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Reproductive epidemiology

Maternal self-reported polycystic ovary syndrome with offspring and maternal cardiometabolic outcomes

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ABSTRACT

STUDY QUESTION: Do children born to mothers with polycystic ovary syndrome (PCOS) have an adverse cardiometabolic profile including arterial stiffness at 9 years of age compared to other children?

SUMMARY ANSWER: Children of mothers with PCOS did not have differing cardiometabolic outcomes than children without exposure.

WHAT IS KNOWN ALREADY: While women with PCOS themselves have higher risk of cardiometabolic conditions such as obesity and diabetes, the evidence on intergenerational impact is unclear. Given *in utero* sequalae of PCOS (e.g. hyperandrogenism, insulin resistance), the increased risk could be to both boys and girls.

STUDY DESIGN, SIZE, DURATION: The Upstate KIDS cohort is a population-based birth cohort established in 2008–2010 to prospectively study the impact of infertility treatment on children's health. After ∼10 years of follow-up, 446 mothers and their 556 children attended clinical visits to measure blood pressure (BP), heart rate, arterial stiffness by pulse wave velocity (PWV), mean arterial pressure, lipids, high-sensitivity C-reactive protein (hsCRP), hemoglobin A1c (HbA1c), and anthropometrics.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women self-reported ever diagnoses of PCOS ∼4 months after delivery of their children in 2008–2010. Linear regression models applying generalized estimating equations to account for correlation within twins were used to examine associations with each childhood cardiometabolic outcome.

MAIN RESULTS AND THE ROLE OF CHANCE: In this cohort with women oversampled on infertility treatment, ∼14% of women reported a PCOS diagnosis (n = 61). We observed similarities in BP, heart rate, PWV, lipids, hsCRP, HbA1c, and anthropometry (*P*-values >0.05) among children born to mothers with and without PCOS. Associations did not differ by child sex.

LIMITATIONS, REASONS FOR CAUTION: The sample size of women with PCOS precluded further separation of subgroups (e.g. by hirsutism). The population-based approach relied on self-reported diagnosis of maternal PCOS even though self-report has been found to be valid. Participants were predominantly non-Hispanic White and a high proportion were using fertility treatment due to the original design. Differences in cardiometabolic health may be apparent later in age, such as after puberty.

WIDER IMPLICATIONS OF THE FINDINGS: Our results provide some reassurance that cardiometabolic factors do not differ in children of women with and without self-reported PCOS during pregnancy.

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogenic disorder in women of reproductive age characterized by hyperandrogenism, oligo-anovulation, and/or polycystic ovarian morphology. The syndrome is a common cause of reduced fertility and is associated with obesity and metabolic comorbidities (Wild *et al.*, 2010; Escobar-Morreale, 2018; Zhang *et al.*, 2020). Evidence suggests that these adverse health effects are perpetuated intergenerationally, not solely by shared inheritance but by *in utero* exposure. Consistent with the developmental origins of health and disease (Barker *et al.*, 1989), PCOS and its sequelae (e.g. excess androgens, insulin resistance) may create a suboptimal intrauterine environment with cardiometabolic health implications for the offspring. Hence, both women with PCOS and their offspring may be at risk of having adverse cardiometabolic profiles.

Previous studies on offspring health of women with PCOS have been inconclusive. A meta-analysis of nine studies reviewed the BMI, systolic (SBP) and diastolic blood pressure (DBP), insulin and glucose, and lipid profiles of 885 children and found higher high-density lipoprotein (HDL)-cholesterol and lower birthweight among children of women with PCOS (n = 298) (Gunning *et al.*, 2020). The researchers also identified sex interactions, suggesting a generally healthier metabolic profile among daughters of women with PCOS (i.e. higher HDL, lower low-density lipoprotein, and lower total cholesterol), inconsistent with the sequalae among adult women. More recently, a Finnish registry study of over a million live births found increased obesity risk in children of women with PCOS or anovulatory infertility (n = 24 682, 2%), with similar risks between boys and girls; but the obesity risk did not persist into adulthood (Chen *et al.*, 2021). Fewer studies have evaluated arterial measures in children of women with PCOS though changes in pulse wave velocity (PWV), a noninvasive measure of arterial stiffness, can be detected beginning in childhood (Stoner *et al.*, 2020). Evaluating childhood risk factors is of import as they have been linked to cardiovascular disease (CVD) risk and events in adulthood (Pool *et al.*, 2021; Jacobs *et al.*, 2022). Compelling evidence from the International Childhood Cardiovascular Cohorts (i3C) consortium study of 38 589 participants showed prospective associations between childhood BMI, total cholesterol, triglycerides, and SBP with incident cardiovascular events in adulthood (Jacobs *et al.*, 2022). Therefore, cardiometabolic and vascular measurements taken in middle childhood are informative of long-term risks.

