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The associations of maternal polycystic ovary syndrome and hirsutism with behavioral problems in offspring

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Abstract

Objective: To study the associations between maternal polycystic ovary syndrome (PCOS) and hirsutism with offspring attention-deficit/hyperactivity disorder (ADHD), anxiety, conduct disorder, and behavioral problems.

Design: Prospective birth cohort study.

Setting: Community sample in upstate New York.

Patient(s): A total of 1915 mother-child dyads.

Intervention(s): N/A

Main Outcome Measure(s): Maternal report of offspring ADHD, anxiety, or conduct disorder diagnosis at 7–8 years; emotional symptoms, behavioral problems (including peer relationship, conduct, hyperactivity/inattention), and prosocial problems measured with the Strengths and Difficulties Questionnaire (SDQ) at 7 years.

Results: Prevalence of PCOS and hirsutism were 12.0% and 3.9%; 84% of women with hirsutism had PCOS. After adjustment for sociodemographic covariates, pre-pregnancy body mass index, and parental history of affective disorders, children born to mothers with PCOS had higher risk of anxiety (aRR 1.62, 95% CI 1.02–2.57) and borderline emotional symptoms (aRR 1.66, 95% CI 1.18–2.33) compared with children born to mothers without PCOS. Associations between maternal PCOS and offspring ADHD were positive but imprecise. Maternal hirsutism was related

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CONFLICTS OF INTEREST

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to higher risk of children's ADHD (aRR 2.33, 95% CI 1.28, 4.24) and conduct disorder (aRR 2.54; 95% CI 1.18–5.47) and borderline emotional symptoms, peer relationship problems, and conduct problems (aRRs 2.61, 95% CI 1.69–4.05; 1.92, 95% CI 1.16–3.17; and 2.22, 95% CI 1.30–3.79, respectively).

Conclusions: Maternal PCOS was associated with offspring anxiety while hirsutism was related to other offspring behavioral problems. These findings should be interpreted with caution as replication is needed in prospective cohort studies which assess PCOS and hirsutism diagnoses using medical records.

Capsule:

Maternal polycystic ovary syndrome is associated with offspring anxiety; maternal hirsutism is related to offspring ADHD, conduct disorder, and other behavioral problems. Despite some diagnostic overlap, offspring behavioral results vary.

Keywords

polycystic ovary syndrome; hirsutism; attention-deficit; hyperactivity disorder; anxiety disorder; behavioral problems

INTRODUCTION

Depressive and conduct disorders are major causes of disability adjusted life years in children and adolescents worldwide (1), yet much remains unknown about their etiology. Recent studies that investigate the association between maternal polycystic ovary syndrome (PCOS) and offspring behavioral disorders may offer evidence on the developmental origins of these childhood conditions.

PCOS is a common endocrine condition known for its association with infertility. Diagnostic criteria for PCOS generally includes having at least two of the following: 1) excess androgens, 2) oligo-anovulation, or 3) polycystic ovaries confirmed by ultrasound (2–4). Hirsutism, a condition marked by excess body hair in a male sex pattern, is often used to indicate a subtype of PCOS with excess androgens. Rodent models of a maternal PCOS-like phenotype induced by injections of androgens find an increase in anxiety-like behavior in offspring (5, 6), potentially mediated by alterations to the androgenic, serotonergic, and *gamma*-Aminobutyric acidergic (GABA) metabolisms in the amygdala (5). Higher levels of circulating inflammatory markers associated with PCOS may also contribute to the behavioral changes seen in animal models (6–8).

Recent epidemiologic studies suggest that maternal PCOS and hirsutism are associated with offspring autism spectrum disorder (ASD) (9–11) and developmental delay (12, 13). Less is known about the associations of maternal PCOS or hirsutism with behavioral problems or mental disorders later in childhood. Using data from the Swedish registry, a population-based case-control study found that offspring of women with PCOS had higher odds of attention-deficit/hyperactivity disorder (ADHD) compared with offspring of women without PCOS (14). This finding was confirmed in a matched cohort study in the United Kingdom; however, the association between maternal PCOS and children's ADHD diagnosis was

attenuated upon controlling for maternal history of mental disorders (10). These findings have not been replicated in a well-characterized prospective cohort, nor has the association between maternal PCOS and other offspring behavioral problems such as anxiety been examined. Further, maternal hirsutism has not been examined as an exposure.

