Prospective Association of Polycystic Ovary Syndrome With Coronary Artery Calcification and Carotid-Intima-Media Thickness

The Coronary Artery Risk Development in Young Adults Women’s Study

Ronit Calderon-Margalit, David Siscovick, Sharon S. Merkin, Erica Wang, Martha L. Daviglus, Pamela J. Schreiner, Barbara Sternfeld, O. Dale Williams, Cora E. Lewis, Ricardo Azziz, Stephen M. Schwartz, Melissa F. Wellons

Objective—To study the independent associations of polycystic ovary syndrome (PCOS), and its 2 components, hyperandrogenism and anovulation, with coronary artery calcification (CAC) and carotid artery intima-media thickness (IMT).

Approach and Results—At the year 20 of the Coronary Artery Risk Development in Young Adults (CARDIA) study, a population-based multicenter cohort of young adults, women (mean age, 45 years) with information on menses and hirsutism in their twenties were assessed for CAC (n=982) and IMT (n=988). We defined PCOS as women who had both irregular menses and hyperandrogenism (n=55); isolated oligomenorrhea (n=103) as women who only had irregular menses; and isolated hyperandrogenism (n=156) as women who had either hirsutism or increased testosterone levels. Logistic regressions and general linear models were used to estimate the associations between components of PCOS and subclinical CVD. The prevalence of CAC was 10.3% overall. Women with PCOS had a multivariable adjusted odds ratio of 2.70 (95% confidence interval, 1.31–5.60) for CAC. Women with either isolated oligomenorrhea or isolated hyperandrogenism had no increased risk of CAC when compared with unexposed women. Women with PCOS had significantly increased bulb and internal carotid-IMT measurements; however, no significant differences were noted in bulb or internal carotid artery IMT among women with either isolated oligomenorrhea or isolated hyperandrogenism when compared with unexposed women. There were no differences in common carotid-IMT among the 4 study groups.

Conclusions—In this study, women with PCOS, manifested as both anovulation and hyperandrogenism, but not women with one of these manifestations alone, were at increased risk for the development of subclinical CVD.

Key Words: carotid intima media thickness • cohort studies • coronary atherosclerosis • electron beam computed tomography • polycystic ovary syndrome • risk
and findings have been inconsistent. Furthermore, previous studies have not assessed whether the overall PCOS phenotype or the individual components of PCOS, ie, isolated hyperandrogenism (IH) and isolated oligomenorrhea (IO), are associated with the development of subclinical CVD.

The aim of this study was to examine the prospective association between PCOS and its components, ie, oligomenorrhea and hyperandrogenism, with subclinical CVD, reflected by measures of CAC and carotid-IMT.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

Coronary Artery Calcifications

Overall, 982 women had CAC assessment at the year 20 examination. They included 55 women with PCOS, 156 women with IH, 103 women with IO, and 668 women with neither oligomenorrhea nor hyperandrogenism (controls; Table 1). This study population, aged 45.3 years, comprised 51% black women (range, 36% among the PCOS group to 56% among the oligomenorrhea group). Body mass index (BMI) ranged between 29.3 (PCOS group) and 30.5 kg/m² (IH group). Glucose and insulin measurements were highest among women with PCOS, leading to Homeostasis Model Assessment-insulin resistance (HOMA-IR) of 5.32 in the PCOS group when compared with that of 3.66 to 3.99 in the other study groups (Table 1).

CAC was present in 10.3% of the controls, 11.7% of women with IO, 6.4% of women with IH, and 23.6% of women with PCOS. Women with PCOS had an odds ratio (OR) of 2.69 (95% confidence interval [CI], 1.37–5.25) for having CAC, whereas no significant association was found for the other study groups (P for interaction between oligomenorrhea and hyperandrogenism, 0.015; Table 2). The association between PCOS and CAC remained similar in multivariable models controlling for age, race, education, smoking, menopausal status, BMI, systolic blood pressure, triglycerides, and HOMA-IR (Table 2). Results were unaltered when treatments for hypercholesterolemia or diabetes mellitus were introduced, and they were slightly attenuated when controlled for the metabolic syndrome (PCOS associated OR, 2.57; 95% CI, 1.28–5.28; not shown). The association became somewhat stronger when Agatston score >10 was considered as CAC positive (adjusted OR, 2.91; 95% CI, 1.21–6.98) rather than Agatston score >0.

