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Searching for Polycystic Ovary Syndrome in Postmenopausal Women: Evidence for a Dose-Effects Association with Prevalent Cardiovascular Disease

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Abstract

Objective—To test the hypothesis that polycystic ovary syndrome (PCOS) is associated with an increased risk of atherosclerotic cardiovascular disease (CVD) in older postmenopausal women.

Design—Cross-sectional study of community-dwelling non-estrogen-using postmenopausal Caucasian women (n=713) mean ($\pm$ SD) age 73.8 ± 7.9 years, mean body mass index 24.0 ± 3.5 kg/m² participating in the Rancho Bernardo Study. A putative PCOS phenotype was defined as the presence of ≥ 3 features: (1) recalled history of irregular menses, (2) symptomatic premenopausal hyperandrogenism *or* biochemical evidence of current biochemical hyperandrogenism, (3) history of infertility or miscarriage, (4) central obesity, or (5) biochemical insulin resistance. Atherosclerotic CVD was determined from clinical history, electrocardiography, and structured interviews using validated techniques. The analysis was stratified by diabetes status, ascertained from medical history or 75 g oral glucose tolerance tests.

Results— The PCOS phenotype was present in 9.3% of the entire cohort and 5.8% of non-diabetic women. The prevalence of CVD was similar between women with the phenotype compared to non-affected women (27.3%, vs. 24.4%). Among women with intact ovaries and no diabetes there was a stepwise graded association between an increasing number of features of the PCOS phenotype (i.e., 0 – ≥ 3) and prevalent CVD (p=0.02) and coronary heart disease alone (p=0.03).

Conclusions— – Among non-diabetic postmenopausal women with intact ovaries, prevalent atherosclerotic CVD is associated with features of a putative PCOS phenotype. This finding supports the thesis that PCOS increases the risk of atherosclerotic CVD years after menopause.

Keywords

Polycystic ovary syndrome; menopause; cardiovascular disease; insulin resistance; hyperandrogenism

Introduction

Polycystic ovary syndrome (PCOS) is held to be the most prevalent endocrine disorder among women of reproductive age¹²³⁴. The syndrome commonly presents in adolescence or early adulthood as hyperandrogenism often in concert with chronic anovulation and infertility⁵⁶⁷.

Cardiovascular disease (CVD) risk in women with PCOS may be enhanced through associations with insulin resistance, diabetes mellitus, and other components of the metabolic syndrome^{89 1011}. Clinical practice guidelines stress the importance of identifying modifiable CVD risk factors in younger women with PCOS⁸⁹. However, few data are available concerning the health implications of PCOS for older women¹².

Among premenopausal women with PCOS, high prevalence rates of dyslipidemia, central obesity, and diabetes^{13, 1415} and evidence of accelerated subclinical atheroma¹³¹⁶ provide *a priori* evidence for an increased risk of atherosclerosis¹⁷¹⁸. To date, however, no clear evidence of an excess of CVD or death has emerged from epidemiologic studies¹⁶¹⁹²⁰. The reasons for this discrepancy have been extensively debated. Some studies included women who had undergone ovarian surgical intervention that might have obscured any association. No studies to date have tested the hypothesis that CVD may become apparent only after the menopause when atherosclerosis is most prevalent¹⁶²¹.

In this study we identified individuals with a putative PCOS phenotype from among a cohort of community-dwelling postmenopausal women. Women taking hormone replacement therapy were excluded. A review of the literature prompted us to stratify our analysis to exclude the potential confounding factors of diabetes and prior oophorectomy.

Methods

Study cohort

Between 1984 and 1987 82% of the surviving participants in the Rancho Bernardo Study, a middle-class Caucasian cohort resident in southern California, participated in a clinical study focusing on diabetes. From this cohort, we identified 713 women aged >50 years who were not taking hormone replacement therapy. All the women were at least one year beyond their last menstrual period and all had plasma estradiol concentrations <100 pmol/L. Height, weight, waist girth, and hip girth were measured in participants wearing lightweight clothing without shoes. Body mass index (BMI) was calculated as weight (kg)/height (m²). Diabetes was diagnosed based on medical history or hyperglycemia, according to American Diabetes Association (ADA) criteria (i.e., fasting plasma glucose ≥ 7.0 and/or 2-h glucose ≥ 11.1 mmol/l after a 75-g oral glucose challenge²²). A history of unilateral or bilateral oophorectomy was sought from all women. Medical records were obtained in 228 of 614 women who reported a history of hysterectomy: 96.5% of the women reporting bilateral oophorectomy and 67.5% of women reporting ovarian conservation had confirmatory medical records²³.