To this end, we examined the relations of maternal self-report of PCOS and hirsutism with children's behavioral problems and mental disorders at 7 and 8 years old in the Upstate KIDS cohort. As our assessment of these associations is limited by maternal self-report of PCOS and hirsutism rather than clinical assessment, our findings should be interpreted as hypothesis-generating and will require replication in future studies.

MATERIALS AND METHODS

Study setting and participants

The Upstate KIDS study is a population-based birth cohort designed to evaluate the effects of infertility treatment on child health and development (15). At approximately 4 months postpartum, mothers of children born between July 2008 and May 2010 in New York State (excluding New York City) were recruited into the study. All infants conceived using fertility treatments and multiple births were invited to participate. Three singletons not conceived by fertility treatment were sampled for every child conceived using fertility treatment, frequency matched to region of birth. In total, 5,034 mothers and 6,171 children were recruited. We did not observe any significant differences in early childhood development by fertility treatment status (16). In this analysis, children with information on behavioral problems or mental disorders are included. Due to low numbers, triplets and quadruplets were excluded (n=134).

The New York State Department of Health and the University of Albany Institutional Review Board (IRB) approved of the study and served as the IRB designated by the National Institutes of Health for this study under a reliance agreement. Parents provided written informed consent prior to enrollment.

Measurements

Baseline questionnaire—At the time of enrollment, 4,886 mothers (97.1%) completed a baseline questionnaire on their reproductive history, familial health status, and sociodemographic information. This survey included questions on parental age, height, weight, and history of affective disorders (i.e., anxiety, mood, or eating disorder), and maternal race/ethnicity, education, insurance type, marital status, parity, history of gynecological medical conditions, history and type of infertility treatment, and smoking use during pregnancy. With regards to maternal gynecological conditions, mothers were asked if they had ever received a diagnosis of PCOS or excessive body hair (hirsutism). If they had received a diagnosis, they specified if the condition was diagnosed but not treated, treated with medication only, or treated with surgery. In addition, we obtained information from birth certificates on the child's sex and plurality, as well as maternal pre-pregnancy height and weight.

Follow-up study—When the children were 7 years old, participants were invited to participate in the Upstate KIDS Follow-Up Study. Mothers completed annual questionnaires pertaining to their children's development. When the children were an average of 7 and 8 years old, mothers reported if their children had ever been diagnosed with attention-deficit disorder (ADD) or ADHD, anxiety, or conduct disorder, and if the child was taking medications for ADD/ADHD or anxiety. In addition, mothers rated their children's behavior with the Strengths and Difficulties Questionnaire (SDQ) (17) at 7 years and a modified version of the Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) (18) at 8 years.

The use of the SDQ in this population has been detailed previously (19). In brief, the SDQ is a validated and reliable questionnaire (17) designed to measure children's behavior in the five domains of emotional symptoms, peer relationship problems, conduct problems, hyperactivity/inattention, and prosocial behaviors. The SDQ consists of 25 statements that mothers rate as not true (0 points), somewhat true (1 point), or certainly true (2 points). From the mother's responses, we obtained domain-specific scores by summing the scores from the five questions pertaining to each behavior domain. To identify children with borderline behavioral problems, we utilized cutoff points recommended by the SDQ developer (emotional symptoms ≥4, peer relationship problems ≥3, conduct problems ≥3, hyperactivity/inattention ≥6, and prosocial behaviors ≤5) (20). In a nationally representative sample in the United States (US), the subscale cutoff points have good specificity (71–91%) and adequate sensitivity (31–85%) (21).

