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Clinical Research Article

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Women With Polycystic Ovary Syndrome Have an Increased Risk of Major Cardiovascular Events: a Population Study

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Abbreviations: BMI, body mass index; BP, blood pressure; CPHM, Cox proportional hazard model; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; HES, Hospital Episode Statistics; HR, hazard ratio; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems classification; IMD, Index of Multiple Deprivation; IQR, interquartile range; ONS, Office for National Statistics; OPCS-4, OPCS Classification of Interventions and Procedures version 4; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

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Abstract

Context: The effects of polycystic ovary syndrome (PCOS) on cardiovascular morbidity and mortality are unclear.

Objective: This work aims to establish the relative risk of myocardial infarction (MI), stroke, angina, revascularization, and cardiovascular mortality for women with PCOS.

Methods: Data were extracted from the Clinical Practice Research Datalink Aurum database. Patients with PCOS were matched to controls (1:1) by age, body mass index (BMI) category, and primary care practice. The primary outcome was the time to major adverse cardiovascular event (MACE); a composite end point incorporating MI, stroke, angina, revascularization and cardiovascular mortality. Secondary outcomes were the individual MACE end points.

Results: Of 219 034 individuals with a diagnosis of PCOS, 174 660 (79.7%) met the eligibility criteria and were matched. Crude rates of the composite end point, MI, stroke, angina, revascularization, and cardiovascular mortality were respectively 82.7, 22.7, 27.4, 32.8, 10.5, and 6.97 per 100 000 patient-years for cases, and 64.3, 15.9, 25.7, 19.8, 7.13, and 7.75 per 100 000 patient-years for controls. In adjusted Cox proportional hazard models (CPHMs), the hazard ratios (HRs) were 1.26 (95% CI, 1.13-1.41), 1.38 (95% CI, 1.11-1.72), 1.60 (95% CI, 1.32-1.94), and 1.50 (95% CI, 1.08-2.07) for the composite outcome, MI, angina, and revascularization, respectively. In a time-dependent CPHM, weight gain

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(HR 1.01; 1.00-1.01), prior type 2 diabetes mellitus (T2DM) (HR 2.40; 1.76-3.30), and social deprivation (HR 1.53; 1.11-2.11) increased risk of progression to the composite end point. **Conclusion:** The risk of incident MI, angina, and revascularization is increased in young women with PCOS. Weight and T2DM are potentially modifiable risk factors amenable to intervention.

Key Words: polycystic ovary syndrome, cardiovascular diseases, mortality, angina, myocardial infarction, stroke

Polycystic ovary syndrome (PCOS), the most common endocrine condition affecting young women, is characterized by hyperandrogenism, menstrual disturbance, and subfertility. In addition to its well-recognized reproductive sequelae, PCOS is now established as a metabolic disorder underpinned by defects in insulin secretion and action. We and others have confirmed that these lead to an increased risk of type 2 diabetes mellitus (T2DM) (1).

In addition to insulin resistance, women with PCOS display a range of metabolic and vascular risk factors, including central obesity (2), hypertension (3), and dyslipidemia (4), which are commonly present at a young age. Studies have shown that surrogate markers of cardiovascular risk are increased in patients with PCOS, including carotid intima media thickness (5), endothelial dysfunction (6), coronary artery calcification (7), and arterial stiffness (8). However, whether these disturbances lead to an increased risk of vascular events and mortality is still unknown. A substudy of the Women's Ischemia Evaluation Study demonstrated that women with PCOS had a higher prevalence of multivessel cardiovascular disease (CVD), and significantly lower cardiovascular event-free survival, than controls (9), results that were later retracted because of a failure to replicate these findings (10) but that have been included in previous meta-analyses (11, 12). Other population-based studies have been limited by comparatively small sample sizes and/or a failure to adjust for important confounders such as obesity (13-20). We (1) and others (21, 22) have previously failed to show an increased risk of cardiovascular events in women with PCOS, although these studies were likely underpowered because the crude incidence of cardiovascular and cerebrovascular events in this young female population is low. Longer-term population-based studies with a large sample size are therefore needed to clarify these risks further.

To address these uncertainties, we reexplored vascular outcomes in women with PCOS in a large primary care research database in the United Kingdom, with a view to exploiting the greater power offered by recent extension of this data set to provide coverage of the population on a much larger scale.

Materials and Methods

This was a retrospective cohort study using primary care data from the Clinical Practice Research Datalink (CPRD) Aurum database, a longitudinal, anonymized research database derived from 883 primary care practices in England. CPRD Aurum contains records for more than 28 million patients and is representative of the English population in terms of age, sex, and deprivation (23). Approximately 70% of practices participate in a linkage scheme, by which their patient records are linked to other data sources, including the Hospital Episode Statistics (HES) data set, which provides data on all inpatient and outpatient contacts occurring within National Health Service hospitals in the United Kingdom, and the Office for National Statistics (ONS) mortality data set. HES and ONS data are available for patients participating in the linkage scheme outside the period of primary care registration.

