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Mediators of the Association between Parental Severe Mental Illness and Offspring Neurodevelopmental Problems

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Abstract

Purpose—Parental severe mental illness (SMI) is associated with an increased risk of offspring Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). We conducted a study to examine the extent to which risk of preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) mediated this association.

Methods—We obtained data on offspring born 1992-2001 in Sweden (n = 870,017) through the linkage of multiple population-based registers. We used logistic and Cox regression to assess the associations between parental SMI, adverse pregnancy outcomes, and offspring ASD and ADHD, as well as tested whether adverse pregnancy outcomes served as mediators.

Results—After controlling for measured covariates, maternal and paternal SMI were associated with an increased risk for PTB, LBW, and SGA, as well as for offspring ASD and ADHD. These pregnancy outcomes were also associated with an increased risk of ASD and ADHD. We found that pregnancy outcomes did not mediate the association between parental SMI and offspring ASD and ADHD, as there was no substantial change in magnitude of the risk estimates after controlling for pregnancy outcomes.

Conclusions—Parental SMI and adverse pregnancy outcomes appear to be independent risk factors for offspring ASD and ADHD.

Keywords

Attention Deficit Hyperactivity Disorder; Autism Spectrum Disorder; infant, small for gestational age; birth weight; gestational age

Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are neurodevelopmental problems whose symptoms often persist into and throughout adulthood, resulting in high societal costs and stress on families [1-5]. ASD encompasses

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COMPETING INTERESTS
None.

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three developmental disorders (i.e., Autism, Asperger's, and Pervasive Developmental Disorder-Not Otherwise Specified) characterized by difficulties in communication and abnormalities in social interaction and behavior, whereas ADHD is described by inattention and hyperactivity [6, 7]. According to recent reports by the Centers for Disease Control and Prevention, the prevalence of ASD and ADHD are rising [6, 7]. Thus, research is needed to understand the etiology of both disorders.

One possible key to understanding the causal mechanisms of ASD and ADHD lies in the association between parental severe mental illness (SMI) and offspring neurodevelopmental problems [8-11]. Individuals with ADHD are at increased risk of having a first degree relative with schizophrenia or bipolar disorder [11]. These associations may be the result of shared genetic factors, as each disorder has been demonstrated to be highly heritable [12, 13]. Studies have also found that genetic factors are shared by numerous forms of severe psychopathology, suggesting that genetic factors typically influence multiple traits pleiotropically [12-14]. However, the current literature does not provide evidence for the causal mechanisms that underlie the association between parental SMI and offspring neurodevelopmental problems [8-11].

Adverse pregnancy outcomes such as preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) are linked to both SMI and childhood neurodevelopmental problems [15-18]. This mutual association with adverse pregnancy outcomes may shed light on the mechanism linking parental SMI with offspring ASD and ADHD. Prescription drug use, alcohol use, and smoking during pregnancy have been cited as potential mechanisms that may explain the link between adult SMI and adverse birth outcomes in their offspring [15, 19]. It is hypothesized that the associations between PTB, LBW, and SGA and offspring ASD and ADHD arise from abnormalities in the developmental of nervous and endocrine systems resultant of restrictions to fetal growth in utero [20-28][29, 30]. Adverse pregnancy outcomes, thus, may serve as mediators in the association between parental SMI and offspring ASD and ADHD [31].

Few studies have examined adverse pregnancy outcomes as mediators in the relation between parental SMI and offspring neurodevelopmental problems, however. One previous study concluded that perinatal factors and parental psychiatric diagnoses were independent risk factors for ASD [10]. This study was limited by the researchers' inability to analyze the independent association between maternal and paternal mental illness and offspring ASD. The results of such an analysis could provide further insights into whether the association between parental SMI and offspring neurodevelopmental problems may result from causal intrauterine effects [32]. And, the previous study only predicted ASD, while much can be gleaned out of additionally predicting ADHD, a condition highly related to ASD [33, 34].