When the children were approximately 8 years old, mothers completed a modified version of the VADPRS, a validated and reliable questionnaire used in the US to measure symptoms related to ADHD (18, 22, 23). The VADPRS consists of 45 statements on children's behavioral symptoms and eight statements on school performance and interpersonal relationships. Of the 45 behavioral statements, nine correspond to DSM-IV behaviors for predominately inattentive subtype of ADHD and nine to the hyperactive/impulsive subtype.

Mothers rated how frequently their children have exhibited each behavior on a 4-point scale (never, occasionally, often, or very often). Mothers then rated their children's scholastic and interpersonal performance on a 5-point scale (excellent, above average, average, somewhat of a problem, or problematic). The VADPRS was scored using the National Institute for Children's Health Quality's criteria (24). To meet criteria for screening for the predominately inattentive or hyperactive/impulsive subtype scales, children must have scored "somewhat of a problem" or "problematic" on any of the eight performance items and "often" or "very often" on at least six behavioral items. To meet criteria to screen for ADHD, a child must screen positive for both the predominately inattentive and hyperactive/impulsive subtype scales.

Data analysis

Exposures assessment—The primary exposures of interest were maternal report of diagnosis of PCOS or hirsutism. To investigate if treatment status impacted the associations between maternal PCOS and child behavior, we also examined treated PCOS (with medication or surgery) and untreated PCOS as separate exposures.

Outcome assessment—Mothers of 1386 children (966 singletons, 420 twins) completed the SDQ at 7 years old and mothers of 1484 children (1067 singletons, 417 twins) responded to the VADPRS at 8 years; mothers of 1915 children (1333 singletons, 582 twins) reported on their child's diagnosis of ADHD, anxiety, or conduct disorder or medication status at either time. We first considered maternal reported diagnosis of ADHD, anxiety, or conduct disorder as outcomes. Diagnosis of ADHD or anxiety was defined by reported diagnosis or use of medications prescribed for that condition at either 7 or 8 years. We also considered children who screened positive with the VADPRS or had ADHD diagnosis as screening for ADHD; children with a positive VADPRS screen were not analyzed as a separate group due to small numbers. We chose not to use the hyperactivity-inattention index of the SDQ to determine ADHD risk as the instrument did not reflect DSM criteria by also accounting for children's performance. Diagnosis of conduct disorder was defined as maternal report of diagnosis. Finally, we considered the subscale borderline behavioral problems defined by the SDQ as behavioral outcomes.

Statistical analysis—Comparisons of participant characteristics by exposure or inclusion status were conducted within a primary cohort of singletons and one randomly selected twin. We first compared participant characteristics according to maternal PCOS and hirsutism status with those of all participants in the primary cohort. Similarly, characteristics of mothers with any annual questionnaire data (n=1651, 33.1%) were compared with those of all mothers at baseline (n=4989).

All singletons and twin pairs were included in multivariable analysis. We estimated risk ratios (RR) and 95% confidence intervals (CI) for dichotomous endpoints using Poisson regression. These analyses were conducted using generalized estimated equations with robust standard errors to account for the correlation among twins. For all multivariable analyses, we imputed missing covariate and exposure information by generating 50 imputed datasets. Among the 1915 children with outcome data at either assessment, mothers of 39 children were missing information on PCOS and hirsutism (2.04%). Covariates with missing data included maternal marital status (3.03%), history of affective disorder (1.78%), smoking during pregnancy (0.16%), body mass index (BMI) (0.05%), and paternal age (5.43%), history of affective disorders (1.78%), and BMI (9.09%). To account for non-response to the follow-up questionnaires, we used inverse probability weighting (IPW). IPW weights were calculated from a multivariable logistic regression model where the outcome was responding to any behavior questions on the 7 year questionnaire for the SDQ (n=1386) or the 7 or 8 year questionnaire for the maternal report of diagnosis or ADHD screening (n=1915). Covariates in the logistic regression model were maternal age, race/ethnicity, education, insurance status, marital status, history of affective disorder, smoking and drinking during pregnancy, BMI, report of gynecological medical conditions; paternal age, history of affective disorder, and BMI; and child sex, plurality, conception using fertility treatment, and parity. Although fertility treatment and parity were included when constructing IPW weights, they were not considered as covariates in the main models as they are likely consequences of PCOS or hirsutism (3) and thus may be mediators on the causal pathway. Adjustment for mediators does not reveal the direct effect of an exposure (e.g., PCOS) on an outcome (e.g., child behavior) and can introduce bias (25, 26).