Laboratory methods

Fasting venous blood samples were obtained and plasma frozen at -70° C. Sex steroid hormones were measured on first-thawed samples between 1992 and 1993 in the Department of Reproductive Medicine Research Laboratory, University of California San Diego, using radioimmunoassay after solvent extraction and celite column chromatography. Steroids are stable for at least 10 years in frozen plasma²⁴. Sex hormone-binding globulin (SHBG) was determined by the method of Rosner²⁵, and bioavailable testosterone and estradiol (the non-SHBG-bound fractions) were measured by a method modified from Tremblay and Dube²⁶. The sensitivity and intra- and inter-assay coefficients of variation have been reported elsewhere²⁷. Plasma glucose was measured using a glucose oxidase assay. Fasting plasma insulin was determined in a substudy of 390 women using a double-antibody radioimmunoassay²⁸. Insulin resistance was assessed using the homeostasis model assessment for insulin resistance (HOMA-IR)--fasting glucose (mmol/l) $\times$ fasting insulin (mU/l)/22.5^{29 30}. Cholesterol and triglycerides were measured by enzymatic methods with an ABA-200 biochromatic analyzer (Abbott). High-density lipoprotein (HDL) cholesterol was measured by

precipitation according to the Lipid Research Clinics protocol³¹; low-density lipoprotein (LDL) cholesterol was calculated using the formula of Friedewald and colleagues³². High-sensitivity C-reactive protein (CRP) was measured by immunoassay (Calbiochem) with a coefficient of variation of 7.7%³³.

Ascertainment of prevalent CVD and CHD

The presence of CHD was defined by any of the following: Rose Questionnaire severe angina score³⁴, history of heart disease diagnosed by a physician (validated for 85% of the 30% subset whose hospital records were requested), history of coronary revascularization, or major electrocardiographic (ECG) abnormalities. A 12-lead resting ECG was performed and coded at the University of Minnesota³⁵. Myocardial infarction was defined by the presence of major ECG Q-wave abnormalities (Minnesota codes 1.1 and 1.2), a history of physician-diagnosed heart attack, or severe chest pain lasting for >30 minutes. Cerebrovascular disease was defined as a history of stroke, transient cerebral ischemic attack, or carotid-intracerebral arterial surgery. Lower extremity arterial disease was identified by claudication using the Rose questionnaire³⁴. CVD was defined as the sum of coronary heart disease, cerebrovascular disease, and lower extremity arterial disease.

Definition of the PCOS phenotype

Clinical and biochemical criteria were selected to identify women with features of PCOS in accordance with the literature^{8, 9, 36}. Because these features cluster together in variable associations in individuals, we defined our phenotype as the presence of ≥ 3 of the following: (1) a history of irregular menses, defined as being 'too irregular to recall' between the ages of 20 and 40 years; (2) hirsutism, defined as excessive facial hair on the chin and/or upper lip or androgenic pattern hair loss (i.e., receding hair line or loss of hair over vertex) before the age of 50 years as reported in a structured self-administered questionnaire, *or* current biochemical evidence of relative hyperandrogenism (i.e., values in the highest quintile for total testosterone or bioavailable testosterone, or the lowest quintile for SHBG); (3) a history of personal infertility (i.e., unable to conceive for reasons not attributable to partner *or* inability to carry pregnancies to term³⁷); (4) central obesity defined as a waist circumference >88 cm³⁸; *or* (5) insulin resistance, defined either as a HOMA-IR value in the top quintile for the cohort²⁹, *or*, in women (n=216) for whom insulin levels were not available, a fasting plasma glucose concentration ≥ 6.1 was used as a proxy marker of insulin resistance as suggested by the 2001 report of the National Cholesterol Education Program (NCEP)³⁸.

