Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Risk of cardiovascular events in patients with polycystic ovary syndrome

S. Iftikhar[1*], M.L. Collazo-Clavell[2], V.L. Roger[3], J. St. Sauver[4], R.D. Brown Jr[5], S. Cha[6], D.J. Rhodes[7]

Divisions of [1]General Internal Medicine, [2]Endocrinology, Diabetes, Metabolism, and Nutrition, [3]Cardiovascular Diseases, [4]Epidemiology, [5]the Department of Neurology, Divisions of [6]Biomedical Statistics and Informatics, [7]Preventive, Occupational, and Aerospace Medicine, Mayo Clinic, Rochester, Minnesota, [*]corresponding author: e-mail: iftikhar.salma@mayo.edu

ABSTRACT

Women with polycystic ovary syndrome (PCOS) have increased prevalence of cardiovascular (CV) risk factors. However, data on the incidence of CV events are lacking in this population.

Using Rochester Epidemiology Project resources, we conducted a retrospective cohort study comparing CV events in women with PCOS with those of women without PCOS in Olmsted County, Minnesota.

Between 1966 and 1988, 309 women with PCOS and 343 without PCOS were identified. Mean (SD) age at PCOS diagnosis was 25.0 (5.3) years; mean age at last follow-up was 46.7 years. Mean (SD) follow-up was 23.7 (13.7) years. Women with PCOS had a higher body mass index (29.4 kg/m^2 vs 28.3 kg/m^2; p=.01). Prevalence of type 2 diabetes mellitus and hypertension and levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides were similar in the two groups. We observed no increase in CV events, including myocardial infarction (adjusted hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.32 to 1.72; p=.48); coronary artery bypass graft surgery (adjusted HR 1.52; 95% CI 0.42 to 5.48; p=.52); death (adjusted HR 1.03; 95% CI, 0.29 to 3.71; p=.96); death due to CV disease (adjusted HR 5.67; 95% CI 0.51 to 63.7; p=.16); or stroke (adjusted HR 1.05; 95% CI 0.28 to 3.92; p=.94).

Although women with PCOS weighed more than controls, there was no increased prevalence of other CV risk factors. Furthermore, we found no increase in CV events. While prospective studies are needed to confirm these findings, women with PCOS do not appear to have adverse CV outcomes in midlife.

KEYWORDS

Cardiovascular disease; polycystic ovary syndrome; Rochester Epidemiology Project

INTRODUCTION

Stein and Leventhal[1] first described polycystic ovary syndrome (PCOS) in 1935 on the basis of case reports of seven women sharing a constellation of signs and symptoms. Today, PCOS is the most common endocrinopathy in women during their childbearing years, with a reported prevalence ranging from 4 to 12%.[2] It is likely that this range significantly under-represents the true prevalence because many cases are unrecognised.[2] Several studies have reported that the prevalence of cardiovascular (CV) risk factors is higher in women with PCOS compared with age-matched controls, including low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, elevated low-density lipoprotein (LDL) cholesterol, elevated homocysteine, and endothelial dysfunction.[3] Patients with PCOS are more likely to be overweight, insulin resistant, and hypertensive.[4] Additionally, Christian *et al.*[5] found an increased prevalence of coronary artery calcification, a surrogate marker for CV disease (CVD), in women with PCOS compared with controls. Other investigators have documented coronary atherosclerosis and increased carotid intimal media thickness among PCOS patients.[6,7]

It has been assumed that PCOS patients are at increased risk for CVD and CV events; Dahlgren and Janson[8] predicted a sevenfold increased risk for myocardial infarction (MI) in women with PCOS. However, few studies have examined actual CV events among

women with PCOS. Pierpoint *et al.*[9] conducted a large, retrospective cohort study among women in the United Kingdom, quoting an increased risk of stroke but no difference in coronary heart disease (CHD) events. The same group did not find an increase in CVD-related deaths, despite the increased prevalence of CV risk factors in women with PCOS.[4,10]

Given the relative lack of data on CVD risk in women with PCOS, it is difficult to provide evidence-based CV management guidelines.[11] We conducted a community-based retrospective cohort study in women with PCOS in Olmsted County, Minnesota, and compared CV risk factors and incidence of CV events with those in women without PCOS.