For the associations of maternal PCOS and hirsutism, we first present an unadjusted model. Model 1 was adjusted for maternal age, race, education, insurance, marital/cohabitation status, and smoking during pregnancy. Model 2 was additionally adjusted for maternal BMI and parental history of affective disorders. Since there is evidence of a bidirectional association between maternal PCOS and BMI or affective disorders (3), we presented these results in a separate model. Finally, Model 3 was additionally adjusted for child's sex to increase statistical efficiency. In supplemental analyses, we examined the relations of PCOS with child behavioral problems separately among women with PCOS who report hirsutism and women with PCOS who do not report hirsutism.

Since maternal PCOS was self-reported, we conducted a sensitivity analysis to assess the robustness of our findings to misclassification. Four different scenarios were simulated, two representing a lower prevalence of PCOS, i.e., overreporting, (7 and 9.5%) and two representing a higher prevalence (14.5 and 17%). For each scenario, we generated 1000 datasets, then calculated the unadjusted and fully adjusted RR in each dataset. We then compared the association based on the observed prevalence in the study with the estimated associations of the 1000 simulated samples for each of the four misclassification errors.

All analysis was conducted with SAS version 9.4 (SAS Institute Inc.).

RESULTS

Prevalence of PCOS and hirsutism was 12.0% and 3.9%, respectively. Twenty-seven percent of women with PCOS had hirsutism and 84% of women with hirsutism had PCOS. Maternal socioeconomic status (SES) markers, and parental weight status were positively associated with PCOS and hirsutism. In addition, maternal history of affective disorders was positively related to hirsutism (Table 1). Compared with all mothers at baseline, mothers who responded to the questionnaires when their child was 7–8 years old were older, had higher SES, were more likely to report a diagnosis of PCOS (Supplemental Table 1).

Maternal PCOS.

In unadjusted analysis, maternal PCOS was positively associated with anxiety disorder diagnosis and borderline emotional symptoms in children (Table 2). Associations were strengthened after adjustment for SES markers, then attenuated upon adjustment for parental history of affective disorders and maternal BMI. After full adjustment (Model 3), children born to mothers with PCOS had higher risk of anxiety disorder diagnosis (adjusted risk ratio [aRR] 1.62, 95% CI 1.02–2.57) and borderline emotional symptoms (1.66, 1.18–2.33) compared with children born to mothers with no reported PCOS. In a sensitivity analysis, the association between maternal PCOS and child anxiety disorder diagnosis was relatively robust to misclassification (Supplemental Figure 1). The relations between PCOS and offspring anxiety disorder diagnosis were similar between women reporting PCOS with and without hirsutism. However, the associations between PCOS and ADHD were stronger among women with PCOS and hirsutism (Supplemental Tables 2 **and** 3). Associations of maternal PCOS with offspring ADHD were positive but not statistically significant.

In most instances, maternal treatment for PCOS did not appear to modify the associations with behavioral problems (Supplemental Table 4). There were suggestive differences in effect estimates for conduct disorder, and borderline emotional symptoms and prosocial problems by treatment status, but confidence intervals generally overlap. For example, children of mothers with untreated PCOS had a higher risk of conduct disorder diagnosis ($aRR_{untreated}$ 2.33, 1.23–4.42; $aRR_{treated}$ 1.18, 0.55–2.53) and borderline prosocial problems ($aRR_{untreated}$ 2.33, 1.24–4.39; $aRR_{treated}$ 0.41, 0.14–1.21) compared with children of mothers with no PCOS while the risk of borderline emotional symptoms was higher in children of mothers with treated PCOS ($aRR_{untreated}$ 1.18, 0.64–2.18; $aRR_{treated}$ 1.96, 1.34–2.87).

