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Coronary heart disease risk factors in adult premenopausal white women with polycystic ovary syndrome compared with a healthy female population

Charles J. Glueck[a,*], John A. Morrison[b], Naila Goldenberg[a], Ping Wang[a]

[a]*Cholesterol Center, Jewish Hospital of Cincinnati, Cincinnati, OH 45229, USA*
[b]*Department of Cardiology, Children's Hospital Medical Center, Cincinnati, OH 45229, USA*

Abstract

Our specific aim was to determine whether coronary heart disease (CHD) risk factors in polycystic ovary syndrome (PCOS) patients were independent of their higher body mass index (BMI) and centripetal obesity. In adult, premenopausal, white women, CHD risk factors were compared between 488 patients with well-defined PCOS and 351 healthy free-living population controls from the Princeton Follow-up Study (PFS). After excluding women with irregular menses (putative PCOS phenotypes), comparisons were also made between the 261 PFS women with a history of regular menses and the 488 women with PCOS. Fasting lipids, insulin, glucose, homeostasis model assessment of insulin resistance (HOMA-IR), HOMA insulin secretion, blood pressure, BMI, and waist circumference were measured. Compared with both the full cohort of 351 PFS women and the subgroup of 261 PFS women with regular menses, women with PCOS had higher BMI, waist circumference, total and low-density lipoprotein cholesterol, triglyceride, systolic blood pressure, diastolic blood pressure, insulin, glucose, and HOMA-IR (all Ps $\leq$ .005). After adjusting for age and BMI, women with PCOS, compared with the 351 and 261 PFS women, had lower high-density lipoprotein cholesterol (P <.0001, .0008) and higher systolic blood pressure (P = .0002, < .0001), insulin (P = .017, .039), HOMA-IR (P = .013, .032), and HOMA insulin secretion (P = .022, .037). The small subgroup of PCOS women with normal BMI (<25 kg/m^2) (36/488, 7%) also had higher age-adjusted insulin, glucose, and HOMA-IR (all Ps < .005) than the subgroup of PFS women with BMI less than 25 kg/m^2 (123/261, 47%). Increased CHD risk factors and high HOMA-IR in PCOS cannot be exclusively attributed to their preponderant centripetal obesity. Identification of women with clinical features of PCOS should alert the clinician to potentially increased risk for CHD and prompt CHD risk factor testing.

1. Introduction

Women with menstrual cycle irregularity, when compared with women with very regular cycles in the Nurses Health Study, had increased risk for nonfatal or fatal coronary heart disease (CHD), with age-adjusted relative risks of 1.25 (95% confidence interval, 1.07-1.47) and 1.67 (95% confidence interval, 1.35-2.06) [1]. In older postmenopausal women with intact ovaries and no diabetes studied by Krentz et al [2], "… there was a stepwise graded association between an increasing number of features of the PCOS [polycystic ovary syndrome] phenotype … and prevalent CVD [cardiovascular disease] (P = .02)." Krentz et al [2] concluded that "this finding supports the thesis that PCOS increases the risk of atherosclerotic CVD after menopause." In middle-aged women, Talbot et al [3] reported that women with PCOS had significantly increased coronary artery calcification compared with controls after adjustment for age, body mass index (BMI), and menopausal status. In women having coronary angiography, those with more extensive coronary artery disease (CAD) were more likely to have polycystic ovaries on ultrasonography than were those with less extensive disease [4]. Recently, Shaw et al [5] studied 390 postmenopausal women seen for ischemia, finding 104 (27%) with clinical features of PCOS, a substantial enrichment beyond the expected population prevalence of 4.7% [6]. Shaw et al reported [5] that women with clinical features of PCOS were more often diabetic (P < .0001), obese (P = .005), and likely to have metabolic syndrome (P < .0001) and to have more angiographic evidence of CAD (P =

* Corresponding author. Tel.: +1 513 585 7800; fax: +1 513 585 7950.
E-mail address: glueckch@healthall.com (C.J. Glueck).