Diagnostic information in CPRD Aurum is recorded using a combination of SNOMED CT (UK Edition) and Read code classification, a UK primary-care practice standard. Diagnoses in HES and ONS data are recorded using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems classification (ICD-10). Surgical procedures in HES are recorded using the OPCS Classification of Interventions and Procedures version 4 (OPCS-4) classification.

Patient Selection and Matching of Controls

The study was undertaken using data from CPRD Aurum and linked HES and ONS mortality data sets. This study included patients identified by CPRD as being of an acceptable research quality (23), who were identified by diagnosis codes both from CPRD Aurum and HES, and who were eligible for linkage to the secondary care data. Patients with a diagnosis of PCOS, recorded in the primary-care data set using SNOMED codes and from HES by ICD-10 code E0.28.2, from 1998 to 2017 were selected. The earliest diagnosis date was selected as the index date and only women aged 18 years or older were included.

Patients with PCOS were then matched at a ratio of 1:1 to a set of non-PCOS controls. Controls were matched by age, body mass index (BMI) category (< 25, 25-30, > 30) and primary care practice. For all survival analysis, cases and controls were excluded if they had any diagnosis of myocardial infarction, stroke, angina, or revascularization before the index date along with their respective matched patient. All patients were then followed up until the earliest of the following: end of CPRD follow-up, end of HES follow-up, death date, or date of outcome.

End Points

The primary outcome was the time to major adverse cardiovascular event, a composite end point incorporating myocardial infarction, stroke, angina, revascularization, and cardiovascular mortality. Secondary end points were the individual major adverse cardiovascular event end points: incident myocardial infarction, stroke, angina, revascularization, and cardiovascular mortality. Myocardial infarction, stroke, and angina were defined by ICD-10 codes in the HES inpatient data set combined with a primary diagnosis and a method of admission code indicative of an emergency admission (codes 21-24). Revascularization was defined by OPCS-4 code in the HES inpatient data set. Cardiovascular mortality was defined by the ICD-10 code (I20-I25) that was considered the underlying cause of death. All outcomes were identified between 1998 and 2019.

Data Analysis

The study was powered to detect a difference in the incidence of cardiovascular events between cases and controls. Based on the results of our previous study (1), we anticipated 0.3% of controls progressing to the primary end point. A previous meta-analysis reported an odds ratio of 1.3 for coronary heart disease in PCOS cases vs controls (24). Based on an α of .05, β of .80, and a 1:1 ratio of cases to controls, this would require a sample size of 38 688 exposed cases and nonexposed controls.

Baseline characteristics between cases and controls were compared using univariate statistics (*t* test for continuous variables and chi-square tests for categorical variables). Crude rates of progression to each cardiovascular outcome were presented, and time to each end point was analyzed using Cox proportional hazards models (CPHMs). Additionally, for the composite end point a time-dependent CPHM was implemented in the PCOS cohort with weight change in kilograms in yearly increments, using a last observation carried forward approach adjusting for patient identifier as a random effect. The CPHM models included the following covariates (all were available and tested for inclusion in each model): age, BMI category, smoking status, alcohol status, T2DM, baseline morbidity represented by the Charlson index (25), systolic blood pressure (BP) and diastolic BP, and relative deprivation based on quintiles of Index of Multiple Deprivation (IMD). The IMD is an area-based measure of social and material deprivation based on various criteria, including income and education. Threshold statistical significance was *P* less than or equal to .05, and 95% CIs were given for hazard ratios (HRs). Outcomes for which the CPHM was violated were not included in the analysis or where possible were censored at an earlier time frame.

Two sensitivity analyses were undertaken. The first included only those patients who had a 3-month "wash-in" from registration date to index date to maximize the likelihood that the case represented an incident PCOS case. The second analysis censored patient follow-up as the earlier of their ONS death date, end of HES follow-up (as defined in secondary care), or date of outcome. This allowed us to follow patients beyond their primary-care registration period.

Studies using CPRD are covered by ethics approval, granted by the Trent Multicentre Research Ethics Committee (Reference 05/MRE04/87). CPRD Independent Scientific Advisory Committee approval was granted for this study (ISAC 19-166).

Results

Patient Selection and Baseline Characteristics

Of 219 034 women identified with a diagnosis of PCOS, 181 916 (83.1%) were eligible after application of the inclusion and matching criteria (Fig. 1). Of these, 174 660 (96.0%) were matched to controls.