Carotid-IMT

Carotid-IMT assessments were conducted in 988 women for whom information on PCOS status was available. Table 3 presents the adjusted means according to the general linear models of carotid-IMT by segment. In analyses examining the associations of PCOS and its components with carotid-IMT at year 20, no association was found among IO, IH, or the combination of oligomenorrhea and hyperandrogenism (PCOS) and the IMT of the common carotid artery (CCA-IMT).

Women with IO or IH had similar IMTs of the bulb or the internal carotid artery (Bulb-IMT and ICA-IMT) when compared with controls. However, women who had PCOS in their twenties had increased Bulb-IMT and ICA-IMT. The adjusted means for Bulb-IMT were 0.96, 0.98, 0.93, and 1.05 mm, for women who were unexposed, with IO, IH, or PCOS, respectively. Adjusted means of ICA-IMT were 0.77, 0.76, 0.78, and 0.83 mm, for women who were controls, with IO, IH, or PCOS, respectively (Table 3). Controlling for the metabolic syndrome did not materially change these results (not shown).

In logistic regression analyses adjusted for age, race, education, smoking, menopausal status, BMI, systolic blood pressure, triglycerides, and HOMA-IR, the ORs for the highest quintile of internal carotid-IMT versus the lowest 4 were 0.70 (0.38–1.30) for oligomenorrhea, 0.80 (0.49, 1.33) for hyperandrogenism, and 2.00 (1.07, 3.75) for PCOS (P for interaction between oligomenorrhea and hyperandrogenism, 0.010; Table 4). Controlling for the metabolic syndrome yielded similar results (not shown).

Discussion

In a population-based, multicenter, biracial cohort of young adult women, we found an increased risk of subclinical CVD, assessed at a mean age of 45 years, among women with evidence of PCOS in their twenties when compared with those who had neither oligomenorrhea nor hyperandrogenism. There was no evidence of increased risk of subclinical CVD among women with either IO or IH.

To date, only few studies have described the association between PCOS and CAC. In a study by Talbott et al, the age- and BMI-adjusted OR for CAC≥210 was 1.90, among 149 women with PCOS and 166 controls; differences in median coronary calcium Agatston score between PCOS cases and controls were modified by menopausal status, with the largest differences observed among postmenopausal women, and especially those with surgically induced menopause. A recent analysis of this study population suggested increased OR also for CAC>0, and no mediation by complement levels. Christian et al reported a similar association with CAC (OR, 1.99) among 36 PCOS women and 142 controls although findings did not remain significant after controlling for BMI. Shroff et al demonstrated an OR of 5.5 (1.03–29.5) for CAC score >0 among 24 women with obesity and PCOS aged 21 to
50 years when compared with 24 obese controls. Conversely, in a recent case–control study nested within the Dallas Heart Study,20 the prevalence of CAC score >10 was similar among women with PCOS defined as having both oligomenorrhea and hyperandrogenism (n=55), or alternately, according to the Rotterdam criteria (n=144) and normal ovulatory controls (n=170), despite a higher prevalence of CVD risk factors among women with PCOS. Although we focused our analyses on a more liberal definition of CAC (Agatston score >0), sensitivity analyses defining CAC positive as Agatston score >10 showed a higher prevalence of CAC among women with PCOS (16.4%) when compared with controls (6.4%), with the association remaining elevated after adjustment for potential confounders. Differences in results between the 2 studies could reflect either differences in prevalence of CVD risk factors or differences in definitions of PCOS (eg, age of testosterone assessment).

We found an association between PCOS and bulb-IMT and ICA-IMT but not with CCA-IMT. The bulb and ICA segments are more common sites for the development of carotid plaques than the CCA.29 Shedding light on the mechanism of ICA- and Bulbar-IMT thickening is important because these segments may be most predictive of future atherosclerotic events. In the CHS study, prevalent atherosclerotic disease in general and coronary heart disease, in particular, were more strongly associated with ICA-IMT than the other 2 segments.30 Furthermore, in a cohort study of 6226 men and women, during 6 years of follow-up, a composite IMT measure of all segments was strongly associated with incident acute myocardial infarction in women, whereas analyses restricted to the CCA-IMT alone showed no association, suggesting that the bulb-IMT and ICA-IMT are the carotid segments that are most useful in predicting atherosclerotic events in women.31

