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Prenatal antidepressant exposure is associated with risk for attention deficit-hyperactivity disorder but not autism spectrum disorder in a large health system

Caitlin C. Clements, BA[1],[2], **Victor M. Castro, MS**[1],[3],[4], **Sarah R. Blumenthal, BS**[1],[2], **Hannah R. Rosenfield, BA**[1],[2], **Shawn N. Murphy, MD, PhD**[3],[4], **Maurizio Fava, MD**[5], **Jane L. Erb, MD**[6], **Susanne E. Churchill, PhD**[7], **Anjali J. Kaimal, MD, MAS**[8], **Alysa E. Doyle, PhD**[1],[2], **Elise B. Robinson, PhD**[1],[9], **Jordan W. Smoller, MD, ScD**[2], **Isaac S. Kohane, MD**[10], and **Roy H. Perlis, MD, MSc**[1],[2],*

[1]Center for Experimental Drugs and Diagnostics, Department of Psychiatry, Massachusetts General Hospital, Simches Research Building 6th Floor, 185 Cambridge St, Boston, MA 02114

[2]Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry, Massachusetts General Hospital, Simches Research Building 6th Floor, 185 Cambridge St, Boston, MA 02114

[3]Partners Research Computing, Partners HealthCare System, One Constitution Center, Boston, MA 02129

[4]Laboratory of Computer Science and Department of Neurology, Massachusetts General Hospital, Boston, MA 02114

[5]Depression Clinic and Research Program, Department of Psychiatry, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114

[6]Department of Psychiatry, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115

*Correspondence: Roy Perlis, MD MSc, Simches Research Building/MGH, 185 Cambridge St, 6th Floor, Boston, MA 02114, Phone: 617 726-7426, Fax: 617-726-0830, rperlis@partners.org.

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[7]Information Systems, Partners HealthCare System, New Research Building 255, 77 Avenue Louis Pasteur, Boston, MA 02115

[8]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114

[9]Analytic and Translational Genomics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Simches Research Building 6th Floor, 185 Cambridge St, Boston, MA 02114

[10]Department of Medicine, Brigham and Women's Hospital, Suite 255, New Research Building, 77 Avenue Louis Pasteur, Boston, MA 02115

Abstract

Previous studies suggested that risk for Autism Spectrum Disorder (ASD) may be increased in children exposed to antidepressants during the prenatal period. The disease-specificity of this risk has not been addressed and possibility of confounding has not been excluded. Children with ASD or attention deficit-hyperactivity disorder (ADHD) delivered in a large New England health care system were identified from electronic health records, and each diagnostic group was matched 1:3 with children without ASD or ADHD. All children were linked with maternal health data using birth certificates and electronic health records to determine prenatal medication exposures. Multiple logistic regression was used to examine association between prenatal antidepressant exposures and ASD or ADHD risk. A total of 1,377 children diagnosed with ASD and 2,243 with ADHD were matched with healthy controls. In models adjusted for sociodemographic features, antidepressant exposure prior to and during pregnancy was associated with ASD risk, but risk associated with exposure during pregnancy was no longer significant after controlling for maternal major depression [OR 1.10 (0.70–1.70)]. Conversely, antidepressant exposure during but not prior to pregnancy was associated with ADHD risk, even after adjustment for maternal depression [OR 1.81 (1.22–2.70)]. These results suggest that the risk of autism observed with prenatal antidepressant exposure is likely confounded by severity of maternal illness, but further indicate that such exposure may still be associated with ADHD risk. This risk, modest in absolute terms, may still be a result of residual confounding and must be balanced against the substantial consequences of untreated maternal depression.

Introduction

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterized by deficits in social function and communication and the presence of repetitive and stereotyped behaviors. An apparently rapid increase in ASD prevalence over the past decade has increased efforts to identify potentially-modifiable risks[1]: While much of the liability for autism is inherited[2, 3], environmental factors also contribute risk[3], although the nature of these factors is not yet well characterized.

Rodent studies nearly a decade ago suggested that prenatal exposure to serotonergic drugs yielded autism-like behaviors in offspring[4]. Subsequently, one health claims-based study[5] and one registry-based study[6] associated in utero exposure to antidepressants with autism liability in children, while a recent large-scale Danish registry-based study did not replicate

this association[7]. In light of the substantial public health implications of this finding, and the contradictory prior results, clarification of this risk is critical: Discontinuation of antidepressants during pregnancy can increase the risk of relapse five-fold[8], and maternal depression during pregnancy is associated with health complications for both the mother and child[9].

Two critical questions were not fully answered by the prior investigations. First, to what extent might the apparent risk be confounded by indication – that is, might antidepressant exposure simply be a proxy for more severe psychiatric illness requiring pharmacologic intervention? Consistent with this alternative hypothesis, previous studies have suggested an independent association between ASD and maternal depression[10, 11]. Second, is the putative risk associated with antidepressants reflected in ASD in particular, or neurodevelopmental disorders more broadly, given that antidepressant exposure has also been associated with ADHD liability in one cohort[12], while a larger one found association with either current or past antidepressant use[13]. To address these questions, we utilized an enhanced pharmacovigiliance approach to examine prenatal exposure to antidepressants as well as other psychotropic medications and subsequent diagnosis of autism or ADHD. We drew maternal and pediatric diagnosis and prescription data from the electronic health record from a large Massachusetts health care system, and integrated the resulting data with birth records from the Massachusetts Registry of Vital Records and Statistics.