Median follow-up was 3.83 years (interquartile range [IQR], 1.89-7.78 years) for patients with PCOS and 3.00 years (IQR, 1.37-6.36 years) for controls. Median age was 29 years (IQR, 24.00-34.00 years) both for cases and controls. There were statistically significant differences between PCOS patients and controls for several baseline variables. A greater proportion of patients with PCOS were classified with extreme obesity (4.65% vs 3.12%). In addition, there were significant differences in smoking and alcohol status, Charlson index, and systolic BP and diastolic BP (Table 1).

Prevalence of Cardiometabolic Comorbidities

At baseline, 5404 (3.09%) patients with PCOS had previously been diagnosed with T2DM compared with 2129

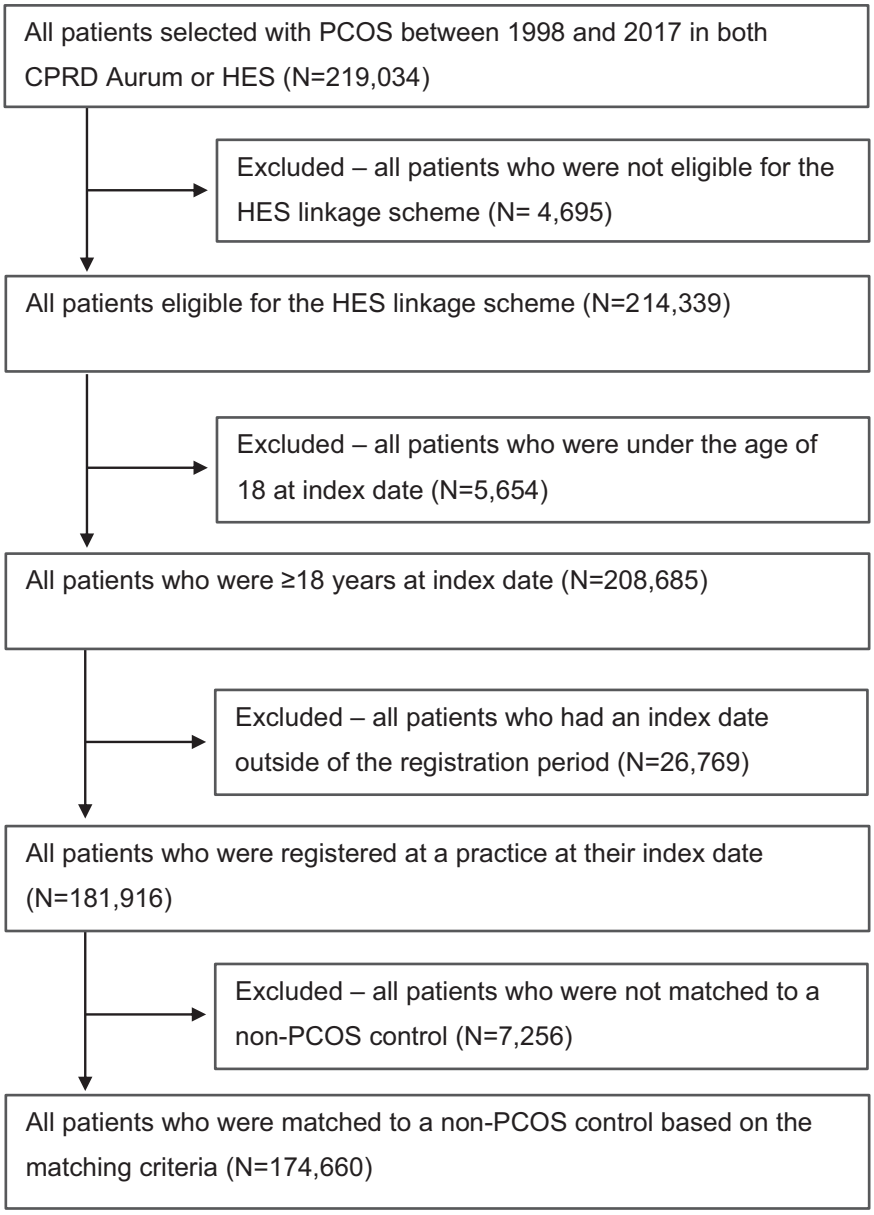

Figure 1. Attrition chart for identification of the polycystic ovary syndrome (PCOS) cohort.

(1.22%) controls ($P < .001$). Prior diagnosis of myocardial infarction was also higher in patients with PCOS (n = 181, 0.10%) compared with controls (n = 87, 0.05%; $P < .001$). There was also a significant increase in a recorded diagnosis of stroke (PCOS 624 [0.36%] vs 525 [0.30%] controls; $P = .004$) and angina (PCOS 328 [0.19%] vs 168 [0.10%] controls; $P < .001$) but not revascularization (PCOS 55 [0.03%] vs 43 [0.02%] controls; $P = .27$).