As maternal and child health are inter-related, due to shared environment and genetics, examining the mothers' own cardiometabolic profiles post-delivery could provide additional insight into any adverse outcomes identified among children. Among women with PCOS, it is established that there is a higher prevalence of cardiovascular risk factors (e.g. obesity, diabetes, hypertension), though whether PCOS itself increases the risk of incident cardiovascular events is debated (Wekker *et al.*, 2020; Zhang *et al.*, 2020; Guan *et al.*, 2022; Mahboobifard *et al.*, 2022). While more research has been done for traditional cardiovascular markers, fewer studies have captured arterial stiffness. PWV can be used to predict future cardiovascular events in adults (Boutouyrie *et al.*, 2008; Vlachopoulos *et al.*, 2010; Ben-Shlomo *et al.*, 2014) and is a biologic marker of vascular function/aging that may be 'accelerated' by cardiometabolic and lifestyle risk factors (Kucharska-Newton *et al.*, 2019). Previous studies examining differences in vascular function among women with and without PCOS have had mixed findings with some finding differences (Kelly *et al.*, 2002; Sasaki *et al.*, 2011) and others not (Moran *et al.*, 2011; Rees *et al.*, 2014; Kim *et al.*, 2019). It remains unclear whether arterial stiffness is affected in women with PCOS. There is some evidence to suggest that excess androgens and/or hyperinsulinemia, as often seen in PCOS, can impact vascular structure through increases in carotid intima-media thickness and calcification in arteries (Luque-Ramírez *et al.*, 2007; Jabbour *et al.*, 2020).

Given the potential elevated cardiovascular risks associated with PCOS for women and their children, the objective of this study was to compare the cardiometabolic profiles of both mothers and their children, 9 years post-delivery, by maternal PCOS status.

Materials and methods

Study design and population

The current investigation is a secondary data analysis. The Upstate KIDS Study is a longitudinal cohort of 5034 mothers and their infants (n = 6171) delivered between 2008 and 2010 in upstate New York. The cohort was designed to study the effects of fertility treatment on childhood growth and development. Using New York State birth certificates, mothers of singleton infants conceived with fertility treatment were approached at a 3:1 ratio to mothers of singletons conceived without treatment while frequency matched by perinatal region of birth (Buck Louis *et al.*, 2014). All mothers of multiples (e.g. twins, triplets, etc.) were invited to participate regardless of fertility treatment status. Additional recruitment and follow-up procedures through age 3, including the validity of this sampling framework, have been published elsewhere (Buck Louis *et al.*, 2014). The cohort has been followed largely through mailed questionnaires. However, beginning in 2017 when the children were around 7–9 years of age, we invited participants to a study clinic visit in order to collect cardiometabolic measures. As such, 4644 children were invited to a study clinic visit at one of four sites (the University at Albany, the University at Buffalo, the University of Rochester, and New York University Langone Health) (Yeung *et al.*, 2022). There were 448 women with their 559 children who participated in the study clinic visit of which 212 children agreed to a blood draw. Study clinic visits concluded in 2019. No differences were identified in clinical measures of children who agreed to a blood draw compared to those who did not. All comparisons of characteristics between those who participated in clinic visits and who provided blood draws along with the finding that child cardiometabolic measures were not associated with fertility treatment has been detailed elsewhere (Yeung *et al.*, 2022).

Ethical approval

The study was approved by the New York State Department of Health and the University at Albany (State University of New York) institutional review boards. Parents provided written informed consent and children assented to clinic visits.

Exposure and covariates assessment

Women self-reported an ever diagnosis of PCOS by a doctor or health care provider on a questionnaire provided ~4 months after delivery of their child. Information on parity, plurality, child sex, gestational age, birth weight, maternal age at delivery, maternal prepregnancy BMI, fertility treatment, gestational hypertension, and gestational diabetes were obtained from birth certificate records. Maternal race/ethnicity, insurance status, maternal education attainment, and smoking during pregnancy were based on maternal report at 4 months after delivery on a questionnaire. The woman's current smoking status and child's

age at time of blood draw were collected during the study clinic visit.

Cardiometabolic assessment

Women and their children attended a study clinic visit for measurements of blood pressure, anthropometrics, arterial stiffness, and to provide blood samples. Height, weight, waist, and hip circumferences were measured by clinic staff in duplicate. A third measurement was taken if the difference between the first two measures exceeded a threshold: 0.5 cm for height, waist, and hip circumferences, and 0.454 kg for weight. The two closest measures of the three were averaged. Using clinically measured height and weight, we calculated BMI as weight over height squared (kg/m^2). For children, age- and sex-specific z-scores for height, weight, and BMI were derived using CDC growth charts to account for age-related developmental changes (Kuczmarski *et al.*, 2002). BMI greater than 90th percentile was used to categorize children as obese (Barlow, 2007). For women, obesity was classified as having a BMI of 30 kg/m^2 or greater. We also used bioelectrical impedance to measure fat (kg), lean dry mass (kg), bone mineral content (kg), lean soft tissue (kg), and fat-free mass (kg). We calculated the fat mass index (FMI) as fat mass over height squared (kg/m^2) and fat-free mass index (FFMI) as fat-free mass over height squared (kg/m^2).

SBP and DBP, mean arterial pressure (MAP), and heart rate were measured at the study clinic visit using an appropriately sized digital blood pressure device prior to blood draw. Per protocol, participants rested in the sitting position for 10 min prior to the measurement being taken from the upper right arm. The first blood pressure measurement was voided, and two others were taken. If the difference between the two measurements exceeded 5 mmHg, a fourth measure was taken. All measures were averaged. For children, pediatric clinical cut offs (95th percentile) were used to assess hypertension based on SBP and DBP. For women, we collected information regarding medication use for a high blood pressure diagnosis during the clinic visit. Women who reported either taking medication or had SBP >130 mmHg or DBP >80 mmHg at the clinic visit were classified as hypertensive. Arterial stiffness was measured by carotid-femoral PWV (SphygmoCor®). The SphygmoCor XCEL performed internal quality control checks which required at least 10 s of high-quality wave forms to be collected before it would initiate each measure (during which another 10 s worth of measures were taken at the carotid and at the femoral cuff). Two measurements were taken in the supine position and a third measure was taken if the difference between the first two measurements exceeded 0.5 m/s. Additional data cleaning steps were taken and coefficients of variation between individuals was 0.1–5.3% for measurements taken on the same day using the difference in measurements (Yeung *et al.*, 2022). Sixteen women were excluded (3.6%; n = 2 with PCOS and n = 14 without PCOS) for having PWV values (range: 2.1–3.65 m/s) below 2 SD (<3.65 m/s) of the mean and outside of typical adult ranges (Reference Values for Arterial Stiffness' Collaboration, 2010).

