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Risk of Cardiovascular Events in Mothers of Women with Polycystic Ovary Syndrome

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Abstract

OBJECTIVE—The purpose of this study was to assess the prevalence of cardiovascular events in an older population of women with polycystic ovary syndrome (PCOS). We took advantage of the high heritability of PCOS and determined the probable PCOS status of mothers of women with PCOS. Prevalence of cardiovascular events in PCOS and non-PCOS mothers was determined.

METHODS—In a single endocrine clinic, 308 women with PCOS were interviewed about their mothers' medical history, and the mothers themselves were interviewed if available. The interview covered menstrual history, fertility, clinical signs of hyperandrogenism, age of incident cardiovascular event, and age of death as reported by daughters. Presence of PCOS in the mothers was defined as history of infertility, irregular menses, or clinical signs of hyperandrogenism. Cardiovascular event was defined as fatal or nonfatal myocardial infarction, any coronary intervention, angina requiring emergency room visits, or cerebrovascular event.

RESULTS—The mothers were predominantly postmenopausal. Among 182 interviewed (n=157) or deceased (n=25) mothers, 59 had probable PCOS. Cardiovascular events were more common (p=0.011) among PCOS mothers (11/59 or 18.6%) than non-PCOS mothers (5/123 or 4.1%). Adjusted for age and race, probable PCOS was an independent predictor of cardiovascular events (OR 5.41 95%CI 1.78−16.40). Cardiovascular events occurred at an early age in mothers of PCOS women, particularly mothers with PCOS themselves.

CONCLUSION—PCOS mothers of women with PCOS are at a higher risk of cardiovascular events compared with non-PCOS mothers, and cardiovascular events appear to occur at an earlier than expected age in PCOS mothers.

Keywords

Polycystic ovary syndrome; cardiovascular risk; cardiovascular events; familial polycystic ovary syndrome

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BACKGROUND

Polycystic ovary syndrome (PCOS) is the most common cause of female anovulatory infertility, affecting 6−10% of women of childbearing age (1;2). The disorder is defined by chronic oligo- or anovulation and hyperandrogenism, with the exclusion of secondary causes for androgen excess or ovulatory dysfunction (3). Recently, the presence of polycystic ovarian morphology was also included as a diagnostic criterion, but only in the concurrent presence of either ovulatory dysfunction or androgen excess (4).

Women with PCOS have substantial insulin resistance (5) and an increased risk for impaired glucose tolerance and type 2 diabetes mellitus (6;7). Perhaps due to the presence of insulin resistance, women with PCOS have a significantly worsened metabolic and cardiovascular risk profile, including the presence of obesity, dyslipidemia, and hypertension (8). In addition, increased levels of surrogate markers for atherosclerosis, such as PAI-I (9), C-reactive protein (10), endothelin-1 (11), and endothelial dysfunction are present in women with PCOS (12-14). Importantly, early subclinical atherosclerotic disease, as evidenced by increased coronary artery calcification (15;16) and carotid intimal media thickness (17) have been noted in women with PCOS.

Despite the evidence supporting a significant cardiovascular risk profile in women with PCOS, whether these women are at increased risk of clinical cardiovascular events is debated (18). In a cohort of 143 women under 60 years of age who underwent catheterization for chest pain or valvular disease, those with polycystic ovaries (42%) by pelvic ultrasonography had more extensive coronary stenosis than women with normal ovaries (19). Another study suggested that lean middle-aged women with PCOS (45−54 years) had a higher prevalence of hypertension, diabetes, and cardiac complaints than non-PCOS women of the same age in a Dutch population database (20).

In contrast, a UK study examining death certificates of PCOS women did not find increased cardiovascular mortality compared with the expected rate from actuarial tables (21). In the much larger Nurses' Health Study, menstrual irregularity, a surrogate marker for PCOS, was independently associated with increased risk of coronary heart disease and fatal myocardial infarction (22). Recently, more advanced angiographic coronary artery disease and worsened cardiovascular event-free survival were reported in postmenopausal women with a premenopausal history of PCOS features and concurrent hyperandrogenemia, as compared with normal postmenopausal women (23).