Methods

Overview and data set generation

The Partners HealthCare electronic health record (EHR) includes sociodemographic data, billing codes, laboratory results, problem lists, medications, vital signs, procedure reports and narrative notes from Massachusetts General Hospital (MGH), Brigham and Women's Hospital (BWH), Newton-Wellesley Hospital (NWH), as well as from community and specialty hospitals which are part of the Partners HealthCare system, and affiliated outpatient clinics. These data can be managed with the i2b2 server software (i2b2 v1.6.04, Boston, MA, USA)[14–16], a scalable computational framework, deployed at over 100 major academic health centers internationally, for managing human health data. The Partners Institutional Review Board approved all aspects of this study. Access to Massachusetts birth certificates was approved by the Massachusetts Department of Public Health Institutional Review Board.

For the present study, children age 2–19 were identified from the EHR for inclusion in the data mart if they had at least one ICD-9 code of 299 (pervasive developmental disorder) between 1997 and 2010, and were delivered at MGH, BWH, or NWH.

Children with ASD were matched 1:3 with non-ASD control children delivered at MGH, BWH, or NWH with the same year of birth, birth hospital, sex, insurance type as a proxy for socioeconomic status, race/ethnicity, and preterm versus full-term status. These children were defined as not having any prior history of ASD, ADHD, or intellectual disability (ICD9 of 299, 314, or 317–319). If fewer than 3 matches could be identified for a case, year of birth was relaxed so that controls were born within 3 years of a given case. 20 ASD cases

were unable to match any controls even after relaxing the birth year criteria and were excluded from the analysis. 81 ASD cases matching fewer than 3 controls were included in the analysis with 1 or 2 matched controls. To account for uneven matching, we adjust for all matching variables in each logistic regression model.

An additional study group was drawn from children with ADHD, defined as at least one ICD-9 code of 314.x between 1997 and 2010 and delivered at MGH, BWH or NWH. Consistent with DSM-IV criteria, children with both ADHD and ASD diagnostic codes were included in the ASD group. This study group was also frequency-matched with healthy control children as for ASD. For ADHD cases, 192 cases were unable to match any controls and were excluded from the analysis. 726 ADHD cases matching fewer than 3 controls were included in the analysis with 1 or 2 matched controls.

As reported in other health systems[5], ICD-9 codes have a high sensitivity and specificity for ASD and ADHD versus healthy control children in the Partners Healthcare system based on blinded review of 60 ASD, ADHD, and healthy control records by an experienced child neuropsychologist (for ASD, sensitivity is 1.00, specificity 0.91; for ADHD, sensitivity is 0.84, specificity 0.90). The impact of variation in sensitivity and specificity was further examined using quantitative bias analysis (see Discussion and Supplemental Table 7).

Mothers were identified on the basis of matching child's date of birth and surname, insurance identifiers, and hospital encounter date. As a further confirmation of match, and to address cases where children might have different last names or where they might have been removed from maternal custody, Massachusetts state birth certificates were queried for all identified children. Where mother-child matches could not be confirmed, those pairs were omitted from analysis. Consistent with prior reports, we restricted the analysis to 1 child per mother, choosing the child with ASD or ADHD when a mother had both a case and control offspring. When two case or two control children were identified we randomly selected one child for inclusion in the study. These queries yielded 1,377 children with ASD matched to 4,022 healthy control children and 2,243 with ADHD (but no ASD diagnosis) matched to 5,631 healthy control children, all delivered at MGH, BWH or NWH.

Exposure definition

Primary analyses examined antidepressant exposure at any time during pregnancy, with presence or absence of exposure included as a predictor in regression models. To maximize comparability with the initial report of association between antidepressant exposure and ASD[5], the same definitions of exposure were utilized to examine time of exposure in greater detail. Specifically, 4 antidepressant exposure times were defined based on the estimated last menstrual period (LMP) calculated from gestational age: preconception (3 months prior to LMP), first trimester (0–90 days after LMP), second trimester (91–180 after LMP) and third trimester (181 days after LMP until delivery). We also report exposure prior to pregnancy (any time before LMP). Prenatal medication exposure was based on prescriptions in the outpatient EHR (95%) and medications dispensed by the inpatient pharmacy (5%). Medication exposure period was estimated based on days of medication provided, calculated using the number of pills provided, frequency, and number of refills; exposure was truncated when medication discontinuation was recorded by the clinician. A mother was considered

exposed at a given time period if her medication exposure overlapped with any point in that time period. Confirmation that agents prescribed were actually dispensed to patients is not available for research purposes.

Analysis

Each sociodemographic or clinical feature was first examined for association with ASD or ADHD in a logistic regression model to yield unadjusted odds ratios. Next, a logistic regression model was fit which included gender, race, birth year, insurance type, maternal age, and median income tertile, yielding an adjusted odds ratio. Finally, a third model was fit including presence or absence of maternal major depressive disorder (ICD9 codes of 296.2x or 296.3x), to address the possibility of confounding by indication. In addition to examining baseline sociodemographic features, we examined effects of obstetric and neonatal complications by incorporating them in regression models; complications were defined according to ICD-9 diagnostic codes and birth certificate data. These included induction of labor, cesarean section, and Apgar scores less than 7. However, we did not include complications in models examining antidepressant exposure and disease outcome, because of the possibility that such complications might lie in the causal path (if any) between exposure and disease.