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.04). The cumulative 5-year cardiovascular event rate was 21.1% for 104 women with clinical features of PCOS vs 11.3% for 286 women without clinical features of PCOS (P = .006) [5]. Shaw et al [5] concluded that, among postmenopausal women evaluated for suspected ischemia, clinical features of PCOS are associated with more angiographic CAD and increased CHD events.

Women with PCOS are characterized by increased risk factors for CHD and are more likely to have coronary events [5], carotid disease [7], and metabolic syndrome [8]. The constellation of CHD risk factors associated with PCOS includes androgen excess [9,10], obesity, centripetal obesity, high low-density lipoprotein cholesterol (LDLC) and triglyceride levels, low high-density lipoprotein cholesterol (HDLC), hypertension, hyperinsulinemia–insulin resistance, and type 2 diabetes mellitus (T2DM) [5,8,10-15]. Identification of women with clinical features of PCOS should alert the clinician to additional health risks and should prompt additional testing, with the ultimate goal being primary and secondary prevention of CAD and CHD events [4,5,8,12,14,16].

Given an increased likelihood of CAD in women with PCOS [3,5] and in women with the PCOS phenotype [1,2,4], our specific aim was to compare CHD risk factors between premenopausal white women with well-documented [17] PCOS and a general, free-living, suburban population of white premenopausal women of similar ages. We hypothesized that there would be consistent evidence of more extreme CHD risk factors and insulin resistance in women with PCOS when compared with free-living suburban women, after excluding women with the putative PCOS phenotype [1,2] and after adjusting for obesity and centripetal obesity, and even women with normal [18] BMI (<25 kg/m^2).

2. Patients and methods

2.1. Women with PCOS (cases)

This study was carried out following a protocol approved by the Children's Hospital Institutional Review Board and by the Jewish Hospital Institutional Review Board with signed informed consent.

From July 1995 to May 2008, 1487 women were referred to the Jewish Hospital Cholesterol Center for diagnosis and treatment of PCOS. Of the 1487 women, 1186 met the revised 2003 Rotterdam European Society for Human Reproduction and Embryology/American Society of Reproductive Medicine 2003 consensus criteria for diagnosis of PCOS, with cases meeting 2 of the following 3 criteria [17]:

1. Oligomenorrhea or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries by pelvic ultrasound

Exclusionary criteria for the current study included serum creatinine greater than 1.5 mg/dL, type 1 DM, pituitary insufficiency, persistent hyperprolactinemia, and congenital adrenal hyperplasia [19]. Of these 1186 women with documented PCOS [17], 1032 were white, of whom 24 (2.3%) had T2DM at pretreatment study entry and 1008 did not. Of the 1032 white women with PCOS, 926 were aged at least 20 years at study entry and 507 were aged 30 to 60 years, of whom 19 were menopausal and 488 were premenopausal. The current report focused on these 488 premenopausal white women (Fig. 1, Tables 1-5).

Women with PCOS who were younger than 30 years were not included in the current report because our free-living Princeton Follow-up Study (PFS) population controls had few women younger than 30 years, most being 30 to 60 years old.

At study entry after an overnight fast, women with PCOS had measures of total and free testosterone, insulin, glucose, cholesterol, triglyceride, HDLC and LDLC, systolic (SBP) and diastolic blood pressure (DBP), height, weight, and waist circumference.

We did not systematically carry out 2-hour postglucose tests.

