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The cardiovascular risk profile of middle-aged women with polycystic ovary syndrome

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Abstract

Objectives: Contradictory results have been reported regarding the association between polycystic ovary syndrome (PCOS) and cardiovascular disease (CVD). We assessed the cardiometabolic phenotype and prevalence of CVD in middle-aged women with PCOS, compared with age-matched controls from the general population, and estimated 10-year CVD risk and cardiovascular health score.

Design: A cross-sectional study.

Participants: 200 women aged >45 with PCOS, and 200 age-matched controls.

Measurements: Anthropometrics, insulin, lipid levels, prevalence of metabolic syndrome and type II diabetes. Ten-year Framingham risk score and the cardiovascular health score were calculated, and carotid intima-media thickness (cIMT) was measured.

Results: Mean age was 50.5 years (SD = 5.5) in women with PCOS and 51.0 years (SD = 5.2) in controls. Increased waist circumference, body mass index and hypertension were more often observed in women with PCOS ($P < .001$). In women with PCOS, the prevalence of type II diabetes and metabolic syndrome was not significantly increased and lipid levels were not different from controls. cIMT was lower in women with PCOS ($P < .001$). Calculated cardiovascular health and 10-year CVD risk were similar in women with PCOS and controls.

Conclusions: Middle-aged women with PCOS exhibit only a moderately unfavourable cardiometabolic profile compared to age-matched controls, even though they present with an increased BMI and waist circumference. Furthermore, we found no evidence for increased (10-year) CVD risk or more severe atherosclerosis compared with controls from the general population. Long-term follow-up of women with PCOS is necessary to provide a definitive answer concerning long-term risk for CVD.

Cindy Meun and Marlise N Gunning consider that the first two authors should be regarded as joint First Authors.

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cardiovascular disease (7), polycystic ovary syndrome

1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in women worldwide.[1] Risk factors for CVD are more prevalent and tend to cluster in women with polycystic ovary syndrome (PCOS).[2,3] This syndrome represents the most common endocrine disorder in women of reproductive age, with a prevalence of up to 15%.[4] PCOS has been associated with cardiometabolic abnormalities such as obesity, dyslipidemia, type II diabetes, hypertension and the metabolic syndrome, which increase the risk for CVD.[5,6] PCOS is a syndrome characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology.[7] The phenotype of PCOS is modified by body mass index (BMI) and ethnicity, generally becomes milder with increasing age, and disappears largely after menopause.[8-10] The cardiometabolic abnormalities associated with PCOS can, however, persist beyond the onset of menopause.[5,8,11]

In the past, it was assumed that women with PCOS would be more prone to develop CVD later in life.[12] The only available long-term follow-up study in women with PCOS did, however, not reveal an increased risk for CVD.[6] More recent studies in postmenopausal women with features of PCOS seem to reinforce these findings.[11,13] At the same time, others suggest an increased incidence of CVD in women with PCOS already at an early age.[14-16] Whether or not women with PCOS are at increased risk to develop CVD still remains uncertain. Long before the onset of cardiovascular events, atherosclerosis can be detected. Carotid intima-media thickness (cIMT) is a marker of subclinical atherosclerosis and can be used to predict future cardiovascular events.[17] In women with PCOS, an increased cIMT has been described, which suggests an increased risk for accelerated atherosclerosis compared to the general population.[18] It remains to be determined to what extent these surrogate markers translate into real cardiovascular events later in life.[19]

In addition to markers used to detect (early) signs of CVD, models have been developed to estimate cardiovascular health and cardiovascular disease risk.[20,21] The Framingham study has provided an algorithm to predict the risk for future CVD, based on factors such as smoking, BMI and cholesterol levels.[21] At the same time, the American Heart Association has identified factors and behaviours, which improve cardiovascular health and reduce death from CVD. The simultaneous presence of ideal health factors and behaviours in an individual is associated with longevity and healthy ageing.[20,21] Not much is known about the performance of women with PCOS in these models.

