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Maternal Polycystic Ovary Syndrome and Risk for Attention-Deficit/Hyperactivity Disorder in the Offspring

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder, and boys are two to three times more likely to develop ADHD. Maternal polycystic ovary syndrome (PCOS), a common metabolic disorder associated with excess circulating androgens, has been associated with increased risk for autism spectrum disorder in the offspring. In this study, we aimed to investigate whether maternal PCOS increases the risk for ADHD in the offspring.

METHODS: We conducted a matched case-control study using health and population data registers for all children born in Sweden from 1984 to 2008. Maternal PCOS was defined by ICD-coded register diagnosis. The outcome of ADHD was defined as an ICD-coded register diagnosis of ADHD and/or registered prescription of medications to treat ADHD. A total of 58,912 ADHD cases (68.8% male) were identified and matched to 499,998 unaffected controls by sex and birth month and year.

RESULTS: Maternal PCOS increased the odds of offspring ADHD by 42% after adjustment for confounders (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.26–1.58). Exclusion of ADHD cases with comorbid autism spectrum disorder attenuated but did not explain the relationship (OR, 1.34; 95% CI, 1.18–1.52). The risk was somewhat elevated for ADHD with comorbid autism spectrum disorder (OR, 1.76; 95% CI, 1.37–2.26). The risk for ADHD was higher among obese mothers with PCOS (OR, 1.68; 95% CI, 1.31–2.17) and was highest among obese mothers with PCOS and other features of metabolic syndrome (OR, 2.59; 95% CI, 1.02–6.58).

CONCLUSIONS: This study provides evidence that maternal PCOS may subtly influence the neurodevelopment of the offspring, resulting in increased risk for neurodevelopmental disorders such as ADHD.

Keywords: Attention-deficit disorder with hyperactivity, Autism spectrum disorder, Comorbidity, Epidemiology, Matched case-control study, Polycystic ovary syndrome, Prospective study

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Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder in childhood, with a prevalence of 4% to 12%, though symptoms often persist into adulthood (1–3). Though there is a substantial genetic component to ADHD risk, multiple environmental factors and gene–environment interactions have been identified (4–6). ADHD is a sexually dimorphic condition, with boys being two to three times more likely to receive a diagnosis (7). Sex hormones can modify brain development (8) and may explain the male-skewed risk for certain neurodevelopmental disorders. Brain regions involved in ADHD, such as the hippocampus, prefrontal cortex, striatum, and amygdala, are influenced by sex hormone signaling during development (9,10). ADHD often co-occurs with autism spectrum disorder (ASD), another male-skewed disorder, and the two conditions may share causal pathways (11). Although increased exposure to prenatal androgens has been noted in ASD (12), the relationship between prenatal hormones and ADHD risk has not been explored.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age, affecting 5% to 15% of women and characterized by hyperandrogenism, ovarian dysfunction, and polycystic ovarian morphology (13). The causes of PCOS are not clear, but there is evidence for a genetic susceptibility to the disorder (14). Some studies support an interaction between genetic susceptibility and the influence of maternal environment, including in utero exposure to excess androgens, in the etiology of PCOS (15,16). Furthermore, weight gain and obesity are of importance for the development of PCOS. Obesity is closely related to the hyperinsulinemia that enhances hyperandrogenemia in women with PCOS (17). Hyperandrogenism in turn contributes to the adiposity, insulin resistance, and hyperinsulinemia that are common in PCOS (13,18). PCOS often emerges during puberty, but it may also develop later in reproductive years, for instance, as a result of weight gain (13,19). Maternal PCOS is a potential source of excess androgen exposure for the

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fetus (20,21). Maternal diagnosis of PCOS is associated with increased risk for ASD in the offspring, particularly in obese mothers (22). We hypothesized that maternal PCOS may also influence the offspring's risk for ADHD.

Here, we test this hypothesis by examining the relationship between maternal diagnosis of PCOS and risk for clinically diagnosed ADHD in the offspring in a Swedish nationwide case-control study using prospectively collected health register data. We explored whether high levels of comorbidity between ADHD and ASD could explain this relationship.