The purpose of the present study was to assess the presence of cardiovascular events in older women who likely had PCOS during their premenopausal years. To capture such a population, we took advantage of the high heritability of PCOS and determined probable PCOS status in mothers of women with PCOS. We then evaluated the occurrence of cardiovascular events in these PCOS and non-PCOS mothers.

SUBJECTS AND METHODS

This is a cross-sectional study, with data obtained via personal interviews. The protocol was approved by the Institutional Review Board at Virginia Commonwealth University.

Subjects

Data regarding mothers of 308 *consecutive* PCOS patients from a single, private endocrine clinic were collected from medical records. In the women with PCOS (daughters), the diagnosis of PCOS was made using criteria from the 1990 NIH Conference (3): ≤8 menses a year, and clinical or biochemical hyperandrogenism, after the exclusion of other possible causes such as

hyperprolactinemia, Cushing's syndrome, androgen-secreting tumors, and non-classical adrenal hyperplasia. PCOS daughters were interviewed to obtain a detailed maternal medical history, as is customary in this practice (see *Interview* below). If the mother was present during the daughter's visit, a medical history was obtained directly from the mother. All mothers were included in analyses unless one of the following exclusion criteria was met: 1) a non-biological maternal relationship; 2) lack of reported medical information to ascertain the probable presence of PCOS or cardiovascular events in the mothers.

Interview

The interviews of the PCOS daughters were conducted in person by a single endocrinologist (W.F.). When mothers accompanied their daughters, the mothers were interviewed at the same time. Otherwise, the daughters were interviewed in detail about their mothers' health. Interview questions included: 1) race and age of mothers at the time of interview; 2) maternal menstrual history (including average number of menses per year during reproductive years, if available); 3) maternal fertility history (number of miscarriages and live-births, difficulty achieving pregnancy, use of fertility drugs or procedures including ovarian wedge resection); 4) maternal clinical signs of hyperandrogenemia (e.g. hirsutism, alopecia, acne); 5) maternal history of coronary events, cerebrovascular events and heart failure; 6) cause and age of death if mothers were deceased.

Definition of PCOS in mothers

Although 7 mothers were patients of the endocrinologist with a confirmed diagnosis of PCOS, in most mothers there was no formal diagnosis of PCOS. The probable presence of PCOS in these mothers was inferred based on menstrual and fertility history and clinical signs of hyperandrogenemia. Probable PCOS in mothers was defined as the presence of one of the following characteristics: 1) irregular menstrual cycles; 2) history of difficulty achieving pregnancy; 3) use of fertility drugs or procedures; 4) maternal clinical signs of hyperandrogenemia. In addition, we also used a more stringent alternate definition of PCOS in the mothers for analyses, defined as the presence of 1) irregular menstrual cycles or history of difficulty achieving pregnancy or use of fertility drugs and procedures; *and* 2) the concurrent presence of clinical signs of hyperandrogenemia.

Definition of cardiovascular events in mothers

Cardiovascular events in the mothers were determined by report from PCOS daughters or via personal interviews with the mothers. Cardiovascular events were defined as fatal or non-fatal myocardial infarction, other coronary events (coronary artery bypass graft, percutaneous coronary interventions, angina necessitating emergency room visits), or cerebrovascular events. Cardiovascular disease was defined as the occurrence of any cardiovascular event or a diagnosis of heart failure.