Among women who consented and children who assented to a blood draw, plasma lipids, C-reactive protein, and average blood sugar over the past 2–3 months via a hemoglobin A1c (HbA1c) test were quantified. Non-fasting blood samples were processed for plasma and packed red blood cells and were subsequently stored at −80°C until analysis. Plasma lipids (mg/dl) and high-sensitivity C-reactive protein (hsCRP, mg/l) were measured using the Roche COBAS 8000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA). Packed red blood cells were used for the HbA1c test using non-porous ion exchange high performance liquid chromatography (Tosoh Automated Analyzer HLC-723G8, Tosoh Bioscience, Inc., South San Francisco, CA, USA).

Statistical analysis

Two women missing PCOS exposure information were excluded, leaving 446/448 women and 556/559 children in the analytic sample. We tabulated data on sample characteristics by PCOS exposure using percentages and means with inference provided by *t*-tests (continuous variables) and chi-square or Fisher's exact tests (categorical variables).

To account for correlation within twins, we applied linear models with generalized estimating equations and an exchangeable correlation structure to examine associations of PCOS exposure with each childhood cardiometabolic outcome. Model adjustments included plurality, child sex, child age at measurement, maternal age at child's birth, maternal race/ethnicity, maternal educational attainment, insurance status, lab site, maternal prepregnancy BMI, fertility treatment, and gestational diabetes. Maternal sociodemographic covariates were selected based on established associations with cardiometabolic risk and from our previous investigations of their associations identified in the larger sample of women with PCOS status in this cohort (Haas *et al.*, 2003; Bell *et al.*, 2018). Infertility treatment was included because of oversampling in the cohort as part of its design (Buck Louis *et al.*, 2014). While there is higher risk of gestational diabetes among women with PCOS, studies suggest it may not be causal but due to shared risk factors (Qiu *et al.*, 2022). Thus, gestational diabetes was included in models to capture the unmeasured impact of factors that may have contributed to endocrine disruption such as genetics and environment (Day *et al.*, 2018; Yao *et al.*, 2023). Child age, sex, clinical site, and plurality were subsequently added to the model as technical covariates for cardiometabolic differences. A sensitivity analysis stratifying offspring by sex was also conducted.

To assess associations of cardiometabolic measures in women by PCOS status, linear regression models were carried out with adjustment for maternal age, race/ethnicity, educational attainment, insurance status, clinic site, infertility treatment, parity, and (separately) current BMI. Again, sociodemographic variables (Mehta *et al.*, 2023), site, and treatment were included by same rationale as above. Childbearing has been found to increase cardiometabolic risk through visceral or body fat changes and therefore parity was included (Gunderson *et al.*, 2008). We modeled BMI separately so that its impact can be delineated from other factors.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Maternal and child characteristics are presented in Table 1. No differences in age, plurality, child sex, or neonatal characteristics, including birth weight or gestational age, were found between children of women with and without PCOS. Women with PCOS were more likely to have been first-time mothers, have private insurance, received fertility treatment, or have had prepregnancy obesity or gestational diabetes.

Approximately 22% of children were obese (n = 97; 10 with and 87 without PCOS exposure, $P = 0.26$) and 18.8% had hypertension by SBP (n = 82; 12 with and 70 without PCOS exposure, $P = 0.75$). Their average HbA1c was 5.1%. Regardless of maternal PCOS exposure, the anthropometric, blood pressure, PWV, lipid, HbA1c, and hsCRP measures were similar among children

Table 1. Study participant characteristics by polycystic ovary syndrome (PCOS) status, Upstate KIDS Study.^

	PCOS	No PCOS	P-value
N (%)	61 (13.7)	385 (86.3)	
Child characteristics			
Plurality, twin, %	20 (32.8)	92 (24.0)	0.1432
Sex, Female, %	30 (49.2)	182 (47.5)	0.8094
Birthweight, grams	3062 (737.9)	3180 (712.2)	0.2447
Low birth weight, <2500 g, %	13 (21.3)	60 (15.7)	0.2692
Gestational age, weeks	37.8 (2.4)	38.0 (2.6)	0.4939
Preterm birth, <37 weeks, %	12 (19.7)	62 (16.2)	0.4977
Age at visit, months	113.0 (7.4)	104.9 (6.9)	0.6256
Maternal characteristics			
Age at delivery, years	30.7 (4.3)	31.4 (6.0)	0.2755
Maternal education, college, %	40 (65.6)	246 (63.9)	0.7996
Maternal race/ethnicity, non-Hispanic White, %	54 (88.5)	331 (86.0)	0.5901
Insurance at birth, private, %	57 (93.4)	319 (82.9)	**0.0347**
Nulliparous, %	43 (71.6)	186 (48.8)	**0.0010**
Infertility treatment			**<0.0001**
Ovulation induction/IUI	30 (49.2)	65 (16.9)	
ART	19 (31.1)	63 (16.4)	
Prepregnancy BMI, kg/m^2	29.2 (7.6)	27.0 (7.0)	**0.0337**
Prepregnancy obesity, %	29 (47.5)	90 (23.4)	**<0.0001**
Gestational diabetes, %	15 (24.6)	40 (10.4)	**0.0017**
Gestational hypertension, %	9 (14.7)	50 (13.0)	0.7051
Smoking during pregnancy, %	2 (3.3)	28 (7.3)	0.4067
Current smoker, %	3 (4.9)	20 (5.4)	1.000

All values reported as mean (SD) unless otherwise stated. Bolding indicates $P < 0.05$.
^ Descriptive statistics reported at the family level including singletons and one randomly selected twin from the twin pair.