Incidence of Vascular Events

Composite end point

In the PCOS group, there were 804 incident events during the follow-up period compared with 522 in the control group. The respective rates per 100 000 patient-years (100 kpy) were 82.7 and 64.3, a relative risk (RR) ratio of 1.29 (95% CI, 1.15-1.44, $P < .001$). In the adjusted CPHM, the HR was 1.26 (95% CI, 1.13-1.41) (Table 2, Fig. 2A). Other covariates that were significant in the model were smoking status, age, BMI category, T2DM, IMD quintile, and systolic BP. In a sensitivity analysis that excluded incident events within 3 months of the index date (n = 75 657), the HR remained significant at 1.33 (95% CI, 1.14-1.55). In a sensitivity analysis that followed patients based on their secondary-care data, the RR and HR both were increased, at 1.50 (95% CI, 1.37-1.63) and 1.40 (95% CI, 1.28-1.53), respectively (Table 3).

Table 1. Baseline characteristics and prior comorbidities for patients with polycystic ovary syndrome and controls

	No.	Cases		Controls		*P*
		174 660		174 660		
Age at index, y	Median	29		29		1.000
	IQR	24.00-34.00		24.00-34.00		
Total follow-up, y	Median	3.83		3.00		< .001
	IQR	1.89-7.78		1.37-6.36		
BMI category, No., %	Underweight, < 18.5	5170	2.96%	6413	3.67%	< .001
	Normal, 18.5-24.9	47 170	27.01%	45 927	26.29%	
	Overweight, 25-29.9	27 543	15.77%	28 482	16.31%	
	Obese, 30-39.9	27 868	15.96%	29 609	16.95%	
	Extremely obese, ≥ 40	8129	4.65%	5449	3.12%	
	Missing	58 780	33.65%	58 780	33.65%	
Smoking status, No., %	Never	103 591	59.31%	102 888	58.91%	< .001
	Prior	23 085	13.22%	20 336	11.64%	
	Current	43 915	25.14%	44 060	25.23%	
	Missing	4069	2.33%	7376	4.22%	
Alcohol status, No., %	Never	22 131	12.67%	19 375	11.09%	< .001
	Prior	1001	0.57%	903	0.52%	
	Current	43 876	25.12%	40 886	23.41%	
	Missing	107 652	61.64%	113 496	64.98%	
Charlson index	Mean	0.37		0.30		< .001
	SD	0.00		0.00		
Systolic BP, No., %, mm Hg	< 120	53 268	30.50%	48 264	27.63%	< .001
	120-139	41 909	23.99%	38 485	22.03%	
	> 139	7678	4.40%	5358	3.07%	
	Missing	71 805	41.11%	82 553	47.26%	
Diastolic BP, No., %, mm Hg	< 80	68 173	39.03%	64 456	36.90%	< .001
	80-89	27 239	15.60%	23 152	13.26%	
	> 89	7443	4.26%	4499	2.58%	
	Missing	71 805	41.11%	82 553	47.26%	
Index of multiple deprivation, No., %, quintile	1	33 732	19.31%	33 643	19.26%	.48
	2	33 338	19.09%	33 102	18.95%	
	3	34 894	19.98%	34 688	19.86%	
	4	38 657	22.13%	38 933	22.29%	
	5	34 039	19.49%	34 294	19.63%	
Prior comorbidities	Type 2 diabetes	5404	3.09%	2129	1.22%	< .001
	Myocardial infarction	181	0.10%	87	0.05%	< .001
	Stroke	624	0.36%	525	0.30%	.004
	Angina	328	0.19%	168	0.10%	< .001
	Revascularization	55	0.03%	43	0.02%	.27

Abbreviations: BMI, body mass index; BP, blood pressure; IQR, interquartile range.

