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Original article

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, low birth weight, and small for gestational age 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 preterm birth, low birth weight, and gestational age, and 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.

Introduction

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 three developmental disorders (i.e., autism, Asperger, 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

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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 [20–30]. 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, whereas much can be gleaned of additionally predicting ADHD, a condition highly related to ASD [33,34].

We used 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.

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 contains annual data since 1990 on income for individuals aged 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 with 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 an SMI were defined as those who had received a diagnosis of schizophrenia, bipolar disorder, or another nonorganic psychosis according to *International Classification of Diseases*, 8th, 9th, and 10th Revision 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 an 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 who had received either an inpatient or outpatient diagnosis of ASD or ADHD according to *International Classification of Diseases* 9th and 10th criteria. Only individuals diagnosed before the age of 18 years 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 2500g (LBW), 2500 to 2999 g, 3000 to 3499 g, 3500 to 3999 g (reference group), and 4000 g and greater and an additional category for missing birth weight. Gestational age was divided into five categories of 23 to 27 weeks 6 days, 28 to 30 weeks 6 days, 31 to 33 weeks 6 days, 34 to 36 weeks 6 days, and 37 to 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 epidemiologic 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 years [44]. We categorized parental highest level of education as an education of 9 years or less (reference category), upper secondary education of 1 to 3 years, and postsecondary and postgraduate 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