Statistical Analysis

Statistical analyses were performed with SAS software version 9.1.3 (SAS Institute, Cary, NC). We performed analyses in all mothers as a whole, and separately in the group of interviewed or deceased mothers. We included deceased mothers in the group of interviewed mothers because it would be reasonably expected for daughters to accurately recall events leading to their mothers' death. Maternal age at the time of interview was compared between PCOS and non-PCOS mothers using a 2-sided Student's *t* test. For deceased mothers, age at death was used as the maternal age. The distributions of cardiovascular events, maternal age categories and race in PCOS vs. non-PCOS mothers were compared using the chi-square test or the Fisher-Exact test. Univariate analyses for cardiovascular events by age, race and probable PCOS were performed. Multivariate logistic regression models were used to determine adjusted odds ratios

for each of the maternal factor, including maternal age, race, and probable PCOS. To determine if interactions exist between maternal age, race, and probable PCOS in predicting cardiovascular events, interaction terms were also entered into the multivariate logistic regression model. For the univariate and multivariate logistic regressions, we also used the more stringent alternative definition of PCOS to determine if the definition of PCOS affects the direction of results. In addition, because our population included a large number of mothers with an Ashkenazi Jewish ancestry, we performed separate analyses with and without specifically considering this ethnicity in the racial mix. For all analyses, p-values of <0.05 were considered significant.

RESULTS

Subjects

There were 308 PCOS daughters who completed interviews regarding their mothers' demographic and medical history. Of the 308 mothers, 157 (51.0%) were personally interviewed to verify the history provided by their daughters. Causes of death were provided by daughters for 25 deceased mothers. Of all 308 mothers, 86 had probable PCOS, and 222 were identified as non-PCOS. Of the 182 interviewed or deceased mothers, 59 had probable PCOS, while 123 were non-PCOS mothers. The mean ages of the two groups were similar (56.5 ± 8.2 years in PCOS mothers vs 58.6±8.2 in non-PCOS mothers, p=0.11). The demographic and reproductive characteristics of interviewed mothers are described in Table 1. Mothers of PCOS women in this study were predominantly postmenopausal.

The causes of death in the 25 deceased mothers were the following: 8 died of cardiovascular causes; 1 died of multiple myeloma; 12 deaths were due to neoplasms; 1 death was due to deep venous thromboembolism; 1 death was due to kidney failure; and 2 deaths were from unknown causes.

Cardiovascular events

When we limited our analysis to the interviewed or deceased mothers (n=182), 8 had a history of myocardial infarction, 8 had other coronary events (coronary artery bypass graft or percutaneous coronary interventions [n=6], angina necessitating emergency room visit [n=2]), 5 mothers had a cerebrovascular accident, and 5 had heart failure, with some mothers having more than one event. There were a total of 16 mothers with cardiovascular events (defined as myocardial infarction, other coronary events, or cerebrovascular accidents), and 18 mothers had cardiovascular disease (defined as having cardiovascular events or heart failure).

In this analysis of only interviewed or deceased mothers (Table 2), mothers with probable PCOS (n=59) had significantly more cardiovascular events (11/59 or 18.6% vs. 5/123 or 4.1%, p=0.011), and any cardiovascular disease (13/59 or 22.0% vs. 5/123 or 4.1% , p=0.0001) compared with non-PCOS mothers (n=123).

When we expanded our analysis and evaluated all 308 mothers as a whole, mothers with probable PCOS (n=86) still had more myocardial infarctions (6/86 or 7.0% vs. 4/222 or 1.8%, p=0.0314), other coronary events (7/86 or 8.1% vs. 3/222 or 1.4%, p=0.0061), any cardiovascular events (14/86 or 16.3% vs. 7/222 or 3.2%, p<0.001), and any cardiovascular disease (16/86 or 18.6% vs. 8/222 or 3.6%, p<0.00001) compared with non-PCOS mothers (n=222).

Regression analyses

In all 308 mothers, univariate logistic regression showed that probable PCOS (OR 5.97, 95% CI 2.32−15.37) was a determinant of cardiovascular events, and cardiovascular disease (OR

6.11, 95%CI 2.51−14.90), which included the diagnosis of heart failure. After adjusting for age and race, probable PCOS was a significant independent predictor of cardiovascular events (OR 6.80, 95%CI 2.55−18.15) and cardiovascular disease (OR 6.97, 95%CI 2.78−17.50).