Maternal hirsutism.

Maternal hirsutism was positively associated with ADHD diagnosis in children and borderline emotional symptoms and conduct problems in unadjusted analysis (Table 3). After adjustment for covariates (Model 3), maternal hirsutism was related to children's ADHD and conduct disorder diagnosis (2.33, 1.28–4.24 and 2.54, 1.18–5.47, respectively), and ADHD screening (2.17, 1.21–3.90). In addition, compared with mothers with no hirsutism, children of mothers with hirsutism had higher risk of borderline emotional symptoms (2.61, 1.69–4.05), peer relationship problems (1.92, 1.16–3.17), and conduct problems (2.22, 1.30–3.79).

DISCUSSION

In this prospective birth cohort of mothers and children in upstate New York, maternal PCOS and hirsutism were associated with behavioral problems and mental disorders at 7 or 8 years in offspring. Maternal PCOS was associated with offspring anxiety and emotional symptoms on the SDQ, though the associations with emotional symptoms may be driven by women reporting both PCOS and hirsutism. Hirsutism was related to offspring ADHD and conduct disorder as well as SDQ emotional symptoms, peer relationship problems, and conduct problems. These associations were independent of parental socioeconomic indicators and history of affective disorders, maternal weight status, and child's sex.

An association between maternal PCOS and offspring anxiety has not been previously reported. One previous study found a relation between maternal PCOS and offspring hospitalization for psychological development (27). Abnormal psychological development can include affective, developmental, and psychotic disorders; therefore, their results may not be comparable with ours. Two European registry linkage studies with thousands of children (10, 14) found a positive association between maternal PCOS and offspring ADHD. Although we did not find a statistically significant association between PCOS and ADHD, our point estimate (aRR=1.34) is similar to the point estimates from these studies (aOR=1.42 (14) and 1.34 (10)), which also controlled for socioeconomic indicators and maternal history of affective disorders. These large studies, however, did not evaluate other behavioral outcomes and our study adds evidence to the broader potential intergenerational impact of maternal PCOS on offspring mental health.

Maternal PCOS is associated with higher circulating androgens and inflammatory cytokines, which may influence the fetal brain development. In rodent models, a maternal PCOS-like phenotype has been related to more anxiety-like behavior (5, 6) and less sociability (28) in offspring. In the amygdala, elevated maternal androgens alter androgen and serotonin receptor expression in female rodents, as well as GABA receptor expression in both sexes (5). Further, corticotropin-releasing hormone and its receptors are altered in the hypothalamus (6). These areas of the brain are associated with regulation of mood and response to stress. Excess inflammation associated with PCOS may also relate to the development of anxiety; in rodent models, chronic and acute inflammation result in more anxiety-like behavior in offspring as well as more activated microglia in the hippocampus (7, 8). Another potential mechanism is through infertility treatment. Women with PCOS are more likely to use fertility treatments, which have been hypothesized to independently relate to child behavioral problems (29, 30).

Metformin, a common treatment for PCOS, may be continued into pregnancy. Metformin increases fetal concentration of sex hormone binding globulin (SHBG) when taken in pregnancy (31) and reduces secretion of inflammatory cytokines from trophoblast cells *in vitro* (32). This may mitigate metabolic irregularities in women with PCOS during pregnancy. However, we did not see consistent differences in the associations between treated and untreated maternal PCOS and offspring behavior. Lack of consistency in these results may reflect the small number of children with behavioral problems or disorders in each group. Alternatively, these varying results could indicate heterogenous treatment regimens or a discontinuation of treatment during pregnancy. For example, oral contraceptives are also commonly prescribed to treat PCOS and would be discontinued prior to attempted pregnancy. We did not have information on which medications women were taking or use during pregnancy, and therefore are not able to investigate these associations further.