Three sets of follow-up analyses expanded these regression models to examine possible indicators of confounding by maternal psychopathology - i.e., confounding by indication. First, we examined whether risk was more strongly associated with more serotonergic antidepressants, as the biological hypothesis would posit (and in contrast to the notable observation in a prior study was association with non-SSRI antidepressants)[5]. Conversely, if risk was associated with agents with lower affinity for the serotonin transporter, often utilized in more severe or treatment-resistant psychiatric illness, it might provide further evidence of confounding by indication. Second, to better understand the role of maternal illness severity, we examined measures of maternal treatment intensity including number of psychopharmacologic visits, number of psychotherapy visits, different antidepressant medications in the prior year, and specific psychiatric disorder or comorbidity, including substance use disorder. Third, we examined risk associated with the non-antidepressant serotonergic agent ondansetron, commonly prescribed for hyperemesis during pregnancy, as well as exposure to antipsychotic medication, which would also be reflective of more severe psychiatric illness – i.e., a positive control for the effects of illness. (Covarying for antipsychotic exposure in primary analyses of antidepressant effects did not meaningfully change results).

For the first follow-up analysis, we examined the association between disease risk and antidepressant serotonin transporter affinity, using definitions consistent with our prior work[17] based upon published affinity constants[18]. These categories distinguish between high affinity (paroxetine, duloxetine, sertraline, escitalopram, fluoxetine); moderate affinity (citalopram, fluvoxamine, venlafaxine); and low affinity (nefazodone, bupropion, mirtazapine). Notably, this latter category includes antidepressants which are generally second- or third-line treatment for depressive episodes, and thus likely to be indicators for more treatment-resistant illness.

All analyses utilized R 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

The ASD, ADHD, and matched healthy control cohorts are described in Table 1A; as cases and controls could not be perfectly matched in all cases, subsequent adjusted models controlled for matching variables as well as maternal age and income tertile. Associations between clinical features and ASD or ADHD are presented in Table 1A. Consistent with prior reports, in adjusted models, advanced paternal and maternal age were significantly associated with ASD risk, while earlier maternal age was associated with ADHD risk. For ADHD but not ASD, the protective effects of greater maternal and paternal education were also observed in adjusted models. Maternal diagnosis of major depressive disorder was associated with risk for both ASD and ADHD, as was first pregnancy. Table 1B depicts details of delivery, with cesarean section associated with autism risk in crude and adjusted models as in prior reports[19]; aspects of delivery were otherwise similar between ASD and ADHD cases and controls.

We next examined ASD risk associated with antidepressant exposure prior to and during pregnancy (Table 2A and B). Antidepressant use *prior* to pregnancy was associated with increase in risk for ASD (OR 1.91 (95% CI 1.41–2.58)). Notably, significant ASD risk with pre-pregnancy antidepressant use persisted after adjustment for history of maternal major depressive disorder. Table 2A presents ASD risk for antidepressant exposure during pregnancy as a whole, and by trimester. In adjusted models which did not include maternal diagnosis, antidepressant exposure was associated with ASD risk, as in some prior reports. However, with the addition of maternal major depression, this association was substantially reduced and no longer statistically significant (OR 1.10 (95% CI 0.70–1.70)). Figure 1 illustrates these risks when antidepressants are divided into low, medium or high-affinity for the serotonin transporter, an approach consistent with prior pharmacovigilance investigations of SSRIs[18] included in our prior work[17] (Table S2). Notably, risk was not greater among high-affinity antidepressants, as would be expected under the original biological hypothesis for ASD.

The pattern of results for ADHD was somewhat different overall. As with ASD, antidepressant exposure prior to pregnancy was associated with risk for ADHD in offspring (OR 1.69 (95% CI 1.25–2.25)) in adjusted models. However, unlike with ASD, the addition of maternal depression to models resulted in this risk no longer remaining statistically significant (OR 1.18 (95% CI 0.86–1.61)). During pregnancy, antidepressant exposure was also associated with ADHD risk; the magnitude of risk was substantially less, but remained significant, after addition of maternal depression to the model. (OR 1.81 (95% CI 1.22–2.70)).

To better understand the potential confounding effects of illness severity, clinical features which could represent more precise measures of illness or treatment indications were examined (Table 3A and B). These features of maternal psychiatric treatment, illness course, or diagnosis were added to the logistic regression models individually. Table 3A indicates the resulting odds ratios for association between antidepressant exposure and ASD risk

examined when each clinical feature was added to the model. Notably, inclusion of elements of treatment intensity led to reduction in observed effect by more than 10%, a common rule of thumb for confounding. Similar results were observed for ADHD: the effect of antidepressant exposure was substantially more modest when measures of psychiatric comorbidity and treatment intensity were included, although adjusted odds ratios with nearly all measures still exceeded 1.7 (Table 3B)(Supplemental tables 6A and B report associations between maternal treatment or diagnosis and ASD or ADHD risk).