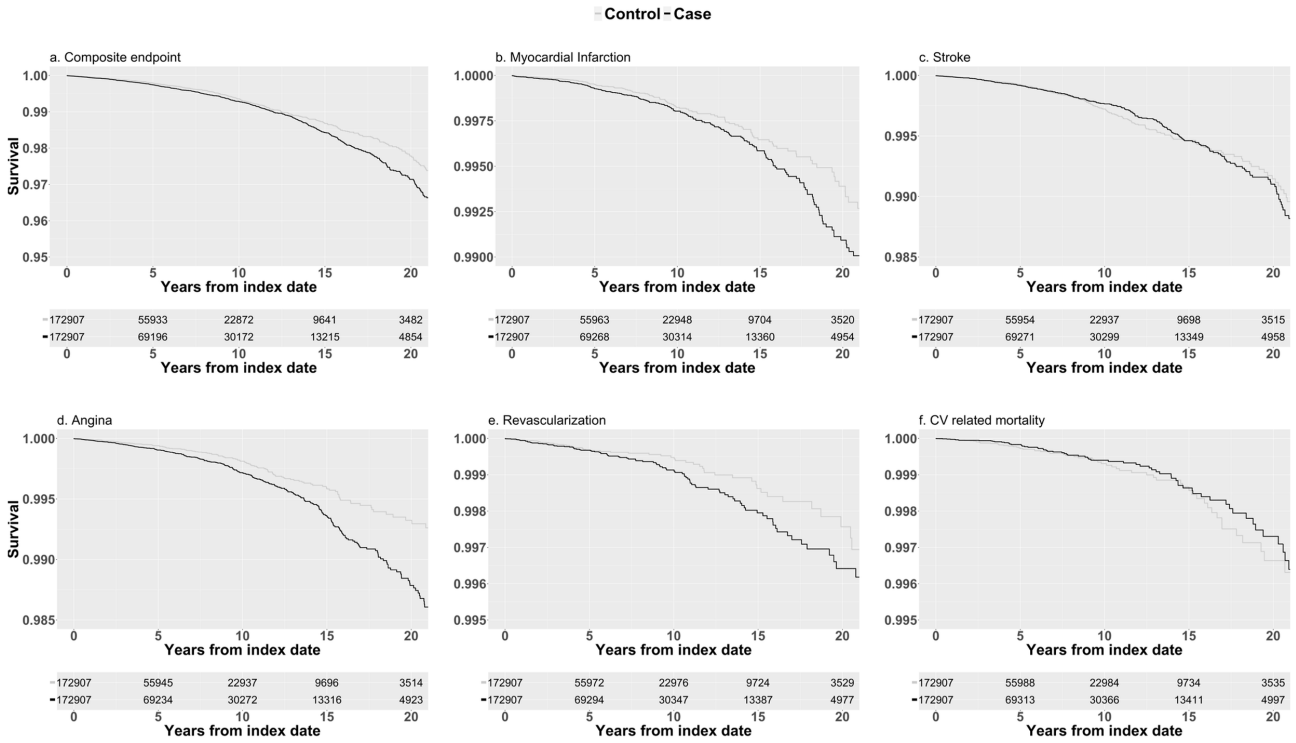

Figure 2. Time from index date to incident composite and individual vascular outcomes.

Additionally, in the time-dependent CPHM, weight increase (per kilogram) was shown to significantly increase risk (HR = 1.01, 95% CI, 1.00-1.01, $P < .001$) along with T2DM prior to index date (HR = 2.40, 95% CI, 1.76-3.30, $P < .001$) and IMD quintile 5 (HR = 1.53, 95% CI, 1.11-2.11, $P = .012$) (Table 4).

Myocardial Infarction

In the PCOS group, there were 221 cases of first-incident myocardial infarction compared with 129 in controls. The respective rates per 100 kpy were 22.7 and 15.9, an RR ratio of 1.43 (95% CI, 1.15-1.78, $P < .001$) (see Table 2). In the adjusted CPHM, the HR was 1.38 (95% CI, 1.11-1.72) (Table 2, Fig. 2B). Other covariates that were significant in the model were age, smoking status, prior T2DM, systolic BP, and IMD quintile. In sensitivity analysis that excluded incident events within 3 months of the index date, the HR no longer remained significant at 1.23 (95% CI, 0.92-1.64). In the additional sensitivity analysis that censored patients on secondary-care data, the RR and HR were significantly increased, at 1.69 (95% CI, 1.42-2.01) and 1.53 (95% CI, 1.29-1.83), respectively (Table 3).

Stroke

In the PCOS group, there were 267 cases of first-incident stroke compared with 209 among the controls. The respective rates per 100 kpy were 27.4 and 25.7, a nonsignificant RR ratio of 1.07 (95% CI, 0.92-1.32, $P = .49$). The CPHM was not calculated because of violation of the proportional hazard assumption (see Table 2, Fig. 2C). In sensitivity analysis that excluded incident events within 3 months of the index date, the respective rates per 100 kpy for PCOS and controls were 31.8 and 27.1, a nonsignificant RR ratio of 1.15 (95% CI, 0.90-1.47, $P = .28$). In the additional sensitivity analysis that censored patients on secondary-care data, the RR and HR were significantly increased, at 1.33 (95% CI, 1.16-1.53) and 1.26 (95% CI, 1.10-1.45), respectively (see Table 3).

Angina

In the PCOS group, there were 319 cases of first-incident angina compared with 161 among the controls. The respective rates per 100 kpy were 32.8 and 19.8, an RR ratio of 1.65 (95% CI, 1.37-2.00, $P < .001$) (see Table 2). In the adjusted CPHM, the HR was 1.60 (95% CI, 1.32-1.94) (see Table 2, Fig. 2D). Other covariates that were significant in the model were age, smoking status, prior T2DM, BMI, systolic BP, and IMD quintile. In sensitivity analysis that excluded incident events within 3 months of the index date, the HR remained significant at 2.01 (95% CI, 1.53-2.64). When patients were followed based on secondary-care data, the RR and HR were also significant at 1.81 (95% CI, 1.56-2.09) and 1.67 (95% CI, 1.44-1.94), respectively (Table 3).