Table 2. Adjusted mean differences (and 95% CIs) of childhood outcomes at age 9 years.[a]

	n	Model 1[b]	Model 2[c]
Systolic blood pressure, mmHg	543	−0.28 (−3.20, 1.49)	−0.38 (−3.07, 2.30)
Diastolic blood pressure, mmHg	543	−0.40 (−2.10, 0.86)	−0.54 (−2.21, 1.13)
Heart rate, bpm	543	−0.29 (−3.64, 1.71)	−0.56 (−3.97, 2.84)
Mean arterial pressure, mmHg	542	−0.34 (−2.29, 1.00)	−0.46 (−2.33, 1.39)
Pulse wave velocity, m/s	494	0.03 (−0.24, 0.14)	0.01 (−0.25, 0.28)
Weight for age z-scores	555	−0.08 (−0.34, 0.13)	−0.07 (−0.33, 0.19)
Height for age z-scores	555	−0.10 (−0.36, 0.13)	−0.10 (−0.35, 0.16)
BMI for age z-scores	555	−0.03 (−0.28, 0.13)	−0.04 (−0.29, 0.21)
Fat mass index, kg/m^2	523	−0.50 (−1.19, 0.35)	−0.67 (−1.36, 0.01)
Fat-free mass index, kg/m^2	492	−0.17 (−0.57, 0.21)	−0.10 (−0.49, 0.28)

[a] Estimates obtained from linear regression with GEE extension to account for correlation among twins.
[b] Model 1 adjusted for maternal age at child's birth, maternal race/ethnicity, maternal educational attainment, insurance status, maternal prepregnancy BMI, fertility treatment, and gestational diabetes.
[c] Model 2 adjusted for plurality, child sex, child age at measurement, maternal age at child's birth, maternal race/ethnicity, maternal educational attainment, insurance status, clinic site, maternal prepregnancy BMI, fertility treatment, and gestational diabetes.

(Table 2, Supplementary Table S1). Children of women with PCOS had marginally lower FMI compared to children of women without PCOS (β: −0.67; 95% CI: −1.36, 0.01) with adjustment for covariates. When stratified by the child's sex, girls exposed to PCOS *in utero* had lower FMI (β: −1.24; 95% CI: −2.07, −0.40) and FFMI (β: −0.59; 95% CI: −1.09, −0.10) than children not exposed (Supplementary Table S2).

Women with PCOS, on average, had a higher heart rate and HbA1c (Supplementary Table S3). In adjusted models, heart rate, HbA1c, and anthropometric measures including BMI (β: 2.11 kg/m^2; 95% CI: 0.004, 4.22) were increased in association with PCOS status (Table 3). Even after further adjustment for current BMI, both heart rate (β: 3.12 bpm; 95% CI: 0.26, 5.97) and HbA1c (β: 0.25; 95% CI: 0.07, 0.43) remained elevated among women with PCOS. Arterial stiffness was also increased (0.32 m/s; 95% CI: −0.03, 0.66) although it did not reach statistical significance and further adjustment for concurrent BMI attenuated the association further (β: 0.25 m/s; −0.08, 0.59). Removal of women who took hypertensive medications did not materially alter the findings for blood pressure or PWV (data not shown). We used false discovery rate (FDR) correction to examine the impact of multiple testing on the maternal cardiometabolic associations.(Benjamini and Hochberg, 1995) Prior to adjustment for BMI, associations with HbA1c remained FDR-significant ($P_{FDR} = 0.04$) and heart rate borderline significant ($P_{FDR} = 0.06$).

Discussion

We first examined cardiometabolic differences of children of women with and without self-reported PCOS during pregnancy. No associations were found with maternal PCOS exposure and anthropometric, blood pressure, PWV, lipid, HbA1c, nor hsCRP outcomes during middle childhood. Further, the associations did not appear to differ substantially by child sex; albeit the finding that the risk of FMI in PCOS exposed children decreased with female sex is interesting but should be interpreted with caution due to small group size. We next assessed the effects of PCOS with multiple CVD risk factors in women. While all mean cardiometabolic values were higher among women with PCOS, only heart rate and HbA1c remained associated with PCOS status after accounting for concurrent BMI.

We found no associations with middle childhood cardiometabolic outcomes among children with and without maternal PCOS exposure. This is in line with our previous finding of no differences in early growth through the first 3 years of life within the Upstate KIDS Study (Bell *et al.*, 2018). Similar to our study, an individual participant data meta-analysis in 2020 of nine case-control studies also found no differences in BMI (Gunning *et al.*, 2020). In contrast, two recent longitudinal studies found increased BMI risk with maternal PCOS exposure, though neither study noted consistent differences by child sex (Chen *et al.*, 2021; Zhang *et al.*, 2022). Specifically, a Finnish registry study found an increased risk of obesity among children 9 years of age or younger and among 10- to 16-year-old offspring with maternal PCOS exposure or anovulatory infertility (Chen *et al.*, 2021). In a study of 198 children of PCOS mothers and 227 of mothers with healthy pregnancies (having been excluded for chronic conditions and any pregnancy complications), maternal PCOS was associated with higher BMI and weight at 5 years of age but not at 4 or 6 years (Zhang *et al.*, 2022). Furthermore, a study combining meta-analysis and mendelian randomization analysis approaches, found that childhood body size and the genetic determinants of body fat increased risk for PCOS independently of adulthood obesity, suggesting a causal influence of body fat in childhood (Dobbie *et al.*, 2023). The authors conjectured that their results point to two distinct PCOS phenotypes, and that the metabolic phenotype, preceded by obesity development, may not drive the reproductive phenotype which can occur in lean women.