Lastly, we examined two other sets of medications that might be expected to contribute to disease risk and/or support confounding by indication. First, we considered exposure to the serotonergic non-antidepressant ondansetron (Table S4). We observed no evidence of association with ASD or ADHD risk. While the total exposure for this episodic intervention is substantially less, rodent models would suggest that even modest serotonergic disruption could be consequential. Second, we examined exposure to typical and atypical antipsychotics during pregnancy, another marker of more severe psychopathology (Table S5). The modest number of exposures led to wide confidence intervals; nonetheless, antipsychotic prescription during pregnancy was associated with numerically greater risk for ASD than antidepressants, although this risk was not observed with ADHD.

Discussion

In a large health care system, using a design distinct from prior reports, which integrates electronic health records with birth certificate data, we identified an association between prenatal antidepressant exposure and risk for ASD which appeared to result from confounding by maternal psychopathology. Convergent evidence of such confounding includes greatest risk with pre-pregnancy exposure, increased magnitude of risk with less- rather than more-serotonergic antidepressants, as well as with antipsychotics, both categories often used in more severely ill patients, and reduction in effect size with inclusion of more detailed measures of psychopathology or treatment intensity.

The magnitude of ASD risk observed with antidepressants overall (adjusted OR ~1.1) is substantially more modest than that observed in two prior studies, with a confidence interval that does not exclude 1. In the first study, which included 298 children with ASD in a northern California health plan, antidepressant exposure was associated with adjusted odds ratio of 2.2 for ASD[5]. In the second, for 1670 ASD cases in a Swedish population cohort, antidepressant exposure was associated with adjusted odds ratio of 1.9[6]. In both of these prior studies, contrary to predictions from rodent models [4], risk was also observed with non-SSRIs. To emphasize the presumed mechanism of risk, we utilized a categorization previously shown to be sensitive to serotonergic effects on gastrointestinal bleeding[17]. Our results are also consistent with the most recent and largest registry-based investigation [7], in that both studies failed to identify risk specifically among SSRI-treated patients. In the analysis by Hviid and colleagues, as in this study, past but not current antidepressant use represents a risk for ASD.

Conversely, for ADHD, we observed persistent risk associated with antidepressant exposure, particularly during the first trimester, which can only partially be explained in regression

models by maternal psychopathology. Here too, effects appeared greatest in the lower-serotonin-affinity treated groups, consistent with a prior investigation of 431 children with ADHD[12] which identified association with bupropion exposure. A larger Danish registry-based study identified a more modest association with antidepressant exposure, which was also observed among offspring of mothers with prior, but not current, antidepressant treatment[13]. Notably, consideration of the first trimester yields adjusted OR >2.0, strongly suggesting that it is the period of greatest risk, although a prior report suggested greatest risk in second trimester[12]. (Analysis of delivery complications also did not identify differences between ADHD cases and controls that might mediate the observed risk, in contrast to the increased rate of cesarean section for ASD cases versus controls).

Our results extend and clarify previous work in multiple important ways. First, these results provide the most direct evidence to date that risk for ASD observed in the two initial reports is likely to represent confounding by indication, with antidepressant-treated mothers experiencing greater psychopathology and treatment intensity overall. Second, they suggest the risk is absent or substantially diminished with highest serotonin-affinity antidepressants as well as a serotonergic non-antidepressant, while it is present and of even greater magnitude with antipsychotic treatment. Third, they indicate that despite a similar pattern of confounding, some risk appears to persist for ADHD, consistent with effects observed in two prior studies, one using claims data, the other a national registry from Denmark[12, 13]. The latter study identified prior antidepressant exposure as a risk factor for ADHD, and suggested that the observed in utero risk represented confounding by indication. However, in the present study, no significant association with prior antidepressant use is noted after adjustment for maternal psychopathology.

A key limitation of any non-randomized investigation of naturalistic data is the risk for confounding. As a randomized, controlled trial to establish risk is unlikely to be conducted for ethical reasons, alternate strategies must be considered because of the public health importance of the clinical question. Of particular concern when treatment exposure is the predictor of interest is confounding by indication. Some, but not all, studies suggest that maternal psychiatric illness is associated with ASD liability[6]. Simply comparing mothers treated with antidepressants to those receiving psychotherapy alone would not address differences in severity which might influence the decision to continue medication.

We note another less apparent contributor to bias rarely addressed directly in pharmacovigilance studies, that arising from systematic misclassification of case/control status – for example, increased sensitivity to autism in offspring based on maternal psychiatric illness. Sensitivity analyses to examine misclassification bias can be helpful in this regard[20]. In our analyses, adjusting for potential sources of biased diagnosis should address this risk. Nonetheless, for illustrative purposes, Supplemental Table 7 depicts the impact on odds ratio for ASD and ADHD of a sensitivity analysis varying sensitivity and specificity using quantitative bias analysis.

While the present data set is among the richest yet examined in terms of availability and resolution of clinical data, because it utilizes longitudinal electronic health records from mothers and children as well as birth certificates, our clinical markers were likely

insufficient to fully capture severity differences between treated and untreated mothers. We considered numerous markers of type and intensity of psychiatric disease, including visit frequency, type of visit, and diagnostic code, with concomitant reductions in estimated ASD risk. Still, these results provide an important cautionary tale for future pharmacovigilance investigations in psychiatric patient populations.