The aim of the current study was to assess the cardiometabolic phenotype and prevalence of CVD in middle-aged women previously diagnosed with PCOS, compared with age-matched controls from the general population. We compared the cardiovascular profile and assessed the presence of subclinical atherosclerosis, by measuring cIMT. In addition, we assessed differences in the estimated cardiovascular health score and 10-year CVD risk between the aforementioned populations.

2 | METHODS

2.1 | Patients

Women aged ≥40 years who were previously diagnosed with PCOS in one of the three participating university hospitals were eligible for inclusion. All patients had in the past underwent a standardized examination, involving a questionnaire, anthropometric measurements, hormonal evaluation and a transvaginal ultrasonography to assess ovarian volume and follicle count. This protocol has been described in detail elsewhere [22] Diagnosis of PCOS was based on the Rotterdam criteria and established during the reproductive years.[10] According to these criteria, PCOS is diagnosed when either two or three of the key features are present: ovulatory dysfunction, polycystic ovarian morphology and clinical and/or biochemical hyperandrogenism.[7] In total, around 850 women had previously been diagnosed and phenotyped by this standardized screening and by now reached the age of 40. Women with a poor ability of speaking or understanding of Dutch or English language or who were currently pregnant were excluded. All other women with PCOS aged >40 were invited to participate in the current study. Women visiting the outpatient clinic underwent an extensive endocrine and cardiovascular assessment, which included general medical, obstetric and family history, education level, smoking status and anthropometric measurements. Visualization of both carotid arteries was done using ultrasound. This study was approved by the institutional review board of the University Medical Center Utrecht, University of Utrecht and registered at www.clinicaltrials.gov, registration number NCT02616510. Written informed consent was obtained from all participants.

2.2 | Controls

The control group was derived from the Rotterdam Study, a prospective population-based cohort study focusing on health and diseases in the elderly. We selected 200 women included in the third cohort of the Rotterdam Study. The third cohort includes inhabitants of the municipality of Ommoord, Rotterdam aged >45 years, and was recruited between 2006 and 2008. Participants are examined extensively at the research centre every 3-5 years. The rationale and design of this study have been described in detail elsewhere.[23] All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. The Rotterdam Study has been approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by

the Ministry of Health, Welfare and Sports of the Netherlands. National trial registry number NTR6831.

2.3 | Endocrine and cardiovascular assessment of women with PCOS and controls

On the day of the assessment, fasting blood samples were collected and assessed.[2,24] We measured cholesterols, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride serum levels. Furthermore, insulin and glucose levels, aspartate transaminasel (ASAT) and alanine transaminase (ALAT), androgens, gonadotropins, sex hormone-binding globulin (SHBG) and oestradiol (E_2) levels were determined. Brain natriuretic peptide (NT-proBNP), a marker for heart failure, was also measured. The free androgen index was calculated as (Testosterone/SHBG)*100. Waist to hip ratio was calculated as waist circumference/hip circumference. Blood pressure was measured once in cases and twice in controls, in sitting position after at least five minutes of rest with a random-zero sphygmomanometer. Insulin resistance was assessed with the homoeostasis model assessment (HOMA-IR). Insulin was converted to mU/L, and next, the HOMA-IR was calculated as: fasting serum insulin (mU/L) x fasting plasma glucose (mmol/L) /22.5. Diabetes was defined as a fasting glucose level of ≥ 7.0 mmol/L, use of anti-diabetic medication or self-reported diagnosis. Hypertension was defined as systolic blood pressure (SBP) >139 mm Hg or diastolic blood pressure (DBP) >89 mm Hg or use of antihypertensive medication. The National Cholesterol Education Program (NCEP) definition was used to determine the presence of the metabolic syndrome.[25] According to this definition, metabolic syndrome is present when ≥3 of the following features are present: waist circumference ≥88 cm, fasting glucose ≥ 6.1 mmol/L, blood pressure >129/84 mm Hg, high-density lipoprotein (HDL) <1.3 mmol/L and triglycerides (TG) ≥ 1.7 mmol/L. Vitamin D deficiency was defined as a 25-OH-D serum of <50 nmol/L.