2.2. PFS control population (controls)

Having selected white women with PCOS, we included only white controls from the same geographic area as the women with PCOS, with recruitment of women with PCOS and controls temporally comparable. No attempt was made to assess cases and controls at the same point in the menstrual cycle. The white premenopausal controls came from the Princeton Lipid Research Clinics (LRC) Follow-up

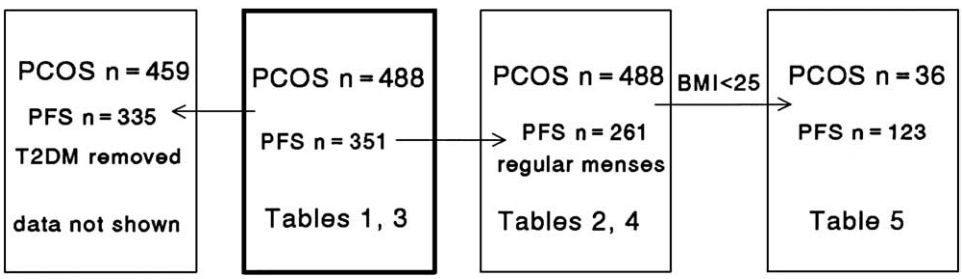

Fig. 1. Analysis groups and subgroups. The 488 PCOS women were compared with the full cohort of 351 PFS women and with 261 PFS women with regular menses. After removal of women with T2DM, 459 PCOS women were compared with 335 PFS women. Restricted to BMI less than 25 kg/m^2, 36 PCOS women were compared with 123 PFS women with normal menses.

Table 1
Coronary heart disease risk factors in white PCOS patients vs white PFS women (all premenopausal), categorized by LRC race-/sex-/age-specific percentiles

Variable	PCOS women (n = 488)	PFS women (n = 351)	
	≥90th percentile[a]	≥90th percentile[a]	
BMI (kg/m^2)	77% (370/480)	27% (93/349)	$\chi^2 = 208.5$, $P < .0001$
Total cholesterol (mg/dL)	19% (92/478)	11% (38/346)	$\chi^2 = 10.3$, $P = .0013$
Triglyceride (mg/dL)	31% (146/478)	19% (67/346)	$\chi^2 = 13.1$, $P = .0003$
LDLC (mg/dL)	14% (66/476)	10% (33/346)	$\chi^2 = 3.5$, $P = .06$
SBP (mm Hg)	49% (198/408)	14% (47/348)	$\chi^2 = 105.2$, $P < .0001$
DBP (mm Hg)	31% (127/408)	15% (51/348)	$\chi^2 = 28.3$, $P < .0001$
	<10th percentile[a]	<10th percentile[a]	
HDLC (mg/dL)	24% (114/480)	22% (76/346)	$\chi^2 = 0.36$, $P = .55$
Age distributions (y)			
30-<40	78% (380/488)	57% (200/351)	Mantel-Haenszel
40-<50	20% (97/488)	40% (139/351)	$\chi^2 = 35.5$, $P < .0001$
50-60	2% (11/488)	3% (12/351)	

Age (y)	BMI 90th (kg/m^2)	Total cholesterol 90th (mg/dL)	Triglycerides 90th (mg/dL)	LDLC 90th (mg/dL)	SBP 90th (mm Hg)	DBP 90th (mm Hg)	HDLC 10th (mm Hg)
30-<35	29.8	215	140	147	124	82	40
35-<40	29.6	233	170	161	128	87	38
40-<45	30.4	241	161	165	133	89	39
45-<50	30.0	256	180	173	138	89	41
50-<55	31.1	267	190	186	151	91	41
55-<60	31.6	278	229	199	158	94	41

[a] LRC white female age-specific 90th/10th percentiles.

Study [20], a 25- to 30-year follow-up of former schoolchildren and their parents from the Cincinnati clinic of the National Institutes of Health–National Heart, Lung, and Blood Institute LRC Prevalence Program (1973-1978), carried out from August 1998 to February 2003. The LRC study was a multistage survey of lipids and other CVD risk factors. The PFS was conducted to assess changes in family CVD risk factor correlations from the period of shared households to separate households and changes in risk factors levels from ages 6 to 18 years into the fourth and fifth decades of life [21]. The Cincinnati LRC Prevalence Study (1973-1978) has been described previously [22,23]. All the LRC study data were collected according to the collaborative LRC protocol [24].