METHODS AND MATERIALS

Study Population

We used similar methods for the population selection and statistical methods as in our recent study that examined the relationship between maternal diagnosis of PCOS and risk for offspring ASD (22). All data are derived from linkages held by Statistics Sweden and the National Board of Health and Welfare, containing routinely collected health and sociodemographic data on the entire population of Sweden and cross-linked by each resident's unique national registration number (23). The eligible study population consisted of all individuals born in Sweden from 1984 to 2011 and followed until December 31, 2011. We matched all cases of ADHD (see below) in the study population with up to 10 living controls who were without an ADHD diagnosis at the end of the follow-up period. Controls were matched by sex and birth month and year. After exclusion of children not born in Sweden, born after 2008, from a multiple birth, adopted, and those with missing covariate data (Figure 1), the final sample consisted of 58,912 ADHD cases matched to 499,998 controls, with a case to control ratio between 1:2 and 1:10. This study was approved by the regional ethical review board at Karolinska Institutet. Informed consent was not required for the analysis of anonymized register data.

ADHD Case Ascertainment

We used a previously validated two-step approach for identifying cases of ADHD (24). First, ADHD case status as of December 31, 2011, was defined as a recorded diagnosis of ICD-10 code F90 or ICD-9 code 314 within the National Patient Register (NPR). The NPR provides data on inpatient care since 1973 and outpatient specialist physician care since 2001. The coverage of the NPR is approximately 99% of all somatic discharge diagnoses, and the validity of the diagnoses is generally high (25). As a second step, we searched the Prescribed Drug Register (PDR) for anyone recorded as receiving prescriptions for ADHD medications (methylphenidate [Anatomical Therapeutic Chemical (ATC) Classification System code N06BA04] or atomoxetin [ATC code N06BA09]). The PDR contains data on medications dispensed to the entire population in Sweden since July 1, 2005. Receipt of a prescription for ADHD medications is a useful proxy for an ADHD diagnosis because Swedish medical guidelines mandate that ADHD medications should only be prescribed by a psychiatric specialist and after other (nonpharmacological) interventions have failed.

Exposure

Maternal PCOS status was classified according to any lifetime recorded diagnosis (ICD-8 code 256.90, ICD-9 code 256E, and ICD-10 code E28.2) within the NPR, supplemented by diagnoses in the Medical Birth Register (MBR). The MBR includes information on pregnancy, delivery, and the neonatal period for approximately 98% of births in Sweden since 1973. We used lifetime diagnoses of PCOS as the exposure because PCOS is a longitudinal disorder with hormonal and metabolic manifestations through the life span (26,27).

Covariates

Covariates were identified a priori as potential confounding factors and/or risk factors for ADHD. Maternal and paternal ages at the time of birth were categorized as $<$25, 25 to 29, 30 to 34, 35 to 39, and $\geq$40 years. Data on family income after deduction of taxes were obtained from the Integrated Database for Labor Market Research, adjusted for family size, and categorized into quintiles according to birth year. The highest education of either parent at the time of birth was classified as years of completed formal education ($\leq$9, 10–12, or $\geq$13 years). Parental history of psychiatric inpatient and outpatient treatment before the birth of the index child (yes/no) was defined as any psychiatric diagnosis (chapter V of ICD-8 and ICD-9 or chapter F of ICD-10) recorded in the NPR. Maternal migrant status was categorized as born in Sweden or not.

We explored whether obstetric complications influenced the findings of our main analysis due to reports of increased obstetric complications in mothers with PCOS (28) and associations of obstetric complications with ADHD (29). Apgar score at 5 minutes was categorized as $<$7 or $\geq$7 and supplemented by Apgar score at 1 minute when data on Apgar score at 5 minutes were not available. Size for gestational age was categorized as small for gestational age or not. Preterm birth was categorized as $<$37 weeks or not. Preeclampsia was classified according to ICD-8 codes 637.03 to 637.04 and 637.09 to 637.10, ICD-9 codes 642E to 642H, and ICD-10 codes O14 to O15 for diagnoses recorded within the MBR or in the NPR during the 9 months before and 1 month after birth of the index child. Birth order was categorized as first born or not according to the MBR.

Obesity and other features of metabolic syndrome are common in PCOS and are related to more severe hyperandrogenemia in women with PCOS (30,31). Furthermore, elevated maternal body mass index (BMI) has been associated with risk for ADHD (32). Thus, we explored the influence of prepregnancy BMI and metabolic syndrome on the relationship between maternal PCOS and offspring ADHD.