Approximately one-third of women with PCOS had hirsutism. Maternal hirsutism was related to offspring ADHD and conduct disorder, as well as borderline emotional symptoms, peer relationship problems, and conduct problems on the SDQ. One previous study found an association between maternal hirsutism and offspring ASD (11). PCOS with hirsutism is often conceptualized as a subtype of PCOS indicative of high androgens. However, hirsutism develops from an interaction between androgens and the sensitivity of the women's hair follicle to androgens (33), and can therefore be present in women with low androgens. Indeed, a recent meta-analysis among women with PCOS found that Ferriman-Gallwey scores, the "gold standard" diagnosis for hirsutism, were positively related to the testosterone and estrogen precursors androstenedione and dehydroepiandrosterone sulfate, but not to other biochemical markers of hyperandrogenism (34). Given this, further evidence is needed to test if the associations seen here between maternal hirsutism and offspring behavioral problems and disorders are mediated by elevated androgens. Replication of these findings in a prospective cohort which uses Ferriman-Gallwey scores or clinical diagnosis to identify hirsutism is necessary as well.

This study has several strengths. Upstate KIDS is a well characterized, prospective birth cohort with information collected on socioeconomic and health indicators. As such, we were

able to control for many potential confounders. Child behavior was measured by maternal report of child diagnosis, the SDQ, and the VADPRS. Use of multiple indicators allowed us to compare associations across different outcome measures to see if the results are consistent.

There are limitations as well. Foremost, diagnosis of maternal gynecological conditions is self-reported. The prevalence of hirsutism among women with PCOS is low in our study, which may be indicative of misclassification of PCOS and/or hirsutism. Although self-report is likely to have high specificity, there may be low sensitivity since women with the condition may not remember their diagnosis; indeed, in a Dutch population the sensitivity and specificity of ovarian factors related to infertility, including ovarian disorders, PCOS, and premature ovarian failure, among others, were 65% and 88%, respectively (35). As such, we addressed the potential impact of measurement error in self-reported diagnoses through a sensitivity analysis which indicated our findings were robust to misclassification. Further, multiple diagnostic criteria were likely used to diagnose women with PCOS in our sample which may result in non-overlapping phenotypes among women who report having PCOS. Mother's report of child behavioral diagnoses may be influenced by recall bias. In addition, non-response to follow-up questionnaires was large. We used IPW to attempt to account for this non-response. We also performed multiple imputations of the exposures and covariates with the assumption that data were missing at random. Finally, generalizability is limited since our sample is primarily Caucasian.

In conclusion, we report here novel associations of maternal PCOS with offspring anxiety, and hirsutism with various offspring behavioral problems and mental disorders. Our findings are limited by self-report of PCOS and hirsutism and, until replication in a study with clinical diagnosis of these conditions, should be interpreted with caution. Treatment for PCOS did not appear to have a consistent effect on offspring behavioral outcomes; however, we were unable to ascertain treatment regimens during pregnancy. Future studies are needed primarily to replicate these findings in well-characterized prospective cohorts which assessed maternal diagnosis of PCOS and/or hirsutism using medical records, and secondarily to explore the role of maternal androgens and inflammatory cytokines during pregnancy, clarify the impact of medication use during pregnancy on child behavior among women with PCOS, and determine if this association varies by diagnostic criteria used to diagnosis PCOS. If replicated, our findings suggest that children of mothers with PCOS should be monitored for the development of behavioral problems to quickly mitigate their potential impact with behavioral or pharmaceutical treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant characteristics according to maternal PCOS[a] and hirsutism status among all singletons and one randomly selected twin of each pair