At the 25- to 30-year follow-up studies of the PFS (1998-2003), data were collected using standard protocols [23,25]. Information was gathered as to menstrual status (yes or no; if yes, regular or irregular). Height and weight were measured with subjects in light indoor clothing and shoes removed. Two measurements of height and weight were made, with a third measurement made if the first 2 differed by more than 0.5 cm (height) and/or 0.3 kg (weight). The mean of replicate measurements was used for analyses. The BMI (in kilograms per square meter) was used to characterize obesity, and waist

Table 2
Coronary heart disease risk factors in white PCOS patients vs white PFS women (all premenopausal, excluding PFS women with irregular menses), categorized by LRC race-/sex-/age-specific percentiles

Variable	PCOS women (n = 488)	PFS women (n = 261)	
	≥90th percentile	≥90th percentile	
BMI (kg/m^2)	77% (370/480)	23% (59/261)	$\chi^2 = 205.8$, $P < .0001$
Total cholesterol (mg/dL)	19% (92/478)	12% (31/259)	$\chi^2 = 6.4$, $P = .011$
Triglyceride (mg/dL)	31% (146/478)	16% (41/259)	$\chi^2 = 19.2$, $P < .0001$
LDLC (mg/dL)	14% (66/476)	10% (27/259)	$\chi^2 = 1.8$, $P = .18$
SBP (mm Hg)	49% (198/408)	12% (31/261)	$\chi^2 = 95.0$, $P < .0001$
DBP (mm Hg)	31% (127/408)	14% (36/261)	$\chi^2 = 26.0$, $P < .0001$
	<10th percentile	<10th percentile	
HDLC (mg/dL)	24% (114/480)	20% (51/259)	$\chi^2 = 1.60$, $P = .21$
Age distributions (y)			
30-<40	78% (380/488)	60% (157/261)	Mantel-Haenszel
40-<50	20% (97/488)	40% (104/261)	$\chi^2 = 16.3$, $P < .0001$
50-60	2% (11/488)	0% (0/261)	

Table 3
White women with PCOS compared with PFS white women, all premenopausal

Variable	PCOS women (n = 488)	PFS women (n = 351)	*P* (Wilcoxon)	*P* adjusted for age	*P* adjusted for age and BMI	*P* adjusted for age and waist circumference
	Median (interquartile range)	Median (interquartile range)				
Age (y)	35.2 (33, 39)	38.9 (36, 42)	<.0001			
BMI (kg/m^2)	36.0 (30.4, 41.5)	25.7 (22.4, 30.1)	<.0001	<.0001		<.0001
Waist circumference (cm)	107 (93, 119)	90 (81, 102)	<.0001	<.0001	<.0001	
Total cholesterol (mg/dL)	192 (170, 216)	184 (164, 210)	.005	<.0001	.057	.061
Triglyceride (mg/dL)	114 (77, 174)	95 (67, 146)	.0004	.0025	.17	.35
HDLC (mg/dL)	46 (39, 54)	48 (40, 58)	.060	.25	<.0001	.0027
LDLC (mg/dL)	119 (97, 140)	110 (93, 131)	.003	.001	.25	.23
SBP (mm Hg)	126 (118, 136)	113 (107, 122)	<.0001	<.0001	.0002	.0001
DBP (mm Hg)	82 (74, 86)	75 (68, 82)	<.0001	<.0001	.58	.067
Insulin (μU/mL)	15.5 (9.4, 25.0)	5.3 (3.6, 7.7) (n = 78)	<.0001	<.0001	.017	.0013
Glucose (mg/dL)	90 (84, 97)	87 (79, 92) (n = 289)	<.0001	<.0001	.11	.039
HOMA-IR	1.7 (1.0, 2.8)	0.6 (0.4, 0.9) (n = 78)	<.0001	<.0001	.013	.0007
HOMA-B	137 (95, 182)	79 (65, 106) (n = 78)	<.0001	<.0001	.022	.018

circumference was used to characterize fat patterning. After sitting for 5 minutes, participants had blood pressure measured by trained certified staff members [23,25].