Because mothers who were interviewed probably provided more reliable information than that obtained from daughters, we focused our analyses on interviewed mothers. In addition, since daughters most reasonably should recall events leading to their mothers' death, we included deceased mothers in the group of interviewed mothers. When we restricted the analysis to this group of mothers, univariate logistic regression again showed probable PCOS (OR 5.41, 95% CI 1.78−16.40) was a determinant of cardiovascular events (Table 3). The relationship between probable PCOS and cardiovascular events remained significant even using the more stringent alternate PCOS criteria that required irregular menses or infertility *and* clinical hyperandrogenemia (OR 3.52, 95%CI 1.10−11.22). For cardiovascular disease (including heart failure), probable PCOS, defined by either criterion, was a significant predictor for this outcome.

All independent variables tested in the univariate model were considered for the multivariate model. In addition, possible interactions among these independent variables were examined and were found not to be of pertinence. Hence, the multivariate model consisted of the terms age, race and PCOS status. In the multivariate model with interviewed mothers, after adjusting for age and race, probable PCOS remained a significant independent predictor of cardiovascular events (OR 5.93, 95%CI 1.87−18.84, Table 4). Using the more stringent PCOS definition, this relationship remained significant (OR 3.42, 95%CI 1.04−11.23). Similarly, probable PCOS by either definition was a significant predictor for cardiovascular disease, which included the diagnosis of heart failure.

If the 25 deceased mothers, including 9 mothers with a history of cardiovascular disease, were further excluded from the above analyses of interviewed mothers, probable PCOS continued to be a significant predictor for cardiovascular events (OR 4.98, 95%CI 1.19−20.80) and cardiovascular disease (OR 6.96, 95%CI 1.76−27.52) in the univariate analysis. In the multivariate analysis, adjusted for age and race, probable PCOS remained a significant predictor for cardiovascular events (OR 6.26, 95%CI 1.32−29.77) and cardiovascular disease (OR 9.59, 95%CI 2.15−42.84).

Because of the substantial number of mothers with an Ashkenazi Jewish ancestry, we also reanalyzed the above univariate and multivariate analyses in all mothers, and in interviewed or deceased mothers, to determine if specifically including this ethnicity strata alters the results. The conclusions of the analyses did not change with these analyses, and the odds ratios remained numerically close to those shown in Tables 3-4.

Age at first cardiovascular event

Mothers with probable PCOS, compared to mothers without PCOS, also appeared to have cardiovascular events at an earlier age. The age at first cardiovascular event for mothers with probable PCOS ranged from 39 years to 69 years, while that for mothers without PCOS ranged from 48 years to 65 years. Although this difference was not statistically different due to the small number of women, mothers of PCOS women, particularly those with probable PCOS themselves, had cardiovascular events at an early age.

DISCUSSION

We set out to assess the presence of cardiovascular events in older women with PCOS. To capture such a population, we took advantage of the high heritability of PCOS and determined the probable PCOS status of mothers of women with PCOS. We then evaluated the occurrence

of cardiovascular events in these PCOS and non-PCOS mothers. The mothers in this study were predominantly postmenopausal.

We found that probable PCOS was a significant independent predictor of cardiovascular events, regardless of whether a broader definition or a more stringent definition of PCOS was used, and regardless of whether all mothers or only mothers who were personally interviewed were considered. In our study, in interviewed or deceased mothers, 11 of 59 (18.6%) mothers with probable PCOS had a cardiovascular event, compared to 5 out of 123 (4.1%) mothers without PCOS (p=0.011). Depending on the definition of probable PCOS used, we observed at least a 3.5 fold increase in the risk of cardiovascular events in mothers with probable PCOS, compared with mothers without PCOS, adjusted for race and age. In addition, cardiovascular events in mothers of women with PCOS appeared to happen at an early age, particularly for mothers who also had features of PCOS themselves.

