Published in final edited form as:
Obstet Gynecol. 2011 January ; 117(1): 6–13. doi:10.1097/AOG.0b013e31820209bb.

Polycystic Ovary Syndrome and Risk for Long-Term Diabetes and Dyslipidemia

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Abstract

Objective—To estimate whether women aged 19–32 who fulfilled National Institutes of Health (NIH) criteria for polycystic ovary syndrome (PCOS) would be at a higher risk for subsequent

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Financial Disclosure: The authors did not report any potential conflicts of interest.

development of incident diabetes, dyslipidemia, and hypertension, and to estimate whether normal-weight women with PCOS would have the same degree of cardiovascular risk as overweight women with PCOS.

Methods—We estimated the association of PCOS with incident diabetes, dyslipidemia, and hypertension over a period of 18 years among 1,127 white women and black women in the Coronary Artery Risk Development In young Adults (CARDIA) cohort. We classified women at baseline (ages 20–32) based on self-reported symptoms and/or biochemical hyperandrogenism using NIH PCOS criteria. We estimated the association of PCOS and subsequent cardiovascular risk factors, independent of baseline body mass index (BMI), using multivariable logistic regression. Additionally, among 746 women with a second assessment of PCOS at ages 34–46, we estimated the association of persistent PCOS with cardiovascular risk factors.

Results—Of 1,127 women, 53 (4.7%) met criteria for PCOS at ages 20–32. PCOS was associated with a twofold higher odds of incident diabetes (23.1% versus 13.1%; adjusted OR (AOR) 2.4, 1.2–4.9) and dyslipidemia (41.9% versus 27.7%; AOR 1.9, 1.0–3.6) over 18 years; the association with incident hypertension was not significant (26.9% versus 26.3%; AOR 1.7, 0.8–3.3). Normal-weight women with PCOS (n=31) had a threefold higher odds of incident diabetes compared to normal weight women without PCOS (AOR 3.1, 1.2–8.0). Compared to those without PCOS (n=11), women with persistent PCOS had the highest odds of diabetes (AOR 7.2, 1.1–46.5).

Conclusions—PCOS is associated with subsequent incident diabetes and dyslipidemia, independent of BMI. Diabetes risk may be greatest for women with persistent PCOS symptoms.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous clinical syndrome among reproductive-aged women; National Institutes of Health (NIH) consensus criteria for the diagnosis of PCOS requires menstrual irregularities due to anovulation, either biochemical or clinical evidence of hyperandrogenism, and the exclusion of other diagnoses (1). Although PCOS is associated with an adverse cardiovascular risk profile, such as obesity, insulin resistance, type 2 diabetes, dyslipidemia, and hypertension in cross-sectional studies (2–5) and natural history studies (6,7), questions remain about the independent association of PCOS with incident cardiovascular disease (CVD) in longitudinal studies. Establishing this relationship is challenging due to the spontaneous resolution of PCOS symptoms over time (8,9) and the higher body mass index (BMI) associated with PCOS (4) that may mediate CVD risk. The determination of PCOS as an independent risk factor for CVD may lead to clearer guidelines for CVD prevention in these women.

We used data from the Coronary Artery Risk Development In young Adults (CARDIA) study – a large, established cohort of young black adults and white adults followed for 20 years – to investigate the association of PCOS and the subsequent development of cardiovascular risk factors. We hypothesized that women who fulfilled NIH criteria for PCOS between ages 20–32 would be at a higher risk for subsequent development of incident diabetes, dyslipidemia, and hypertension. Additionally, we hypothesized that normal weight women with PCOS would have the same degree of cardiovascular risk as overweight women with PCOS and that the persistence of PCOS symptomatology over time would be associated with increased cardiovascular risk.

MATERIALS AND METHODS

Study Design and Sample

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective investigation of cardiovascular risk factors in a U.S. population of black and white young adults (10). The study enrolled 5115 men and women, aged 18–30 years at baseline in 1985–1986, who were recruited from four cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). The institutional review board at each of the study sites approved the study protocols, and written informed consent was obtained from all participants. The sampling strategy yielded a cohort balanced by age, gender (54% women), education (40% ≤ 12 years of education), and race (52% black). Participants underwent a baseline exam and follow-up exams at Years 2, 5, 7, 10, 15, and 20 with retention rates of 91, 88, 81, 79, 74, and 72%, respectively. The CARDIA Women's Study (CWS) is an ancillary study of women who attended an additional examination at Year 16; CWS was designed to examine the role of androgens and polycystic ovaries in the development of cardiovascular disease. To be eligible for CWS, women had to have attended the Year 15 examination, have at least one ovary, and not be pregnant. Approximately 86% of eligible CARDIA women were successfully recruited and examined for CWS during Year 16 (n = 1163).