Statistical analysis

Data were analyzed using SPSS for Windows® version 11.5 (SPSS Inc, Chicago, IL). Immunoreactive insulin, HOMA-IR, and sex steroid hormones did not follow a normal distribution. However, because results did not differ between analyses based on untransformed and log-transformed variables, untransformed data are presented. For quintile analysis, the highest or lowest quintile, depending on the variable, was compared with the remaining four quintiles. Unadjusted associations between potential predictors and cardiovascular disease were evaluated using Student's *t* test and χ^2 tests, as appropriate. One-way analysis of variance was used to examine differences between the means of more than two groups, followed by *post hoc* tests where appropriate. Binary logistic regression was used to examine the effect of covariates on the association between PCOS and prevalent CVD. Since some of the variables that defined the PCOS phenotype are closely associated with diabetes--itself a powerful risk factor for CVD--the analysis was stratified by diabetes status. Data were analyzed before and after exclusion of women with a history of unilateral or bilateral oophorectomy. All *P* values are two-tailed. Statistical significance was defined as $p < 0.05$.

Ethics approval

Written, informed consent was obtained from all participants. The study was approved by the institutional review board of University of California, San Diego.

Results

Clinical and biochemical characteristics of the cohort

The mean ($\pm$ SD) age of the 713 women was 74 ± 8 years (range: 51–89); mean body mass index (BMI) was 24.0 ± 3.5 kg/m². Diabetes mellitus was present in 107 women (15% of total). Among the women with diabetes, 29 were already known to have the disorder and the remainder were new cases identified by glucose tolerance tests. Of the women with known diabetes, 16 were being treated with antidiabetic agents at the time of the study. Among the 601 non-diabetic women, 310 (43.5%) had normal glucose tolerance; the remaining women had either impaired glucose tolerance ($n=195$; 27.3%), or impaired fasting plasma glucose as defined by ADA criteria²²; glucose tolerance status was unclassifiable in 5 women (0.7%). A history of single ($n=47$) or bilateral ($n=120$) oophorectomy was reported by a total of 167 (23.4%) women. Total testosterone concentration was significantly lower in women with a history of either single or bilateral ($p<0.05$ for each) oophorectomy compared with intact women (0.35 ± 0.24 vs. 0.54 ± 0.47 vs. 0.65 ± 0.46 nmol/l, respectively; $F=24.9$, $p<0.01$ between the groups).

Association of PCOS phenotype with cardiovascular risk factors

The prevalence of the putative PCOS phenotype (i.e., ≥ 3 criteria as defined above) among the entire cohort was 9.3%; among non-diabetic women, the prevalence of the phenotype was lower at 5.8%. Clinical and biochemical data for the PCOS vs. non-affected women are presented in Table 1. As expected from the selection criteria, statistically significant differences were observed between those with versus those without PCOS for waist circumference, bioavailable testosterone, SHBG, and HOMA-R. Plasma total and bioavailable estradiol concentrations were significantly higher in women with the PCOS phenotype compared to unaffected women ($p<0.01$; Table 1). The proportion of women reporting a history of cigarette smoking or estrogen-progestogen use, current physical activity or exercise three or more times weekly, and single or bilateral oophorectomy did not differ according to the presence or absence of the PCOS phenotype (Table 1).

The percentage of affected and non-affected women with each of the main features of the PCOS phenotype is presented in Table 2. Among women with the PCOS phenotype, the frequency of relevant symptoms did not differ by diabetes status (Figure 1). However, high waist circumference, hyperandrogenism, and insulin resistance were more common in diabetic women with the PCOS phenotype than in non-diabetic women with the phenotype ($p<0.01$ for each; Figure 1).

Relationship of the PCOS phenotype to prevalent CVD

The prevalence of CVD was similar between women with PCOS status and non-affected women (27.3% vs. 24.4%). When the analysis was confined to non-diabetic women with intact ovaries, a significant age-adjusted stepwise graded association was observed between an increasing number of features of the PCOS phenotype (i.e., $0 - \geq 3$) and prevalent CVD ($p=0.02$; Table 3). This association was also evident for CHD alone ($p=0.03$; Table 3).

Discussion

Our objective was to identify major clinical and biochemical features of PCOS among a well-characterized cohort of non-hormone using postmenopausal women and examine the PCOS

association with CVD. For non-diabetic women with intact ovaries we observed a stepwise graded association between key features of our putative PCOS phenotype and prevalent CVD. We believe that our study is the first to describe PCOS and CVD in exclusively postmenopausal women, and to provide support for the thesis that PCOS increases the risk of CVD in later life. In addition, prevalent CVD increases as a function of the number of features of the syndrome.