METHODS

Setting and participants

By using the Rochester Epidemiology Project resources,[12] a unique system that links and indexes the records of virtually all medical providers in Olmsted County, investigators can electronically identify and review records for all patients who received a particular diagnosis during a defined time period. Previous studies have shown that about 89 to 96% of all care within the county is delivered at one of the participating sites, allowing for population-based studies. This study was approved by the Mayo Clinic and the Olmsted Medical Center Institutional Review Boards. The study cohort was identified between 1966 and 1988 and medical records were abstracted for events through 2005. A follow-up survey was done to update their CV health status through 2007.

Identification of PCOS Cases

Cases were defined as patients aged 18 to 40 years, residing in Olmsted County, who were diagnosed with PCOS between 1966 and 1988, using Hospital International Classification of Diseases Adapted code 02568, International Classification of Diseases 9 code 256.4, and Berkson code 027904. The keywords used were polycystic ovaries, Stein-Leventhal syndrome, and sclerocystic ovaries.

Once other causes (listed below) had been excluded, we used the current Rotterdam consensus criteria[13,14] for diagnosis. PCOS was defined as meeting two of the following three criteria: presence of oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism (not due to pituitary, adrenal, or tumour-related causes), and presence of polycystic ovaries by ultrasound. Chronic anovulation was defined as amenorrhoea of 3 months' duration or oligomenorrhoea (i.e. intermenstrual intervals >35 days). Excluded were women with active thyroid disease, prolactin elevation, adrenal or ovarian tumours, or late-onset 21-hydroxylase deficiency (as shown by either a basal serum 17-hydroxyprogesterone >2.0 ng/ml or an elevated one-hour adrenocorticotropic hormone stimulation test). Follow-up for more than five years without evidence for another disorder contributing to the clinical characteristics was accepted as evidence for inclusion.

Identification of women without PCOS

Ten control subjects for each case were first identified using an established computerised matching algorithm,[15] where age and calendar year during their clinic visit plus three years were matching factors. The matching scheme ensured that both groups received medical care in Olmsted County during the same time period. However, for 115 cases, none of the control subjects had available data for this study. For the other cases, one to three control subjects had available survey data.

Outcome measures

Information on CV events and deaths (due to CVD or another cause) was collected according to the following definitions.

MI, percutaneous coronary intervention, coronary artery bypass grafting

Standard epidemiological criteria were applied to assign a diagnosis of MI on the basis of cardiac pain, biomarker elevation,[16] and Minnesota Code for Electrocardiograms. Information on percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) was also collected.

Stroke and transient ischaemic attack

Strokes and transient ischaemic attacks (TIAs) were identified by criteria described previously.[17] Briefly, stroke was defined as the acute onset, over minutes to hours, of a focal neurological deficit persisting for longer than 24 hours, with or without computed tomographic or magnetic resonance imaging documentation. TIA included an episode of focal neurological symptoms with abrupt onset and rapid resolution lasting less than 24 hours. Cases were confirmed by the study neurologist (R.D.B.).

CV death

CV death was identified as the primary or secondary cause of death on the death certificates.

Risk factor identification

Hypertension and type 2 diabetes mellitus

Hypertension and type 2 diabetes mellitus (T2DM) were defined by the most current physician-identified diagnosis, prescription of medication for hypertension or T2DM, or self-report of either diagnosis on patient survey.

Body mass index

Body mass index (BMI) was calculated using the most recent weight (kilograms) documented in the medical record divided by the height (metres squared).

Framingham Risk Score

The Framingham Risk Score is the risk assessment tool that predicts a person's chance of having a heart attack in the next 10 years. This tool was designed for adults aged 20 years or older without heart disease or T2DM. We incorporated gender and most recent complete data on age, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, and use of antihypertensive medications into a risk score calculator.[18] In the absence of records on systolic blood pressure readings on all patients, we used physician diagnosis of hypertension or use of antihypertensive medications as evidence of hypertension. For hypertension, T2DM, BMI and Framingham risk score, we used the last documented measure for analysis. If multiple measures were recorded during the period of analysis, we used only the most recent measure during the study period.

Follow-up procedures

Passive

The cohort was gathered from 1966 to 1988. Retrospective chart reviews were performed through 2005.

Active

In December 2006, a survey was mailed to the last documented address for study subjects requesting updated clinical information on CV risk factors and outcomes pertinent to this study. Surveys were sent to all cases unless there was documentation that the patient had died. Surveys were sent to all control subjects for whom adequate documentation through to at least the year 2000 was not available. Survey recipients received a follow-up phone call if the survey had not been returned within three months.