Sociodemographic characteristics	All	PCOS	Hirsutism
Overall, *n* (%)	1651 (100)	194 (11.8)	63 (3.8)
Maternal Characteristics			
Age, year, mean ± SD	31.3 ± 5.9	31.5 ± 4.7	32.2 ± 4.5
Non-Hispanic white, *n* (%)	1412 (85.5)	168 (86.6)	57 (90.5)
Education, *n* (%)			
Less than high school	53 (3.2)	1 (0.5)	0 (0.0)
High school or GED equivalent	158 (9.6)	11 (5.7)	4 (6.3)
Some college	421 (25.5)	60 (30.9)	21 (33.3)
College	414 (25.1)	55 (28.4)	18 (28.6)
Advanced degree	605 (36.6)	67 (34.5)	20 (31.7)
Private insurance, *n* (%)	1354 (82.0)	175 (90.2)	56 (88.9)
Married or living as married, *n* (%)	1468 (91.4)	184 (95.3)	59 (93.7)
History of affective disorder, *n* (%)	288 (17.7)	43 (22.2)	19 (30.2)
Smoking during pregnancy, *n* (%)	162 (9.8)	14 (7.2)	3 (4.8)
BMI, kg/m^2, mean ± SD	26.9 ± 7.0	30.4 ± 8.2	32.2 ± 8.7
Paternal characteristics			
Age, year, mean ± SD	33.6 ± 6.7	33.4 ± 5.5	34.1 ± 5.4
History of affective disorder, *n* (%)	127 (7.8)	16 (8.2)	6 (9.5)
BMI, kg/m^2, mean ± SD	28.3 ± 5.5	30.4 ± 6.1	31.5 ± 6.5
Child characteristics			
Child sex, male, *n* (%)	876 (53.1)	100 (51.5)	29 (46.0)
Maternal reported diagnosis			
ADHD, *n* (%)	148 (9.1)	22 (11.7)	11 (19.0)
Anxiety, *n* (%)	125 (7.7)	23 (12.2)	7 (12.1)
Conduct disorder, *n* (%)	99 (6.1)	15 (8.0)	8 (13.8)
Maternal reported diagnosis or screen on VADPRS			
ADHD, *n* (%)	164 (10.1)	24 (12.8)	11 (19.0)
Borderline behavioral problems, SDQ			
Emotional symptoms, *n* (%)	167 (14.1)	31 (21.2)	17 (37.8)
Peer relationship problems, *n* (%)	185 (15.7)	25 (17.1)	12 (26.7)
Conduct problems, *n* (%)	172 (14.6)	21 (14.4)	12 (26.7)
Hyperactivity/inattention, *n* (%)	188 (15.9)	29 (19.9)	11 (24.4)
Prosocial problems, *n* (%)	73 (6.2)	12 (8.2)	3 (6.7)

[a]ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; PCOS, polycystic ovary syndrome; SDQ, Strengths and Difficulties Questionnaire; VADPRS, Vanderbilt ADHD Diagnostic Parent Rating Scale

Table 2.

Childhood behavioral problems and disorders according to maternal polycystic ovary syndrome (PCOS) status in the Upstate KIDS Study

	n	*n, cases*	Reference	Unadjusted RR (95% CI)[a]	Model 1 RR (95% CI)[b]	Model 2 RR (95% CI)	Model 3 RR (95% CI)
Maternal reported diagnosis							
ADHD[c]	1906	173	1	1.25 (0.77, 2.04)	1.56 (1.00, 2.44)	1.33 (0.84, 2.09)	1.34 (0.86, 2.09)
Anxiety	1909	139	1	1.67 (1.05, 2.64)	1.87 (1.18, 2.97)	1.63 (1.02, 2.59)	1.62 (1.02, 2.57)
Conduct disorder	1905	116	1	1.29 (0.71, 2.35)	1.90 (1.10, 3.30)	1.59 (0.92, 2.75)	1.64 (0.96, 2.79)
Maternal reported diagnosis or screen on VADPRS							
ADHD	1915	193	1	1.18 (0.75, 1.86)	1.52 (1.00, 2.32)	1.31 (0.86, 2.01)	1.33 (0.87, 2.03)
Borderline behavioral problems, SDQ							
Emotional symptoms	1386	193	1	1.61 (1.14, 2.28)	1.89 (1.33, 2.68)	1.68 (1.19, 2.36)	1.66 (1.18, 2.33)
Peer relationship problems	1386	211	1	0.95 (0.63, 1.44)	1.15 (0.76, 1.72)	1.08 (0.72, 1.62)	1.08 (0.72, 1.62)
Conduct problems	1386	201	1	0.98 (0.66, 1.47)	1.17 (0.79, 1.74)	1.11 (0.74, 1.66)	1.10 (0.73, 1.66)
Hyperactivity/inattention	1386	214	1	1.23 (0.85, 1.76)	1.40 (0.98, 2.02)	1.24 (0.85, 1.82)	1.22 (0.83, 1.81)
Prosocial problems	1386	86	1	1.21 (0.66, 2.23)	1.35 (0.75, 2.43)	1.21 (0.67, 2.21)	1.18 (0.64, 2.18)