To calculate maternal baseline BMI (in kg/m^2), we used weight and height data recorded at the first visit to a maternal health clinic (33). Data were available on 71% of the mother-child pairs in our analytical sample (Figure 1). Maternal baseline BMI was categorized by standard convention (34): underweight (BMI $<$ 18.5 kg/m^2), normal (18.5 $\leq$ BMI $<$ 25 kg/m^2), overweight (25 $\leq$ BMI $<$ 30 kg/m^2), and obese (BMI $\geq$ 30 kg/m^2). Mothers were classified as having a prior diagnosis of diabetes mellitus according to the codes ICD-8 250; ICD-9 250, 648A, and 790C; and ICD-10 E10 to E11 and O24.0 to O24.1 if at least one diagnosis was recorded prior to and

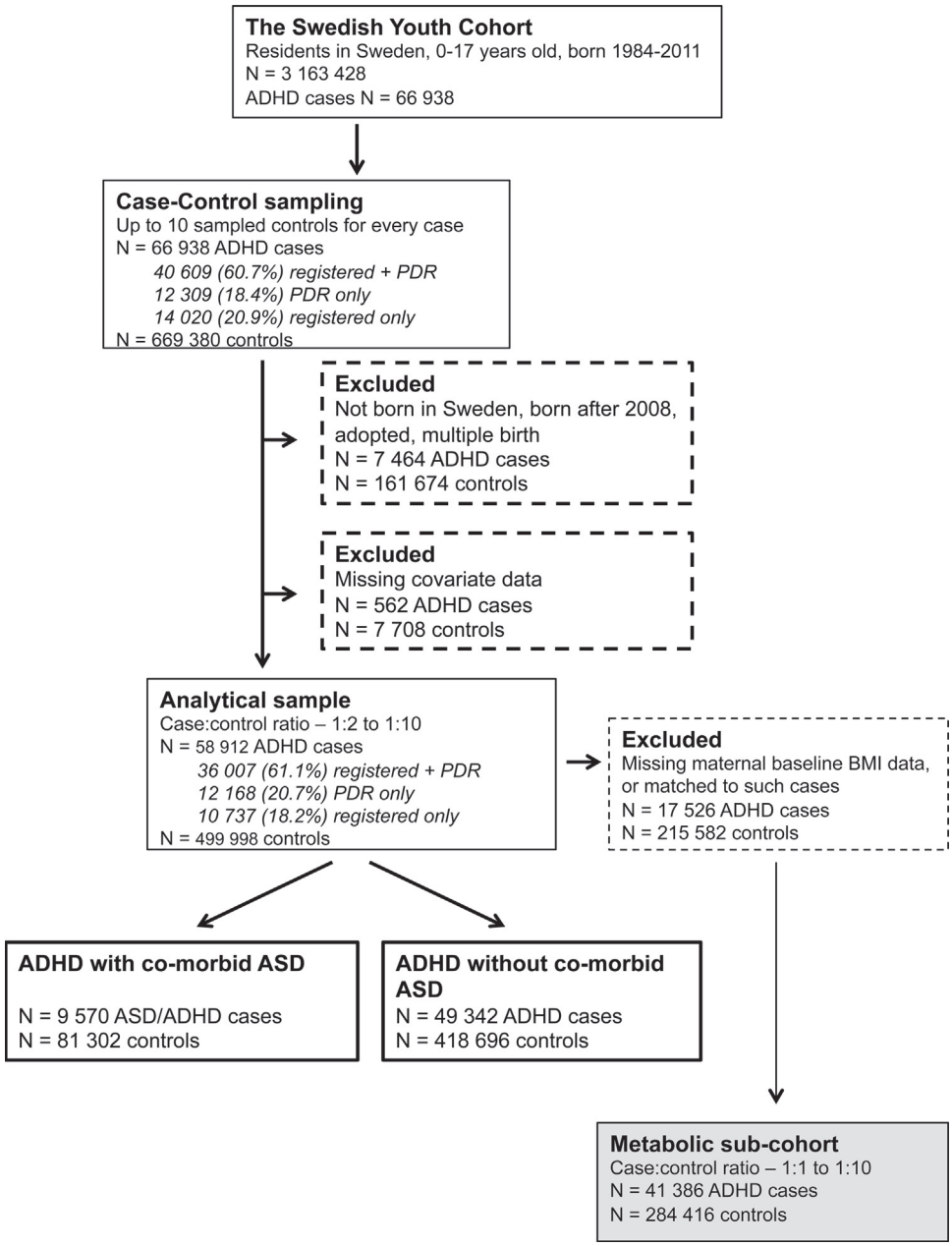

Figure 1. Derivation of the Swedish Youth Cohort analytical sample. Cases classified as to whether identification occurred through a registered ICD diagnosis, through the Prescribed Drug Register (PDR), or both. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index.