Our study sample included 1127 women present at both the Year 2 (ages 20–32) and Year 16 (ages 34–46) examinations. The Year 2 examination was considered to be baseline unless otherwise noted.

Defining PCOS

We used NIH consensus criteria for the diagnosis of PCOS, which includes menstrual irregularities due to anovulation and either biochemical or clinical evidence of hyperandrogenism (1). PCOS was determined by self-report of clinical symptoms, including oligomenorrhea and hirsutism, and serum androgen measures. At the Year 16 examination, women were queried about symptoms at two time frames – past (ages 20–30) and current (ages 34–46). Women were asked about the length and regularity of menstrual cycles. Those who indicated either regular or irregular menstrual cycles ≥34 days were considered to fulfill criteria for oligomenorrhea. Women, who reported unwanted hair growth, excluding the lower leg and underarm, were considered to fulfill criteria for the clinical symptom of hirsutism. Androgen measures were obtained from Year 2 stored sera (ages 20–32) and newly collected Year 16 sera (ages 34–46). Androgens were assayed by the OB/GYN Research and Diagnostic Laboratory at the University of Alabama, Birmingham. Total testosterone (T) was measured using a competitive immunoassay (Beckman Coulter, Fullerton, CA) using direct chemiluminescent technology on the Beckman Access Automated System. Sex hormone binding globulin (SHBG) was determined using equilibrium analysis, and free T was calculated on the basis of measured total T and SHBG (11). Given that testosterone levels are known to decrease as women with PCOS age (8), we used age-specific cut-offs to define biochemical hyperandrogenism. Biochemical hyperandrogenism at Year 2 was defined as ≥80 ng/dL of total T or ≥0.65 ng/dL of free T based on the 95th percentile for the non-oligomenorrheic, non-hirsute women at Year 2. Biochemical hyperandrogenism at Year 16 was defined as 55 ng/dL of total T or 0.44 ng/dL of free T based on the same criteria at Year 16.

For our main analysis, participants were classified as having PCOS at ages 20–32 if they reported oligomenorrhea between 20–30 years of age and either reported hirsutism between 20–30 years of age or fulfilled criteria for biochemical hyperandrogenism at Year 2.

Persistent PCOS

Participants were classified as having PCOS at Year 16 if they reported current oligomenorrhea and either reported current hirsutism or fulfilled criteria for biochemical hyperandrogenism at Year 16. We classified women with persistent PCOS based on the two time frames – Year 2 (ages 20–32) and Year 16 (ages 34–46): 1) "never PCOS" – women who did not fulfill criteria for PCOS at either time frame, 2) "early PCOS" – women who fulfilled criteria at Year 2 only, and 3) "persistent PCOS" – women who fulfilled criteria for PCOS at both time frames. To reduce the possibility of post-menopausal symptoms limiting true assessment of PCOS, we excluded women based on follicle-stimulating hormone (FSH) >40mIU/mL (n=77) and self-report of no menses within the last 12 months (n=116) at the Year 16 examination. Women using hormonal contraception (n=148) were also excluded. Additionally, the 40 women who fulfilled criteria for PCOS at Year 16 only were excluded to prevent possible inclusion of women with irregular menstrual cycles due to perimenopause.

Covariates

Self-reported sociodemographic data (age, race, maximally obtained education, and parity) and lifestyle information (physical activity, alcohol abuse, and cigarette status) were collected using self- and interviewer-administered questionnaires. For parity, participants were categorized as either nulliparous (0 births) or parous (≥ 1 birth). Physical activity was reported as total exercise units based on the CARDIA Physical Activity History Questionnaire, which assessed intensity and frequency of participation in a variety of leisure and occupational activities (12). For alcohol abuse, participants were dichotomized based on the at-risk consensus threshold of the National Institute on Alcohol Abuse and Alcoholism, which were met if a woman consumed more than seven drinks per week. For cigarette status, participants were categorized as current users if they smoked more than five cigarettes per week. Family history of diabetes was defined as ≥1 first degree relative(s) with diabetes.