[a] Values are risk ratios and their 95% confidence intervals from a Poisson regression model.

[b] Model 1 is adjusted for maternal age, race, education, insurance status, marital status, smoking, and father's age difference; Model 2 is additionally adjusted for maternal and paternal history of affective disorder and maternal body mass index; and Model 3 is additionally adjusted for child's sex.

[c] ADHD, attention-deficit/hyperactivity disorder; VADPRS, Vanderbilt ADHD Diagnostic Parent Rating Scale; and SDQ, Strengths and Difficulties Questionnaire

Table 3.

Childhood behavioral problems and disorders according to maternal hirsutism status in the Upstate KIDS Study

	n	*n, cases*	Reference	Unadjusted RR (95% CI)[a]	Model 1 RR (95% CI)[b]	Model 2 RR (95% CI)	Model 3 RR (95% CI)
Maternal reported diagnosis							
ADHD[c]	1906	173	1	2.12 (1.08, 4.16)	2.53 (1.40, 4.59)	2.06 (1.11, 3.81)	2.33 (1.28, 4.24)
Anxiety	1909	139	1	1.45 (0.63, 3.38)	1.59 (0.68, 3.72)	1.28 (0.55, 2.94)	1.30 (0.56, 3.01)
Conduct disorder	1905	116	1	2.15 (0.90, 5.14)	2.74 (1.26, 5.97)	2.18 (1.00, 4.75)	2.54 (1.18, 5.47)
Maternal reported diagnosis or screen on VADPRS							
ADHD	1915	193	1	1.88 (0.99, 3.57)	2.31 (1.29, 4.16)	1.91 (1.04, 3.50)	2.17 (1.21, 3.90)
Borderline behavioral problems, SDQ							
Emotional symptoms	1386	193	1	2.86 (1.90, 4.28)	3.42 (2.33, 5.01)	2.72 (1.75, 4.23)	2.61 (1.69, 4.05)
Peer relationship problems	1386	211	1	1.71 (0.94, 3.10)	1.98 (1.22, 3.21)	1.81 (1.10, 2.97)	1.92 (1.16, 3.17)
Conduct problems	1386	201	1	1.86 (1.10, 3.12)	2.25 (1.40, 3.62)	2.06 (1.22, 3.48)	2.22 (1.30, 3.79)
Hyperactivity/inattention	1386	214	1	1.48 (0.87, 2.52)	1.66 (0.97, 2.84)	1.34 (0.74, 2.43)	1.46 (0.81, 2.64)
Prosocial problems	1386	86	1	1.11 (0.42, 2.93)	1.23 (0.47, 3.28)	1.01 (0.37, 2.70)	1.08 (0.42, 2.83)

[a] Values are risk ratios (RR) and their 95% confidence intervals from a Poisson regression model.

[b] Model 1 is adjusted for maternal age, race, education, insurance status, marital status, smoking, and father's age difference; Model 2 is additionally adjusted for maternal and paternal history of affective disorder and maternal body mass index; and Model 3 is additionally adjusted for child's sex.

[c] ADHD, attention-deficit/hyperactivity disorder; VADPRS, Vanderbilt ADHD Diagnostic Parent Rating Scale; and SDQ, Strengths and Difficulties Questionnaire