We utilized prospectively-collected, population-based Swedish registers and logistic and Cox regression models to examine the extent to which adverse pregnancy outcomes act as mediators of the association between parental SMI and offspring ASD and ADHD. We hypothesized that adverse pregnancy outcomes would mediate, at least in part, the association between parental SMI and offspring ASD and ADHD.

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METHODS

Study population

The study sample was obtained by linking information available in multiple Swedish population-based registers. Specifically, the Multi-Generation Register provides information on familial relationships in Sweden since 1933 [35]; the Medical Birth Registry contains data on more than 99% of births since 1973 [36]; the National Patient Register provides information on inpatient psychiatric diagnoses since 1973 and outpatient diagnoses since 2001; the Education Register provides information on the highest level of education completed; the Longitudinal Integration Database for Health Insurance and Social Studies (LISA) contains annual data since 1990 on income for individuals 15 years and older [37].

The initial cohort consisted of 980,046 offspring born in Sweden between 1992 and 2001. We excluded offspring who either died (4,255; 0.4%) or emigrated from Sweden (36,195; 3.7%). We also excluded offspring with a recorded gestational age under 23 weeks or over 42 weeks 6 days (7,228; 0.7%) in case gestational age was incorrectly recorded. Individuals born with congenital malformations (32,754; 3.3%) were then dropped, as were multiple births (26,210; 2.7%), given their increased risk of adverse pregnancy outcomes in comparison to singleton births [38]. Finally, we dropped individuals missing maternal (48; 0.005%) or paternal (3,339; 0.3%) identification numbers. The final sample of eligible Swedish births included data for 870,017 individuals born to 597,264 distinct mothers and 599,747 distinct fathers.

Measures

Maternal and paternal SMI—Cases of parental SMI were identified from well-validated inpatient data available in the National Patient Register [39]. Parents with a SMI were defined as those that had received a diagnosis of schizophrenia, bipolar disorder, or another non-organic psychosis according to ICD-8/9/10 criteria as a result of at least one hospital admission. Parents had to be at least 12 years old at the time of diagnosis. Parents with a SMI were included regardless of the timing of diagnosis in relation to childbirth. We explored SMI separately for both parents and constructed an index of parental SMI that included situations in which either or both parents had a diagnosis.

Offspring Neurodevelopmental Problems—Cases of offspring ASD and ADHD were identified using the National Patient Register [40] and defined as those that had received either an inpatient or outpatient diagnosis of ASD or ADHD according to ICD-9/10 criteria. Only individuals diagnosed before the age of 18 were included. We have documented the validity the diagnoses of ADHD [41], and the cases of ASD have been shown to be valid by our research group [42] and others [43].

Adverse pregnancy outcomes—Adverse pregnancy outcome data were obtained from the Medical Birth Registry. Birth weight was divided into five ordinal categories including less than 2,500g (LBW), 2,500-2,999g, 3,000-3,499g, 3,500-3,999g (reference group), and 4,000g and greater and an additional category for missing birth weight. Gestational age was divided into five categories of 23 weeks-27 weeks 6 days, 28 weeks-30 weeks 6 days, 31

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weeks-33 weeks 6 days, 34 weeks-36 weeks 6 days, and 37 weeks-42 weeks 6 days (reference). An additional category of PTB was created as a combined measure of any birth before 37 weeks of gestation. The gestational age data recorded in the Medical Birth Registry is based on ultrasound estimates of gestational age during the second trimester and/or mother's report of last menstruation at her first antenatal visit. Offspring born greater than two standard deviations below the average birth weight for a given gestational age were recorded in the Medical Birth Registry as being born SGA. We used a binary indicator of SGA status and included a missing category. These measures have been widely used in epidemiological studies and have been well validated [36].