We note several additional limitations of the present study. First, there is some risk of misclassification because the Partners healthcare system is not a closed system: some control subjects may actually have ASD diagnosed elsewhere. To address this risk, we matched controls by primary hospital, increasing the likelihood that ASD would be documented if it was present. Further, with the notable exception of systematic misclassification noted above, misclassification would tend to bias us towards the null hypothesis, underestimating rather than inflating true effects.

Despite these caveats, these results provide important clarification from prior cohort studies which examined prenatal antidepressant exposure and ASD risk. In particular, we demonstrate the likelihood of confounding by indication. The persistence of risk for ADHD, despite some evidence of confounding, suggests the importance of investigating risk for that disorder in additional cohorts to more precisely estimate antidepressant effects, if any. In particular, further characterization of potential residual confounding effects which may inflate the observed ADHD risk is a high priority.

The consequences of failing to treat depression in pregnancy warrant emphasis. One study found that rates of depressive relapse were increased 5-fold when antidepressants were discontinued during pregnancy[8]; the postpartum period is known to be particularly high risk. Moreover, maternal depression during pregnancy is associated with health complications for both the mother and child[9]. The present study adds to a body of evidence suggesting that the apparent risk of depression treatment during pregnancy may actually reflect maternal psychopathology; moreover, in absolute terms any incremental risk must be weighed against the serious consequences of failing to adequately treat depression and related disorders. Decision-making about antidepressant utilization in pregnancy requires that these emerging risks, as well as benefits, be weighed in the context of the individual patient and family.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1A.

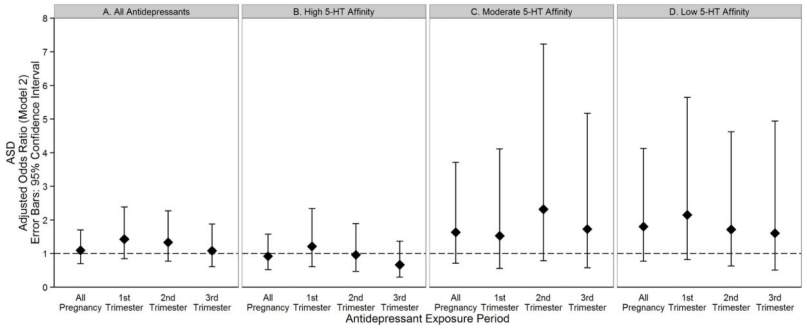

Figure 1B.

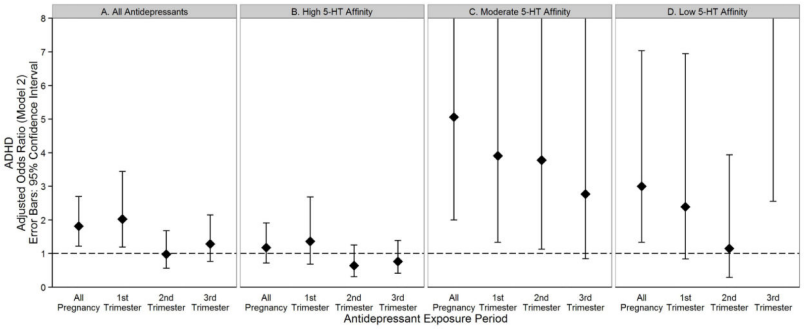

Figure 1.

Figure 1A: ASD risk associated with maternal antidepressant exposure during pregnancy stratified by serotonin transporter affinity

Figure 1B: ADHD risk associated with maternal antidepressant exposure during pregnancy stratified by serotonin transporter affinity

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Table 1A

Sociodemographic and medical history of children and parents in ASD, ADHD and matched control study groups