Several retrospective studies have suggested an increased risk of atherosclerotic CVD in women with PCOS^{39,40}. In case-control studies the severity of surrogate markers of atherosclerosis in premenopausal women, including coronary calcification scores^{17,41}, carotid intima media thickness, and adverse electrocardiographic features⁴² was increased in women with PCOS compared with controls⁴³. However, a higher prevalence of undiagnosed glucose intolerance and/or diabetes in women with PCOS⁹ might partially explain these findings⁴⁴. In a small single-center study of women with a mean age of ~60 years undergoing coronary angiography, hirsutism was more commonly reported by women with stenotic coronary disease³⁹. However, assessment of coronary disease by angiography is now recognized to be a relatively poor indicator of the true extent of coronary atherosclerosis⁴⁵.

Prospective studies have produced equivocal results. In a UK study of 786 women with PCOS diagnosed on macroscopic or histological criteria, Pierpoint et al⁴⁶ found no increased risk of CVD compared with national rates. Additional follow-up of this cohort in middle-age¹⁵ found no excess of CHD morbidity or mortality, but elevated rates of self-reported cerebrovascular disease and diabetes were observed. Of note, a high proportion (75%) of the women in this cohort had a history of surgical ovarian wedge resection⁴⁶. We hypothesized that high rates of ovarian surgery in western countries may confound epidemiologic studies of the association between PCOS and CVD. The high rates of oophorectomy in the U.S. provide support for this contention: more than 25% of women have had a hysterectomy before age 60⁴⁷; this procedure is often accompanied by elective oophorectomy.⁴⁸ Even wedge resection of the ovaries can reportedly improve menstrual patterns for decades⁴⁹. However, it is not known whether cardiovascular risk is modified by hysterectomy or oophorectomy.^{50,51} Levels of endogenous androgens may be pertinent to this issue, although testosterone is generally thought to contribute little to the insulin resistance of PCOS⁵². It has been reported that relative hyperandrogenism may persist into the postmenopausal years among women with PCOS who have intact ovaries⁵³. The association between endogenous androgens and cardiovascular risk remains uncertain⁵⁴, and it is unclear whether reduced testosterone levels following oophorectomy alter the link between PCOS and CVD²⁰. In a previous report from the Rancho Bernardo study, testosterone levels were about 40% lower in postmenopausal women who had a history of hysterectomy and bilateral oophorectomy compared to intact women⁵⁵. In the present study testosterone levels were significantly lower in women with unilateral or bilateral oophorectomy, with a dose-effect association.

There is a clear need for further studies. Diagnosing PCOS retrospectively in oophorectomized women is clearly fraught with theoretical and practical difficulties. Other steroid hormones may be relevant to CVD risk. Adrenal androgen production is reportedly increased in some women with PCOS⁵⁶. It has been suggested that higher levels of DHEAS might protect women with PCOS against atherosclerosis⁵⁷. We found no increase in DHEAS levels in women with the PCOS phenotype, as we defined it. Total and bioavailable estradiol levels were significantly higher in the women with the PCOS phenotype, a difference that possibly reflects the presence of greater adiposity or diabetes⁵⁸.

Among premenopausal women, the absence of universally agreed-on diagnostic criteria for PCOS and the paucity of long-term follow-up studies have contributed to uncertainty about the long-term risk of CVD^{16,59,60}. Although the diagnosis of PCOS may be more reliable in premenopausal than postmenopausal women, the absolute CVD risk in this age group is

intrinsically low⁴. The risk of CVD is higher after the menopause yet the diagnosis of PCOS in postmenopausal women presents investigators with additional challenges. Using current knowledge we aimed to identify a phenotype that incorporated the major clinico-pathologic features associated with PCOS, particularly those likely to be associated with CVD risk.

Recent studies have suggested that self-reported symptoms of oligomenorrhea and hirsutism can identify women at elevated risk of CVD⁶¹. Longitudinal cohort studies have shown that a history of irregular menses predicts the development of both CVD⁶² and diabetes⁶³. A recent cross-sectional study from Finland reported that premenopausal women with oligomenorrhea and/or hirsutism were more likely to have adverse cardiovascular risk profiles than asymptomatic women.⁶⁴ A recent U.S. study found that menstrual irregularity identified mothers of women with PCOS who also have features of the syndrome¹². An association between irregular periods and insulin resistance has been reported⁶⁵, which suggests a potential mechanism by which menstrual irregularity might affect CVD risk. Accordingly, we found an unfavorable plasma lipid profile among the women with the putative PCOS phenotype^{16, 19}: fasting triglycerides were elevated while mean HDL-cholesterol concentrations were reduced; these changes were independent of diabetes status. Other studies have shown that reduced HDL-cholesterol levels are associated with obesity, insulin resistance,⁶⁶ and low concentrations of SHBG in women with PCOS⁶⁷.