Table 2. Number, crude rates, and associated hazard ratios for incident cardiovascular events in women with polycystic ovary syndrome and matched controls

CV outcome	Cases (N = 172 907)		Controls (N = 172 907)		RR (95% CI)	*P*	HR (95% CI)	*P*
	No.	Rate, 100 kpy	No.	Rate, 100 kpy				
Composite end point	804	82.7	522	64.3	1.29 (1.15-1.44)	< .001	1.26 (1.13-1.41)	< .001
MI	221	22.7	129	15.9	1.43 (1.15-1.78)	.001	1.38 (1.11-1.72)	.004
Stroke[a]	267	27.4	209	25.7	1.07 (0.92-1.32)	.492	–	–
Angina	319	32.8	161	19.8	1.65 (1.37-2.00)	< .001	1.60 (1.32-1.94)	< .001
Revascularization	102	10.5	58	7.13	1.46 (1.06-2.02)	.019	1.50 (1.08-2.07)	.02
CV mortality[a]	68	6.97	63	7.75	0.90 (0.64-1.27)	.547	–	–

Abbreviations: 100 kpy, 100 000 patient-years; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; RR, relative risk.
[a]The Cox proportional hazards model was not presented because it violated the assumptions of proportional hazards.

Table 3. Number, crude rates, and associated hazard ratios for incident cardiovascular events in women with polycystic ovary syndrome and matched controls—sensitivity analysis censoring patients based on secondary care data

CV outcome	Cases (N = 172 907)		Controls (N = 172 907)		RR (95% CI)	*P*	HR (95% CI)	*P*
	No.	Rate, 100 kpy	No.	Rate, 100 kpy				
Composite end point	1305	81.0	872	54.1	1.50 (1.37-1.63)	< .001	1.40 (1.28-1.53)	< .001
MI	345	21.4	204	12.6	1.69 (1.42-2.01)	< .001	1.53 (1.29-1.83)	< .001
Stroke	463	28.7	347	21.5	1.33 (1.16-1.53)	< .001	1.26 (1.10-1.45)	.001
Angina	512	31.7	283	17.5	1.81 (1.56-2.09)	< .001	1.67 (1.44-1.94)	< .001
Revascularization	144	8.9	111	6.9	1.30 (1.01-1.66)	.039	1.26 (0.98-1.62)	.04
CV mortality[a]	119	7.4	106	6.6	1.12 (0.86-1.46)	.389	–	–

Abbreviations: 100 kpy, 100 000 patient-years; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; RR, relative risk.
[a]The Cox proportional hazards model was not presented because it violated the assumptions of proportional hazards.

Table 4. Hazard ratios derived from the time-dependent Cox proportional hazard model for the composite end point in the polycystic ovary syndrome cohort

Variables	HR (95% CI)	*P*
Wt increase, kg	1.01 (1.00-1.01)	< .001
Prior type 2 diabetes	2.40 (1.76-3.30)	< .001
IMD (reference = quintile 1), quintile		
2	0.97 (0.68-1.38)	.88
3	1.26 (0.91-1.75)	.09
4	1.14 (1.82-1.60)	.45
5	1.53 (1.11-2.11)	.012

Abbreviations: HR, hazard ratio; IMD, Index of Multiple Deprivation.

Revascularization

In the PCOS group, there were 102 cases of incident revascularization compared with 58 among the controls. The respective rates per 100 kpy were 10.5 and 7.13, an RR ratio of 1.46 (95% CI, 1.06-2.02, *P* = .019) (see Table 2). In the adjusted CPHM, the HR was 1.50 (95% CI, 1.08-2.07) (see Table 2, Fig. 2E). Other covariates that were significant in the model were age and prior T2DM. In the wash-in sensitivity analysis, the HR no longer remained significant at 1.31 (95% CI, 0.82-2.10). For the secondary-care follow-up analysis, the RR and HR were significantly increased at 1.30 (95% CI, 1.01-1.66) and 1.26 (95% CI, 0.98-1.62), respectively (see Table 3).

Cardiovascular Mortality

In the PCOS group, there were 68 deaths during the follow-up period compared with 63 among the controls. The respective rates per 100 kpy were 6.97 and 7.75, a nonsignificant RR ratio of 0.90 (95% CI, 0.64-1.27, *P* = .55). The CPHM was not calculated because of violation of the proportional hazard assumption (see Table 2, Fig. 2F). In the wash-in and secondary-care follow-up sensitivity analyses, the RR ratio remained nonsignificant at 1.12 (95% CI, 0.86-1.46) (see Table 3).