Covariates—We controlled for offspring sex and coded parental country of origin as Sweden or not Sweden (reference category). Parental cohabitation status at birth was categorized as cohabitating (reference) or not cohabitating. We categorized parity as first-born (reference), second-born, third-born, and fourth-born or higher. Maternal and paternal ages at childbirth were separated into categories of under 21, 21 to 24, 25 to 29 (reference), 30 to 35, and above 35 years old. Parental criminality was a dichotomous variable indicating conviction of any crime at or after the age of 15 [44]. We categorized parental highest level of education as an education of less than or equal to 9 years (reference category), upper secondary education of 1 to 3 years, and post-secondary and post-graduate education. We coded maternal, paternal, and average parental income at childbirth as percentiles of 0 to 20 (reference), 20 to 40, 40 to 60, 60 to 80, and 80 to 100. A category of "missing" was included as a dummy code for all covariates when appropriate.

Statistical analyses

We estimated statistical associations using either logistic regression (for binary response variables) or Cox proportional hazards models (for right-censored variables). In the first set of analyses, we measured the associations between maternal and paternal SMI and offspring PTB, LBW, and SGA using three logistic regression models. The baseline model estimated the association between maternal and paternal SMI and each pregnancy outcome while controlling for offspring year of birth, sex, and parity. The SMI adjusted model accounted for the previous covariates, as well as SMI in the other parent. Finally, the adjusted model accounted for all measured covariates.

In the second set of analyses, we estimated hazard ratios (HR) for the associations between the pregnancy outcomes (PTB, LBW, and SGA) and offspring ASD and ADHD using two Cox regression models. The baseline model adjusted for offspring sex and parity and the adjusted model accounted for all covariates. We included all measures of adverse birth outcome in the models in order to capture multiple aspects of problematic fetal development.

Finally, four Cox regression models were used to predict offspring ASD and ADHD from parental SMI. In Model 1 we measured the association between maternal and paternal SMI and offspring ASD and ADHD while controlling for offspring sex and parity. Model 2, similar to the previously described SMI adjusted model, assessed the association while also adjusting for SMI in the other parent. Model 3 measured the association while controlling

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for all covariates. Finally, Model 4 measured the association between maternal and paternal SMI and offspring ASD and ADHD while adjusting for all covariates, as well as gestational age, birth weight, and SGA, to examine whether pregnancy outcomes mediate the association between parental SMI and offspring neurodevelopmental problems. If pregnancy-related problems mediate the association, we would expect that the association between parental SMI and offspring ASD and ADHD would be attenuated in Model 4 as compared with the other models.

RESULTS

Demographics

Table 1 provides descriptive statistics for all eligible offspring born between 1992 and 2001 in Sweden. Of these offspring, 7,236 (0.8%) have received a diagnosis of ASD, 15,254 (1.8%) have received a diagnosis of ADHD, 19,288 (2.2%) were born SGA, 25,748 (3.0%) were born LBW, and 37,451 (4.3%) were PTB. A total of 9,134 (1.5%) mothers and 8,285 (1.4%) fathers were diagnosed with a SMI.

Parental SMI and adverse pregnancy outcomes

Table 2 provides the results of logistic regression analyses for maternal and paternal SMI predicting PTB, LBW, and SGA. Even in the adjusted models, both maternal and paternal SMI were associated with an increased risk for PTB (adjusted OR (aOR)$_{maternal}$=1.26; 95% CI=1.16-1.37; aOR$_{paternal}$ = 1.10; 95% CI=1.01-1.21) and SGA (aOR$_{maternal}$=1.13; 95% CI=1.01-1.26; aOR$_{paternal}$ = 1.13; 95% CI=1.01-1.28). With respect to LBW, maternal SMI continued to predict an increased risk (aOR$_{maternal}$=1.31; 95% CI=1.19-1.45), while associations between paternal SMI and LBW were attenuated in the adjusted model (aOR$_{paternal}$=1.11; 95% CI=0.99-1.23). Similar results were obtained when using parental SMI as a combined measure of maternal and paternal SMI, such that parental SMI was associated with an increased risk of each outcome (results available upon request).