### Table 1. Characteristics of Coronary Artery Risk Development in Young Adults Women’s Study Participants, by PCOS Status, Those With Coronary Artery Calcification Measurements

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control n=668</th>
<th>Isolated Oligomenorrhea n=103</th>
<th>Isolated Hyperandrogenism n=156</th>
<th>PCOS n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.4 (3.57)</td>
<td>45.0 (3.79)</td>
<td>45.1 (3.76)</td>
<td>45.4(3.44)</td>
</tr>
<tr>
<td>Race black, n (%)</td>
<td>344 (51.5)</td>
<td>58 (56.3)</td>
<td>80 (51.3)</td>
<td>20 (36.4)</td>
</tr>
<tr>
<td>Education ≤12 y, n (%)</td>
<td>151 (22.6)</td>
<td>32 (31.1)</td>
<td>29 (18.6)</td>
<td>8 (14.5)</td>
</tr>
<tr>
<td>Ever smoking, n (%)</td>
<td>287 (37.0)</td>
<td>46 (39.7)</td>
<td>64 (35.0)</td>
<td>23 (35.9)</td>
</tr>
<tr>
<td>Height, m</td>
<td>165 (7.15)</td>
<td>165 (7.62)</td>
<td>165 (6.76)</td>
<td>163 (5.72)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.1 (20.3)</td>
<td>81.0 (23.0)</td>
<td>82.9 (19.3)</td>
<td>78.7 (19.1)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.9 (7.47)</td>
<td>29.8 (8.22)</td>
<td>30.5 (7.16)</td>
<td>29.3 (6.50)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>88.3 (14.7)</td>
<td>88.3 (15.9)</td>
<td>89.1 (14.3)</td>
<td>89.0 (16.2)</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>95.4 (22.4)</td>
<td>96.0 (17.3)</td>
<td>93.3 (18.7)</td>
<td>100 (36.3)</td>
</tr>
<tr>
<td>Fasting insulin, mU/L</td>
<td>10.7 (6.88)</td>
<td>11.4 (9.82)</td>
<td>11.9 (8.29)</td>
<td>13.1 (6.99)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.86 (2.96)</td>
<td>3.99 (3.20)</td>
<td>3.66 (2.58)</td>
<td>5.32 (9.13)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.08 (0.79)</td>
<td>1.05 (0.51)</td>
<td>1.03 (0.52)</td>
<td>1.22 (0.96)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.77 (0.87)</td>
<td>4.89 (0.92)</td>
<td>4.89 (0.85)</td>
<td>4.90 (0.79)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.76 (0.76)</td>
<td>2.90 (0.90)</td>
<td>2.81 (0.81)</td>
<td>2.79 (0.78)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.52 (0.41)</td>
<td>1.51 (0.43)</td>
<td>1.60 (0.45)</td>
<td>1.55 (0.46)</td>
</tr>
<tr>
<td>LDL/HDL cholesterol</td>
<td>1.95 (0.76)</td>
<td>2.11 (0.95)</td>
<td>1.92 (0.82)</td>
<td>1.98 (0.88)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>115 (16.3)</td>
<td>114 (17.7)</td>
<td>113 (14.9)</td>
<td>113 (15.9)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>72.7 (11.7)</td>
<td>72.0 (12.3)</td>
<td>72.2 (12.2)</td>
<td>71.6 (11.8)</td>
</tr>
<tr>
<td>Menopause, n (%)</td>
<td>153 (23.2)</td>
<td>30 (29.4)</td>
<td>21 (13.6)</td>
<td>7 (12.7)</td>
</tr>
</tbody>
</table>

Numbers represent means (SD), unless stated otherwise. BMI indicates body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment-insulin resistance; LDL-C, low-density lipoprotein cholesterol; PCOS, polycystic ovary syndrome; and SBP, systolic blood pressure.

*Defined according to medical treatments for the condition.

†Defined according to the joint interim definition (2009) as having ≥3 of waist circumference (>88 cm), increased blood pressure (SBP≥135, DBP≥85, or treatment for hypertension), increased glucose (fasting glucose≥100 mg/dL or taking medications for diabetes), increased triglycerides (≥1.7 mmol/L), and decreased HDL-C (<1.3 mmol/L).