Several lines of evidence support the concept that women with PCOS are at high risk for cardiovascular and metabolic consequences (8). Many recognized cardiovascular risk factors, such as type 2 diabetes mellitus, impaired glucose tolerance, hypertension, increased LDL, small dense LDL and triglyceride levels, and decreased HDL cholesterol, are present in women with PCOS (8). Increased levels of surrogate markers for atherosclerosis, such as increased levels of PAI-I (9), C-reactive protein (10), endothelin-1 (11), and endothelial dysfunction (12-14) have also been noted in women with PCOS. Women with PCOS also exhibit lower left ventricular ejection fraction (24) and reduced cardiopulmonary functional capacity as evaluated by oxygen consumption during exercise testing (25). Imaging cardiac studies often showed worse coronary calcification scores and carotid intima-media thickness, indicative of underlying cardiovascular disease, even in young women with PCOS, compared to age-matched control subjects (15-17;26).

Several prevalence studies have also suggested an increased risk of coronary artery disease in women with PCOS. More severe coronary stenosis as determined by angiography were found in women with androgen excess or polycystic ovaries on pelvic ultrasonography (19;27). However, epidemiologic evaluations to date have not consistently shown evidence of increased cardiovascular events in women with PCOS (8;18;21;28). This lack of a consistent association may be due to the design of these studies. Some studies included women who had undergone ovarian wedge resections or other ovarian surgeries, or had a lower BMI, which are potential confounding factors that could obscure an association between PCOS and increased cardiovascular events (21;28). Ovarian wedge resection may improve menstrual patterns for decades (29). Although it is not extensively known whether hysterectomy, oophorectomy or wedge resection changes cardiovascular risk, at least one study suggested that oophorectomy may obscure the association between PCOS and cardiovascular events (30).

Few studies to date examined whether cardiovascular events may become evident in older women with PCOS, as the risk of cardiovascular disease rises substantially after menopause (18;31). Our hypothesis was that the study of mothers of women with PCOS, who also had a putative diagnosis of PCOS, compared to mothers who likely did not have PCOS, may offer insight into the frequency of cardiovascular events in PCOS women as they age. Our findings are in agreement with a prior study of postmenopausal women with probable PCOS, in which atherosclerotic disease was found to be more prevalent in women with PCOS than control subjects (30), and with the recently published Women's Ischemia Syndrome Evaluation study, in which postmenopausal women with a premenopausal history of PCOS features and concurrent hyperandrogenemia were found to have more angiographically advanced coronary lesions and worse cardiovascular event-free survival compared with postmenopausal women without PCOS features (23). In our current study, we observed that cardiovascular events may

not be a problem only after menopause, but could occur in women with PCOS in their late thirties and early forties.

While we targeted an older and predominantly postmenopausal PCOS population, there is no standard definition for the diagnosis of PCOS in older women. In this study, we incorporated the major clinical features associated with PCOS that may be more recallable, namely clinical features of hyperandrogenemia, history of infertility and irregular menses. A recent study reported that menstrual irregularity identified mothers of women with PCOS who also have features of the syndrome (32). In addition, menstrual irregularity and/or hirsutism have been reported to be a good surrogate for identifying individuals with polycystic ovaries (33). Our definition of probable PCOS therefore included either menstrual irregularity, or hirsutism, or a history of infertility. In addition, analyses were also performed using a more stringent definition of probable PCOS, namely, irregular menses or infertility *and* clinical features of hyperandrogenemia. In our study, the association between PCOS and increased cardiovascular events remained significant even using the more stringent definition of PCOS.

Familial aggregation of PCOS demonstrates a distinct genetic susceptibility to this disorder (32;34;35). The prevalence of the putative PCOS phenotype among the 182 interviewed or deceased mothers in this study is 32.4%, which is similar to the prevalence rates in first degree relatives reported by others. In 132 probands with PCOS aged 19 to 37 years, prevalence of PCOS in mothers was 31.8%, and 31% in sisters (35). In another study of 93 probands with PCOS with their 78 mothers and 50 sisters, the prevalence of PCOS in mothers was 24% and 32% in sisters (34).

The metabolic abnormalities in PCOS are also heritable. Previous studies have suggested that first degree relatives of women with PCOS have an increased prevalence of insulin resistance (36-38), impaired glucose tolerance (36), and type 2 diabetes mellitus (39). In addition, dyslipidemia was also more prevalent in mothers of women with PCOS as compared to normal mothers (32). Hence, even first-degree relatives without PCOS features may be at increased cardiovascular risk. In this study, we compared mothers of women with PCOS, who also have features of the syndrome themselves, with mothers without PCOS. Because the control group was derived from mothers of women with PCOS, we probably have underestimated the true risk of cardiovascular events in PCOS mothers.