2.4 | Carotid intima-media thickness for women with PCOS and controls

We used cIMT to assess subclinical atherosclerosis in middle-aged women with PCOS and age-matched controls from the general population. cIMT was defined as the distance between the lumen intima and the media-adventitia and measured three times at both sides over 1 centimetre length and at least 0.5 centimetres proximal of the bifurcation of the common carotid artery, or at the beginning of the dilatation of the distal common carotid artery across a length of 1 centimetre.[26-28] The mean of the right and left carotid arteries was used for analysis. Ultrasound measurements were performed by trained professionals at the respective research centre. Multiple devices were used for ultrasound measurements. In women with PCOS, the Panasonic CardioHealthStation (Yokohoma, Japan), Esaote MyLabTMOne and the ToshibaAplioArtida Medical System were used. Measurements with the various machines yielded similar results across the different research centres (Table S1). In controls, the ATL UltraMark IV (Advanced Technology Laboratories, Bothell) was used.

2.5 | Other measurements

Women with PCOS with FSH serum levels of >40 (U/L) in combination with an amenorrhoea were labelled as postmenopausal. In controls, postmenopausal status was self-reported via questionnaire. Information on prevalent CVD (stroke, myocardial infarction and/or coronary heart disease) was self-reported or obtained through general practitioners or hospital discharge reports. Smoking status was labelled as ever or never smoker. Former smokers and current smokers were grouped as 'ever smokers' as it was not known how long ago women had stopped smoking. Ethnicity was self-reported.

The 10-year CVD risk was calculated according to the Framingham Risk Score (FRS), and based on age, SBP, HDL and total cholesterol, smoking and the presence of type II diabetes.[21] Low risk was defined as a 10-year CVD risk <10%, 10%-20% as intermediate 10-year CVD risk, and >20% was marked as high 10-year CVD risk CVD. Next, we calculated the CHS in women with PCOS and controls.[20] The CHS was introduced by the American Heart Association and encompasses health factors (cholesterol and glucose serum levels, blood pressure and BMI) and behavioural factors (smoking, dietary intake and physical activity). Information on 5 out of the 7 factors (cholesterol, glucose, blood pressure, smoking status and BMI) was available in our study population. We did not have information on dietary intake and physical activity. However, measures of these parameters have been marked to be prone to sampling variability and misclassification.[29,30] Therefore, we calculated a composite CHS based on the 5 available parameters and assessed the mean CHS and performance of cases and controls on each of the health metrics.

2.6 | Statistical analysis

For each case, a control was age-matched 1:1, from the Rotterdam study cohort, using propensity score matching (PSM) greedy approach. PSM was based on a logistic regression model that includes PCOS vs no PCOS as a dichotomous outcome and age as the only covariate under study. Hosmer-Lemeshow test was used to evaluate goodness-or-fit of the models. Transformation of age was used based on lowess graph in order to choose the best fitting model. Standardized differences and plots of propensity scores distribution between PCOS and control group, before and after matching procedure, were made to evaluate the balance achieved.

All statistical analysis were performed with IBM SPSS statistics version 24 (IBM Corp.) and STATA version 14.2 (Station College). A two-sided $P < .05$ denoted statistical significance. Baseline characteristics were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and as proportions (%) for dichotomous variables. Continuous variables with a normal distribution were compared with the student t test and with Mann-Whitney U for nonnormally distributed variables. Chi-square test or Fisher's exact test were used for categorical variables. Linear

regression was used to assess cIMT. cIMT was log transformed to obtain a normal distribution. Results were expressed as regression coefficients (β) and corresponding 95% confidence intervals (95%CI). To eliminate the effect of possible confounders, we adjusted for BMI, smoking status, education level, research centre and menopausal status.