For both PFS and PCOS women, fasting blood was drawn into Vacutainers containing EDTA, kept on cold packs, and delivered to the laboratory within 3 hours for processing for measurement of lipid profiles in a laboratory participating in the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute Lipid Standardization Program to ensure accuracy and acceptable within-day and between-day coefficients of variation. For both PFS and PCOS women, serum insulin was measured using the ALPCO (Salem, NH) Insulin EIA sandwich-type immunoassay; and glucose was measured using a hexokinase-glucose-6-phosphate dehydrogenase method. Between-day coefficients of variation were 6.5% and 4% for insulin and glucose, respectively.

Homeostasis model assessment of insulin resistance (HOMA-IR), which correlates with estimates of IR measured by the euglycemic clamp technique, was used as an index of IR and, along with HOMA insulin secretion (HOMA-B), was calculated by the HOMA-IR calculator (http://www.dtu.ox.ac.uk/homa/, version 2.2). Although the HOMA-IR measure is less accurate than the euglycemic clamp method, in large epidemiologic studies, it is a reasonable alternative to the complicated clamp method that requires continuous intravenous administration of insulin and glucose for 3 hours for calculation of insulin sensitivity [26].

Assessments of waist circumferences, weight and height (to calculate BMI), and blood pressure were done uniformly in the PCOS and PFS cohorts.

In the PFS, there were 351 premenopausal white women aged 30 to 60 years who were compared with the 488 premenopausal white women with PCOS aged 30 to 60 years (Tables 1 and 3) Of the 351 women in the PFS, fasting plasma insulin was measured in 78 seen during a 3-month window; and glucose, in 289. Among the 351 premenopausal women in the PFS, to identify a subset who might have a

Table 4
White women with PCOS compared with PFS white women, all premenopausal, excluding PFS women with irregular menses

Variable	PCOS women (n = 488)	PFS women (n = 261)	*P* (Wilcoxon)	*P* adjusted for age	*P* adjusted for age and BMI	*P* adjusted for age and waist circumference
	Median (interquartile range)	Median (interquartile range)				
Age (y)	35.2 (33, 39)	38.7 (36, 42)	<.0001			
BMI (kg/m^2)	36.0 (30.4, 41.5)	25.4 (22.4, 29.3)	<.0001	<.0001		<.0001
Waist circumference (cm)	107 (93, 119)	89 (80, 99)	<.0001	<.0001	.0004	
Total cholesterol (mg/dL)	192 (170, 216)	182 (163, 210)	.0016	<.0001	.038	.065
Triglyceride (mg/dL)	114 (77, 174)	92 (66, 135)	<.0001	<.0001	.38	.17
HDLC (mg/dL)	46 (39, 54)	48 (40, 58)	.033	.13	.0008	.014
LDLC (mg/dL)	119 (97, 140)	110 (93, 131)	.0058	.0033	.40	.47
SBP (mm Hg)	126 (118, 136)	112 (106, 120)	<.0001	<.0001	<.0001	<.0001
DBP (mm Hg)	82 (74, 86)	74 (66, 82)	<.0001	<.0001	.14	.015
Insulin (μU/mL)	15.5 (9.4, 25.0)	5.2 (3.4, 7.7) (n = 59)	<.0001	<.0001	.039	.0042
Glucose (mg/dL)	90 (84, 97)	85 (79, 91) (n = 218)	<.0001	<.0001	.018	.0021
HOMA-IR	1.7 (1.0, 2.8)	0.6 (0.4, 0.9) (n = 59)	<.0001	<.0001	.032	.0026
HOMA-B	137 (95, 182)	80 (65, 100) (n = 59)	<.0001	<.0001	.037	.025