Measurements of weight, height, and waist circumference were obtained by trained and certified clinical staff according to standardized protocols previously described (13). Body weight was measured with participants wearing light clothing using a calibrated balance beam scale to the nearest 0.2 kg. Height, without shoes, was measured with a vertical ruler to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by squared height in meters. Waist circumference was measured at the minimum abdominal girth to the nearest 0.5 cm.

Cardiovascular Risk Factors

Cardiovascular risk factors were assessed at each CARDIA exam. Diabetes was defined as a fasting plasma glucose ≥ 126 mg/dL or use of diabetic medications. Fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured, and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation (14). Dyslipidemia was defined as LDL > 160 mg/dL, HDL < 40 mg/dL, triglycerides > 200 mg/dL, or use of cholesterol-lowering medications. Blood pressure was measured by trained and certified clinical staff. After a 5-minute rest, blood pressure was measured three times at one-minute intervals in the right arm of the seated participant using a Hawksley random zero sphygmomanometer (W.A. Baum Co., Copaigue, NY) and an appropriate-sized cuff (13). The mean of the last two blood pressure values were used in the analyses. Hypertension was defined as blood pressure ≥ 140/90 mmHg or the use of antihypertensive medications.

For each outcome, cumulative incident diabetes, dyslipidemia, or hypertension was defined as the development of these conditions at any exam visit through Year 20 excluding those cases present at Year 2.

Statistical analyses

Descriptive statistics included means (± standard deviation) and the Wilcoxon rank sum test for continuous variables and proportions for categorical variables. Differences between means or proportions were compared using *t*-tests for continuous variables and χ^2 tests for categorical variables.

For the main analysis, multivariable logistic regression was used to assess the odds of cumulative incident diabetes, dyslipidemia, and hypertension based on PCOS classification at 20–32 years of age. Prevalent cases at baseline were specifically excluded for each outcome. The first model (Model 1) adjusted for age, race, BMI, education, parity, and family history of diabetes obtained at baseline. The second model (Model 2) adjusted for the same covariates as Model 1 plus Year 20 BMI. We also assessed the association between PCOS and diabetes based Model 1 by adjusting for fasting insulin levels at baseline. Likewise, we further explored the association between PCOS and dyslipidemia based on Model 1 by adjusting for fasting LDL cholesterol, HDL cholesterol, and triglyceride levels at baseline.

Next, we investigated the effect of PCOS and BMI as a combined risk factor for cumulative incident diabetes and dyslipidemia. We used a categorical variable with four groups the predictor – 1) women without PCOS at ages 20–32 and baseline BMI <25 kg/m^2 (reference group), 2) women without PCOS at ages 20–32 and baseline BMI >25 kg/m^2, 3) women with PCOS at ages 20–32 and baseline BMI <25 kg/m^2, and 4) women with PCOS at ages 20–32 and baseline BMI >25 kg/m^2. All the other elements of the analysis were identical to the main analysis.

As an additional analysis, we used the PCOS classification of “never PCOS”, “early PCOS”, and “persistent PCOS” as previously described to assess the odds of developing diabetes and dyslipidemia between the Year 15 examination and the Year 20 examination. The reference group was considered to be the “never PCOS” women for this analysis. Prevalent cases at Year 15 were specifically excluded for each outcome. The logistic regression model was adjusted with covariates obtained at the Year 15 examination.

Stata (version 10, 2007, StataCorp, College Station, Texas) was used for all statistical analyses.

RESULTS

Of the 1127 women included in the analyses, 53 (4.7%) fulfilled criteria for PCOS at ages 20–32 (Table 1). White race, nulliparity, and a higher mean fasting insulin level were more common among women with PCOS. The two groups did not differ by maximally obtained education, BMI, waist circumference, physical activity, alcohol use, and current tobacco use. Women with PCOS also did not differ significantly from those without PCOS for the presence of hypertension, diabetes, or dyslipidemia at baseline.

Women with PCOS at ages 20–32 were more likely to develop incident diabetes by the time they reached 38–50 years of age (Table 2). PCOS was associated with a two-fold higher odds of incident diabetes, which persisted after adjusting for potential confounders including baseline BMI and Year 20 BMI. When baseline BMI was excluded from the multivariable model, the association of PCOS with diabetes remained (adjusted OR 2.6, 1.3–5.2).