Finally, using the propensity score matching (greedy approach), we also matched cases and controls on both age and BMI and repeated all the analyses to examine the effect of BMI on the cardiometabolic profile of women with PCOS.

3 | RESULTS

3.1 | General and cardiometabolic characteristics

In this cross-sectional study, we compared 200 women diagnosed with PCOS with 200 age-matched controls from the general population. The baseline characteristics of the total study population are presented in Table 1. The mean age was similar in women with PCOS (50.5 years, SD = 5.5) and controls (51.0 years, SD = 5.2). Women with PCOS had experienced menarche at a later age (13.7, SD = 2.6 vs 12.8, SD = 1.6 [$P < .001$]) and had more often experienced cycle irregularities in the past (69.8% vs 12.5% [$P < .001$]). Compared to women with PCOS, a much larger proportion of the control population was already postmenopausal (40.5% vs 12.6% [$P < .001$]). Women with PCOS were less often smokers (41.5% vs 64.8% [$P < .001$]) and had more often attended higher general education or university ($P < .001$). The free androgen index was significantly higher in women with PCOS (1.9 IQR 1.2-2.9 vs 1.2, IQR 0.8-1.7 [$P < .001$]), as well as serum levels of E_2 ($P = .028$), whereas SHBG levels were significantly lower ($P < .001$).

We observed a higher BMI (28.4, IQR 23.8-32.9 vs 26.3, IQR 23.7-29.8 [$P = .015$]), higher SBP (130.0, IQR 120.0-140.0 vs 122.0, IQR 112.0-136.0 [$P = .003$]) and increased waist circumference (93.0, IQR 84.5-107.0 vs 85.9, IQR 79.5-94.6 [$P < .001$]) in women with PCOS. Moreover, the prevalence of hypertension (48.2% vs 26.5% [$P < .001$]) was increased and we observed higher glucose levels (5.3, IQR 5.0-5.7 vs 5.1, IQR 4.8-5.5 [$P = .019$]). No differences were found in serum lipid levels, NT-pro-BNP and vitamin D levels, prevalence of cardiovascular disease or type II diabetes. The prevalence of the metabolic syndrome was higher in women with PCOS, but this result did not reach statistical significance. The HOMA assessment of insulin resistance yielded similar results ($P = .647$). When we repeated the analyses in an age and BMI matched control population of 171 women, the analyses yielded similar results (data not shown).

3.2 | Carotid intima-media thickness

We observed a lower mean cIMT (um) in women diagnosed with PCOS compared to age-matched controls (612.8, SD = 93.6 vs 721.7, SD = 118.4 [$P < .001$]). The latter was consistent across all participating university hospitals (Table S1). In a linear regression model after adjusting for BMI, smoking, SBP, education, measurement centre and menopausal status, we found that PCOS was associated with a lower cIMT β (95%CI) −0.212 (−0.283-0.142, $P < .001$).

3.3 | Ten-year cardiovascular disease risk and the cardiovascular health score

The median 10-year CVD risk was 5.79% in women with PCOS and 7.38% in controls ($P = .214$). Next, we categorized women into low (<10%), intermediate (10%-20%) and high (>20%) risk for a cardiovascular event in the subsequent 10 years. We observed no significant differences in the proportion of women with PCOS and controls in each risk category ($P = .388$, Figure 1).

The composite cardiovascular health score was calculated in all patients and controls with available information on all health metrics. We used information on BMI, blood pressure, glucose and cholesterol serum level and smoking status. We were able to calculate the CHS in 158 cases and 199 controls. The mean (SD) CHS in PCOS women was 5.69 (2.18) and 5.71 (1.99) in controls ($P = .915$). The performance of women with PCOS and controls on each of the separate cardiovascular health metrics are presented in Figure 2.