including the birth year of the index child (in the NPR or MBR). Type 1 and type 2 diabetes were grouped together because these distinctions were not recorded before the use of ICD-10 coding. A similar strategy was used to identify essential hypertension using the following ICD codes: ICD-8 400 to 404; ICD-9 401 to 404 and 642A to 642C; and ICD-10 I10 to I13 and O10 to O11.

Women with PCOS more often use fertility treatments (13). Information on fertility treatment, including in vitro fertilization, intracytoplasmic injection, ovulation induction, or other treatment, was available in the MBR from 1995 onward.

Medications such as valproate (ATC code N03AG01) and antipsychotics (ATC code N05A) are reported to induce features of PCOS in women (35,36). Use of these medications during pregnancy has been associated with neurodevelopmental disorders in the offspring (37). Pharmacological interventions for mothers with PCOS, such as spironolactone (ATC code C03DA01) and metformin (ATC code A10BA02), might lower androgen and insulin levels and attenuate risk for ADHD (38,39). Information on mothers' medication during pregnancy was available in the PDR from 2005 onward.

Statistical Analysis

Analyses were performed using SPSS, version 20 (IBM Corp., Armonk, NY). Conditional logistic regression was used to

Table 1. Selected Characteristics of Birth Cohorts From 1984 to 2008 in the Swedish Population

Characteristic	ADHD Cases, *n* (%) (*N* = 58,912)	Controls, *n* (%) (*N* = 499,998)	Analysis *p*[a]
ASD Diagnosis	9570 (16.2)	3970 (0.8)	<.001
Maternal PCOS	404 (0.7)	1937 (0.4)	<.001
Mother's Country of Birth			<.001
Sweden	52,411 (89)	425,919 (85.2)	
Other	6501 (11)	74,079 (14.8)	
Parental History of Psychiatric Care			
Mother	24,584 (41.7)	102,914 (20.6)	<.001
Father	18,280 (31)	78,691 (15.7)	<.001
Lowest Quintile for Family Income	10,403 (17.7)	78,936 (15.8)	<.001
Parents With ≤9 Years of Schooling	16,055 (27.3)	81,831 (16.4)	<.001
Born First	25,404 (43.1)	208,436 (41.7)	<.001
Preeclampsia	2320 (3.9)	15,931 (3.2)	<.001
Apgar Score <7 at 5 Minutes	753 (1.3)	4667 (0.9)	<.001
Missing data	426 (0.7)	3006 (0.6)	
Gestational Age			<.001
Preterm birth (<37 weeks)	4123 (7.0)	24,660 (4.9)	
Postterm birth (≥42 weeks)	4113 (7.0)	37,413 (7.5)	
Missing data	122 (0.2)	641 (0.1)	
Size for Gestational Age			<.001
Small for gestational age	2216 (3.8)	11,820(2.4)	
Large for gestational age	2211 (3.8)	17,716 (3.5)	
Missing data	326 (0.6)	2052 (0.4)	
Maternal BMI in Early Pregnancy			<.001
BMI < 18.5 kg/m^2	1651 (2.8)	13,378 (2.7)	
18.5 ≤ BMI < 25 kg/m^2	25,480 (43.3)	244,238 (48.8)	
25 ≤ BMI < 30 kg/m^2	9440 (16)	72,835 (14.6)	
BMI ≥ 30 kg/m^2	4815 (8.2)	24,895 (5)	
Missing data	17,526 (29.7)	144,652 (28.9)	
Parental Age at Delivery, Years	Mean (SD)	Mean (SD)	*p*[b]
Maternal	27.65 (5.43)	28.77 (5.06)	<.001
Paternal	30.71 (6.54)	31.65 (6.04)	<.001