Additional adjustment for fasting insulin levels did not change this association (adjusted OR 2.1, 1.0–4.4). In the adjusted logistic regression model with or without Year 20 BMI, women with PCOS also had a two-fold higher odds of incident dyslipidemia over 18 years of follow-up (Table 2). After additional adjustment for baseline LDL cholesterol, HDL cholesterol, and triglyceride levels, the magnitude of the association remained unchanged, but was no longer statistically significant (adjusted OR 1.9, 0.9–3.8). Given the race differences suggested in Table 1, we examined potential effect modification by race and found that the association between PCOS and either incident diabetes or incident dyslipidemia did not differ between the two race groups (p for interaction = 0.4 and 0.2, respectively). The association between PCOS and incident hypertension was not statistically significant (Table 2).

Because of the lack of a significant association between PCOS and incident hypertension, the subsequent analyses focused on incident diabetes and dyslipidemia. Using PCOS classification and baseline BMI as a combined predictor, PCOS was associated with a three-fold higher odds of developing diabetes among normal weight women with PCOS compared to normal weight women without PCOS over 18 years of follow-up (Table 3). Although these results are limited by wide confidence intervals, the magnitude of this risk appeared to be greater than that of overweight women without PCOS, but less than that of overweight women with PCOS. After further adjustment with Year 20 BMI, the independent association for PCOS and diabetes regardless of baseline BMI category remained. The same pattern of association was observed for dyslipidemia, although some associations did not reach the level of statistical significance in this analysis (Table 3).

Of the 746 women available for the secondary analysis of persistent PCOS, 2.0% (15/746) met criteria for “persistent PCOS” and 3.5% (26/746) were classified as “early PCOS”. Thus, spontaneous resolution of PCOS symptomatology over 14 years occurred in 63% of women classified with PCOS at ages 20–32 (26/41). Women with “persistent PCOS” had a seven-fold higher odds of developing diabetes over the subsequent five years compared to women without PCOS, although wide confidence intervals limit the precision of the point estimate. Those with “early PCOS” did not demonstrate a statistically significant increased odds of diabetes (Table 4). In contrast, women with “early PCOS”, but not “persistent PCOS”, had a significantly increased odds of incident dyslipidemia, compared to those without PCOS.

DISCUSSION

In a large biracial cohort of young U.S. women, we found that PCOS among women in their 20’s was associated with an increased odds of subsequent incident diabetes and dyslipidemia, but not hypertension, by the fifth decade of life. We observed that even normal weight women with PCOS were at an increased risk for diabetes compared to normal weight women without PCOS. In addition, women with persistent PCOS symptomatology had the highest risk of diabetes. The results of these longitudinal analyses support the hypothesis that PCOS places women at an increased risk for CVD and have important implications for screening, surveillance, and risk factor modification in these young women.

Natural history studies have followed small cohorts of PCOS women identified by ovarian wedge resection and noted an increased risk for diabetes (6,7), hypertriglyceridemia (6), and hypercholesterolemia (6) compared with rates in the general population. The Nurses’ Health Study II, a prospective cohort study, assessed menstrual cycle history between 18–22 years based on recall in 101,073 women, and found that women with long or irregular cycles had a two-fold increase risk of incident diabetes after adjusting for self-reported BMI at 18 years and other confounders (15).

Our study supports the existing natural history studies and extends the Nurses' Health Study in several ways. We studied a large and well-characterized cohort of white women and black women that have been followed for over 18 years. We used a standardized definition of PCOS, supported by measures of serum androgen levels as well as participant self-report. We were also able to assess PCOS at two time points, allowing for the assessment of persistent symptomatology. Furthermore, we examined the incidence of three important CVD risk factors over this 18 year period - diabetes, dyslipidemia, and hypertension.

PCOS as an independent risk factor for diabetes can be explained by several mechanisms. Studies have shown a unique post-binding defect in insulin signal transduction in skeletal muscle of women with PCOS, resulting in increased serine phosphorylation of the insulin receptor and insulin receptor substrate-1 (16). We did not see a change in the association between PCOS and diabetes after adjusting for fasting insulin levels; however, this does not account for the significant insulin resistance observed in women with PCOS compared to controls as demonstrated in euglycemic clamp studies. Hyperandrogenism may also play a role in insulin resistance as insulin and androgen levels are known to be positively correlated in women with PCOS (17). Androgen administration to healthy women has been shown to be associated with the development of insulin resistance; conversely, the blockade of androgen action led to improved insulin sensitivity (18).