Prior evidence has also indicated no differences in fasting glucose or insulin in children, but increased insulin following an oral glucose tolerance test, particularly in girls (Kent *et al.*, 2008; Sir-Petermann *et al.*, 2009). Some studies have also examined blood pressure and lipid metabolism, including the recent meta-

Table 3. Adjusted mean differences (and 95% CIs) of maternal cardiovascular measures taken ~9 years postpartum by polycystic ovary syndrome (PCOS) status.[a]

	N	Model 0[b]	N	Model 1[c]
Systolic blood pressure, mmHg	429	0.97 (−2.81, 4.75)	419	−0.62 (−4.21, 2.98)
Diastolic blood pressure, mmHg	429	1.11 (−1.50, 3.73)	419	−0.09 (−2.56, 2.39)
Heart rate, bpm	429	**4.00 (1.02, 6.98)**	419	**3.12 (0.26, 5.97)**
Mean arterial pressure, mmHg	429	0.90 (−2.01, 3.82)	419	−0.42 (−3.17, 2.33)
Pulse wave velocity, m/s	383	0.32 (−0.03, 0.66)	378	0.25 (−0.08, 0.59)
Weight, kg	424	**7.05 (1.17, 12.94)**	423	1.47 (−0.42, 3.36)
Height, cm	432	1.44 (−0.44, 3.32)	423	1.48 (−0.42, 3.38)
Waist, cm	429	**6.34 (1.30, 11.38)**	422	2.27 (−0.25, 4.78)
Hip	428	**4.43 (−0.003, 8.86)**	422	0.96 (−1.23, 3.14)
BMI, kg/m^2	423	**2.11 (0.004, 4.22)**		n/a
Fat, kg	407	**4.43 (0.20, 8.67)**	398	0.38 (−1.15, 1.91)
Lean dry mass, kg	403	**1.09 (0.18, 1.99)**	394	0.64 (−0.18, 1.45)
Bone mineral content, kg	403	**0.38 (0.06, 0.70)**	394	1.35 (−0.46, 3.17)
Fat-free mass, kg	387	**3.47 (0.89, 6.05)**	379	1.39 (−0.45, 3.23)
Fat mass index, kg/m^2	407	1.41 (−0.17, 2.99)	398	−0.08 (−0.62, 0.47)
Fat-free mass index, kg/m^2	387	**0.95 (0.15, 1.75)**	379	0.20 (−0.19, 0.59)
HbA1c, %	363	**0.30 (0.12, 0.49)**	355	**0.25 (0.07, 0.43)**
Total cholesterol, mg/dl	365	3.92 (−7.17, 15.02)	356	2.60 (−8.52, 13.72)
High-density lipoprotein, mg/dl	365	0.96 (−4.32, 6.24)	357	3.29 (−1.42, 8.00)
Low-density lipoprotein, mg/dl	365	1.25 (−8.72, 11.22)	358	−0.50 (−10.43, 9.42)
Triglycerides, mg/dl	365	17.79 (−6.58, 42.16)	359	7.68 (−15.00, 30.37)
C-reactive protein, mg/dl	344	0.78 (−0.95, 2.51)	360	0.05 (−1.48, 1.59)
Non-HDL cholesterol, mg/dl	365	2.96 (−8.86, 14.78)	361	−0.69 (−12.14, 10.76)

Bolding indicates $P < 0.05$.
[a] Estimates obtained from linear regression.
[b] Model 0 adjusted for maternal age, race/ethnicity, educational attainment, insurance status, clinic site, fertility treatment, parity.
[c] Model 1 additionally adjusted for measured BMI.

analysis, but did not find differences (Gunning et al., 2020). Lastly, Wilde et al. (2018) found carotid intima-media thickness was significantly higher in 6- to 8-year-old children in a PCOS group versus a reference population (Wilde et al., 2018). However, at a younger age when the children were 2–5 years old, they found no differences in PWV as measured at the aorta. The lack of association is similar to our observation even though they measured PWV slightly higher than ours (averaging 5.6 m/s vs 4.4 m/s in the reference groups). As carotid intima-media thickness and arterial stiffness target different parts of the vasculature, it's possible these measures reflect different aspects of early CVD progression (Pettersson-Pablo et al., 2020; Heffernan et al., 2023).