Indeed, if we were to compare our predominantly Caucasian and postmenopausal non-PCOS and PCOS mothers to the predominantly Caucasian and postmenopausal women from the Artherosclerosis Risk in Communities (ARIC) Study (40), the standardized risk ratio of cardiovascular events in mothers of PCOS women would be 1.38, indicating that the pooled mothers of PCOS women, regardless of whether they also had PCOS symptoms themselves, had a risk of cardiovascular events 38% greater than women in the general population. Since outcomes in the ARIC study included silent (EKG) MI, which was not included as an outcome in our study, this standardized ratio is probably a conservative estimate of the true risk of mothers of PCOS women compared to a general population of women. Hence, even without stratifying by mothers' PCOS status, mothers of PCOS women are at increased risk of cardiovascular events, suggesting the heritable cardiovascular risk of PCOS.

There are several limitations to this study. One of the most challenging issues is the definition of probable PCOS in older women. Because no diagnostic criteria exist in this age group, we have based our definition on the most common clinical features of PCOS. The reported premenopausal history of clinical signs of hyperandrogenism (e.g. hirsutism) and oligomenorrhea may not have been correctly recalled by older women, and were not confirmed by laboratory assays or ovarian imaging. In addition, we were unable to exclude secondary causes of oligomenorrhea or hyperandrogenism. However, these are unlikely to have been

common among community-dwelling women (41). Importantly, menstrual irregularity and/or hirsutism have been reported to be good surrogate indicators for PCOS (32;33;42). Thus our definition of probable PCOS is consonant with existing data. Nevertheless, since misclassification of PCOS status is possible, we have used two definitions of probable PCOS, and the results were similar regardless of which definition was used. In addition, since *consecutive* PCOS women and their mothers were interviewed, and these interviews were performed as part of the private clinic's routine medical care, mothers did not self-select to participate in this study, which would minimize selection bias. Cardiovascular events were also by self-report in this study, which may be unreliable. In addition, accuracy of information may be different when a daughter was reporting about their mothers as compared to when mothers were personally interviewed. We addressed this limitation by performing analyses on all mothers, and only mothers who were interviewed. Lastly, because the data was obtained by interviews, interviewer bias was possible. That is, it is possible that mothers with probable PCOS may have been given a more detailed interview, hence discovering more cardiovascular events. Although the same questions were asked during each interview to address the problem of interviewer bias, this bias cannot be completely eliminated.

Since established cardiovascular risk factors, such as a history of diabetes mellitus, hypertension, and dyslipidemia in mothers, and duration of hormone replacement use, if any, were not readily recallable or available, we were not able to adjust our risk estimate of increased cardiovascular events with these established cardiovascular risk factors. In addition, we did not collect data on the exact time of menopause or whether a woman had had a hysterectomy or oopherectomy. We envision that were information on these risk factors available, the adjusted risk estimate of cardiovascular events would be lower. However, in this study, we used non-PCOS mothers as the control group to be compared with mothers with probable PCOS. Our results probably underestimated the risk of cardiovascular events in PCOS mothers in this regard, since mothers of women with PCOS, even in the absence of a history of menstrual irregularity, may be at increased cardiovascular risk (32).

CONCLUSION

Mothers of women with PCOS, who themselves have features of PCOS, may be at increased risk for cardiovascular events, when compared to normal mothers of women with PCOS. Since mothers are in a more advanced age group, this suggests that women with PCOS may have an increased risk of cardiovascular events as they age. However, prospective longitudinal studies to assess cardiovascular outcomes in PCOS should provide definitive evidence on the association between PCOS and increased cardiovascular risk. Based on our current findings and previous reports by others indicating an increased cardiovascular risk in women with PCOS, women with PCOS should undergo early evaluation for cardiovascular risk factors and receive appropriate lifestyle and pharmacologic prevention as well as careful systemic medical assessment by their internist and/or cardiologist.