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; PCOS, polycystic ovary syndrome.
[a]Case-control differences were tested using a χ^2 test.
[b]Case-control differences were tested using an independent-sample *t* test.

evaluate the association between maternal diagnosis with PCOS and offspring ADHD, first as an unadjusted estimate (model 1) and then in a model adjusted for maternal and paternal age, parental psychiatric history, parental income and education, birth order, and maternal country of birth (model 2). Mothers without PCOS were used as the referent group. To explore the influence of obstetric complications on the maternal PCOS–offspring ADHD relationship, we used a model additionally adjusted for the following obstetric factors: Apgar score, preterm birth, small for gestational age, and preeclampsia (model 3). Results were examined for the total analytical sample, in sex-stratified models, and in the metabolic subcohort (Figure 1). For the metabolic subcohort, we additionally adjusted for maternal BMI in early pregnancy (model 4).

Because ASD is often diagnosed with ADHD and maternal PCOS may increase the risk for ASD (22), we tested whether associations observed between maternal PCOS and offspring ADHD were driven by the comorbidity between the disorders by stratifying ADHD cases on the basis of comorbid ASD and their controls (Figure 1) and repeating the analysis of maternal PCOS (models 1–3).

Last, we tested for the effects of worsening cardiometabolic risk profiles among women with PCOS. We explored whether the risk for offspring ADHD was different among mothers with the following a priori defined mutually exclusive categories: no PCOS (referent), PCOS, PCOS with overweight, PCOS with obesity, and PCOS with obesity and indications of metabolic syndrome. Mothers without PCOS were used as the referent group (including women without PCOS but affected by overweight, obesity, diabetes, or essential hypertension).

Sensitivity Analyses

Because it is possible that cases ascertained by prescription drug records only may differ from cases with a recorded diagnosis, we excluded cases ascertained by PDR records only and repeated models 1 to 3.

PCOS increases the risk for infertility and fertility treatments might influence offspring health. Therefore, we repeated the analysis for children born after 1995 (27,194 cases, 227,324 controls), with further adjustment of model 2 for use of fertility treatment.

Because migrants to Sweden may experience differential access to care and thus may be less likely to receive diagnoses of ADHD or PCOS, we excluded all children with mothers born outside of Sweden and repeated models 1 to 3 for the remaining 52,411 cases and 379,071 controls.

Because information on mothers' medication use during pregnancy was available for only a subsample of children born in 2005 to 2008, we tabulated cases and controls exposed to maternal PCOS and valproate, antipsychotic, spironolactone, or metformin use during pregnancy without further analyses.

Finally, to assess whether more detailed information on parental psychiatric history influenced the relationship between maternal PCOS and offspring ADHD, model 2 was repeated including the following specific diagnoses in the mother and father: affective disorders (bipolar), nonaffective psychosis, ADHD, and other psychiatric diagnoses.

RESULTS

A higher proportion of mothers of ADHD cases had a diagnosis of PCOS compared with mothers of noncases (Table 1). ADHD cases were more likely to have younger parents, a mother born in Sweden, parental history of psychiatric care, lower household income, lower parental education, and obstetric complications and to be second born or later.

Maternal diagnosis of PCOS was associated with higher odds of ADHD in both unadjusted (model 1 odds ratio [OR], 1.75; 95% confidence interval [CI], 1.58–1.95) and adjusted (model 2 OR, 1.42; 95% CI, 1.26–1.58) models (Table 2). Further adjustment for obstetric complications did not substantially attenuate the OR for ADHD. Excluding cases of ADHD with comorbid ASD attenuated the associations between maternal PCOS and offspring ADHD (model 2 OR, 1.34; 95% CI, 1.18–1.52), and ORs were somewhat higher for ADHD with comorbid ASD (model 2 OR, 1.76; 95% CI, 1.37–2.26; Table 2). In sex-stratified analyses, ORs tended to be higher among girls compared with boys (Table 3).