It is well-recognized that central adiposity may be present even in the absence of generalized obesity in women with PCOS^{68,69}. We used a waist girth of >88 cm as a proxy measure of abdominal obesity, as recommended in the 2001 NCEP Adult Treatment Panel³⁸ and subsequently adopted by the 2003 Rotterdam Consensus Conference on PCOS⁸. Abdominal obesity is associated with activation of the innate immune system, a defect implicated in atherogenesis^{70,71}. However, we found no increase in CRP levels in women with the PCOS phenotype compared to non-affected women (data not shown).

The prevalence of the PCOS phenotype in our study was 5.8% among non-diabetic women. This figure is very similar to prevalence rates reported in the literature^{12, 4}, although women in the Rancho Bernardo Study are almost exclusively Caucasian and leaner than a representative sample of white U.S. women⁷². Azziz and colleagues reported a cumulative prevalence of 6.6% in a mixed-race sample of U.S. women³, while Diamanti-Kandarakis and colleagues⁷³ and Ascunio and colleagues⁷⁴ found prevalence rates of 6.8% and 6.5% among premenopausal Greek and Spanish women, respectively.

Previous studies that examined the association between PCOS and CVD have not always rigorously excluded women with undiagnosed diabetes. This is important because several components of the PCOS phenotype, i.e., menstrual irregularity⁶³, hyperandrogenism^{5, 58}, central obesity⁷⁵, and insulin resistance^{9,76}, are associated with diabetes. The prevalence of PCOS in our cohort increased to 9.3% when women with diabetes were included^{4, 5}. The majority of women with diabetes in our study were identified using oral glucose tolerance tests, currently the most sensitive diagnostic method²².

We acknowledge several limitations of our study. First, ovarian imaging and a medical record of physician-confirmed PCOS were not available. However, appearances on pelvic ultrasonography do not necessarily correlate well with clinical and biochemical features, and ovarian imaging is not required to make a diagnosis of PCOS^{8, 77}. In fact, up to 25% of apparently healthy women with regular menstrual cycles have polycystic ovary morphology⁹ accompanied by degrees of insulin resistance⁷⁸. Second, the reported premenopausal clinical history (hirsutism, oligomenorrhea) may not have been correctly recalled by older women. While we were also unable to exclude alternative causes of oligomenorrhea or hyperandrogenism, clinical practice suggests that these are likely to have

been uncommon among community-dwelling women⁷⁹. Similarly, reported infertility or inability to take a pregnancy to term may have had causes other than PCOS. Third, we included clinical and subclinical CVD in our analysis when it is acknowledged that the diagnosis of CHD can be problematic in women⁸⁰. To reduce the non-specificity of chest pain in women, we included only those individuals with severe angina scores on the Rose questionnaire³⁴. We used HOMA-IR in place of the gold standard euglycemic hyperinsulinemic clamp technique⁸¹ to measure insulin resistance⁸². HOMA-IR appears to be a valid marker of insulin resistance and is generally regarded as a practical alternative to the clamp technique in epidemiologic studies⁸³. However, there are some reservations about the reliability of HOMA-IR in the presence of hyperglycemia. The cross-sectional design of our study cannot exclude selective cardiovascular mortality in more severely affected women. Such a survivor effect would reduce the ability to identify an association between PCOS and CVD. Perhaps the most challenging issue is that of defining a PCOS phenotype in older women. Since no gold standard diagnostic criteria exist, of necessity we have had to base our definition on current views of the pathophysiology of PCOS. Because there is overlap between PCOS and the broader metabolic syndrome of cardiovascular risk¹¹⁹, our study should be regarded as an exploratory attempt to identify PCOS in postmenopausal women. Strengths of our study include the well-characterized cohort, exclusion of women taking hormone replacement therapy, accurate ascertainment of diabetes status, and the validated history of oophorectomy.

In summary, we found a stepwise graded association between components of a PCOS phenotype and prevalent atherosclerotic CVD in a cohort of non-estrogen using postmenopausal women. This association was evident only in non-diabetic women and was obscured by a history of oophorectomy. The latter observation suggests that oophorectomy may be a confounding factor in studies of the association between PCOS and CVD. In conclusion, we believe our findings provide support for the thesis that PCOS increases the risk of CVD in postmenopausal women.