The lack of differences observed among children is consistent with their mothers also having similar cardiometabolic measures 8–10 years after delivery, after accounting for BMI. MAP and HbA1c were higher despite adjusting for BMI. A tendency for arterial stiffness to be increased was also observed. Two case-control studies among women with and without PCOS found positive associations with brachial artery PWV, but Kelly et al., did not find associations with carotid-femoral PWV as measured in our study (Kelly et al., 2002; Sasaki et al., 2011). Carotid-femoral and brachial artery PWV are strongly correlated indices of central artery stiffness, though on average, brachial artery PWV is higher than carotid-femoral PWV, suggesting it is partially influenced by peripheral (muscular) arterial stiffness (Tanaka et al., 2009). In contrast, three cross-sectional studies found no differences in PWV though the analyses only accounted for participant age and BMI (Moran et al., 2011; Rees et al., 2014; Kim et al., 2019). These differences in findings may be attributed to variations in genetic background and the heterogeneity in PCOS phenotypes in different studies, for example, by severity of hyperandrogenism or insulin resistance (Lizneva et al., 2016), which has been linked to PWV (Armeni et al., 2013). The association with HbA1c is in line with evidence that PCOS heightens risk of diabetes due to insulin resistance, although whether the risk is independent on BMI remains debated (Glintborg et al., 2022). We also recognize that diet and exercise could improve cardiometabolic health among women with PCOS (Patten et al., 2020). Mothers were asked about their own physical activity about 2 years prior to the exam and a subgroup who attended the clinic visit had provided information (n = 268). In this subgroup, no differences in reported level of activity were found by PCOS status ($P > 0.5$). Nevertheless, lifestyle interventions remain important in this high-risk group.

An important strength of the current study is the longitudinal cohort design that benefited from a nearly 10-year follow-up period. In addition, we were able to assess a number of cardiometabolic clinical measures taken by trained staff rather than relying solely on self-report for these important outcomes. Limitations in this study include the small sample size, which for instance, precluded us from further evaluating subgroups of PCOS with hirsutism (n = 14, 3.14%) separately from PCOS without hirsutism (n = 47, 10.54%), even though research suggests hyperandrogenism may be an important driver of cardiometabolic risk. The sample size may also limit detection of small differences in some cardiovascular outcomes in children with high variability. For instance, we could only rule out differences in blood pressure of over 2.7 mmHg DBP and 3.9 mmHg SBP based on minimally detectable differences (from two sample tests assuming $\alpha = 0.05$, power = 0.80, 61 PCOS and 385; excluding one twin from each family due to correlations). However, other factors such as BMI z-score and PWV with standard deviations near 1 would have been detectable at 0.4 units difference and we observed near zero mean differences between children of differing PCOS exposure groups in their adjusted analysis, suggesting they were not due to sample size limitations. PCOS exposure was based on maternal report of a physician diagnosis rather than well-established diagnostic criteria (e.g. NIH (Zawadzki and Dunaif, 1995), Rotterdam (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004)). As a result of being selected from a population-based source it's also possible that we identified milder phenotypes of PCOS compared to a clinically recruited population (Lizneva et al., 2016). However, in large epidemiologic studies,

clinically verifying PCOS is often not feasible and in practice clinical information such as that regarding anovulation or hirsutism is essentially self-reported (given women shave, etc.) and self-reported PCOS has been found to be a valid alternative for population-based research.(de Boer *et al.*, 2005; Piltonen *et al.*, 2023) We relied on a single study visit in middle childhood, while daughters of women with PCOS are more likely to develop PCOS (Risal *et al.*, 2019) though clinical manifestations often present after puberty (Hudnut-Beumler *et al.*, 2021). We did not track physical changes of puberty (e.g. Tanner scale) in children enrolled in this study and puberty could affect metabolic parameters. Further follow-up to explore these associations is warranted as puberty may alter cardiometabolic risk. We lacked dietary and physical activity data for adjustment. However, we suspect that adjustment for maternal BMI may have captured the impact of excess calories or low physical activity on cardiometabolic outcomes.

Conclusions

This study demonstrated that cardiometabolic factors did not differ in children of women with and without self-reported PCOS during pregnancy. Secondly, this study confirmed independent associations of maternal cardiovascular risk factors, apart from BMI, with history of PCOS. Future investigations in larger studies with long follow-up may provide useful information on the contributions of maternal PCOS exposure on both offspring and maternal cardiometabolic outcomes.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data that support the findings of this study are available on request from the corresponding author [E.H.Y.]. The data are not on a public database due to New York State restrictions (i.e. releasing information that could compromise participant privacy/consent).

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Authors' roles

K.J.P. analyzed the data and drafted the manuscript; S.L.R., P.J., and V.G.-L. designed the analytic plan and critically interpreted and revised the manuscript for important intellectual content; D. L.P. interpreted the data and revised the manuscript for important intellectual content; R.S., A.G., and E.M.B. acquired the data, interpreted the results and critically revised the manuscript for important intellectual content. E.H.Y. designed the study, acquired the data, analyzed the data, interpreted the data and critically revised the manuscript for important intellectual content.

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Conflict of interest

None to declare.

References

Armeni E, Stamatelopoulos K, Rizos D, Georgiopoulos G, Kazani M, Kazani A, Kolyviras A, Stellos K, Panoulis K, Alexandrou A *et al.* Arterial stiffness is increased in asymptomatic nondiabetic postmenopausal women with a polycystic ovary syndrome phenotype. *J Hypertens* 2013;**31**:1998–2004.

Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;**298**:564–567.

Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007;**120**(Suppl 4):S164–S192.

Bell GA, Sundaram R, Mumford SL, Park H, Broadney M, Mills JL, Bell EM, Yeung EH. Maternal polycystic ovarian syndrome and offspring growth: the Upstate KIDS Study. *J Epidemiol Community Health* 2018;**72**:852–855.

Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen C-H, Cruickshank JK *et al.* Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014;**63**:636–646.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol* 1995;**57**:289–300.