The association between PCOS and hypertension has been less clear in the literature. Some studies show that PCOS is associated with hypertension based on ambulatory 24-hour monitoring or outpatient diagnoses (4,6,19), whereas other studies have not reached the same conclusion (7). The use of different diagnostic criteria for PCOS may account for these inconsistent findings. Our results suggest that PCOS is not associated with incident hypertension; however, this does not exclude the possibility of an association between a history of PCOS and future hypertension as this cohort continues to age and transition through menopause. However, we do note that hypertension is not uncommon by the Year 20 exam, affecting 28.4% of women in our cohort.

Our study indicates that PCOS is an independent risk factor for subsequent disease, most notably diabetes. The results of this study support the recommendation by a consensus panel representing the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine (20), as well as the Androgen Excess Society (21), to screen all women with PCOS for diabetes. Although retrospective data suggest that metformin therapy may protect against impaired glucose tolerance and diabetes in women with PCOS (22), clinical trials are needed before metformin can be routinely recommended for women with PCOS with normal glucose tolerance.

Certain limitations should be noted when interpreting our study results. Although the use of questionnaires for the diagnosis of PCOS according to symptomatology has been validated (23), misclassification of cases may occur. Additionally, the retrospective diagnosis of PCOS for women at ages 20–32 is subject to recall bias. However, the ascertainment of cases in these women is complemented by serum androgen levels and the prevalence of PCOS noted in this study is consistent with the literature. Furthermore, misclassification is likely to have resulted in bias to the null. The considerable strengths of our study include the standardized definition of PCOS, the large cohort of both black women and white women, the long follow-up period, and the adequacy of our outcome assessment. The 18-year follow-up period is further strengthened by an overall retention rate of 72% within the CARDIA cohort.

In conclusion, in this large biracial cohort with extensive follow-up, we find that PCOS in early adulthood is associated with an increased long-term risk of diabetes and dyslipidemia, independent of BMI.

Acknowledgments

Supported by the National Heart, Lung and Blood Institute (N01-HC-95095, N01-HC-48047, N01-HC-48048, N-01-HC-48049, N01-HC-48050, N01-HC-05187, N01-HC-45205, N01-HC-45204, N01-HC-45134), as was the CARDIA Women's Study (R01-HL-065611).

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Table 1

Baseline (Year 2) characteristics of the CWS cohort by PCOS classification at ages 20–32

Characteristics	No PCOS (n=1074)	PCOS (n=53)	p-value[a]
Age, mean (SD), y	27.3 (3.6)	26.8 (3.7)	0.38
Race, No. (%)			0.001
Black	580 (54.0)	16 (30.2)	
White	494 (46.0)	37 (69.8)	
Maximally obtained education, No. (%)			0.10
≤ High school	336 (31.5)	11 (20.8)	
> High school	729 (68.5)	42 (79.3)	
Body mass index, No. (%)			0.79
< 25 kg/m^2	620 (58.2)	31 (58.5)	
25–30 kg/m^2	235 (22.1)	10 (18.9)	
>30 kg/m^2	210 (19.7)	12 (22.6)	
Waist circumference, mean (SD), cm	77.0 ± 12.5	78.5 ± 13.9	0.39
Physical activity, median (IQR), total exercise units	246 (125–408)	287 (186–447)	0.07
Alcohol abuse (>7 drinks/week), No. (%)	104 (9.8)	4 (7.6)	0.59
Cigarette status, No. (%)	291 (27.1)	11 (21.2)	0.35
Parity, No. (%)			0.003
Nulliparous	606 (56.4)	41 (77.4)	
Parous	468 (43.6)	12 (22.6)	
≥1 first degree relative with diabetes, No. (%)[b]	204 (19.0)	8 (15.1)	0.48
Fasting plasma glucose, mean (SD), mg/dL[e]	80.8 (15.2)	81.8 (8.9)	0.61
Fasting insulin, mean (SD), μu/mL[e]	11.0 (7.5)	13.4 (9.4)	0.02
LDL cholesterol, mean (SD), mg/dL	111.1 (32.0)	115.9 (35.4)	0.30
HDL cholesterol, mean (SD), mg/dL	58.1 (14.4)	56.3 (15.8)	0.40
Triglycerides, mean (SD), mg/dL	71.7 (40.0)	78.4 (45.9)	0.25
Systolic blood pressure, mean (SD), mmHg	104.3 (9.8)	101.6 (10.2)	0.05
Diastolic blood pressure, mean (SD), mmHg	65.9 (9.4)	65.3 (9.4)	0.65