Among mothers with PCOS, 1.8% were underweight, 39.1% were normal weight, 32.4% were overweight, and 26.7% were obese in early pregnancy. Corresponding proportions among mothers without PCOS were 3.7%, 67.7%, 20.9%, and 7.7%, respectively. Maternal PCOS was associated with higher odds of ADHD in the subset of women with BMI data; estimated ORs were similar compared with the entire study sample (Supplemental Table S1). The ORs were attenuated after adjustment for BMI (model 4 OR, 1.25; 95% CI, 1.09–1.43; Supplemental Table S1). In stratified analysis, we observed the highest odds of offspring ADHD among obese women with PCOS and symptoms of metabolic syndrome (Table 4). Trend analysis indicated that the odds of ADHD increased with worsening cardiometabolic profiles (Table 4).

In sensitivity analyses, excluding cases identified only by record of prescription of ADHD medication did not substantially change the OR (model 2 OR, 1.44; 95% CI, 1.27–1.63), nor did adjusting for fertility treatment (model 2 OR, 1.44; 95% CI, 1.25–1.65), excluding children with mothers born outside of Sweden (model 2 OR, 1.47; 95% CI, 1.3–1.67), or including detailed information on parental psychiatric history (model 2 OR, 1.41; 95% CI, 1.25–1.58). Last, of the 9492 children (955 cases, 8537 controls) born in 2005 to 2008 in the study population, no cases were exposed to maternal PCOS and maternal use of valproate, antipsychotics, or spironolactone during gestation. Three control individuals were exposed to both maternal PCOS and metformin; no control individuals were exposed to any of the other listed medications and maternal PCOS.

DISCUSSION

Maternal diagnosis of PCOS increased the risk for clinically diagnosed ADHD in the offspring even after adjustment for potential confounders. The increase in risk for ADHD remained after excluding cases with comorbid ASD, indicating that maternal PCOS increases the risk for ADHD independent of comorbidity between ADHD and ASD. Our results show that the risk for ADHD grew higher with worsening cardiometabolic profiles among mothers with PCOS, such that children of mothers affected by PCOS, obesity, and other features of metabolic syndrome had a greater than twofold increased risk for ADHD.

To our knowledge, no previous study has examined the relationship between maternal PCOS and offspring ADHD. PCOS is the leading cause of anovulatory infertility, and prior studies have found a relationship between fertility treatments, particularly ovulation induction, and offspring ADHD (40,41). Recent evidence suggests that the risk associated with fertility treatments originates from the underlying causes of infertility rather than the treatment itself (40).

Maternal PCOS increased the risk for ASD in a recent study (22), and our results indicate that ADHD is associated with maternal PCOS independent of comorbidity with ASD. Taken together, these results suggest that maternal PCOS may have broader detrimental effects on neurodevelopment. We hypothesize that these effects may be mediated by excess prenatal androgen exposure. Most women with PCOS have clinical hypernadrogenemia that is aggravated by obesity (42,43). During pregnancy, women with PCOS display increased circulating androgen levels (21). Placentas of women with PCOS show abnormal steroidogenesis and increased capacity for producing androgens (20). Newborns of women with PCOS have atypical levels of sex steroids, including elevated androgen levels (44,45).

Prenatal exposure to sex hormones may influence neurodevelopment and increase susceptibility for ADHD through a range of mechanisms. During neurodevelopment, steroids influence the formation of brain regions (9,10,46) and neurological processes, including the reward system, motor function, and spatial memory (46–48), that are impaired in ADHD. Fetal testosterone levels are linked to abnormal brain lateralization and reduced volume of the right hemisphere, as seen in ADHD (49–51). Fetal steroids influence neuronal spine density and synaptic plasticity that also appear aberrant in ADHD (52,53). Aberrations in brain dopaminergic activity, a major biological underpinning of ADHD, have been related to prenatal sex hormone exposure in animal models (54,55). Maternal polymorphisms in the sex steroid pathway have been

Table 2. ORs and 95% CIs of ADHD for Maternal PCOS in Birth Cohorts From 1984 to 2008 in the Swedish Population

	Any ADHD		ADHD With No ASD Comorbidity		ADHD With ASD Comorbidity	
	No PCOS	Maternal PCOS	No PCOS	Maternal PCOS	No PCOS	Maternal PCOS
Cases, *n* (%)	58,508 (99.3)	404 (0.7)	49,023 (99.4)	319 (0.6)	9485 (99.1)	85 (0.9)
Controls, *n* (%)	498,061 (99.6)	1937 (0.4)	417,085 (99.6)	1611 (0.4)	80,976 (99.6)	326 (0.4)
Model 1, OR (95% CI)[a]	Ref	1.75 (1.58–1.95)	Ref	1.66 (1.48–1.88)	Ref	2.20 (1.73–2.80)
Model 2, OR (95% CI)[b]	Ref	1.42 (1.26–1.58)	Ref	1.34 (1.18–1.52)	Ref	1.76 (1.37–2.26)
Model 3, OR (95% CI)[c]	Ref	1.40 (1.25–1.56)	Ref	1.32 (1.17–1.50)	Ref	1.75 (1.36–2.24)

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio; PCOS, polycystic ovary syndrome; Ref, reference.