Quality control

All outcomes of interest were identified using standardised methods.[16] Furthermore, previous work from our centre indicated that this case-finding approach yielded results similar to those of a cohort approach, confirming the robustness of our method of ascertainment.[19]

Statistical method

Demographic and cardiovascular disease risk factor data were summarised using standard descriptive measures. For continuous variables, two-sample t tests or Wilcoxon rank-sum tests were used to compare cases and controls. For categorical variables, χ^2 tests or Fisher's exact tests were used to compare the two groups. Overall survival and CVD event-free survival were compared using log-rank tests. Multivariate Cox proportional hazards analyses were used to assess the effects of potential confounders in the survival models. Assessed confounders included age; BMI; smoking status; presence of T2DM, hypertension or hyperlipidaemia; and family history of CVD, hypertension or T2DM. Due to low event rates, especially in women without PCOS, p values were derived from the likelihood ratio test.[20] Our sample size provided 80% power at α=.05 to detect a hazard ratio of 1.2. Thus, 287 patients were needed per group. Although a smaller effect might have been missed, the study was powered to detect effects of clinical and public health importance.[21]

RESULTS

We identified 400 potential PCOS cases diagnosed between 1966 and 1988 (*figure 1*). Ninety were excluded; 44 did not meet the Rotterdam consensus criteria; 39 were not residents of Olmsted County; and seven did not provide research authorisation. One patient was lost to follow-up. The resultant study cohort numbered 309 cases. We identified 343 women without PCOS to serve as controls. Following data abstraction, 426 surveys were sent to 298 cases with 149 returned (50%) and 128 controls with 27 returned (21%). Thus, data on CV risk factors and events were updated at least through the year 2000 from data abstraction, survey results, or a combination of both.

The mean follow-up time for both groups was 23.7 years. The mean (SD) age at diagnosis for women with PCOS was 25.0 (5.3) years (*table 1*). Mean age at the end of study was 46.7 years.

Women with PCOS weighed more than women without PCOS (74.4 kg *vs* 71.2 kg; p=.05) and had a higher BMI (29.4 kg/m^2 *vs* 28.3 kg/m^2; p=.01). More women with PCOS were obese compared with women without PCOS (36 *vs* 30%, with BMI >30 kg/m^2; p=.19) (*table 2*), but this difference was not statistically significant. We found no significant differences in total cholesterol, HDL cholesterol, triglyceride, LDL cholesterol, or fasting blood

Figure 1. *Flow chart of cases and controls. PCOS indicates polycystic ovary syndrome.*

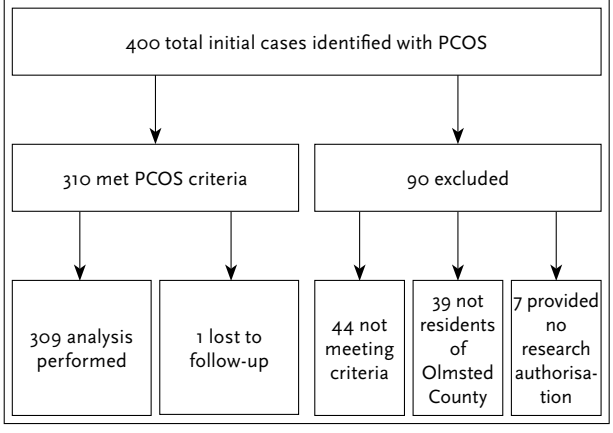

Table 1. *Baseline characteristics of patients with and without PCOS*

Variable	No. used	Overall (n=652)	No. used	No PCOS (n=343)	No. used	PCOS (n=309)	p value
Age at diagnosis, mean (SD), y	309	25.0 (5.3)	...	...	309	25.0 (5.3)	...
Age at last FU, mean (SD), y	652	46.7 (11.8)	343	48.8 (10.2)	309	44.4 (12.9)	<.001[a]
Length of FU, mean (SD), y	652	23.7 (13.7)	343	23.7 (12.3)	309	23.7 (22.7)	.98[a]
Weight, median (range), kg	525	72.5 (37-184)	294	71.2 (43-184)	231	74.4 (37-179)	.05[b]
Height, median (range), cm	525	164.0 (123-249)	294	164.0 (132-183)	231	164.0 (123-249)	.66[b]
No. of pregnancies, median (range)	499	2 (0-10)	295	2 (0-6)	204	2 (0-10)	<.001[b]
No. of births, median (range)	486	2 (0-7)	291	2 (0-6)	195	2 (0-7)	<.001[b]
Infertility treatment, no. (%)	652	91 (14)	343	10 (3)	309	81 (26)	<.001[c]

PCOS = polycystic ovary syndrome; [a]two-sample *t* test; [b]Wilcoxon rank sum test; [c]Fisher's exact test.

