evaluation of vascular health is the Agatston score[26] (Table 3). This score is used for quantification of coronary artery calcium (CAC). Coronary atherosclerosis in its turn is related to coronary heart disease and all-cause mortality[27,28]. Women with PCOS appear to have increased presence of any coronary arteriosclerosis compared to non-PCOS controls[29]. When looking at continuous data of Agatston scores, higher Agatston scores are reported in women with PCOS, compared to controls[30,31]. Another small study of 48 patients reports that obese PCOS patients and obese controls with quite similar cardiovascular risk profiles do differ in prevalence of coronary atherosclerosis, to the disadvantage of the obese PCOS patient group[31]. This finding suggests that PCOS influences atherosclerosis, disregarding BMI, adiposity distribution, inflammation and metabolic markers. This all leads to the hypothesis that older women with PCOS have an increased risk for developing cardiovascular disease.

Long-term cardiovascular outcomes and implications

The long-term health implications of metabolic dysfunction in women with PCOS have remained uncertain until now. PCOS is diagnosed during the reproductive lifespan, mostly in a woman's early twenties and thirties when there is a wish to conceive. However, cardiovascular disease becomes manifest three to four decades later. Due to this large time gap, large, well-phenotyped cohorts of women with PCOS with sufficient long-term follow-up are lacking. We are restricted to using surrogate outcomes or small follow-up studies in women previously diagnosed with PCOS, or cross-sectional studies in postmenopausal women with a presumed PCOS history. Selecting the best suitable surrogate outcomes for cardiovascular disease (CVD) is only possible when we fully understand the mechanism underlying CVD in women. This mechanism differs from the pathophysiology seen in males[32,33].

Unfortunately, the majority of conducted research was based on the male concept of CVD. It is generally known that CVD in women is present approximately 10 years later compared to men and is more often of functional nature: less obstructive and more diffuse patterns of coronary artery disease and microvascular coronary artery disease. Males typically have focal calcified plaques, while in females more soft plaques are observed[32,34–36]. Despite later onset, and less obstructive CVD, the clinical outcome in women is not better than in men[36].

Several retrospective cohort studies have been published on long-term health outcomes (for overview, see Table 4). Three small retrospective studies found no evidence of an increased risk for coronary heart disease (CHD) and mortality in women with polycystic ovaries. These studies were all prone to selection and/or information bias due to their design and heterogeneous inclusion criteria. The largest retrospective study on this subject was conducted by retrieving all women for which a PCOS diagnosis ($n = 2560$) was registered at hospitalization in Western Australia. A similar number of age-matched controls were selected from the same source. These data were combined with national registries on pregnancy, cancer and mortality. In contrast to the previously three mentioned smaller studies, Hart and Doherty showed that ischemic heart disease (hazard ratio (HR) 2.89; 95% CI 1.68–4.97) and all-cause mortality (HR 1.89; 95% CI 1.12–3.17) were higher in women with PCOS[37] (Table 4). However, the use of a hospital registry as the starting point for this study may give rise to inclusion bias.

Data on CVD and mortality in peri- and postmenopausal women with PCOS remain scarce and inconsistent (Table 5). A study from the 1990s reports that the estimated risk for a myocardial infarction was increased seven times in peri- and postmenopausal women with PCOS compared to healthy controls[47]. After re-analysis of these data and extended follow-up, no significant difference was found in CVD between women with PCOS and healthy controls[38].

Table 4. Retrospective studies regarding women with polycystic ovarian syndrome (PCOS): intermediate and cardiovascular disease (CVD) outcomes.

Authors, year	*PCOS vs. controls. Mean or median age at follow-up (years)*	*Diagnostic criteria for PCOS*	*Intermediate outcomes*	*CVD outcomes*
Pierpoint *et al.*, 1998[44]	$n = 786$, compared to national rates, mean age 26.4 years, mean follow-up at 30 years	Histological or macroscopic evidence of polycystic ovaries, clinical signs of ovarian dysfunction including signs of androgen excess	Similar diabetes mellitus	All-cause mortality and mortality due to circulatory disease were similar, increased diabetes-related mortality within PCOS group
Wild *et al.*, 2000[a][45]	$n = 61$ vs. 63, mean age at endpoint 56.7 years (38–98), follow-up at 31 years	AE-PCOS, Rotterdam criteria	More diabetes, hyperlipidemia, obesity, hypertension	Coronary heart disease similar
Elting *et al.*, 2001[41]	$n = 345$ vs. 8950, mean age 38.7 years, follow-up at 45–54 years	Oligo- or amenorrhea and elevated LH	More hypertension and diabetes mellitus	Similar cardiac complaints (defined as: 'serious cardiac complaints or cardiac arrest')
Hart & Doherty, 2015[37]	$n = 2566$ vs. 25 660, median age 35.8 years	Rotterdam criteria used from 2004, not for inclusions between 1997 and 2004	More diabetes mellitus, obesity, hypertensive disorders, depression	More ischemic heart disease, cerebrovascular attack, all-cause mortality

n, number of patients; AE-PCOS, Androgen Excess and PCOS Society; LH, luteinizing hormone.
[a], Additional analyses with additional inclusions from Pierpoint and colleagues.

Table 5. Cross-sectional studies in postmenopausal women with polycystic ovarian syndrome (PCOS) versus controls.