Table 5
White women with PCOS compared with PFS white women, all premenopausal, all with BMI < 25 kg/m^2, excluding PFS women with irregular menses

Variable	PCOS women (n = 36)	PFS women (n = 123)	*P* (Wilcoxon)	*P* adjusted for age	*P* adjusted for age and BMI	*P* adjusted for age and waist circumference
	Median (interquartile range)	Median (interquartile range)				
Age (y)	34.2 (32, 38)	38.2 (36, 42)	<.0001			
BMI (kg/m^2)	22.9 (20.9, 24.2)	22.1 (20.7, 23.4)	.094	.080		.094
Waist circumference (cm)	79 (70, 86)	80 (75, 86)	.47	.80	.19	
Total cholesterol (mg/dL)	163 (146, 201)	181 (162, 199)	.10	.69	.58	.65
Triglyceride (mg/dL)	61 (45, 94)	75 (60, 105)	.034	.98	.80	.26
HDLC (mg/dL)	57 (50, 73)	55 (45, 64)	.16	.13	.057	.41
LDLC (mg/dL)	91 (77, 112)	107 (90, 124)	.027	.22	.15	.63
SBP (mm Hg)	110 (106, 122)	109 (100, 115)	.072	.0012	.0018	.056
DBP (mm Hg)	70 (68, 78)	69 (64, 76)	.24	.054	.067	.044
Insulin (μU/mL)	6.6 (4.8, 9.0)	4.2 (3.3, 5.3) (n = 29)	.0006	.0038	.0032	.037
Glucose (mg/dL)	85 (81, 90)	85 (77, 89) (n = 103)	.13	.0021	.0025	.0091
HOMA-IR	0.7 (0.5, 1.0)	0.5 (0.3, 0.6) (n = 29)	.0005	.0031	.0027	.022
HOMA-B	84 (68, 107)	72 (61, 87) (n = 29)	.086	.11	.13	.64

putative PCOS phenotype [1,2], we excluded women who had no information on menses or had menses but reported irregular or very irregular cycles [1], leaving 261 PFS women with regular menses as a second control group (Tables 2 and 4).

2.3. Statistical methods

After defining CHD risk factors by the age-/race-/sex-specific LRC 90th percentile or 10th percentile for HDLC [24], χ^2 analyses or Fisher exact tests were used to compare premenopausal PCOS and PFS women (Tables 1 and 2). Without adjustment, CHD risk factors in PCOS women and PFS controls were compared by the Wilcoxon test (Tables 3-5). After adjusting for age, after adjusting for age and BMI, and after adjusting for age and waist circumference, CHD risk factors were compared between PCOS women and controls using analysis of variance (Tables 3-5).

Fig. 1 displays the analysis groups and subgroups. The 488 PCOS women were compared with the full cohort of 351 PFS women (Tables 1 and 3) and with 261 PFS women with regular menses (Tables 2 and 4). After removal of women with T2DM, 459 PCOS women were compared with 335 PFS women (Fig. 1). Furthermore, restricted to BMI less than 25 kg/m^2, 36 PCOS women were compared with 123 PFS women with normal menses (Table 5, Fig. 1).

3. Results

Of the 351 premenopausal women in the PFS, 47 reported having no menses (31 hysterectomy, 3 pregnant, 13 other), 22 provided no information, and 282 reported on menstrual status (ie, 261 regular [Table 4] and 21 irregular [7.4%]).

Using LRC Prevalence population [24] age-/race-/sex-specific top decile cut points, women with PCOS were significantly more likely than PFS women (unselected or selected by regular menses) to have top decile BMI, total cholesterol, triglyceride, SBP, and DBP (Tables 1 and 2). The pattern of case-control differences was very similar whether the controls were 351 unselected PFS women (Table 1) or 261 selected PFS women, with putative PCOS phenotypes excluded (Table 2).