Boutouyrie P, Vermersch S, Laurent S, Briet M. Cardiovascular risk assessment through target organ damage: role of carotid to femoral pulse wave velocity. *Clin Exp Pharmacol Physiol* 2008;**35**:530–533.

Buck Louis GM, Hediger ML, Bell EM, Kus CA, Sundaram R, McLain AC, Yeung E, Hills EA, Thoma ME, Druschel CM. Methodology for establishing a population-based birth cohort focusing on couple fertility and children's development, the Upstate KIDS Study. *Paediatr Perinat Epidemiol* 2014;**28**:191–202.

Chen X, Koivuaho E, Piltonen TT, Gissler M, Lavebratt C. Association of maternal polycystic ovary syndrome or anovulatory infertility with obesity and diabetes in offspring: a population-based cohort study. *Hum Reprod* 2021;**37**:193–194.

Day F, Karaderi T, Jones MR, Meun C, He C, Drong A, Kraft P, Lin N, Huang H, Broer L *et al.*; 23andMe Research Team. Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. *PLoS Genet* 2018;**14**:e1007813.

de Boer EJ, den Tonkelaar I, Burger CW, van Leeuwen FE; OMEGA Project Group. Validity of self-reported causes of subfertility. *Am J Epidemiol* 2005;**161**:978–986.

Dobbie LJ, Pittam B, Zhao SS, Alam U, Hydes TJ, Barber TM, Cuthbertson DJ. Childhood, adolescent, and adulthood adiposity are associated with risk of PCOS: a Mendelian randomization study with meta-analysis. *Hum Reprod* 2023;**38**:1168–1182.

Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol* 2018;**14**:270–284.

Glintborg D, Kolster ND, Ravn P, Andersen MS. Prospective risk of type 2 diabetes in normal weight women with polycystic ovary

syndrome. *Biomedicines* 2022;**10**:1455. https://doi.org/10.3390/biomedicines10061455.

Guan C, Zahid S, Minhas AS, Ouyang P, Vaught A, Baker VL, Michos ED. Polycystic ovary syndrome: a "risk-enhancing" factor for cardiovascular disease. *Fertil Steril* 2022;**117**:924–935.

Gunderson EP, Sternfeld B, Wellons MF, Whitmer RA, Chiang V, Quesenberry CP, Lewis CE, Sidney S. Childbearing may increase visceral adipose tissue independent of overall increase in body fat. *Obesity (Silver Spring)* 2008;**16**:1078–1084.

Gunning MN, Sir Petermann T, Crisosto N, van Rijn BB, de Wilde MA, Christ JP, Uiterwaal C, de Jager W, Eijkemans MJC, Kunselman AR *et al.* Cardiometabolic health in offspring of women with PCOS compared to healthy controls: a systematic review and individual participant data meta-analysis. *Hum Reprod Update* 2020;**26**:103–117.

Haas JS, Lee LB, Kaplan CP, Sonneborn D, Phillips KA, Liang SY. The association of race, socioeconomic status, and health insurance status with the prevalence of overweight among children and adolescents. *Am J Public Health* 2003;**93**:2105–2110.

Heffernan KS, Stoner L, London AS, Augustine JA, Lefferts WK. Estimated pulse wave velocity as a measure of vascular aging. *PLoS One* 2023;**18**:e0280896.

Hudnut-Beumler J, Kaar JL, Taylor A, Kelsey MM, Nadeau KJ, Zeitler P, Snell-Bergeon J, Pyle L, Cree-Green M. Development of type 2 diabetes in adolescent girls with polycystic ovary syndrome and obesity. *Pediatr Diabetes* 2021;**22**:699–706.

Jabbour R, Ott J, Eppel W, Frigo P. Carotid intima-media thickness in polycystic ovary syndrome and its association with hormone and lipid profiles. *PLoS One* 2020;**15**:e0232299.

Jacobs DR, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, Kartiosuo N, Lehtimäki T, Magnussen CG, Viikari JSA *et al.* Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med* 2022;**386**:1877–1888.

Kelly CJ, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JM. Altered vascular function in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;**87**:742–746.

Kent SC, Gnatuk CL, Kunselman AR, Demers LM, Lee PA, Legro RS. Hyperandrogenism and hyperinsulinism in children of women with polycystic ovary syndrome: a controlled study. *J Clin Endocrinol Metab* 2008;**93**:1662–1669.

Kim J, Choi S-Y, Park B, Park HE, Lee H, Kim MJ, Kim SM, Hwang KR, Choi YM. Arterial stiffness measured by cardio-ankle vascular index in Korean women with polycystic ovary syndrome. *J Obstet Gynaecol* 2019;**39**:681–686.

Kucharska-Newton AM, Stoner L, Meyer ML. Determinants of vascular age: an epidemiological perspective. *Clin Chem* 2019;**65**:108–118.

Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11* 2002;**246**:1–190.

Lizneva D, Kirubakaran R, Mykhalchenko K, Suturina L, Chernukha G, Diamond MP, Azziz R. Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis. *Fertil Steril* 2016;**106**:1510–1520.e12.

Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil Steril* 2016;**106**:6–15.

Luque-Ramírez M, Mendieta-Azcona C, Alvarez-Blasco F, Escobar-Morreale HF. Androgen excess is associated with the increased carotid intima-media thickness observed in young women with polycystic ovary syndrome. *Hum Reprod* 2007;**22**:3197–3203.

Mahboobifard F, Rahmati M, Niknam A, Rojhani E, Momenan AA, Azizi F, Ramezani Tehrani F. Impact of polycystic ovary syndrome on silent coronary artery disease and cardiovascular events; a long-term population-based cohort study. *Arch Med Res* 2022;**53**:312–322.