Adverse pregnancy outcomes and offspring neurodevelopmental problems

Table 3 presents the results of Cox regression analyses predicting ASD and ADHD from PTB, LBW, and SGA. Each birth outcome was associated with an increased risk of ASD that was independent of measured covariates (e.g., adjusted HR (aHR)$_{LBW}$=1.79; CI=1.60-2.00). PTB, LBW, and SGA were also predictive of similar magnitudes of increased risk for ADHD (e.g., aHR$_{LBW}$=1.73; CI=1.61-1.87). Comparable results were obtained when using ordinal outcomes of gestational age and birth weight, presented in Table A1 online.

Parental SMI and offspring neurodevelopmental problems

Table 4 provides the results of models 1-4 predicting ASD and ADHD from parental SMI. In Models 1 and 2, maternal and paternal SMI were associated with an increased risk of offspring ASD and ADHD. These associations were attenuated, but remained after controlling for all covariates in Model 3 for both mothers (aHR$_{ASD}$=1.73; 95% CI=1.50-1.99; aHR$_{ADHD}$=1.59; 95% CI=1.44-1.79) and fathers (aHR$_{ASD}$=1.59, 95% CI=1.37-1.85; aHR$_{ADHD}$=1.47; 95% CI=1.32-1.62). The increased risk of offspring ASD

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and ADHD remained largely unchanged after controlling for birth outcomes in addition to all covariates in Model 4 for mothers (HR_{ASD}=1.72, 95% CI=1.46-2.02; HR_{ADHD}=1.56, 95% CI=1.39-1.74) and fathers (HR_{ASD}=1.56, 95% CI=1.31-1.86; HR_{ADHD}=1.36; 95% CI=1.21-1.54). Again, similar results were obtained when using a combined measure of parental SMI, such that parental SMI was associated with offspring ASD and ADHD and adverse pregnancy outcomes did not mediate the association.

Sensitivity Analyses—Parental SMI variables were limited to instances where the parent received the SMI diagnosis prior to childbirth in order to clarify the directionality of association. This limited the exposures to (XXX) maternal SMI and (XXX) paternal SMI instances. With this more restrictive definition or parental SMI and while adjusting for the other parents' SMI, maternal ($aOR_{maternal}$=1.13; 95% CI=1.01-1.26) and paternal ($aOR_{paternal}$ = 1.10; 95% CI=1.01-1.21) SMI continued to predict offspring ASD. Maternal ($aOR_{maternal}$=1.13; 95% CI=1.01-1.26) and paternal ($aOR_{paternal}$ = 1.10; 95% CI=1.01-1.21) SMI also continued to predict offspring ADHD in the adjusted model. When testing for mediation by adverse birth outcome, increased risk of offspring ASD and ADHD was robust after controlling for birth outcomes in addition to all covariates for mothers (HR_{ASD}=1.72, 95% CI=1.46-2.02; HR_{ADHD}=1.56, 95% CI=1.39-1.74) and fathers (HR_{ASD}=1.56, 95% CI=1.31-1.86; HR_{ADHD}=1.36; 95% CI=1.21-1.54).

DISCUSSION

The current study utilized a large, Swedish population-based sample to examine the associations between parental SMI, adverse pregnancy outcomes, and offspring neurodevelopmental problems. The results suggest that adverse pregnancy outcomes do not mediate the association between maternal and paternal SMI and offspring ASD and ADHD. More specifically, in agreement with previous research [15-18], we found that the risk of offspring PTB, LBW, and SGA are elevated if the mother and/or father has a SMI. With the exception of the association between paternal SMI and offspring LBW, these associations remained robust in the adjusted models. Although not statistically different, the variation in magnitude of association between mothers and fathers suggests that future research may benefit from continuing to explore if the relation between maternal SMI and pregnancy outcomes is partially influenced by the prenatal environment [15, 19, 32].