Abbreviations: SD, standard deviation; IQR, interquartile range, HDL, high-density lipoprotein; LDL, low density lipoprotein

[a] P-value calculated by χ^2 test for categorical variables; *t*-test or Wilcoxon rank sum test for continuous variables

[b] Data obtained at Year 0

Table 2

Baseline (Year 2) and cumulative incident cardiovascular risk factors in the CWS cohort based on PCOS classification at ages 20–32

	No PCOS (n=1074)	PCOS (n=53)	n[a]	Model 1[b]	Model 2[c]
Diabetes					
Baseline Diabetes, No. (%)	26 (2.4)	1 (1.9)			
Cumulative Incident Diabetes, No. (%)	137 (13.1)	12 (23.1)	1100	2.4 (1.2–4.9)	2.6 (1.3–5.3)
Dyslipidemia					
Baseline Dyslipidemia, No. (%)	215 (20.1)	10 (18.9)			
Cumulative Incident Dyslipidemia, No. (%)	238 (27.7)	18 (41.9)	902	1.9 (1.0–3.6)	2.0 (1.0–3.9)
Hypertension					
Baseline Hypertension, No. (%)	31 (2.9)	1 (1.9)			
Cumulative Incident Hypertension, No. (%)	274 (26.3)	14 (26.9)	1095	1.7 (0.8–3.3)	1.8 (0.9–3.6)

Diabetes: fasting plasma glucose ≥ 126 mg/dL or use of diabetic medications; Dyslipidemia: LDL cholesterol > 160 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides > 200 mg/dL, or use of cholesterol-lowering medications; Hypertension: blood pressure ≥ 140/90 mmHg or the use of antihypertensive medications.

[a] Sample size for logistic regression models for each outcome.

[b] Logistic regression model adjusted for age, race, BMI, education, and parity obtained at Year 2, and family history of diabetes obtained at Year 0. Values represent odds ratio (95% confidence interval) of women with PCOS compared to women without PCOS.

[c] Logistic regression model adjusted for the covariates in Model 1 plus BMI at Year 20

Table 3

Odds ratio (95% confidence interval) of cumulative incident diabetes and dyslipidemia according to baseline BMI (Year 2) and PCOS classification at ages 20–32

		Diabetes			Dyslipidemia	
	n	Model 1[a]	Model 2[b]	N	Model 1	Model 2
No PCOS, normal weight[c]	610	1.0	1.0	531	1.0	1.0
No PCOS, overweight[d]	428	2.0 (1.3–2.9)	1.4 (0.8–2.2)	320	1.7 (1.2–2.3)	0.9 (0.6–1.3)
PCOS, normal weight	31	3.1 (1.2–8.0)	3.2 (1.2–8.3)	28	1.9 (0.8–4.3)	2.0 (0.8–4.5)
PCOS, overweight	21	4.0 (1.5–11.0)	3.0 (1.0–8.6)	15	3.5 (1.2–9.8)	1.8 (0.6–5.4)

[a] Logistic regression model adjusted for age, race, education, parity, and family history of diabetes at baseline.

[b] Logistic regression model adjusted for the covariates in Model 1 plus BMI at Year 20

[c] Normal weight defined as BMI <25 kg/m^2

[d] Overweight defined as BMI ≥25 kg/m^2

Table 4

Odds ratio (95% confidence interval) of incident[a] diabetes and dyslipidemia based on persistence of PCOS diagnosis within the CWS cohort

	Diabetes		Dyslipidemia	
	n	Adjusted OR[b]	n	Adjusted OR
Never PCOS	620	1.0	441	1.0
Early PCOS	24	4.9 (0.9–25.4)	17	5.4 (1.6–18.7)
Persistent PCOS	11	7.2 (1.1–46.5)	7	2.1 (0.2–19.8)

[a] Number of new cases at Year 20 excluding the number of cases at Year 15

[b] Logistic regression model adjusted for age, race, BMI, education, and parity obtained at Year 15, and family history of diabetes obtained at Year 10.