Mehta LS, Velarde GP, Lewey J, Sharma G, Bond RM, Navas-Acien A, Fretts AM, Magwood GS, Yang E, Blumenthal RS *et al.*; American Heart Association Cardiovascular Disease and Stroke in Women and Underrepresented Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Hypertension; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Cardiovascular disease risk factors in women: the impact of race and ethnicity: a scientific statement from the American Heart Association. *Circulation* 2023;**147**:1471–1487.

Moran LJ, Cameron JD, Strauss BJ, Teede HJ. Vascular function in the diagnostic categories of polycystic ovary syndrome. *Hum Reprod* 2011;**26**:2192–2199.

Patten RK, Boyle RA, Moholdt T, Kiel I, Hopkins WG, Harrison CL, Stepto NK. Exercise interventions in polycystic ovary syndrome: a systematic review and meta-analysis. *Front Physiol* 2020;**11**:606.

Pettersson-Pablo P, Cao Y, Breimer LH, Nilsson TK, Hurtig-Wennlof A. Pulse wave velocity, augmentation index, and carotid intima-media thickness are each associated with different inflammatory protein signatures in young healthy adults: the lifestyle, biomarkers and atherosclerosis study. *Atherosclerosis* 2020;**313**:150–155.

Piltonen T, Morin-Papunen L, Ollila MM, Tapanainen J, Arffman R, Jarvelin MR, Franks S. Women self-reporting PCOS symptoms should not be overlooked. *Hum Reprod* 2023;**38**:189–190.

Pool LR, Aguayo L, Brzezinski M, Perak AM, Davis MM, Greenland P, Hou L, Marino BS, Van Horn L, Wakschlag L *et al.* Childhood risk factors and adulthood cardiovascular disease: a systematic review. *J Pediatr* 2021;**232**:118–126.e23.

Qiu Y, Zhang X, Ni Y. Association between polycystic ovarian syndrome and risk of gestational diabetes mellitus: a meta-analysis. *Gynecol Obstet Invest* 2022;**87**:150–158.

Rees E, Coulson R, Dunstan F, Evans WD, Blundell HL, Luzio SD, Dunseath G, Halcox JP, Fraser AG, Rees DA. Central arterial stiffness and diastolic dysfunction are associated with insulin resistance and abdominal obesity in young women but polycystic ovary syndrome does not confer additional risk. *Hum Reprod* 2014;**29**:2041–2049.

Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;**31**:2338–2350.

Risal S, Pei Y, Lu H, Manti M, Fornes R, Pui HP, Zhao Z, Massart J, Ohlsson C, Lindgren E *et al.* Prenatal androgen exposure and transgenerational susceptibility to polycystic ovary syndrome. *Nat Med* 2019;**25**:1894–1904.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;**19**:41–47.

Sasaki A, Emi Y, Matsuda M, Sharula, Kamada Y, Chekir C, Hiramatsu Y, Nakatsuka M. Increased arterial stiffness in mildly-hypertensive women with polycystic ovary syndrome. *J Obstet Gynaecol Res* 2011;**37**:402–411.

Sir-Petermann T, Codner E, Pérez V, Echiburú B, Maliqueo M, Ladrón de Guevara A, Preisler J, Crisosto N, Sánchez F, Cassorla F *et al.* Metabolic and reproductive features before and during puberty

in daughters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2009;**94**:1923–1930.

Stoner L, Kucharska-Newton A, Meyer ML. Cardiometabolic health and carotid-femoral pulse wave velocity in children: a systematic review and meta-regression. *J Pediatr* 2020;**218**:98–105.e103.

Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T *et al.* Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *J Hypertens* 2009; **27**:2022–2027.

Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; **55**:1318–1327.

Wekker V, van Dammen L, Koning A, Heida KY, Painter RC, Limpens J, Laven JSE, Roeters van Lennep JE, Roseboom TJ, Hoek A. Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. *Hum Reprod Update* 2020;**26**:942–960.

Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab* 2010;**95**:2038–2049.

Wilde MA, Eising JB, Gunning MN, Koster MPH, Evelein AMV, Dalmeijer GW, Uiterwaal C, Eijkemans MJC, Ent CKV, Meijboom FJ *et al.* Cardiovascular and metabolic health of 74 children from women previously diagnosed with polycystic ovary syndrome in comparison with a population-based reference cohort. *Reprod Sci* 2018;**25**:1492–1500.

Yao X, Geng S, Zhu L, Jiang H, Wen J. Environmental pollutants exposure and gestational diabetes mellitus: evidence from epidemiological and experimental studies. *Chemosphere* 2023; **332**:138866.

Yeung EH, Mendola P, Sundaram R, Lin TC, Broadney MM, Putnick DL, Robinson SL, Polinski KJ, Wactawski-Wende J, Ghassabian A *et al.* Conception by fertility treatment and cardiometabolic risk in middle childhood. *Fertil Steril* 2022;**118**:349–359.

Zawadzki J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. *Polycystic Ovary Syndrome* 1995;377–384.

Zhang F, Ying L, Zhang Q, Wang F, Qu F. Association between maternal polycystic ovary syndrome and early childhood growth: a continuous observation from 3 months to 6 years of age. *J Assist Reprod Genet* 2022;**39**:461–471.

Zhang J, Xu JH, Qu QQ, Zhong GQ. Risk of cardiovascular and cerebrovascular events in polycystic ovarian syndrome women: a meta-analysis of cohort studies. *Front Cardiovasc Med* 2020; **7**:552421.