4 | DISCUSSION

In this large cross-sectional study in women with PCOS around the age of 50, we observed that women with PCOS exhibit only a moderately unfavourable cardiometabolic profile compared to age-matched controls, despite a higher BMI and larger waist circumference. The prevalence of major risk factors for CVD or CVD itself was not increased, and we found no evidence for more severe atherosclerosis in women suffering from PCOS. Finally, the aggregated measure of 10-year CVD risk and overall performance on cardiovascular health metrics in women with PCOS were similar to age-matched controls from the general population.

PCOS is associated with cardiometabolic disturbances, which can persist throughout life.[5,11] Indeed, we observed that compared with age-matched controls, waist circumference, BMI, SBP and androgen levels were all significantly higher and the prevalence of hypertension was nearly 50%. At the same time, we observed no differences in lipid levels of women with PCOS and age-matched controls. In addition, neither HOMA-assessed insulin resistance, nor the prevalence of type II diabetes, metabolic syndrome or CVD was significantly increased at the age of 50, despite of a higher BMI and blood pressure in women with PCOS. Atherosclerosis can be detected with cIMT and used as a predictor for future CVD. In the current study, we measured a lower cIMT in women with PCOS. Variability in measuring techniques and devices may have influenced our results, baring reason for caution. However, this finding indicates that atherosclerosis is not more advanced in women with PCOS.[17,31] In line with this, both the estimated Framingham 10-year CVD risk and the cardiovascular health score, used to predict longevity and healthy ageing, were similar in women with PCOS and age-matched controls. Of note, repeating all analyses with an age-BMI matched control

TABLE 1 Characteristics of the total study population

	PCOS (N = 200)	Control (N = 200)	*P*-value
General/Obstetric parameters			
Age (years)	50.5 (5.5)	51.0 (5.2)	.35
BMI (kg/m^2)	28.4 (23.8-32.9)	26.3 (23.7-29.8)	.02
Ethnicity (Northern-European)	170 (85.4%)	175 (87.5%)	.50
Ever smoker	78 (41.5%)	129 (64.8%)	<.001
Age at menarche (years)	13.7 (2.6)	12.8 (1.6)	<.001
Postmenopausal	25 (16.0%)	81 (40.5%)	<.001
OCP use (ever)	166 (83.4%)	182 (91%)	.02
Amenorrhoea (at age 25)	14 (6.9%)	3 (1.5%)	<.001
Oligomenorrhea (at age 25)	127 (62.9%)	22 (11.0%)	
Regular cycle (at age 25)	35 (17.3%)	131 (65.0%)	
Education			
Primary	2 (1.1%)	18 (9.0%)	<.001*
Lower/intermediate or lower vocational	34 (18.0%)	77 (38.7%)	
Intermediate vocational or higher general	70 (37.0%)	54 (27.1%)	
Higher vocational or university	79 (31.8%)	50 (25.1%)	
Anthropometrics			
Waist (cm)	93.0 (84.5-107.0)	85.9 (79.5-94.6)	<.001
Hip (cm)	107.0 (99.5-114.0)	106.5 (100.8-112.6)	.68
Waist/Hip ratio	0.88 (0.83-0.93)	0.81 (0.77-0.86)	<.001
Cardiometabolic parameters			
Systolic BP (mm Hg)	130.0 (120.0-140.0)	122 (112.0-136.0)	<.01
Diastolic BP (mm Hg)	82.7 (11.3)	81.2 (11.3)	.19
Hypertension	96 (48.2%)	53 (26.5%)	<.001
Prevalent CVD	3 (1.5%)	3 (1.5%)	1.00
Lipid lowering medication	13 (6.5%)	31 (15.6%)	<.01
Total cholesterol (mmol/L)	5.3 (4.5-6.0)	5.3 (4.8-6.1)	.44
HDL cholesterol (mmol/L)	1.5 (1.2-1.8)	1.5 (1.2-1.8)	.68
LDL cholesterol (mmol/L)	3.3 (2.7-4.0)	3.1 (2.6-3.9)	.42
Triglycerides (mmol/L)	1.0 (0.8-1.6)	1.1 (0.8-1.5)	.35
ASAT (U/L)	22.0 (19.0-25.0)	21.0 (18.0-23.0)	.09
ALAT (U/L)	21.0 (16.0-30.0)	20.0 (17.0-25.0)	.38
Gamma-GT (U/L)	20.0 (15.0-29.0)	17.0 (13.0-27.0)	.02
NT-pro-BNP (pmol/L)	7.0 (4.0-13.0)	6.2 (4.1-11.1)	.40
Elevated NT-pro-BNP (>15 pmol/L)	27 (14.2%)	27 (18.8%)	.26
Insulin (pmol/L)	74.0 (47.0-117.0)	72.0 (55.0-105.0)	.83
Glucose (mmol/L)	5.3 (5.0-5.7)	5.1 (4.8-5.5)	.02
HOMA-IR	2.68 (1.54-4.33)	2.43 (1.71-3.69)	.65
Diabetes	22 (11.1%)	13 (6.5%)	.11
Metabolic syndrome (NCEP definition)	45 (25.0%)	34 (17%)	.06
Mean carotid cIMT (um)	612.8 (93.6)	721.7 (118.4)	<.001
Endocrine parameters			
FAI	1.9 (1.2-2.9)	1.2 (0.8-1.7)	<.001
Testosterone (nmol/L)	0.9 (0.6-1.2)	0.8 (0.6-1.1)	.041
SHBG (nmol/L)	48.5 (34.3-70.7)	69.6 (46.7-100.4)	<.001