We also identified associations between PTB, LBW, and SGA and offspring ASD and ADHD that were independent of measured covariates. These findings are largely consistent with other studies assessing adverse pregnancy outcomes as risk factors for ASD and ADHD [20-27, 45]. A recent sibling-comparison study has supported the independent association between PTB and offspring ASD [28], and researchers have suggested that abnormalities in the brain development of offspring born preterm are associated with an increased risk of ADHD [46]. LBW and SGA also are associated with many diseases later in life, including mental illness, which may be the result of fetal growth restriction [29, 30]. Thus, the association between adverse pregnancy outcomes and neurodevelopmental problems found in this study may be explained by similar mechanisms. For example, previous research has found that LBW is associated with white matter abnormalities and cortical surface area and brain volume shows variation even across normal birth weights [47, 48]. Poor maternal

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nutrition during pregnancy may also be contributing to fetal growth and altered brain development [49].

In addition, our results suggest that offspring of parents with a SMI are at an increased risk of ASD and ADHD. These associations were largely unchanged after controlling for birth outcomes, suggesting that adverse pregnancy outcomes do not mediate the association between parental SMI and offspring neurodevelopmental problems. This finding supports those of a smaller study that found parental SMI and adverse pregnancy outcomes to be independent risk factors for ASD [10]. The current study extends this previous research by showing that maternal and paternal SMI are independent risk factors for ASD [10] and shows a novel parallel association with offspring ADHD, a highly related outcome [34]. However, future research should explore the association between paternal SMI, ADHD, and possible mediation by adverse birth outcomes because unlike the other associations, this association was slightly reduced in magnitude with the additional control of adverse birth outcomes (HR of 1.47 vs. 1.36). Environmental or genetic vulnerability may be responsible for partial mediation, if found in future research.

The similarity in magnitudes of the increased risk of offspring neurodevelopmental problems for maternal and paternal SMI suggests that observed associations are likely due to genetic and/or environmental factors rather than causal intrauterine effects [32]. If the association were due to intrauterine effects, maternal SMI would have showed a stronger association with offspring ASD than with paternal SMI, thus mental illnesses may share common etiological factors, such as genetic risk [8, 11, 14, 34].

Limitations

Despite using a large, population-based sample with well-validated measures and controlling for several offspring and parental characteristics, our findings must be interpreted in light of a number of limitations. First, Swedish health care and diagnostic practices may differ from other countries. Second, our definition of parental SMI required that individuals be diagnosed in an inpatient setting, which may lead to over or underestimation of the magnitude of associations. Future research is needed to examine the studied relations using parental SMI prior to childbirth, indexed at disease onset, and including outpatient diagnoses. Additionally, including other measures of neurodevelopmental disorders will help to determine the specificity of our findings. Finally, while PTB, LBW, and SGA are important indices, they are merely proxies for restricted fetal growth and brain development. We included all three measures of adverse birth outcome to capture the most complete measure of problematic fetal development. However, fetal insults that are not indexed by PTB, LBW, or SGA may still mediate the association between parental SMI and offspring neurodevelopmental problems.

Conclusion

Adverse pregnancy outcomes and maternal and paternal SMI are independent risk factors for ASD and ADHD. The similarity in moderate association magnitude between maternal and paternal SMI and offspring ASD and ADHD indicates that the associations are likely not due to causal intrauterine effects [32]. Our results provide evidence consistent with the

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theory that genetic factors may explain much of the association between parental SMI and offspring ASD and ADHD [14]. Future research should continue to focus on elucidating the mechanisms underlying the independent associations between parental SMI, adverse pregnancy outcomes, and offspring ASD and ADHD, as this could provide etiological information about these neurodevelopmental problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

SMI	Parental severe mental illness
ASD	Autism Spectrum Disorder
ADHD	Attention Deficit Hyperactivity Disorder
PTB	preterm birth
LBW	low birth weight
SGA	small for gestational age