	ASD	ASD Controls	ASD vs Matched Controls		ADHD	ADHD Controls	ADHD vs Matched Controls	
	1,377	4,022	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	2,243	5,631	Unadjusted OR (95% CI)	Model 1 OR (95% CI)
Child Demographics								
Age at first ASD/ADHD diagnosis, years [mean (sd)]	5.1 (3.0)	n/a	n/a	n/a	8.3 (2.9)	n/a	n/a	n/a
Male gender	81.3%	81.6%	0.98 (0.84–1.15)	1.02 (0.86–1.21)	71.2%	73.5%	0.89 (0.80–1.00) *	0.87 (0.78–0.98) *
Race								
White	71.5%	72.3%	0.96 (0.84–1.10)	1.02 (0.78–1.35)	66.3%	71.3%	0.79 (0.71–0.88) ***	0.97 (0.78–1.22)
Black	6.5%	6.0%	1.09 (0.84–1.39)	1.02 (0.76–1.35)	7.1%	6.4%	1.11 (0.92–1.35)	0.89 (0.71–1.10)
Hispanic	11.5%	11.5%	1.00 (0.82–1.20)	0.95 (0.74–1.22)	18.5%	14.1%	1.38 (1.21–1.57) ***	0.90 (0.75–1.07)
Asian	4.2%	4.0%	1.06 (0.78–1.43)	1.05 (0.74–1.45)	2.2%	2.5%	0.89 (0.64–1.23)	0.84 (0.59–1.19)
Other	6.3%	6.3%	1.01 (0.78–1.29)	0.98 (0.74–1.28)	5.9%	5.7%	1.05 (0.85–1.29)	1.03 (0.82–1.28)
Median household income								
1st tertile (< $32,136)	33.3%	32.9%	1.02 (0.88–1.17)	1.17 (0.97–1.41)	38.4%	30.9%	1.40 (1.26–1.56) ***	1.29 (1.11–1.51) **
2nd tertile ($32,136–$41,820)	35.3%	32.2%	1.15 (1.00–1.32) *	1.07 (0.89–1.28)	33.4%	32.8%	1.03 (0.92–1.15)	0.94 (0.82–1.08)
3rd tertile (> $41,820)	31.4%	34.9%	0.85 (0.74–0.98) *	0.86 (0.71–1.04)	28.1%	36.3%	0.69 (0.61–0.77) ***	0.77 (0.66–0.90) **
Multiple birth	7.9%	6.4%	1.25 (0.99–1.57)	1.16 (0.89–1.50)	4.9%	6.5%	0.75 (0.60–0.93) **	0.84 (0.66–1.05)
Parent Demographics								
Mother age at delivery, years [mean (sd)]	32.3 (5.4)	31.8 (5.4)	1.02 (1.01–1.03) **	1.03 (1.02–1.04) ***	29.9 (6.6)	31.3 (5.5)	0.96 (0.95–0.97) ***	0.97 (0.96–0.98) ***
Father age at delivery, years [mean (sd)]	34.9 (6.7)	34.1 (6.2)	1.02 (1.01–1.03) ***	1.02 (1.01–1.04) **	32.5 (7.2)	33.5 (6.1)	0.98 (0.97–0.98) ***	0.99 (0.98–1.01)
Mother - government insurance	17.8%	15.4%	1.19 (1.01–1.40) *	1.29 (1.05–1.59) *	27.0%	17.7%	1.72 (1.53–1.93) ***	1.41 (1.21–1.63) ***
Mother, 4+ years of college	62.8%	66.0%	0.87 (0.77–0.99) *	0.86 (0.72–1.01)	46.6%	60.8%	0.56 (0.51–0.62) ***	0.70 (0.62–0.80) ***
Father, 4+ years of college	64.0%	66.3%	0.90 (0.79–1.03)	0.86 (0.72–1.02)	48.2%	62.4%	0.56 (0.50–0.62) ***	0.64 (0.56–0.73) ***
Mother Past Medical History								
Diabetes	2.8%	2.4%	1.18 (0.80–1.72)	1.22 (0.80–1.82)	3.2%	2.4%	1.33 (0.99–1.77)	1.23 (0.90–1.67)
Chronic hypertension	1.3%	1.6%	0.82 (0.47–1.35)	0.74 (0.40–1.29)	1.5%	1.7%	0.88 (0.58–1.29)	0.89 (0.58–1.33)
Major depressive disorder	9.3%	5.6%	1.72 (1.37–2.15) ***	1.74 (1.35–2.23) ***	8.2%	3.8%	2.25 (1.84–2.76) ***	2.29 (1.84–2.85) ***
Parity								

	ASD	ASD Controls	ASD vs Matched Controls		ADHD	ADHD Controls	ADHD vs Matched Controls	
	1,377	4,022	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	2,243	5,631	Unadjusted OR (95% CI)	Model 1 OR (95% CI)
1	62.1%	52.6%	1.48 (1.30–1.68) ***	1.62 (1.41–1.87) ***	56.8%	53.1%	1.16 (1.05–1.28) **	1.15 (1.03–1.28) *
2	28.6%	35.0%	0.74 (0.65–0.85) ***	0.72 (0.62–0.84) ***	33.2%	34.5%	0.94 (0.85–1.05)	0.96 (0.86–1.08)
3+	9.2%	12.4%	0.72 (0.58–0.88) **	0.63 (0.50–0.80) ***	10.0%	12.4%	0.78 (0.67–0.92) **	0.79 (0.66–0.94) **

[1] Child age of first ASD or ADHD diagnosis, child diagnosis and maternal history of major depression were extracted from electronic medical records. All other variables were extracted from birth certificates.

[2] Values indicate percent of study group unless otherwise indicated.

[3] Unadjusted and adjusted risk of ASD or ADHD compared to ASD-matched controls;

Significance at alpha < 0.05 (*), <0.01 (**), <0.001 (***). Model 1 is adjusted for gender, race, birth year, insurance type, maternal age, and median income tertile.

Table 1B

Antepartum, intrapartum and neonatal history of children and parents in ASD, ADHD and matched control study groups