Author, year	*PCOS vs. controls, age at follow-up (years)*	*Diagnostic criteria for PCOS*	*Intermediate outcomes*	*Cardiovascular disease outcomes*
Dahlgren *et al.*, 1992[47]	$n = 33$ vs. 132 age 40–61	Histological evidence of PCOS	Triglycerides ns, increased risk for type 2 diabetes mellitus, hypertension and increased waist–hip ratio	Estimated relative risk of 7.4 for myocardial infarction, based on severity of present risk factors
Cibula *et al.*, 2000[48]	$n = 28$ vs. 752 age 45–59	Histological evidence of PCOS with oligo- or amenorrhea, hirsutism, anovulatory infertility	Increased BMI, waist circumference, waist–hip ratio, hyperlipidemia; arterial hypertension ns	Non-insulin-dependent diabetes mellitus and coronary artery disease increased in PCOS
Krentz *et al.*, 2007[39]	$n = 66$ vs. 647 mean age 72 ± 9 vs. 74 ± 8	Putative PCOS phenotype[c]	Increased BMI, waist circumference, cholesterol (total, LDL, HDL), free testosterone, plasma glucose, HOMA-IR; systolic and diastolic blood pressures ns	Cardiovascular disease ns
Shaw *et al.*, 2008[51] *Retracted*	$n = 104$ vs. 286 mean age 62.5 ± 10 vs. 65.8 ± 9	NIH, Rotterdam, AE-PCOS	Increased hypertension, diabetes mellitus, triglycerides, BMI, waist–hip ratio, HOMA-IR	Increased angiographic coronary artery disease, 5-year cardiovascular event-free survival of 78.9% vs. 88.7% ($p = 0.006$) (cardiovascular event: myocardial infarction, cerebrovascular accident both fatal and non-fatal)
Schmidt *et al.*, 2011[b][38]	$n = 32$ vs. 95 age 61–79	Rotterdam	BMI, waist circumference ns	Myocardial infarction, stroke, all-cause mortality ns
Armeni *et al.*, 2013[46]	$n = 43$ vs. 286 mean age 55.6 ± 7.8 vs. 55.3 ± 5.5	Putative PCOS phenotype[c]	Increased BMI, waist–hip ratio, (central) systolic blood pressure, insulin, free androgen index and pulse wave velocity ($p < 0.001$); carotid intima-media thickness ns	Presence of plaques in common carotid artery, carotid bulb and internal carotid artery ns, subclinical atherosclerosis[d] ns
Polotsky *et al.*, 2014[50]	$n = 497$ vs. 20 249 age 57–59 years	Hyperandrogenism and irregular menses	Metabolic syndrome ns	Self-reported myocardial infarction and stroke ns
Merz *et al.*, 2016[a][49]	$n = 25$ vs. 270 mean age 62.6 ± 11.6 vs. 64.8 ± 9.6	Clinical or biochemical hyperandrogenism and irregular menses	Not applicable	Coronary artery disease and 10-year mortality ns

BMI, body mass index; HOMA-IR, insulin resistance; ns, not significant; LDL, low density lipoprotein; HDL, high density lipoprotein; *n*, number of patients; *p*, *p*-value.
[a], Re-analyses of Shaw *et al.*; [b], follow-up on similar population as the Dahlgren *et al.* publication; [c], putative PCOS phenotype = two out of three criteria: irregular menses, infertility not attributed to the partner, insulin resistance or fasting plasma in the highest quintile, central obesity (waist circumference >88 cm) and clinical or biochemical hyperandrogenism (excessive facial hair or androgenic pattern hair loss, free testosterone in the highest quintile or sex hormone binding globulin in the lowest quintile); [d], subclinical atherosclerosis = intima-media thickness >0.9 mm and/or atherosclerotic plaque in the common carotid artery, carotid bulb or internal carotid artery.

A small study of 28 PCOS patients and 752 controls, in which an increased rate of non-insulin-dependent diabetes mellitus was seen in PCOS patients, supports that women with PCOS have an increased risk for coronary artery disease (CAD)[48]. A larger study in non-diabetic postmenopausal women ($n = 713$) reports that the number of present features of the putative PCOS phenotype is also associated with CAD. However, this association is not significant in the total PCOS population consisting of women with and without diabetes[39]. Postmenopausal women ($n = 497$) with a history of irregular menses and hyperandrogenism, disregarding ovarian morphology, show an increased risk for

self-reported myocardial infarction and stroke, compared to controls ($n = 20\,249$)[50].

There are multiple possible hypotheses concerning possible mechanisms behind the absence of increased CVD in postmenopausal women with PCOS despite the metabolic derangements present early in life[11]. The increased androgen concentrations in women with PCOS could have an influence on CVD in later life. In a large cohort in Sweden consisting of 6440 perimenopausal women (aged between 50 and 59 years), lower serum androgen concentrations were found in women with PCOS who had CAD compared to women without CAD. This might suggest that androgens have a protective role in progression to CAD in women with PCOS[40]. In the general Dutch female population (34–55 years old), the prevalence of diabetes mellitus increases with age. This was also the case in women with PCOS. However, cardiac complaints were not more often reported by women with PCOS, but were more often reported in the general Dutch population as age increases. Another remarkable observation was that BMI differences between PCOS patients and the general population lose their significance as age increases[41]. This phenomenon could also play a role in similar CVD risk among woman with PCOS and healthy controls. It should be noted in this context that the normalization of regular menstrual cycles with increasing age, along with a later age of menopause in women with PCOS, may also affect cardiovascular risk. Finally, other – as yet unknown – protective factors may exist.

Conclusion

Women with PCOS have increased risk for cardiovascular disease based on an unfavorable cardiovascular profile and surrogate markers for cardiovascular disease such as flow-mediated dilation, carotid intima-media thickness and coronary artery calcium. Whether these women truly have an increased risk for cardiovascular disease and mortality is still unknown. Large cohorts, all subjected to multiple biases, show contrasting results on the prevalence of cardiovascular disease in peri- and postmenopausal women with PCOS. The role of androgens in later life of women with PCOS remains unclear and must be clarified. More important is the need for large, prospective cohort studies with well-phenotyped women with PCOS and standardized long-term follow-up.

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