[a]Model 1: unadjusted.

[b]Model 2: adjusted for maternal age, paternal age, birth order, parental psychiatric history, household income, parental education, and mother's country of birth.

[c]Model 3: adjusted as above, with further adjustment for obstetric complications (Apgar score at 5 minutes, preterm birth, small for gestational age, and preeclampsia).

associated with inattention and disruptive behavior in boys (56). Somewhat surprisingly, the risk associated with PCOS appeared slightly elevated for girls compared with boys, though risk estimates for boys and girls overlapped.

We observed that maternal PCOS was associated with a somewhat higher risk for ADHD with comorbid ASD compared to ADHD only. There has been increasing focus on the comorbidity between ADHD and ASD in recent years. Overlap between the disorders has been noted in terms of shared risk factors, similarities in brain structure, and shared dimensions of each disorder (11,57–59). Given the possibility that ADHD with comorbid ASD represents a distinct subtype of ADHD, current DSM-5 guidelines allow for clinicians to make an ASD diagnosis in the context of ADHD (57,60). To date, more research has been conducted regarding hormone exposures in the prenatal environment for ASD compared to ADHD (12). Our study adds further evidence of shared risk factors for these disorders and highlights the utility of considering comorbid diagnostic status because the relationship between the prenatal environment and neurodevelopmental outcomes may vary by subtypes of each disorder.

In addition to androgen excess, there are a host of metabolic disturbances concomitant with PCOS, including adiposity, insulin resistance, and hyperinsulinemia (13). Prenatal exposure to maternal overweight or obesity (32,61) and hyperinsulinemia (62) have been associated with the risk for offspring ADHD. Adjusting for BMI attenuated but did not fully explain the relationship between PCOS and risk for ADHD in our study, indicating that some of the risk could be attributed to elevated BMI in mothers with PCOS. Recent evidence suggests that the association between maternal elevated BMI and ADHD could be due to confounding by time-stable familial factors (32). The hormonal and metabolic disturbances associated with PCOS would be conserved over time within mothers, and thus we were not able to use family-based study designs to parse this question further. We observed a trend of increasing risk for ADHD with worsening cardiometabolic risk profiles of mothers with PCOS. Mothers with PCOS, obesity, and other features of metabolic syndrome had the highest risk. In women with PCOS, the androgen excess collaborates with insulin resistance and hyperinsulinemia in increasing adiposity and risk for metabolic syndrome, which in turn exacerbate hormonal disturbances of PCOS in a positive-feedback loop (43,63). As a result, obese women with PCOS have more severe hyperandrogenemia and metabolic disturbances as compared with their normal-weight counterparts (31,63). Apart from maternal hyperandrogenemia, maternal obesity and hyperinsulinemia also influence the hormonal and metabolic environment of the fetus by modulating placental aromatase activity and potentially by modulating fetal steroidogenesis and gonadal programming (64–66). Maternal obesity and metabolic syndrome also increase circulating levels of inflammatory factors; maternal inflammation has been proposed to play a role in the development of ADHD and ASD (67–69). Further studies measuring biomarkers of the hormonal, inflammatory, and metabolic environment of the mother and fetus are necessary to understand the mechanisms linking maternal PCOS to ADHD and its subtypes in the offspring.

Table 3. ORs and 95% CIs of Maternal PCOS for ADHD Stratified by Sex of the Child in Birth Cohorts From 1984 to 2008 in the Swedish Population

	Male		Female	
	No PCOS	Maternal PCOS	No PCOS	Maternal PCOS
Cases, *n* (%)	40,191 (99.3)	282 (0.7)	18,317 (99.3)	122 (0.7)
Controls, *n* (%)	341,444 (99.6)	1402 (0.4)	156,617 (99.7)	535 (0.3)
Model 1, OR (95% CI)[a]	Ref	1.69 (1.49–1.92)	Ref	1.92 (1.58–2.35)
Model 2, OR (95% CI)[b]	Ref	1.37 (1.20–1.57)	Ref	1.53 (1.24–1.88)

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio; PCOS, polycystic ovary syndrome; Ref, reference.