‡Self-reported history of acute myocardial infarction or angina.
these CVD risk factors seem to contribute more to the thickening of the CCA than to the thickening of the ICA and bulb segments. In an earlier report from the CARDIA study that used data from both men and women, cardiovascular risk factors explained a larger proportion of the CCA-IMT variability (26.8%) than the bulb (11.2%) or ICA (8.0%). Furthermore, in The Vascular Aging (EVA) study, systolic blood pressure and hypertension were associated with both CCA-IMT and plaques at the Bulb and ICA; however, diabetes mellitus, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were associated only with CCA-IMT. Similarly, among Taiwanese women, the metabolic syndrome was only associated with CCA-IMT, but not with the bulb or ICA-IMT. However, in the Multi-Ethnic Study of Atherosclerosis (MESA) study, among 997 adults aged 45 to 84 years, the metabolic syndrome was associated with both CCA-IMT and the ICA-IMT. Finally, these associations may be age and sex related, as shown in a recent meta-analysis that demonstrated associations of triglycerides and high-density lipoprotein cholesterol with CCA-IMT. However, the association of triglycerides was not evident among women, and the negative association of high-density lipoprotein cholesterol was not evident among those aged <60 years. The few previous studies that have investigated the association between PCOS and subclinical CVD include the study by Solomon et al, where the time period when PCOS women appear at highest risk of atherosclerotic progression.

To the best of our knowledge, our study is the first study to examine the associations of PCOS and its 2 major components, ie, oligomenorrhea and hyperandrogenism, with subclinical CVD. Previous studies investigated either women diagnosed with PCOS or women with either oligomenorrhea or hyperandrogenism, but not as isolated characteristics. Studies of the association of irregular menses, a proxy for oligomenorrhea, with CVD include the study by Solomon et al.

Table 2. Association Between Components of PCOS With CAC at the Year 20 CARDIA Examination

<table>
<thead>
<tr>
<th>PCOS Components</th>
<th>CAC+</th>
<th>CAC−</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>69</td>
<td>599</td>
<td>1.00</td>
<td>Reference</td>
<td>0.007</td>
<td>1.00</td>
<td>Reference</td>
<td>0.009</td>
<td>1.00</td>
<td>Reference</td>
<td>0.022</td>
</tr>
<tr>
<td>Isolated oligomenorrhea</td>
<td>12</td>
<td>91</td>
<td>1.15</td>
<td>0.60–2.20</td>
<td>…</td>
<td>1.16</td>
<td>0.59–2.26</td>
<td>…</td>
<td>1.15</td>
<td>0.59–2.28</td>
<td>…</td>
</tr>
<tr>
<td>Isolated hyperandrogenism</td>
<td>10</td>
<td>146</td>
<td>0.59</td>
<td>0.30–1.18</td>
<td>…</td>
<td>0.63</td>
<td>0.31–1.26</td>
<td>…</td>
<td>0.66</td>
<td>0.33–1.33</td>
<td>…</td>
</tr>
<tr>
<td>PCOS</td>
<td>13</td>
<td>42</td>
<td>2.69</td>
<td>1.37–5.25</td>
<td>…</td>
<td>2.81</td>
<td>1.40–5.63</td>
<td>…</td>
<td>2.70</td>
<td>1.31–5.60</td>
<td>…</td>
</tr>
</tbody>
</table>

P for the interaction between oligomenorrhea × hyperandrogenism

Table 3. Association Between Components of PCOS With the Log-Transformed Carotid-IMT Measurements at the Year 20 CARDIA Examination

<table>
<thead>
<tr>
<th></th>
<th>CCA Mean of the Maximum IMT</th>
<th>Bulb Mean of the Maximum IMT</th>
<th>ICA Mean of the Maximum IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β*</td>
<td>P Value</td>
<td>Mean IMT</td>
</tr>
<tr>
<td>Control</td>
<td>…</td>
<td>…</td>
<td>0.779</td>
</tr>
<tr>
<td>Isolated oligomenorrhea</td>
<td>−0.003</td>
<td>0.827</td>
<td>0.777</td>
</tr>
<tr>
<td>Isolated hyperandrogenism</td>
<td>0.013</td>
<td>0.236</td>
<td>0.789</td>
</tr>
<tr>
<td>PCOS</td>
<td>−0.020</td>
<td>0.259</td>
<td>0.764</td>
</tr>
</tbody>
</table>

P for the interaction between oligomenorrhea × hyperandrogenism

Adjusted for age, race, education, smoking, menopausal status, body mass index, systolic blood pressure, triglycerides, and Homeostasis Model Assessment-insulin resistance. CCA indicates common carotid artery; ICA, internal carotid artery; IMT, intima-media thickness; and PCOS, polycystic ovary syndrome.