Discussion

In this large, retrospective analysis of electronic health record data, we found a significantly increased risk of cardiovascular events in women with PCOS compared with matched controls. The risk was increased for our composite outcome and for each of myocardial infarction, angina, and revascularization individually. This is the largest study to confirm an increased incidence of major cardiovascular morbidity in patients with PCOS and emphasizes the importance of recognizing the disorder as a higher-risk vascular condition.

The biological mechanisms linking PCOS with increased vascular risk are multifactorial. Insulin resistance, which is highly prevalent in lean as well as obese women with PCOS, increases adipose tissue lipolysis (26), leading to dyslipidemia, and vasoconstriction, due to reduced endothelial nitric oxide production (27). Hyperinsulinemia may also lead to sympathoexcitation, with consequent actions on increased renal water retention and BP elevation (28), while defects in insulin secretion as well as insulin action contribute to an increased risk of T2DM (1). Accordingly, PCOS is associated with increased endothelial dysfunction (6), arterial stiffness (8), and carotid intima media thickness (5), yet it is unclear whether these surrogate measures translate into increased vascular morbidity and mortality.

Our finding of an increased risk of cardiovascular events is consistent with some (11, 24, 29-31), but not all (12, 32), previous meta-analyses that have examined the risk of coronary heart disease, stroke, and/or cardiovascular mortality in this population. However, 2 of the earlier meta-analyses were compromised by the inclusion of data that were later retracted (11, 12), while adjustment for BMI, a potentially major confounder in this patient population, abolished the increased risk of stroke reported in another (30). At baseline, patients with PCOS in our study had a significantly increased risk of a recorded diagnosis of T2DM, myocardial infarction, stroke, and angina. Our findings are largely in agreement with another population-based study, in which patients with PCOS had a higher prevalence of a recorded diagnosis of stroke, diabetes, dyslipidemia, and hypertension than controls, whereas the risks of a diagnosis of CVD, myocardial infarction, and transitory cerebral ischemia were not significantly different (13). This contrasts with the findings of Lo et al, who compared the prevalence of diagnosed CVD (coronary heart disease, cerebrovascular disease, and peripheral vascular disease) among 11 035 women with PCOS and 55 175 age-matched controls in an integrated health care delivery system in northern California (33). Despite a higher frequency of diabetes, hypertension, and known dyslipidemia in women with PCOS, the prevalence of a recorded diagnosis of CVD was not different between groups, although clinically diagnosed CVD as expected was very rare.

In contrast to cross-sectional comparisons, longitudinal studies have largely failed to confirm an increase in incident cardiovascular events in women with PCOS, likely because of studies being underpowered as a result of the low absolute risk of CVD in this young female population. This contrasts with the higher relative and absolute risk reported in young patients with rheumatoid arthritis (34). In our previous examination of the CPRD data set, we found no evidence of an increased incidence of large-vessel disease in women with PCOS (1), although the number of patients

studied was considerably smaller (n = 21 740) than the present study. As in this study, the crude incidence of CVD was low, reflecting the young mean age of the cohort and relatively limited median follow-up due to a greater number of patients being identified in recent years. In a Danish national register-based study (35), involving 18 112 patients and 52 769 controls, the adjusted HR for incident CVD (excluding hypertension and dyslipidemia) was 1.4 (95% CI, 1.3-1.5) in PCOS patients compared with matched controls. However, the researchers' definition of CVD was very broad and included venous thrombosis/pulmonary embolism or prescription of drugs for dyslipidemia or hypertension, in addition to the more recognized definitions of CVD of myocardial infarction, angina, heart failure, or cerebrovascular disease. Nevertheless, the incidence was individually increased for angina/myocardial infarction and heart failure but not stroke. In this regard, their findings are similar to ours. Hart and Doherty reported an increased risk of hospitalization for ischemic heart disease and cerebrovascular disease in their study of 2566 women with PCOS and 25 660 age-matched women without a diagnosis of PCOS in Western Australia (15). However, they were unable to control for BMI in their study, and the selection of hospitalized patients may have led to risk inflation. In a recent systematic review and meta-analysis of observational longitudinal studies comparing fatal and nonfatal CVD events in women with and without PCOS (32), the risk of coronary events was not different between groups, whereas nonfatal cerebrovascular events were higher in women with PCOS. However, in sensitivity analyses restricted to high-quality studies, neither coronary nor cerebrovascular event risk was increased. In another meta-analysis the increased risk of cardiovascular events was noted only in reproductive-age rather than menopausal women with PCOS, although the number of studies conducted in older populations is low (31). Our observations, comprising a significantly larger number of events than any of the component studies that informed these meta-analyses, thus add important new data on cardiovascular morbidity in patients with PCOS.