Table 2. *Distribution of cardiovascular disease risk factors in patients with and without PCOS*

Variable	No. used	Overall (n=652)	No. used	No PCOS (n=343)	No. used	PCOS (n=309)	p value
TC, median (range), mg/dl	482	198 (0-369)	286	199 (0-369)	196	197 (92-330)	.82[a]
HDL, median (range), mg/dl	464	58 (23-129)	283	59 (30-129)	181	57 (23-106)	.16[a]
TG, median (range), mg/dl	478	109 (29-473)	285	110 (33-431)	193	107 (29-473)	.75[a]
LDL, median (range), mg/dl	442	110 (26-225)	278	111 (38-211)	164	108 (26-225)	.74[a]
Fasting blood glucose, median (range), mg/dl	455	94 (39-338)	276	94 (68-208)	179	94 (39-338)	.51[a]
History of diabetes	652	11 (1.7)	343	9 (2.6)	309	2 (0.7)	.07[b]
Framingham risk score, median (range)	464	4 (−9-19)	283	4 (−4-17)	181	4 (−9-19)	.76[a]
BMI, mean (SD)	519	28.8 (7.61)	291	28.3 (7.47)	228	29.4 (7.77)	.01[c]
BMI categories	519		291		228		.19[b]
≤30 kg/m²		351 (68)		204 (70)		147 (64)	
>30 kg/m²		168 (32)		87 (30)		81 (36)	
Oestrogen/progesterone treatment	652	451 (69)	343	200 (58)	309	251 (81)	<.001[b]
Duration of oestrogen /progesterone treatment	440		197		243		.28[d]
0-1 y		115 (26)		43 (22)		72 (30)	
1-3 y		93 (21)		45 (23)		48 (20)	
3-5 y		66 (15)		33 (17)		33 (14)	
>5 y		166 (38)		76 (39)		90 (37)	
Hypertension	652	133 (20)	343	73 (21)	309	80 (26)	.20[b]
Antihypertensive treatment	652	130 (20)	343	72 (21)	309	73 (24)	.45[b]
Smoking	547		312		235		.67[d]
Never		314 (57)		182 (58)		132 (56)	
Ex-smoker		153 (28)		88 (28)		65 (28)	
Current smoker		80 (15)		42 (13)		38 (16)	
Postmenopausal hormonal treatment	652		343		309		.01[d]
None		502 (77)		249 (73)		253 (82)	
Current user		71 (11)		47 (14)		24 (8)	
Past user		79 (12)		47 (14)		32 (10)	
Family history of heart disease	542	444 (82)	302	249 (82)	240	195 (81)	.74[b]
Family history of hypertension	541	399 (74)	300	209 (70)	241	190 (79)	.02[b]
Family history of diabetes	532	297 (56)	300	155 (52)	232	142 (61)	.03[b]

The data are presented as numbers (percentages) unless otherwise stated. BMI = body mass index; HDL = high density lipoprotein; PCOS = polycystic ovary syndrome; TC = total cholesterol; TG = triglycerides; [a]Wilcoxon rank sum test; [b]Fisher's exact test; [c]Two-sample *t* test; [d]Pearson χ^2 p value.

glucose levels or the presence of T2DM and hypertension between women with and without PCOS. Parameters of insulin resistance were not available. Women with PCOS were more likely than those without PCOS to have a family history of hypertension (79 vs 70%; p=.02) and T2DM (61 vs 52%; p=.03). Use of statins, antihypertensive medications, and anti-T2DM medications was similar, as was smoking status. The Framingham coronary disease risk scores were similar for both groups (4 and 4; p=.76). The only significantly different variables were BMI, family history of hypertension, family history of T2DM, oestrogen use, and postmenopausal hormone therapy.