Compared with both the full cohort of 351 PFS women and the subgroup of 261 PFS women with regular menses, women with PCOS had higher BMI, waist circumference, total cholesterol, LDLC, triglyceride, SBP, DBP, insulin, glucose, and HOMA-IR by Wilcoxon test ($P \leq .005$ for all, Tables 3 and 4). As displayed in Tables 3 and 4, after adjusting for age, women with PCOS vs PFS women had higher BMI, waist circumference, total cholesterol, LDLC, triglycerides, SBP, DBP, insulin, glucose, HOMA-IR, and HOMA-B. The pattern of case-control differences was very similar whether the controls were unselected women (Table 3) or selected, with putative PCOS phenotypes excluded (Table 4).

After further adjusting for BMI as well as age, women with PCOS had greater waist circumference, higher total cholesterol, lower HDLC, higher SBP, higher insulin, higher HOMA-IR, and higher HOMA-B (Tables 3, 4). After adjusting for waist circumference and age, women with PCOS had lower HDLC, higher SBP, higher insulin, higher glucose, higher HOMA-IR, and higher HOMA-B (Tables 3, 4). The pattern of case-control differences was very similar whether the controls were unselected women (Table 3) or selected, with putative PCOS phenotypes excluded (Table 4).

Subgroup analyses of the PCOS and PFS cohorts after removing women with T2DM (Fig. 1) revealed case-control differences that were virtually identical to the full cohort analyses (data not shown).

The small group of PCOS women with normal BMI (<25 kg/m^2), 36 of 488 (7%), had higher age-adjusted insulin, glucose, and HOMA-IR (all *P*s < .005, Table 5) than the 123 of 261 (47%) PFS women with BMI less than 25 kg/m^2.

4. Discussion

Because it has been estimated that 4.7% of white women and 3.4% of black women have PCOS [6], PCOS may be the most common endocrine disorder in women and, by extension [3,5], one of the most common disorders associated with increased CHD risk in women. Modifiable risk factors for CHD associated with PCOS include high total cholesterol and LDLC, high SBP and DBP, obesity, centripetal obesity, hyperglycemia and T2DM, insulin resistance, hyperinsulinemia, and the metabolic syndrome [4,8,11,13,14,27-30]. In the current study, compared with healthy women originally recruited from a suburban Cincinnati school district, women with PCOS were much more likely to have higher BMI, waist circumference, total cholesterol, LDLC, triglyceride, SBP, DBP, insulin, glucose, and HOMA-IR. After adjusting for age and BMI, or age and waist circumference, women with PCOS had lower HDL, higher SBP, higher insulin, higher HOMA-IR, and higher HOMA-B. Premenopausal women with PCOS have higher serum testosterone than free-living women [14], and testosterone is inversely associated with HDLC and positively associated with LDLC [31,32]. At the same time, premenopausal women with PCOS have lower estradiol than controls [14]; and endogenous estradiol is positively associated with HDLC and inversely associated with LDLC.

In the current study, PCOS-control differences were not materially different when controls were free-living, unselected women in the PFS or, after exclusion of PFS women who might have had the putative PCOS phenotype [1,2], those with menstrual irregularity (7.4% of those reporting menses). Our finding of 7.4% of the PFS cohort with irregular menses and the putative PCOS phenotype was comparable with the 9.5% reported by Krentz et al [2] using more inclusive criteria. Our study suggested that increased CHD risk in women with PCOS cannot be exclusively attributed to their preponderant centripetal obesity.