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Table 1

Descriptive characteristics of offspring born in Sweden 1992-2001

Variable	N	% of Total Sample
Offspring Characteristics (N = 870,017)		
Sex		
Female	425,218	48.9%
Male[a]	444,799	51.1%
Parity		
First[a]	356,593	41.0%
Second	322,893	37.1%
Third	131,831	15.2%
Fourth or higher	58,700	6.7%
Maternal Age at Childbirth (years)		
under 21	17,941	2.1%
21-24	150,268	17.3%
25-29[a]	319,598	36.7%
30-35	259,498	29.8%
over 35	122,712	14.1%
Paternal Age at Childbirth (years)		
under 21	4,967	0.6%
21-24	73,633	8.5%
25-29[a]	253,988	29.2%
30-35	286,383	32.9%
over 35	249,813	28.7%
Missing	1,233	0.1%
Maternal Disposable Income at Birth (percentile)		
0-20[a]	92,742	10.7%
20-40	161,367	18.5%
40-60	231,371	26.6%
60-80	212,402	24.4%
80-100	167,436	19.2%
Missing	4,699	0.5%
Paternal Disposable Income at Birth (percentile)		
0-20[a]	95,940	11.0%
20-40	163,917	18.8%
40-60	228,221	26.2%
60-80	210,774	24.2%
80-100	162,782	18.7%
Missing	8,383	1.0%
Parental Disposable Income at Birth (percentile)		

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Variable	N	% of Total Sample
0-20[a]	96,797	11.1%
20-40	163,430	18.8%
40-60	222,190	25.5%
60-80	207,746	23.9%
80-100	176,622	20.3%
Missing	3,232	0.4%
Parental Cohabitation Status at Birth		
Cohabitation[a]	772,180	88.8%
No Cohabitation	38,985	4.5%
Missing	58,852	6.8%
Gestational Age		
23 weeks to 27 weeks 6 days	1,016	0.1%
28 weeks to 30 weeks 6 days	2,148	0.2%
31 weeks to 33 weeks 6 days	5,685	0.7%
34 weeks to 36 weeks 6 days	28,602	3.3%
37 weeks to 42 weeks 6 days[a]	832,556	95.7%
Birth weight (grams)		
less than 2500	25,748	3.0%
2500-3000	86,836	10.0%
3000-3500	271,963	31.3%
3500-4000[a]	311,723	35.8%
greater than 4000	171,176	19.7%
Missing BW	2,571	0.3%
Small for Gestational Age		
Not SGA[a]	846,984	97.4%
SGA	19,288	2.2%
Missing	3,745	0.4%
ASD		
No ASD[a]	862,781	99.2%
ASD	7,236	0.8%
ADHD		
No ADHD[a]	854,763	98.2%
ADHD	15,254	1.8%
Maternal Characteristics (N=597,264)		
Country of Origin		
Sweden	505,249	84.6%
Not Sweden[a]	91,461	15.3%
Missing	554	0.1%
Highest Level of Education		

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Variable	N	% of Total Sample
Less than 9 years[a]	56,985	9.5%
Upper secondary education of 1-3 years	301,904	50.5%
Post-secondary and post-graduate education	236,614	39.6%
Missing	1,761	0.3%
Criminality		
No Criminality[a]	523,772	87.7%
Criminality	73,492	12.3%
Severe Mental Illness		
No Severe Mental Illness[a]	588,130	98.5%
Severe Mental Illness	9,134	1.5%
Paternal Characteristics (N=599,747)		
Country of Origin		
Sweden[a]	503,514	84.1%
Not Sweden	95,388	15.9%
Missing	845	0.1%
Highest Level of Education		
Less than 9 years[a]	86,555	14.4%
Upper secondary education of 1-3 years	323,004	53.9%
Post-secondary and post-graduate education	187,729	31.3%
Missing	2,459	0.4%
Criminality		
No Criminality[a]	344,971	57.5%
Criminality	254,776	42.5%
Severe Mental Illness		
No Severe Mental Illness[a]	591,462	98.6%
Severe Mental Illness	8,285	1.4%