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Table 1

Demographic and reproductive characteristics among interviewed or deceased mothers with and without cardiovascular events

	Total		No CV Events		CV Events	
	N	%	N	%	N	%
Race						
Asian	2	1.1	2	1.2	0	0
African American	5	2.8	5	3.0	0	0
Hispanic	8	4.4	5	3.0	3	18.8
Caucasian without Ashkenazi Jewish background	132	72.5	122	73.5	10	62.5
Caucasian with Ashkenazi Jewish background	35	19.2	32	19.3	3	18.8
Age						
<50 years	26	14.4	24	14.6	2	12.5
50−59.9 years	82	45.6	76	46.3	6	37.5
60−69.9 years	55	30.6	49	29.9	6	37.5
≥70 years	17	9.4	15	9.2	2	12.5
Clinical features of hyperandrogenism						
No	139	76.4	132	79.5	7	43.8
Yes	43	23.6	34	20.5	9	56.3
History of infertility						
No	162	89.0	150	90.4	12	75.0
Yes	20	11.1	16	9.6	4	25.0
Menstrual history						
Irregular	24	13.2	22	13.3	2	12.5
Regular	158	86.8	144	86.8	14	87.5
History of Infertility or irregular menses						
No	144	79.1	134	80.7	10	62.5
Yes	38	20.9	32	19.3	6	37.5
Menopausal Status						
Premenopausal	20	11.4	19	11.9	1	6.7
Peri-menopausal	10	5.7	10	6.3	0	0
Postmenopausal	145	82.9	131	81.9	14	93.3
Probable PCOS[1]						

	Total		No CV Events		CV Events	
	N	%	N	%	N	%
No	123	67.6	118	71.1	5	31.3
Yes	59	32.4	48	28.9	11	68.8
Probable PCOS[2] (alternate definition)						
No	158	86.8	147	88.6	11	68.8
Yes	24	13.2	19	11.5	5	31.3

CV events = Cardiovascular events. Any cardiovascular event was defined as any fatal or non-fatal myocardial infarction, other coronary events (coronary artery bypass graft, percutaneous coronary interventions, angina that necessitated emergency room visits), or cerebrovascular events.

[1]Probable PCOS in mothers was defined as the presence of one of the following characteristics: (1) irregular menstrual cycles; (2) reported history of difficulty achieving pregnancy; (3) use of fertility drugs or procedures; (4) maternal clinical signs of hyperandrogenemia.

[2]The alternate definition of probable PCOS was defined as (1) irregular menstrual cycles or reported history of difficulty achieving pregnancy or use of fertility drugs or procedures AND (2) maternal clinical signs of hyperandrogenemia.

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Table 2

Distribution of demographic and outcome parameters among interviewed or deceased mothers who had probable PCOS (N=59) or did not have PCOS (N=123)

	Non-PCOS N	%	Probable PCOS N	%	Total	P-value
Race						
Caucasians	116	69.5	51	30.5	167	0.0866
Non-Caucasians	7	46.7	8	53.3	15	
Age						
<50 years	17	65.4	9	34.6	26	0.4430
50−59.9 years	52	63.4	30	36.6	82	
60−69.9 years	39	70.9	16	29.1	55	
≥70 years	14	82.4	3	17.7	17	
Menopausal Status						
Pre- or Peri-menopausal	21	70.0	9	30.0	30	0.9702
Postmenopausal	101	69.7	44	30.3	145	
Any cardiovascular event[ϕ]						
No	118	71.1	48	289	166	0.0011
Yes	5	31.3	11	68.8	16	
Any cardiovascular disease[ǂ]						
No	118	72.0	46	28.0	164	0.0001
Yes	5	27.8	13	72.2	18	
CVA						
No	121	68.4	56	31.6	177	0.3309
Yes	2	40.0	3	60.0	5	
MI						
No	120	69.0	54	31.0	174	0.1146
Yes	3	37.5	5	62.5	8	
Other coronary events						
No	120	69.0	54	31.0	174	0.1146
Yes	3	37.5	5	62.5	8	
Heart failure						
No	121	68.4	56	31.6	177	0.3309
Yes	2	40.0	3	60.0	5	