(Continues)

TABLE 1 (Continued)

	PCOS (N = 200)	Control (N = 200)	*P*-value
Androstenedione (nmol/L)	2.6 (1.9-3.7)	3.0 (2.1-4.0)	.02
DHEA (nmol/L)	9.8 (6.1-14.3)	13.9 (9.5-20.9)	<.001
E2 (pmol/L)	150.5 (41.3-383.3)	78.8 (18.4-346.1)	.03
Vitamin D deficiency	55 (36.9%)	78 (41.7%)	.48

Note: Values are displayed as Means (standard deviation) or medians (interquartile range), or as numbers (percentage). Differences were tested with Student's t test for variables with a normal distribution, and Mann-Whitney U test was used for variables with a skewed distribution. Chi-square test or Fisher's exact test were used for categorical variables Abbreviations: Body mass index (BMI), oral contraceptive pill (OCP), blood pressure (BP), cardiovascular disease (CVD), high-density lipoprotein (HDL), low-density protein (LDL), aspartate aminotransferase (ASAT and, alanine aminotransferase (ALAT).
*use of Fisher's exact test.

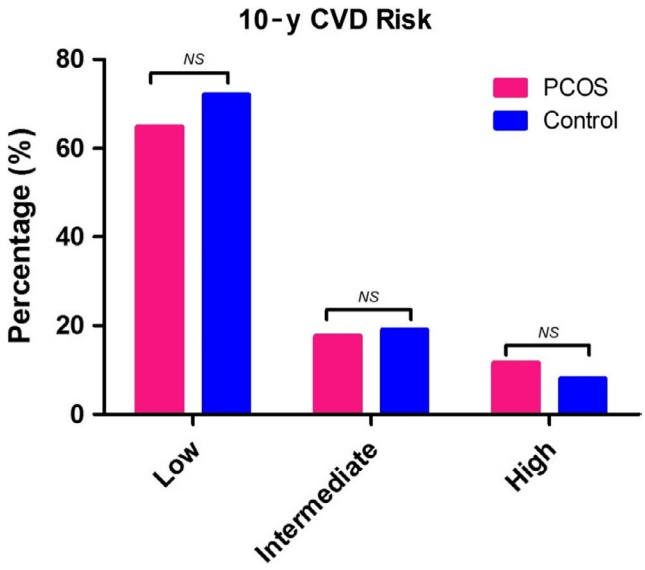

FIGURE 1 Ten-year risk for CVD in women with PCOS and controls. The 10-year risk for CVD in women with PCOS and age-matched controls. A risk of <10% was marked as low risk, 10%-20% as intermediate and >20% as high risk. Abbreviations: polycystic ovary syndrome (PCOS), not significant (NS)