[a]Reference

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Table 2

Results of parental severe mental illness predicting pregnancy outcomes

	BASELINE		SMI ADJUSTED		ADJUSTED	
Outcomes	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Preterm Birth						
- Maternal SMI	1.39*	1.29-1.50	1.38*	1.28-1.49	1.26*	1.16-1.37
- Paternal SMI	1.21*	1.11-1.32	1.20*	1.10-1.30	1.10*	1.01-1.21
Low Birth Weight						
- Maternal SMI	1.52*	1.39-1.66	1.51*	1.38-1.65	1.31*	1.19-1.45
- Paternal SMI	1.28*	1.16-1.41	1.26*	1.14-1.39	1.11	0.99-1.23
Small for Gestational Age						
- Maternal SMI	1.39*	1.25-1.54	1.37*	1.23-1.53	1.13*	1.01-1.26
- Paternal SMI	1.37*	1.22-1.53	1.35*	1.21-1.51	1.13*	1.01-1.28

Note: SMI= severe mental illness, OR = odds ratio, CI = confidence interval,

* $p<0.05$. The baseline model controlled for offspring year of birth, sex, and parity. The SMI adjusted model additionally controlled for SMI in the other parent. The adjusted model additionally controlled for all measured covariates.

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Table 3

Results of pregnancy outcomes predicting ASD and ADHD

Predictors	BASELINE		ADJUSTED	
	HR	95% CI	HR	95% CI
ASD				
Preterm Birth	1.53*	1.40-1.67	1.47*	1.34-1.62
Low Birth Weight[a]	1.92*	1.74-2.13	1.79*	1.60-2.00
Small for Gestational Age[a]	1.69*	1.50-1.91	1.50*	1.32-1.71
ADHD				
Preterm Birth	1.53*	1.43-1.62	1.42*	1.31-1.51
Low Birth Weight[a]	1.90*	1.77-2.04	1.73*	1.61-1.87
Small for Gestational Age[a]	1.71*	1.57-1.86	1.58*	1.45-1.73

Note: None of the cases missing birth weight or SGA had a diagnosis of ASD or ADHD, so missing birth weight and SGA were dropped from the analyses; ASD = Autism Spectrum Disorder, ADHD = Attention Deficit Hyperactivity Disorder, HR = hazard ratio, CI = confidence interval,

*$p<0.05$. The baseline model controlled for offspring sex and parity. The adjusted model additionally controlled for all measured covariates.

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Table 4

Results of models 1-4 of maternal and paternal SMI predicting ASD and ADHD

Predictors	Model 1		Model 2		Model 3		Model 4	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ASD								
Maternal SMI	2.04*	1.78-2.34	1.99*	1.74-2.28	1.73*	1.50-1.99	1.72*	1.46-2.02
Paternal SMI	1.98*	1.72-2.28	1.92*	1.66-2.21	1.59*	1.37-1.85	1.56*	1.31-1.86
ADHD								
Maternal SMI	2.16*	1.97-2.37	2.09*	1.90-2.29	1.59*	1.44-1.75	1.56*	1.39-1.74
Paternal SMI	2.21*	2.01-2.43	2.13*	1.94-2.35	1.47*	1.32-1.62	1.36*	1.21-1.54

Note: SMI= severe mental illness, ASD = Autism Spectrum Disorder, ADHD = Attention Deficit Hyperactivity Disorder, HR = hazard ratio, CI = confidence interval,

*p<0.05. Model 1 controlled for offspring sex and parity. Model 2 additionally controlled for SMI in the other parent. Model 3 additionally controlled for all measured covariates. Model 4 additionally controlled for gestational age, birth weight, and small for gestational age.

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