There was no increased risk of CV events in the women with PCOS as defined by MI (adjusted hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.32 to 1.72; p=.48); CABG (adjusted HR 1.52; 95% CI 0.42 to 5.48; p=.52); overall deaths (adjusted HR 1.03; 95% CI 0.29 to 3.71; p=.96); and death due to CVD (adjusted HR 5.67; 95% CI 0.51 to 63.7; p=.16). Incidence of stroke too was not different (adjusted HR 1.05; 95% CI 0.28 to 3.92; p=.94) (*table 3*). After adjusting for age, BMI, infertility, and history of hypertension no significant difference in CV events remained. All CV events were identified from the medical index database, and when compared with survey results, no additional CV events were identified.

DISCUSSION

In our retrospective cohort study of 309 women with PCOS and 343 women without PCOS, we found few differences in CV risk factors and no overall difference in CV events (MI, unstable angina, stroke, TIA, CABG, or PTCA or death due to CVD) during a mean follow-up of 23 years (through the ages of 45 to 50 years). Relative to women without PCOS, women with PCOS had a higher BMI, but were not significantly different in total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, or fasting blood glucose measurements. We are unable to comment on the prevalence of insulin resistance in the cohort because parameters for insulin resistance were not routinely measured as part of clinical practice. There was no significant difference in the prevalence of T2DM and hypertension between the two groups, although women with PCOS were more likely than those without PCOS to have a family history of T2DM and hypertension.

Our findings challenge conclusions of previous studies. For example, the sevenfold increased risk of CHD suggested by Dahlgren and Janson[8] on the basis of calculations from their model may represent an overestimation of CHD risk among women with PCOS. Review of that study must take into consideration the limitations imposed by the small cohort of only 34 women with PCOS and 132 controls. Actual CV events were rare (one MI in each group, stroke in two women with PCOS and three without PCOS) and were not statistically significant. Yet, when CHD risk factors, triglycerides, waist-to-hip ratio, T2DM, and hypertension were applied to a risk factor assessment model, the estimated risk ratio for MI was 4.2 in women with PCOS aged 40 to 49 years and 11 for those aged 50 to 61 years. This risk factor model remains unvalidated and does not include the many other recognised risk factors for CHD. Cases relied on ovarian biopsies for definition, likely including women with cystic ovaries but not PCOS and excluding women who had PCOS but did not have ovarian biopsy.

In contrast, our study is a population-based study with consistent and validated case-finding criteria based on International Classification of Diseases and Hospital International Classification of Diseases Adapted coding, clear definitions for women with PCOS, event verification by the study's principal investigator (S.I.) and endocrinologist (M.L.C.-C.), use of a validated risk

Table 3. *Cardiovascular events, overall deaths, and deaths due to CVD*

Events	Total No. (%) (n=652)	PCOS No. (%) (n=309)	No PCOS No. (%) (n=343)	Hazard ratio (95% CI)	p value[a]	Adjusted hazard ratio[b] (95% CI)	p value[a]
Myocardial infarction	31 (4.8)	15 (4.9)	16 (4.7)	0.82 (0.39-1.69)	.58	0.74 (0.32-1.72)	.48
Unstable angina	16 (2.5)	10 (3.2)	6 (1.8)	1.44 (0.51-4.07)	.49	1.32 (0.42-4.13)	.63
Stroke	13 (2.0)	6 (1.9)	7 (2.0)	0.75 (0.25-2.27)	.61	1.05 (0.28-3.92)	.94
CABG	12 (1.8)	7 (2.3)	5 (1.5)	0.99 (0.31-3.19)	.99	1.52 (0.42-5.48)	.52
At least 1 CV event	54 (8.3)	26 (8.4)	28 (8.2)	0.87 (0.51-1.50)	.62	0.82 (0.44-1.54)	.54
Overall deaths	19 (2.9)	11 (3.6)	8 (2.3)	1.16 (0.46-2.90)	.76	1.03 (0.29-3.71)	.96
Deaths due to CVD	6 (0.9)	4 (1.3)	2 (0.6)	1.57 (0.28-8.75)	.61	5.67 (0.51-63.7)	.16

BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; PCOS = polycystic ovary syndrome; [a]*P* values came from the likelihood ratio test; [b]Adjusted for age at last follow-up, BMI, infertility treatment, postmenopausal hormone therapy, and family history of hypertension.

assessment tool (the Framingham Risk Assessment Tool), and a long follow-up period.

Our findings agree with those of a previous retrospective study by Pierpoint *et al.*,[9] who reported prevalence of CHD risk factors and CHD mortality in 760 women followed for more than 30 years in a predominantly white population in the United Kingdom. Based on review of death records, they reported an increased prevalence of CV risk factors, including T2DM and insulin resistance, but no excess risk of CHD mortality. Our study population was similar (predominantly white); we believe that the strict requirement for PCOS diagnosis (based on laparotomy, laparoscopy, and wedge resection) used in their study may have excluded the less severe cases.