*β* is the regression coefficient of components of PCOS with the log-transformed segment-specific IMT measures. The mean values were back transformed to yield the mean IMT values adjusted for the study covariates.
Resistant or to other cardiometabolic derangements. This points potentially to other hormones or combinations of hormones of the PCOS milieu (such as progesterone, estrogen, and their ratios with androgens) rather than isolated hyperandrogenism as contributors to subclinical CVD associated with PCOS. A hormonal derangement as the cause of the increased risk of CVD in women with PCOS is plausible because the presence of insulin resistance and the metabolic syndrome does not seem to explain much of the association between PCOS and subclinical CVD. This statement is supported by the fact that adjustments for HOMA-IR and other cardiometabolic risk factors only modified the association between PCOS and subclinical CVD measures slightly.

Limitations include the small number of women with PCOS. The definitions of oligomenorrhea and hirsutism when the women were in their twenties were based on self-report and recall. However, self-reported hirsutism and oligomenorrhea have been shown to correlate both with sonographic findings of polycystic ovaries and with hormone levels, supporting their validity in the diagnosis of PCOS.51,52 In this study, we found associations of PCOS with ICA and Bulb-IMT, but not with the CCA-IMT. Although the CCA-IMT is the segment most studied that has the highest interobserver reliability, any misclassification of measurements in the bulbar- or the ICA-IMT would be nondifferential by PCOS group, and thus bias the association to the null.

Strengths of this study include a population-based, multicenter study design, with 20 years of follow-up. The classification of women as having PCOS, IH, and isolated anovulation, or none of these conditions was not based on symptoms that motivated women to be referred for clinical diagnosis, but rather on applying a set of criteria to the whole study population.

Our study suggests that women in their twenties with both components of PCOS, but not with either IO or IH, are at increased risk for the development of subclinical CVD. Additional studies are needed to confirm these results and identify the mechanisms that underlie these associations.

Acknowledgments

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Table 4. Association Between Components of PCOS With Upper Quintiles of Carotid-IMT Measurements at the Year 20 CARDIA Examination

<table>
<thead>
<tr>
<th></th>
<th>CCA-IMT</th>
<th></th>
<th>Bulb-IMT</th>
<th></th>
<th>ICA-IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence,* %</td>
<td>OR</td>
<td>95% CI</td>
<td>P Value</td>
<td>Prevalence,* %</td>
</tr>
<tr>
<td>Control</td>
<td>20.8</td>
<td>1.00 Reference</td>
<td>0.071</td>
<td></td>
<td>20.0</td>
</tr>
<tr>
<td>Isolated oligomenorrhea</td>
<td>15.4</td>
<td>0.65 0.35 0.21</td>
<td>...</td>
<td></td>
<td>24.2</td>
</tr>
<tr>
<td>Isolated hyperandrogenism</td>
<td>22.7</td>
<td>1.30 0.82 2.07</td>
<td>...</td>
<td></td>
<td>14.0</td>
</tr>
<tr>
<td>PCOS</td>
<td>9.4</td>
<td>0.40 0.15 1.07</td>
<td>...</td>
<td></td>
<td>28.3</td>
</tr>
</tbody>
</table>

P for interaction between oligomenorrhea and hyperandrogenism

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.228</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.250</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*Prevalence of the upper quintile of the segment specific IMT.

Adjusted for age, race, education, smoking, menopausal status, body mass index, systolic blood pressure, triglycerides, and Homeostasis Model Assessment-insulin resistance. CCA indicates common carotid artery; CI, confidence interval; IMT, intima-media thickness; OR, odds ratio; and PCOS, polycystic ovary syndrome.

al12 that found an increased risk of CHD (hazard ratio, 1.53; 95% CI, 1.24–1.90) and a nonsignificantly increased risk of stroke (hazard ratio, 1.30; 95% CI, 0.97–1.74). Wang et al13 found an increased risk of CHD mortality among women with irregular menses when compared with controls; however, this finding became nonsignificant with adjustment for BMI; risk of mortality from stroke did not differ between the 2 study groups. Both studies referred to irregular menses as a proxy to PCOS.