In contrast to morbidity, we found no evidence of an increased risk of cardiovascular mortality in women with PCOS in our study. In keeping with previous studies (29, 31, 32), however, the number of fatal cardiovascular or cerebrovascular events in this young premenopausal population was very low. Owing to the relatively short follow-up of this young population of PCOS women, we undertook a sensitivity analysis that followed patients beyond their primary-care registration period. This increased overall follow-up from a median of 3.4 years to 8.3 years, with a consequent increase in vascular events and a significantly increased HR for all our individual morbidity outcomes. An important limitation, however, is that clinical data emanating from primary care might have been lost in any women who left their practice prior to the end of the sensitivity follow-up period. This may introduce some uncertainty in the data, since some control women may have been diagnosed with PCOS during this time, and some patients may have left England, leading to unrecognized loss of follow-up in the HES and ONS data sets. Larger studies with an extended follow-up period are therefore needed to allow us to draw meaningful conclusions on cardiovascular mortality.

In our previous analysis of cardiometabolic outcomes in patients with PCOS, we found that weight gain was associated with worsening glucose tolerance; a 1% increase in BMI led to a 2% increase in diabetes risk (1). Hypothesizing that a similar effect might be observed with respect to vascular risk, we undertook a time-dependent CPHM analyzing weight change over time on the risk of our composite outcome. This analysis identified weight increase, a diagnosis of T2DM, and relative deprivation (IMD quintile 5) as significant risk factors in the model, with a 1-kg weight gain increasing the risk of the composite end point by 1%. These observations imply that prevention of weight gain, prevention of T2DM, and targeting resources and risk factor management to the most socially and materially deprived patients might carry the greatest traction in preventing CVD in this population. It is unclear how this might be best achieved in women with PCOS, although evidence from other patient groups with prediabetes suggests that intensive lifestyle interventions and/or metformin therapy might be clinically beneficial and cost-effective in reducing the subsequent incidence of T2DM (36, 37). Intervention at an early age may be especially important in light of data showing increased weight gain in early adulthood in women with PCOS compared to controls (38).

International PCOS guidelines recommend an assessment of cardiovascular risk factors and global CVD risk as part of long-term patient management (39). While our data provide convincing evidence of an increased risk of cardiovascular events in this condition, it is worth recognizing that the absolute risk of CVD is low, hence the case for screening is not entirely clear. Screening would be beneficial only if it led to the earlier identification of risk factors amenable to modification, in turn leading to improved outcomes (40). Furthermore, in a relatively low-risk population CVD screening may be costly, of low yield, and potentially harmful because of overdiagnosis. A randomized trial of screening for cardiometabolic risk factors vs usual care in women with PCOS might help provide an answer but may be practically challenging to deliver in view of the long-term follow-up needed to demonstrate an effect on event rates. Until such data are forthcoming, clinicians should at least inform patients of an increased risk of cardiometabolic

disease and use clinic visits to opportunistically target modifiable risk factors, such as smoking, weight, and BP that were significant covariates in our individual disease models.

Our study has a number of strengths and limitations. The strengths of our study include the very large sample size, the controlled design, population setting, comparatively long follow-up period, and adjustment for BMI as an important confounder in disease risk. Nevertheless, our study has several limitations, including missing data and coding imperfections due to the collation of data from routine practice. BMI was not available in one-third of the cases. To compensate for this, we modeled BMI as a categorical variable, with "missing" included as a category, but it should be considered that different levels of BMI within the missing category could partially explain some of the observed results. Waist and hip circumference were additionally unavailable for analysis. Such data might offer greater insight into the risks of central compared to general obesity on event rates, although regional fat distribution may not be altered in women with PCOS (41). As with all database studies, there is also the potential for residual confounding and bias. We were also unable to study any influence of ethnicity on risk because this is poorly recorded in the CPRD database. This is an important area of further study in view of the recognized influence of ethnicity on cardiometabolic risk factors in women with PCOS as in the general population (42, 43). An analysis of any effect on vascular events in PCOS patients after the menopausal transition would also be of interest, since hyperandrogenism and metabolic disturbances persist despite amelioration of the clinical features with age (18). Finally, we were unable to study any effects of the different PCOS phenotypes on incident vascular risk. Previous studies have suggested that cardiovascular risk factors are more prevalent in PCOS patients with irregular cycles (44), but additional studies are needed to establish whether this leads to differences among phenotypes in clinical events.

In conclusion, our study demonstrates that young women with a diagnosis of PCOS have an increased incidence of major cardiovascular events, whether captured as a composite outcome or as myocardial infarction, angina, and revascularization individually. High-quality longitudinal studies are now needed to understand any effect of disease phenotype and ethnicity on risk, and whether screening strategies with targeted intervention can lead to improved cardiovascular outcomes.

Additional Information

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Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. CPRD data are available on application after ISAC approval through a licensed organization (Pharmatelligence). Source data are not publicly available. This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone.

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