Using the same cohort in the United Kingdom, Wild *et al.*[10,22] conducted a follow-up study on 319 PCOS cases looking for cardiac events and reported an increased risk of stroke but no difference in coronary events. This study was limited by a large dropout rate, reporting on less than 50% of the study subjects, which may limit conclusions.

We found no difference in the use of antihypertensive or anti-T2DM agents or statins between the two groups, suggesting that the women with PCOS were not more diligently managed compared with women without PCOS, despite elevated BMI. We cannot address the possibility that women with PCOS received and followed lifestyle change recommendations (exercise and diet) more aggressively potentially impacting insulin resistance and the prevalence of CV risk factors.

Compared with women without PCOS, women with PCOS used hormone preparations more frequently before menopause but less frequently after menopause. The possibility that these differences in hormone therapy could have provided some protective benefit to women with PCOS is interesting but impossible to conclude from our study.

Another consideration for the findings observed in our study is that PCOS may actually offer some protective benefits that lower the risk of CV events in an unrecognised way. This was also suggested by Wild *et al.*[10] and Pierpoint *et al.*[9] Additionally, the majority of the women in this study have not yet reached ages at which CV events are common. Therefore, we cannot rule out the possibility that the incidence of CV events will increase in women with PCOS at older ages. However, our data do suggest that women with PCOS are not at an increased risk of CV events compared with the general population, at least through midlife. These findings are consistent with the recent Androgen Excess and PCOS Society statement[23] and the Dallas Heart Study (a cross-sectional analysis of a US obese PCOS cohort in the Dallas Heart Study),[24] which reported no difference in subclinical markers of coronary artery disease or abdominal atherosclerosis between PCOS patients and controls, thus supporting our findings.

Limitations and strengths

The primary limitation of this study is the retrospective design. However, this allowed us to follow individuals over an extended time (nearly 24 years). Additionally, for individuals who were lost to follow-up, we attempted contact via a survey to ascertain their outcomes. The survey response rates differed between cases and controls. However, updated medical information was available from the medical records for more than 63% of controls, with an additional 21% updated from the survey, thus yielding updated data on 84% of the control subjects, similar to the rate for the case patients. No additional CV events were discovered, but we must acknowledge potential bias introduced by unrecognised differences between responders and nonresponders. The likelihood of this is low, as Rochester Epidemiology Project records are updated at least with death data even if the subject moved away.

Additionally, as the calculated Framingham Risk scores did not differ between women with and without PCOS, our data also suggest that ten-year risks of CV events will be similar in both groups. Finally, based on the 1990 census, until recently the population of Rochester has been predominantly white, hence generalisability may be limited to white women aged between 18 and 50 years.

Strengths included a population-based cohort study in a defined geographic area, limiting the biases that can occur in studying referral populations. Additionally, we were able to take advantage of the extensive patient information available through the Rochester Epidemiology Project and supplemented these data with active follow-up of study participants who had relocated from Olmsted County, Minnesota. This retrospective cohort study design also represented the best and most feasible method to answer our study question. A prospective study is conceivable but would take decades and substantial funding to complete. Additionally, using the survey to update our data mitigated the bias from subjects being lost to follow-up and gave us information on the recent health status of the cohort.

Conclusions

In this community-based cohort, women with PCOS were significantly more likely than controls to be overweight. However, there were no statistically significant differences in other CV risk factors between cases and controls, including total cholesterol, HDL cholesterol, triglyceride, LDL cholesterol, and fasting blood glucose levels or the presence of T2DM and hypertension. This result contradicts those of other studies, which have reported an increased prevalence of T2DM, dyslipidaemia, and hypertension in women with PCOS. Furthermore, there was no observed increase in CV events in this cohort through midlife. Prospective community-based studies are needed to confirm this lower-than-anticipated prevalence of

CV risk factors and events and to determine whether this prevalence persists in later decades of life.

ACKNOWLEDGMENTS

We thank the Survey Research Centre for help with formatting, collection, and compilation of the surveys and Kathryn Trana for help with manuscript preparation.
Grant support: This study was funded by Solvay Pharmaceuticals through Women's Health Fellowship (S.I.) funds and was made possible by the Rochester Epidemiology Project (grant AR30582 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases).

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