Studies of the associations between androgens and subclinical CVD have yielded mixed results. A population-based cross-sectional study of postmenopausal women demonstrated a positive association of total and bioavailable testosterone with CCA-IMT.43 Conversely, negative results for the association with CCA-IMT were demonstrated by a population-based, cross-sectional study of 483 middle-aged women44 and in a longitudinal study of 180 postmenopausal women.45 Moreover, inverse associations of androgens with subclinical CVD were suggested by a cross-sectional study of 101 pre- and postmenopausal women in Italy,46 and by a nested case–control study within the Atherosclerosis Risk In Communities cohort, where postmenopausal women who had total testosterone levels at the highest quartile had an OR of 0.34 (95% CI, 0.16–0.70) for the highest 5th percentile of a combined IMT measure.57 We have previously evaluated the association of the total and free testosterone as continuous variables with subclinical CVD in the CARDIA Women’s Study and found no association for testosterone with either CAC or carotid artery IMT.48 Women with PCOS in our study tended to have higher fasting insulin and glucose levels (hence higher HOMA-IR), higher triglycerides, and higher prevalence of diabetes mellitus and the metabolic syndrome when compared with the other study groups. Previous studies that looked into different phenotypes of PCOS according to the Rotterdam criteria have found that unlike phenotypes that included both anovulation and hyperandrogenism, the phenotype of hyperandrogenism and sonographic polycystic ovaries was not associated with insulin resistance.49,50 It is worth mentioning that in the case of our study, the Rotterdam hyperandrogenism with sonographic polycystic ovaries phenotype is encompassed in our IH group. Thus, combined, ours and other studies suggest that IH does not seem to contribute to insulin resistance or to other cardiometabolic derangements.
References


Significance

This is the first cohort study of largely premenopausal women that assessed the association between features of the polycystic ovary syndrome (PCOS) and subclinical cardiovascular disease, namely coronary artery calcification and intima-media thickness of the common carotid artery, internal carotid artery, and the carotid artery bifurcation. Having a population-based cohort enabled to study these features in a community setting, rather than identifying women with PCOS in clinical settings, minimizing selection bias. In this prospective study, history of PCOS, but not the distinct components of the syndrome, was associated with subclinical cardiovascular disease. Therefore, our study suggests that the effect of PCOS is beyond the effects of either hyperandrogenism or oligomenorrhea. Furthermore, the association was independent of the effects of body mass index, insulin resistance, and menopausal status, suggesting that women with PCOS comprise a unique group at risk for the development of cardiovascular disease.
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METHODS

Analyses were conducted using data from the CARDIA Women’s Study (CWS), an ancillary study to CARDIA (Coronary Artery Risk Development in Young Adults). The CARDIA study was initiated in 1985-6 and included 5115 adults aged 18-30 years recruited from four centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA [1, 2]. The CARDIA study population was balanced at baseline in terms of age (45% aged 18-24), sex (54% women), race (52% black, 48% white), and education (40% completed up to 12 years of education). The CWS was designed to assess the role of androgens and ovaries in the development of subclinical cardiovascular disease in young adult women. At the CWS examination in year 16 of the CARDIA study, 1163 women (of 1227 who were invited) responded to a self-administered reproductive-health questionnaire. The questionnaire collected data, among others, on patterns of menstruation and unwanted hair at age 20-30 years. Additionally, stored serum samples from year 2 of the CARDIA study were used to measure androgens. Study protocols were approved by the IRB committees of the participating institutions, and all participants provided written informed consent.

Definition of characteristics of PCOS:

Oligomenorrhea was defined as irregular menstrual cycles at age 20-30, as reported by women at the year 16 exam. Hyperandrogenism was defined as either hirsutism or increased levels of serum testosterone. Hirsutism was considered present if a woman reported having excess unwanted hair at age 20-30. Free and total testosterone measures were assessed using stored samples from CARDIA Year 2 (ages 20-34) by the OB/GYN Research and Diagnostic Laboratory at the University of Alabama, Birmingham. Total testosterone 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 dialysis, and free testosterone was calculated on the basis of measured total testosterone and SHBG [3]. Abnormal testosterone levels were defined as total testosterone of >80ng/dL or free testosterone of >0.75ng/dL, which corresponds with the 95th percentile, among women who were not pregnant and did not use oral contraceptives at the year 2 exam. Measurements of testosterone were available for 83% of the study population, however for the current analysis we considered measurements available only for 55.3% of the women who were not pregnant or did not use oral contraceptives at the time of year 2 examination. For these 612 women who had both valid androgen measurements and information on unwanted hair in their twenties, 455 had neither hirsutism nor hyperandrogenemia, 111 had only reported on hirsutism, 24 had only evidence of hyperandrogenemia, and 16 had both. The study population was divided into four groups: women who had PCOS based on having both oligomenorrhea and hyperandrogenism (n=64), women who had only (isolated) hyperandrogenism (either biochemical or according to history of hirsutism; n=183) (IH), women who had only (isolated)
oligomenorrhea (n=116) (IO), and women who had none of these symptoms (control group; n=776). For 24 women (2%), the study group could not be determined and they were excluded from the analysis.