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Figure 1. Prevalence (%) of clinical and biochemical components of the putative polycystic ovary syndrome phenotype stratified by diabetes status

High waist circumference, hyperandrogenism, and insulin resistance were more common in diabetic women with the PCOS phenotype than in non-diabetic women with the phenotype ($p < 0.01$ for each).

See text for definitions of composite clinical features.

Androgens – Composite of testosterone or bioavailable testosterone in highest quintile or sex hormone-binding globulin in lowest quintile

Insulin resistance – Composite of HOMA value in highest quintile or fasting venous plasma glucose ≥ 6.1 mmol/l

Table 1

Clinical and biochemical characteristics of women with a putative PCOS phenotype and non-affected women.

	PCOS	No PCOS	P
n	66	647	-
Age	72 ± 9	74 ± 8	0.034
Body mass index (kg/m ²)	28.0 ± 4.8	23.9 ± 3.3	<0.001
Waist circumference (cm)	89.5 ± 12.2	78.5 ± 8.9	<0.001
Total cholesterol [*] (mmol/l)	6.3 ± 1.0	6.0 ± 1.0	0.01
LDL-cholesterol [*] (mmol/l)	4.0 ± 1.0	3.7 ± 1.0	0.013
HDL-cholesterol [*] (mmol/l)	1.5 ± 0.4	1.7 ± 0.5	<0.001
Triglycerides [*] (mmol/l)	1.9 ± 1.2	1.3 ± 0.7	<0.001
Total testosterone (nmol/L)	0.66 ± 0.52	0.58 ± 0.42	NS
Bioavailable testosterone (nmol/l)	0.21 ± 0.14	0.15 ± 0.13	<0.001
Total estrogen (pmol/l)	27.37 ± 15.96	20.39 ± 11.67	<0.001
Bioavailable estrogen (pmol/l)	17.10 ± 10.18	10.74 ± 7.43	<0.001
Sex hormone-binding globulin (nmol/l)	3.61 ± 2.17	6.32 ± 2.98	<0.001
DHEAS (μmol/l)	1.52 ± 1.02	1.52 ± 1.11	NS
Androstenedione (nmol/l)	1.21 ± 0.59	1.16 ± 0.55	NS
Plasma glucose [*] (mmol/l)	6.51 ± 1.51	5.36 ± 0.83	<0.01
Plasma immunoreactive insulin (pmol/l) [*]	129.2 ± 78.7	83.7 ± 54.2	<0.01
HOMA-IR	5.36 ± 3.88	2.83 ± 2.04	<0.01
Systolic blood pressure (mmHg)	142 ± 17	145 ± 22	NS
Diastolic blood pressure (mmHg)	76 ± 9	76 ± 10	NS
Exercise (%) [#]	27.3	23.0	NS
History of cigarette smoking (%)	43.9	52.7	NS
Reported past use of estrogen-progesterone (%)	7.7	12.1	NS

Data are mean ± SD unless otherwise indicated.

^{*} Fasting values

LDL, Low-density lipoprotein

HDL, High-density lipoprotein

HOMA-IR, homeostasis model assessment

[#] Current physical activity or exercise three or more times per week

Table 2

Prevalence of individual and composite features of a putative PCOS phenotype among affected (i.e., those with ≥ 3 features) and non-affected women*. See text for details of definitions.

	PCOS	No PCOS	P
Menstrual irregularity	13.6	3.6	<0.01
Biochemical hyperandrogenism	95.5	34.2	<0.01
Infertility or miscarriage	31.8	3.9	<0.01
Central obesity	68.2	12.8	<0.01
Biochemical insulin resistance	75.6	18.4	<0.01

* All values are percentages.

Table 3

Binary logistic regression of cardiovascular disease and coronary heart disease: association with age and number of components of the PCOS phenotype in non-diabetic non-oophorectomized women (N=601).

	Exp (B)	95% confidence interval	p
Cardiovascular disease			
Age	1.056	1.021–1.093	<0.01
PCOS	1.362	1.052–1.762	0.02
Coronary heart disease			
Age	1.050	1.012–1.090	<0.01
PCOS	1.360	1.030–1.796	0.03

PCOS = Increasing number of components of PCOS (i.e., 0 – ≥ 3).

Exp (B) = Estimated odds ratio