	ASD	ASD Controls	ASD vs Matched Controls		ADHD	ADHD Controls	ADHD vs Matched Controls	
	1,377	4,022	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	2,243	5,631	Unadjusted OR (95% CI)	Model 1 OR (95% CI)
Mother Prenatal								
Adequacy of prenatal care Kotelcheck Index < adequate	9.3%	10.1%	0.92 (0.73–1.15)	0.84 (0.65–1.08)	10.9%	10.2%	1.08 (0.92–1.27)	0.94 (0.79–1.12)
Gestational diabetes	5.0%	4.4%	1.16 (0.87–1.53)	1.24 (0.91–1.67)	3.7%	3.4%	1.09 (0.84–1.42)	1.08 (0.80–1.44)
Pregnancy weight gain, pounds, [mean (sd)]	29.9 (12.1)	29.3 (12.9)	1.00 (1.00–1.01)	1.00 (1.00–1.01)	29.0 (12.5)	29.4 (13.2)	1.00 (0.99–1.00)	1.00 (1.00–1.00)
Labor and Delivery								
C-section delivery	38.2%	31.0%	1.38 (1.21–1.56) ***	1.28 (1.11–1.47) **	28.4%	29.7%	0.94 (0.84–1.04)	1.03 (0.91–1.15)
Induction of labor	17.5%	17.9%	0.97 (0.83–1.14)	0.98 (0.82–1.17)	17.3%	16.2%	1.09 (0.95–1.24)	1.14 (0.99–1.31)
Neonatal								
Gestational age								
20–32 weeks	3.2%	3.7%	0.86 (0.61–1.21)	0.91 (0.63–1.28)	3.6%	3.3%	1.07 (0.82–1.39)	1.05 (0.78–1.39)
33–36 weeks	9.1%	8.4%	1.09 (0.87–1.34)	1.08 (0.85–1.37)	7.3%	7.0%	1.04 (0.85–1.25)	1.02 (0.83–1.25)
37–43 weeks (reference)	87.7%	87.9%	0.98 (0.82–1.19)	0.98 (0.80–1.20)	89.2%	89.6%	0.95 (0.81–1.12)	0.97 (0.82–1.15)
1 minute Apgar < 7	10.2%	9.0%	1.14 (0.93–1.40)	1.12 (0.89–1.39)	9.1%	9.1%	1.00 (0.84–1.18)	0.98 (0.81–1.17)
5 minute Apgar < 7	1.7%	1.5%	1.13 (0.69–1.79)	1.07 (0.63–1.73)	1.7%	1.7%	0.99 (0.66–1.44)	0.96 (0.64–1.42)
Birth weight								
< 1,500 grams	2.4%	2.3%	1.05 (0.69–1.55)	1.14 (0.75–1.71)	90.0%	90.0%	0.99 (0.71–1.36)	1.01 (0.70–1.43)
1,500 – 2,499 grams	8.5%	7.9%	1.09 (0.87–1.35)	0.99 (0.77–1.26)	2.3%	2.3%	1.00 (0.83–1.20)	0.98 (0.80–1.19)
2,500 + grams	89.1%	89.9%	0.92 (0.76–1.13)	0.97 (0.79–1.21)	7.7%	7.7%	1.00 (0.85–1.18)	1.01 (0.85–1.21)

[1] All variables were extracted from birth certificates.

[2] Values indicate percent of study group unless otherwise indicated.

[3] Unadjusted and adjusted risk of ASD or ADHD compared to ASD-matched controls;

Significance at alpha < 0.05 (*), <0.01 (**), <0.001 (***). Model 1 is adjusted for gender, race, birth year, insurance type, maternal age, and median income tertile.

Table 2A

ASD risk associated with maternal antidepressant exposure during pregnancy

	ASD	Controls	ASD vs. ASD-matched Controls[3]		
Antidepressant exposure	**1,377**	**4,022**	**Unadjusted OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**
Time period					
Prepregnancy	6.6%	3.5%	1.98 (1.50–2.59) ***	1.91 (1.41–2.58) ***	1.62 (1.17–2.23) **
Preconception (conception - 30 days)	1.7%	1.0%	1.72 (1.02–2.84) *	1.89 (1.07–3.30) *	1.47 (0.81–2.61)
1st Trimester	2.3%	1.3%	1.76 (1.11–2.74) *	1.84 (1.11–3.00) *	1.43 (0.85–2.38)
2nd Trimester	2.0%	1.2%	1.76 (1.08–2.79) *	1.81 (1.07–3.00) *	1.34 (0.77–2.27)
3rd Trimester	1.8%	1.1%	1.60 (0.96–2.59)	1.48 (0.85–2.50)	1.08 (0.61–1.88)
Pregnancy (preconception - delivery)	2.9%	2.0%	1.49 (1.01–2.18) *	1.45 (0.94–2.19)	1.10 (0.70–1.70)

[1] Unadjusted and adjusted risk of ASD compared to ASD-matched controls;

Significance at alpha < 0.05 (*), <0.01 (**), <0.001 (***). Model 1 is adjusted for gender, race, birth year, insurance type, maternal age, and median income tertile. Model 2 is adjusted for variables in model 1 and past history of maternal depression.

Table 2B

ADHD risk associated with maternal antidepressant exposure during pregnancy

	ADHD	Controls	ADHD vs. ADHD-matched Controls[3]		
Antidepressant exposure	**2,243**	**5,631**	**Unadjusted OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**
Time period					
Prepregnancy	4.1%	2.6%	1.60 (1.23–2.08) ***	1.69 (1.25–2.25) ***	1.18 (0.86–1.61)
Preconception (conception - 30 days)	1.3%	0.6%	2.37 (1.42–3.94) **	2.92 (1.68–5.11) ***	2.15 (1.21–3.82) **
1st Trimester	1.6%	0.6%	2.61 (1.62–4.21) ***	2.79 (1.67–4.66) ***	2.03 (1.19–3.44) **
2nd Trimester	1.3%	0.8%	1.72 (1.07–2.73) *	1.51 (0.89–2.52)	0.98 (0.56–1.68)
3rd Trimester	1.6%	0.8%	1.99 (1.28–3.07) **	2.02 (1.23–3.28) **	1.29 (0.76–2.15)
Pregnancy (preconception - delivery)	2.8%	1.2%	2.30 (1.62–3.24) ***	2.53 (1.73–3.69) ***	1.81 (1.22–2.70) **

[1]Unadjusted and adjusted risk of ADHD compared to ASD-matched controls;

Significance at alpha < 0.05 (*), <0.01 (**), <0.001 (***). Model 1 is adjusted for gender, race, birth year, insurance type, maternal age, and median income tertile. Model 2 is adjusted for variables in model 1 and past history of maternal depression.