Even in the small minority of PCOS women with normal [18] BMI (<25 kg/m^2), 7%, compared with the 47% of PFS women with BMI less than 25 kg/m^2, women with PCOS retained higher age-adjusted insulin, glucose, and HOMA-IR. In the Prediction of Cardiovascular Events in Asymptomatic Patients With Type 2 Diabetes (PREDICT) study of 589 patients with T2DM, HOMA-IR predicted primary end points independently of the coronary artery calcification score (P = .01). The HOMA-IR has a positive, significant relationship to increased myocardial infarction and stroke events in older women [33] and was a significant independent predictor of cardiovascular events in Danish men and women [34]. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study of gemfibrozil in men with elevated triglycerides and low HDLC, the occurrence of a new cardiovascular event and the benefit of fibrate therapy were much less dependent on levels of HDLC or triglycerides than on the presence or absence of insulin resistance. In 543 patients with T2DM randomized to the insulin secretogogue glimepiride or to the peroxisome proliferator–activated receptor insulin sensitizer pioglitazone, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with treatment with glimepiride [35]. This suggests that pioglitazone-mediated reduction of insulin resistance may slow the progression of CAD [35]. In a study of 4555 elderly subjects, β-cell function as measured by HOMA-B was a significant predictor of incident cardiovascular events and mortality after controlling for HOMA-IR and sociodemographic and clinical confounders [36].

Maintenance of higher HOMA-IR in women with PCOS vs normal women in the current study, after adjusting for age, BMI, and waist circumference, is concordant with increased CHD risk [33-35].

We agree with Shroff et al [37] that evidence of early coronary atherosclerosis in young women with PCOS underscores the need to "… screen and aggressively counsel and treat those women to prevent symptomatic CV disease." Christian et al [38] used electron beam computed tomography to noninvasively measure coronary artery calcium, a marker for coronary atherosclerosis. Coronary artery calcium was measured by electron beam computed tomography in 30- to 45-year–old premenopausal PCOS women (n = 36) compared with normal ovulatory volunteers (n = 36) matched by age and weight and with community-dwelling women (n = 71) of similar age and BMI [38]. Coronary artery calcium was more prevalent in PCOS women (39%) than in matched controls (21%; odds ratio, 2.4; P = .05) or community-dwelling women (9.9%; odds ratio, 5.9; P < .001). Christian et al [38] concluded that "… PCOS women are at increased risk for atherosclerosis and should be targeted for primary prevention of CHD." Recently, among 390 postmenopausal women in a myocardial ischemia study, 104 with clinical features of PCOS, Shaw et al [5] reported that PCOS was a significant predictor (P < .01) of adverse CHD outcome in prognostic models including diabetes, waist circumference, hypertension, and angiographic CAD as covariates. Shaw et al [5] concluded that, among postmenopausal women evaluated for suspected ischemia, clinical features of PCOS are associated with more angiographic CAD and reduced survival free of CV events.

The main weakness of this study was that it examined only basic risk factors such as lipids, blood pressure, insulin resistance, and obesity, not CVD. Because our PCOS population (and the PFS controls) are both young female cohorts, we did not have enough cardiac or stroke events to be able to distinguish a different event rate in the PCOS vs PFS controls. In addition, we did not study surrogate end points, carotid intimal-medial thickness or coronary artery calcium [37], or inflammatory markers (high-specificity C reactive protein) that are more common in young women with PCOS than in age- and body mass–matched controls [37], findings independent of traditional CVD risk factors

[37]. We did not have adequate frozen serum to allow measurement of metabolic risk markers including adiponectin, resistin, visfatin [39], asymmetric dimethylarginine [40], vaspin [41], and cystatin [42-44].

Major CHD risk factors and insulin resistance associated with PCOS can, to a large extent, be ameliorated by diet and Glucophage (Bristol Myers Squibb, New York, NY) [8,13-15,27,29,45-51]. To prevent adverse CHD outcomes, diagnosis and recognition of PCOS should alert the clinician to identify and treat major CHD risk factors including diet-drug regimens designed to lower insulin and insulin resistance; to reduce BMI, triglyceride, LDLC, SBP, and DBP; and to raise HDLC. Even if the preponderant obesity in women with PCOS can be ameliorated, they are likely to retain most CHD risk factors and insulin resistance, all of which will require intervention.

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