population yielded similar results, suggesting the outcomes of our study were not driven by the higher BMI in women with PCOS.

Previous studies report an increase of CVD risk factors in women with PCOS, such as dyslipidemia, insulin resistance, type II diabetes and metabolic syndrome. This risk is increased by the presence of PCOS per se, but also strongly correlated with BMI as overweight and obese women with PCOS are most at risk.[6,16,32,33] The relatively low BMI in our PCOS cohort could explain the seemingly contradictory results in the prevalence of metabolic syndrome and type II diabetes.[32,33] However, it also seems as if some metabolic disturbances associated with PCOS are detectable at any age, whilst others seem to disappear over time.[2,5,6,34] Evidence suggests that of the lipid disturbances associated with PCOS, increased triglyceride levels are the only lipid abnormality still detectable at older age.[5,6,11,13] The same pattern seems to apply to the metabolic syndrome, which has been described to be five times as prevalent in young women with PCOS, but to remain only two times as prevalent after the age of 39.[5,13] Another possible explanation for this could also be that these women were already diagnosed early on during their reproductive years and were also informed about their long-term health risks, which they might have adjusted accordingly in the years following initial diagnosis.

Conflicting results have been reported on cIMT and CVD in women with PCOS.[3,18,35] Data on cIMT in middle-aged and older women with (features of) PCOS are scarce, but most evidence suggests a higher cIMT.[3,11,36] The lower cIMT in women with PCOS compared to age-matched controls in our study could be explained by the small proportion of women with PCOS who were postmenopausal at the age of 50. The menopausal transition is associated with an increase in cIMT.[31] The fact that on average, women with PCOS enter menopause at a later age could have a protective effect on the development of atherosclerosis and risk for future CVD.[37,38] Indeed, most evidence points into the direction that the risk for CVD in women with PCOS is not increased. A recent large Danish study in women with PCOS, however, demonstrated higher incidence rates of CVD already an early age.[14] In this study, hypertension and dyslipidemia were considered cardiovascular diseases and comprised the majority of CVD diagnosis. The event rate for stroke was not increased and the event rate for ischaemic heart disease in women with PCOS was slightly increased but included milder forms of ischaemic heart disease (angina) in the definition.[14] Similarly, in the current study we detected a much higher prevalence of hypertension in women with PCOS, but the prevalence of cardiovascular events was similar to the general population and NT-proBNP as a marker for heart failure was not increased. We believe most evidence still points into the direction that long-term risk for CVD events (stroke, myocardial infarction and/or coronary heart disease) in women with PCOS might not be increased.[6,11,13]

How is it possible that so many known risk factors for CVD cluster in women with PCOS already at an early age, yet this does this not seem to translate into an increased risk for cardiovascular disease later in life? It might be that there is an early worsening in risk factors for CVD in women with PCOS, which does not seem to progress much over the years.[5,6] Again the latter might be due to the fact that women are aware of these risk factors and do anticipate accordingly to them. This in contrast to controls who seem to develop metabolic abnormalities gradually over time and apparently end at a similar level as women with PCOS. Furthermore, genetic studies have provided us