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Table 3A

Confounding effects of maternal psychiatric morbidity in ASD cases compared to controls

Depression Severity Models	ASD 1,377 %	Controls 4,022 %	Model 1 + Severity Measure[1] Adjusted OR (95% CI)
ASD risk of antidepressant exposure during pregnancy not adjusted for depression severity variables (reference from Table 2A)	2.9%	2.0%	1.45 (0.94–2.19)
ASD risk of antidepressant exposure during pregnancy adjusted for mental health treatments during pregnancy			
Distinct antidepressants (2 or more)	1.2%	0.5%	1.16 (0.71–1.86)
Psychotherapy visits (1 or more)	3.1%	1.4%	1.24 (0.79–1.91)
Psychotherapy visits (2 or more)	1.9%	0.8%	1.26 (0.80–1.95)
Psychopharmacology visits (1 or more)	1.7%	0.8%	1.15 (0.72–1.81)
ASD risk of antidepressant exposure during pregnancy adjusted for past psychiatric history			
Bipolar Disorder	1.0%	0.5%	1.42 (0.91–2.16)
History of Substance/Alcohol Abuse	4.5%	2.9%	1.37 (0.88–2.09)
Past Suicide Attempt	0.5%	0.3%	1.47 (0.95–2.22)
Schizophrenia or schizoaffective disorder	0.1%	0.1%	1.48 (0.96–2.25)
Post-traumatic Stress Disorder (PTSD)	1.7%	0.6%	1.31 (0.84–2.01)
Obsessive Compulsive Disorder (OCD)	0.7%	0.2%	1.39 (0.90–2.13)
Generalized Anxiety Disorder (GAD)	1.5%	0.5%	1.34 (0.86–2.05)
Depressive Disorder (ICD-9 311)	8.1%	4.6%	1.06 (0.66–1.65)
Panic Disorder	2.1%	1.1%	1.33 (0.85–2.04)
Any psychiatric history of the above or MDD	16.8%	11.1%	1.07 (0.68–1.67)

[1]Odds ratio (95% confidence interval) of antidepressant exposure during pregnancy association with ASD when adjusted by the severity measure in addition to Model 1 covariates. Model 1 is adjusted for gender, race, birth year, insurance type, maternal age, and median income tertile.

Table 3B

Confounding effects of maternal psychiatric morbidity in ADHD cases compared to controls

Depression Severity Models	ADHD 2,243 %	Controls 5,631 %	Model 1 + Severity Measure[1] Adjusted OR (95% CI)
ADHD risk of antidepressant exposure during pregnancy not adjusted for depression severity variables (reference from Table 2B)	2.8%	1.2%	2.53 (1.73–3.69) ***
ADHD risk of antidepressant exposure during pregnancy adjusted for mental health treatments during pregnancy			
Distinct antidepressants (2 or more)	0.8%	0.4%	2.01 (0.76–5.18)
Psychotherapy visits (1 or more)	4.0%	1.8%	1.77 (0.74–4.06)
Psychotherapy visits (2 or more)	2.5%	0.9%	1.75 (0.73–4.02)
Psychopharmacolgy visits (1 or more)	1.2%	0.5%	1.73 (0.72–3.99)
ADHD risk of antidepressant exposure during pregnancy adjusted for past psychiatric history			
Bipolar Disorder	1.2%	0.4%	1.74 (0.72–4.04)
History of Substance/Alcohol Abuse	7.0%	3.1%	1.79 (0.75–4.15)
Past Suicide Attempt	0.8%	0.3%	1.91 (0.81–4.36)
Schizophrenia or schizoaffective disorder	0.5%	0.1%	1.93 (0.82–4.39)
Post-traumatic Stress Disorder (PTSD)	1.7%	0.6%	1.65 (0.68–3.85)
Obsessive Compulsive Disorder (OCD)	0.6%	0.1%	1.93 (0.82–4.39)
Generalized Anxiety Disorder (GAD)	1.6%	0.6%	1.85 (0.78–4.25)
Depressive Disorder (ICD-9 311)	8.2%	4.6%	1.72 (0.72–3.97)
Panic Disorder	2.5%	1.0%	1.69 (0.70–3.91)
Any psychiatric history of the above or MDD	17.6%	9.7%	1.60 (0.66–3.71)

[1]Odds ratio (95% confidence interval) of antidepressant exposure during pregnancy association with ADHD when adjusted by the severity measure in addition to Model 1 covariates. Model 1 is adjusted for gender, race, birth year, insurance type, maternal age, and median income tertile.