[a]Model 1: unadjusted.

[b]Model 2: adjusted for maternal age, paternal age, birth order, parental psychiatric history, household income, parental education, and mother's country of birth.

Table 4. ORs and 95% CIs by Maternal PCOS Symptom Severity for ADHD in Birth Cohorts From 1984 to 2008 in the Swedish Population

	No PCOS	Maternal PCOS	Maternal PCOS + Overweight	Maternal PCOS + Obesity	Maternal PCOS + Obesity + Metabolic Syndrome[a]	*p* Trend
Cases, *n* (%)	41,084 (99.3)	106 (0.3)	101 (0.2)	88 (0.2)	7 (<0.1)	
Controls, *n* (%)	283,185 (99.6)	521 (0.2)	396 (0.1)	297 (0.1)	17 (<0.1)	
Model 1, OR (95% CI)[b]	Ref	1.42 (1.15–1.75)	1.82 (1.46–2.27)	2.09 (1.65–2.66)	2.97 (1.23–7.18)	<.001
Model 2, OR (95% CI)[c]	Ref	1.11 (0.89–1.39)	1.56 (1.24–1.96)	1.68 (1.31–2.17)	2.59 (1.02–6.58)	<.001

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio; PCOS, polycystic ovary syndrome; Ref, reference.

[a]Metabolic syndrome defined as obesity and a diagnosis of essential hypertonia and/or diabetes.

[b]Model 1: unadjusted.

[c]Model 2: adjusted for maternal age, paternal age, birth order, parental psychiatric history, household income, parental education, and mother's country of birth.

Genetic factors related to risk for PCOS and risk for ADHD may explain some of the associations observed in this study. A small clinical study compared ADHD rating scale scores among women with PCOS and healthy controls and found the former to have more ADHD symptoms (70), indicating that there may be some shared genetic risk between the two disorders. We observed little evidence that the association is explained by increased risk for obstetric complications among mothers with PCOS.

Strengths of our study are the large population-based sample within a publicly funded universal access health care setting, prospectively collected outcome data, and information on many potential confounders. Our study has a number of limitations. The observed prevalence of PCOS was lower than previous estimates, suggesting that PCOS may be unrecognized in many Swedish women. Although register-based diagnoses are objective and not subject to recall bias, we might have captured women with more severe PCOS as exposed and thus our findings may not be generalizable to all women with PCOS. Likewise, case ascertainment was based on registered diagnoses and drug treatment for ADHD and may reflect more severe cases. Data on mothers' medication during pregnancy were available for only a small subsample of the study population. Thus, it was not possible to examine whether pharmacological interventions for mothers with PCOS, such as metformin use, could attenuate risk. Further, it is not possible to rule out that valproate or antipsychotic use during pregnancy might confound the relationship between maternal PCOS and offspring ADHD. In this study, there was little evidence of use of these medications during pregnancy among mothers with PCOS for the subsample of children born in 2005 to 2008. The question of whether maternal medication use modulates the risks for neurodevelopmental disorders in the offspring associated with maternal PCOS remains an important goal for future research in this area. Data on BMI were available for only a subsample of the study population. However, there are few differences between women with and without baseline BMI data in characteristics such as socioeconomic factors, suggesting that BMI data are missing at random (33).

Conclusions

Maternal PCOS may subtly influence the neurodevelopment of the offspring, resulting in increased risk for neurodevelopmental disorders such as ADHD. The apparent risk increased with worsening maternal cardiometabolic profiles. Encouraging women with PCOS to begin pregnancy at a healthy weight and to adhere closely to gestational weight gain guidelines could potentially decrease the risk for ADHD for their offspring. Given the impact that ADHD has globally, there is a need for delineation of the mechanisms underlying the relationship with maternal PCOS, particularly the role of prenatal androgens and metabolic disturbances in the etiology of neurodevelopmental disorders.

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ARTICLE INFORMATION

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