	Non-PCOS N	%	Probable PCOS N	%	Total	P-value

CVA = cerebrovascular accident; MI = myocardial infarction

ϕAny cardiovascular event was defined as in Table 1, which included any fatal or non-fatal myocardial infarction, other coronary events (coronary artery bypass graft, percutaneous coronary interventions, angina that necessitated emergency room visits), or cerebrovascular events.

$\ddagger$Any cardiovascular disease was defined as the occurrence of any cardiovascular event or a diagnosis of heart failure.

Table 3

Univariate odds ratios cardiovascular outcomes by maternal factors in interviewed mothers (including deceased mothers)

			ANY CARDIOVASCULAR EVENT[ϕ]				ANY CARDIOVACSULAR DISEASE[ǂ]			
				95% CI				95% CI		
		Total (N)	Any CV Events (N)	OR	Lower	Upper	Any CVD (N)	OR	Lower	Upper
Race										
	Caucasian	167	13	referent			15	referent		
	Non-Caucasian	15	3	2.96	0.74	11.84	3	2.53	0.64	10.00
Age										
	<50 years	26	2	referent			2	referent		
	50−59.9 years	82	6	0.95	0.18	5.01	6	0.95	0.18	5.01
	60−69.9 years	55	6	1.48	0.28	7.83	8	2.04	0.40	10.38
	≥70 years	17	2	1.60	0.20	12.60	2	1.60	0.20	12.60
Probable PCOS[1]										
	No	123	5	referent			5	referent		
	Yes	59	11	5.41	1.78	16.40	13	6.67	2.25	19.76
Probable PCOS[2] (alternate definition)										
	No	158	11	referent			11	referent		
	Yes	24	5	3.52	1.10	11.22	7	5.50	1.88	16.08

[1] Probable PCOS

[2] alternate definition of probable PCOS were defined as in Table 1.

[ϕ] Any cardiovascular event

[ǂ] any cardiovascular disease were defined as in Table 2.

Table 4

Adjusted odds ratios for cardiovascular outcomes by maternal factors in interviewed mothers (including deceased mothers)

	Adjusted OR*	95% CI Lower	95% CI Upper
Any Cardiovascular Event[ϕ]			
Age			
<50 years	referent		
50−59.9 years	0.77	0.13	4.38
60−69.9 years	1.66	0.30	9.33
≥70 years	2.43	0.28	20.98
Race			
Caucasian	referent		
Non-Caucasian	2.62	0.59	11.68
Probable PCOS[1]			
No	referent		
Yes	5.93	1.87	18.84
Probable PCOS[2] (alternate definition)			
No	referent		
Yes	3.42	1.04	11.23
Any Cardiovascular Disease[‡]			
Age			
<50 years	referent		
50−59.9 years	0.77	0.13	4.46
60−69.9 years	2.47	0.45	13.52
≥70 years	2.62	0.30	23.34
Race			
Caucasian	referent		
Non-Caucasian	2.34	0.52	10.62
Probable PCOS[1]			
No	referent		
Yes	7.78	2.49	24.30
Probable PCOS[2] (alternate definition)			
No	referent		
Yes	5.43	1.80	16.39

[1] Probable PCOS

[2] the alternate definition of probable PCOS were defined as in Table 1.

[ϕ] Any cardiovascular event

[‡] any cardiovascular disease were defined as in Table 2.

* Multivariate odds ratios shown for the factors age and race were derived from a logistic regression model with the following terms: age, race, and probable PCOS1. The multivariate odds ratio shown for probable PCOS2 (alternate definition) were derived from a logistic regression model of the following

terms: age, race, and probable PCOS[2] (alternate definition). The multivariate ORs for age and race status are not shown for the later model with probable PCOS[2] (alternate definition).