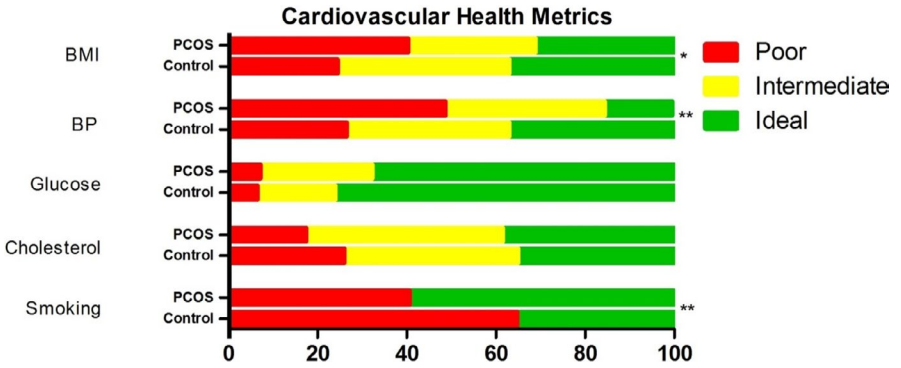

FIGURE 2 Performance of women with PCOS and controls on cardiovascular health metrics. Prevalence (%) of poor, intermediate and ideal cardiovascular heath metrics in women diagnosed with PCOS and controls. A *denotes statistical significance of <0.01, **denotes a statistical significance of <0.001. Abbreviations: BMI, body mass index; BP, blood pressure; PCOS, polycystic ovary syndrome

with clues suggesting women with PCOS might be able to compensate the damage caused by this unfavourable accumulation of risk factors. Genetic variants associated with late menopause and associated with better DNA repair and maintenance are more prevalent in women with PCOS. These variants are correlated with long-term health and longevity, suggesting a potential evolutionary advantage for women with PCOS.[39,40] Indeed, in our study the majority of middle-aged women with PCOS were not yet postmenopausal at the age of 50. Finally, hyperandrogenism is present in the majority of women with PCOS and associated with cardiometabolic abnormalities at a younger age. In the past, hyperandrogenism was suggested as a main driver for the CVD risk in PCOS.[2,34] The effects of hyperandrogenism after menopause are still heavily debated. Whilst some consider hyperandrogenism to be a risk factor for CVD, other studies have shown that hyperandrogenism is not associated with a higher risk for CVD and could even be protective against CVD.[9,11,13,41]

All of these proposed mechanisms could protect women with PCOS from developing CVD. Despite of their unfavourable profile at a younger age, long-term cardiovascular health in women with PCOS seems to be similar to that of the general population. Based on the selective enrichment with better DNA repair and maintenance genes, one could hypothesize that these women should actually be healthier compared to the general population provided that they had received proper preventive treatment in combination with a healthy lifestyle from an early age on.

This is one of the largest clinical studies assessing the cardiometabolic profile and prevalence of CVD in women diagnosed with PCOS around the age of 50. Besides availability of several subclinical measures of atherosclerosis, detailed information on study subjects made it possible to comprehensively address the cardiometabolic profile of these women and to estimate their risk for future CVD. The limitations of our study also merit consideration. Our data set is quite precise and complete; unfortunately, we were still sometimes faced with missing data. Although this was only the case for a small proportion of the data, this may have led to an underestimation of the true prevalence of for instance the metabolic syndrome, as we were not able to assess all parameters in all patients. In addition, although our study population comprised a large population of meticulously phenotyped women with PCOS, we might still have lacked sufficient power to detect small associations. Our findings therefore still need to be validated in a large cohort of women with PCOS followed up until old age.

Studies following women with PCOS until very old age will eventually provide definitive answers on the risk for CVD and the involved mechanisms. Therefore, cardiovascular assessment and follow-up of women with PCOS are still necessary. At this time, however, we conclude that although some metabolic disturbances were present in our large cohort of middle-aged women with PCOS, we found no evidence for premature atherosclerosis or an increased risk for future CVD. Only, time will tell whether this will indeed translate into a better cardiovascular health in women with PCOS than was previously anticipated.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX

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