**Coronary Artery Calcified plaques (CAC)**

CAC was assessed by computed tomography (CT) of the chest. Electron beam CT (Imatron C-150) or multidetector CT scanners (GE Lightspeed or Siemens VZ/Siemens Biograph 16) were used to obtain consecutive 2.5 -3mm-thick transverse images from the root of the aorta to the apex of the heart in two sequential electrocardiogram-gated scans. Experienced image analysts measured calcified plaques in the epicardial coronary arteries (left main, left circumflex, left anterior descending, and right) at a central reading center (Wake Forest University Health Sciences, Winston Salem, NC). A total calcium score, using a modified Agatston method to account for slice thickness, was calculated on an FDA-approved workstation (TeraRecon Aquarius Workstation, San Mateo, CA) for each of the two sequential scans and averaged. Review and adjudication by an expert physician in cardiovascular imaging was performed for all participants with discordant scan pairs, a change in calcium status from the previous CAC evaluation, indications of possible surgically intervention, concerns identified by the reader, and calcium scores >200. CT analysts were blinded to participant information.

For these analyses, the CAC score was used as a dichotomous variable (CAC-negative stands for a score of zero, whereas any value above zero was considered as CAC-positive), as has been previously shown to predict CVD in low-risk women [4]. In sensitivity analyses, we also examined associations with CAC-positive was defined as modified Agatston score >10.

**Intima-Media Thickness (IMT)**

IMT measures of the common carotid artery (CCA), the carotid bifurcation (Bulb), and the internal carotid artery (ICA) were obtained at the CARDIA Year 20 examination. Carotid B-mode ultrasound examinations were conducted by trained sonographers at each field center employing a standard protocol using the GE Logiq 700 device. Magnified longitudinal images in gray-scale of the far and near wall of the distal CCA, the CB, and the proximal ICA were obtained on the right and left sides. Images were read at the ultrasound reading center (Tufts Medical Center, Boston, MA). The maximum IMT of each segment was defined as the mean of the maximal IMT of the near and far wall of both the left and right sides.

**Data analysis:**

Year 20 characteristics by study group were described as means (SD) or proportion distribution, as suitable. Multivariable logistic-regressions models were fit to compare the prevalence of positive CAC at year 20 among the study groups taking into account potential confounders. Since PCOS is the combination of both
oligomenorrhea and hyperandrogenism, we estimated the interaction between these components. We therefore constructed in addition models that included instead of a variable of PCOS, the components oligomenorrhea, hyperandrogenism and an interaction term between them, to yield the p for interaction. Similar models were fit to study the associations of the components of PCOS with the upper quintile (compared with the lower four quintiles) of the IMT of the CCA (CCA-IMT), Bulb (Bulb-IMT) and the ICA (ICA-IMT). General linear models were fit to study the associations of the different components of PCOS with the logistic transformations of carotid IMT as a continuous variable. Models were adjusted for age (continuous), race (Black vs. White), highest education achieved by year 20 (<12 vs ≥12 years), and smoking (ever vs. never). Additional models controlled for measurements of systolic blood pressure, triglycerides (logistic transformation), menopausal status, and the year 20 homeostatic model assessment of insulin resistance (HOMA-IR, calculated as: fasting glucose in mass units×fasting insulin/405). Sensitivity analyses controlled also for medically treated diabetes or hypercholesterolemia, and additional models controlled for the metabolic syndrome [defined according to ref. #5]. We present ORs for logistic regression models, parameter estimates (betas) and adjusted means for GLM regression models, 95% confidence intervals (CI) and two sided p-values.

REFERENCES