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Offspring psychopathology following preconception, prenatal, and postnatal maternal bereavement stress

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Abstract

Background—Preconception, prenatal, and postnatal maternal stress are associated with increased offspring psychopathology, but findings are inconsistent and need replication. We estimated associations between maternal bereavement stress and offspring autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, suicide attempt, and completed suicide.

Methods—Using Swedish registers, we conducted the largest population-based study to date examining associations between stress exposure in 738,144 offspring born 1992–2000 for childhood outcomes and 2,155,221 offspring born 1973–1997 for adult outcomes with follow-up through 2009. Maternal stress was defined as death of a first degree relative during 6 months before conception, across pregnancy, or the first two postnatal years. Cox proportional survival analyses were used to obtain hazard ratios (HR) in unadjusted and adjusted analyses.

Results—Marginal increased risk of bipolar disorder and schizophrenia following preconception bereavement stress was not significant. Third trimester prenatal stress increased risk of ASD (adjusted HR=1.58, 95% CI: 1.15–2.17) and ADHD (adjusted HR=1.31, 95% CI: 1.04–1.66). First postnatal year stress increased risk for offspring suicide attempt (adjusted HR=1.13, 95% CI: 1.02–1.25) and completed suicide (adjusted HR=1.51, 95% CI: 1.08–2.11). Bereavement stress during the second postnatal year increased risk of ASD (adjusted HR=1.30, 95% CI: 1.09–1.55).

Conclusions—Further research is needed on associations between preconception stress and psychopathological outcomes. Prenatal bereavement stress increases risk of offspring ASD and ADHD. Postnatal bereavement stress moderately increases risk of offspring suicide attempt, completed suicide, and ASD. Smaller previous studies may have overestimated associations between early stress and psychopathological outcomes.

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Keywords

stress; preconception; prenatal; postnatal; psychiatric; psychopathology; autism; attention-deficit/hyperactivity disorder; schizophrenia; suicide

In support of the developmental origins of disease hypothesis (Barker, 1998), accumulating evidence links maternal stress to increased risk of psychopathological morbidity in offspring (Khashan et al., 2008a, Li et al., 2010, Khashan et al., 2011, Van Os and Selten, 1998, Ronald et al., 2011, Huttunen and Niskanen, 1978, Rodriguez and Bohlin, 2005). Studies have identified associations with severe, impairing, and costly psychiatric disorders, including autism spectrum disorder (ASD; Ganz, 2007, Beversdorf et al., 2005), attention-deficit/hyperactivity disorder (ADHD; Rodriguez and Bohlin, 2005, Polanczyk et al., 2007, Pelham et al., 2007), and schizophrenia (Jablensky, 2000, Khashan et al., 2008a). Associations with adverse psychopathological outcomes have been reported following maternal exposure to physical stressors, such as famine (Brown et al., 2000, Brown et al., 1995), and psychological stressors, such as bereavement (Khashan et al., 2008a, Khashan et al., 2011, Li et al., 2010), trauma (Brand et al., 2006), war (Van Os and Selten, 1998), and natural disaster (Glynn et al., 2001, King and Laplante, 2005, Kinney et al., 2008a). Assessing the effect of timing of an individual level, objective psychological stress on psychiatric outcomes is particularly important because linkage with a specifically-timed effect increases the likelihood that an association might be causal (Smith, 2008).

Previous research suggests that exposure during sensitive critical periods may exist for certain psychiatric disorders. For example, in humans *preconception* stress may be associated with an increased risk of childhood ADHD (Li et al., 2010) and adult affective disorder (Khashan et al., 2011), but only in male offspring. In rodents, preconception stress is associated with altered adult offspring memory functioning (Schelar et al., 2007) and differences in affective and social behaviour (Shachar-Dadon et al., 2009). In humans, evidence indicates that *prenatal* maternal stress is associated with psychopathological outcomes across stressors and populations (Khashan et al., 2008a, Li et al., 2010, Khashan et al., 2011, Van Os and Selten, 1998, Ronald et al., 2011, Huttunen and Niskanen, 1978, Rodriguez and Bohlin, 2005, Talge et al., 2007, Bale et al., 2010, O'Connor et al., 2003, Beydoun and Saftlas, 2008, Beversdorf et al., 2005, Kinney et al., 2008a). Additionally, *postnatal* stress exposure is associated with increased risk of offspring psychiatric outcomes (Brent and Mann, 2006, Heim et al., 2008, Landau et al., 2010, Rosenberg et al., 2007, Mortensen et al., 2003, Epstein et al., 2008, Guinchat et al., 2012, Rai et al., 2012).

While associations between early stress exposure and perinatal outcomes show relative consistency (Beydoun and Saftlas, 2008), associations between early maternal stress exposure and major psychopathological outcomes remain inconsistent and need focused and continued exploration for several reasons. First, there is a paucity of evidence for the effect of preconception maternal exposure to severe stress; where these do exist, effect sizes are modest at best (Khashan et al., 2008a, Khashan et al., 2011). Second, replication is needed for a number of reported effects. For example, a meta-analysis did not support an association between prenatal stress and schizophrenia (Selten et al., 2003), and studies predicting autism from prenatal stress also have been inconsistent (Li et al., 2009, Beversdorf et al., 2005, Rai et al., 2012, Ronald et al., 2011). Finally, several important methodological issues limit the quality of much of the evidence to date. For example, measurement difficulties abound, such as the use of retrospective self-reports in small and biased samples (Beversdorf et al., 2005). In famine studies, individuals are exposed to psychological as well as nutritional stressors, while women that conceive and complete pregnancy during famine may represent an unusual group (Dunkel-Schetter and Glynn, 2011, Rodriguez and Bohlin, 2005, Brown et

al., 2000, St. Clair et al., 2005). These limitations are of enough concern to render current evidence for robust and/or causal associations between preconception, prenatal, and postnatal maternal stress exposure and offspring psychopathological outcomes inconclusive.

We set out to address sample size, measurement, and timing limitations in previous studies by analysing data from Swedish national registers. These data provide one of the largest and most comprehensive population registers currently available for psychiatric research. Utilising the highest quality and largest data set possible was necessary to draw conclusions regarding associations between rare risks and outcomes across several early risk periods in one population. We decided to focus on psychopathological outcomes with the best evidence to date (ASD, ADHD, and schizophrenia), associated outcomes of suicidal behaviour (suicide attempt and completed suicide), and bipolar disorder, which has not been directly examined previously. We defined exposure to maternal stress as the occurrence of the death of a first degree relative of the mother which we considered an objective measure of psychological stress. We also utilised the random nature of the timing of the exposure to bereavement stress in a quasi-experimental design (Academy of Medical Sciences Working Group, 2007), while statistically controlling for measured covariates to help account for alternative explanations.

We hypothesised that the findings would support prior positive findings by timing of exposure, as well as reveal novel associations with previously unstudied outcomes. In particular, we hypothesized that preconception bereavement stress would be associated with increased risk for offspring ADHD but not other outcomes (Li et al., 2010, Khashan et al., 2008a, Li et al., 2009). We hypothesized that prenatal bereavement stress would be associated with increased risk for ADHD and schizophrenia (Kinney et al., 2008b, Ronald et al., 2011, Li et al., 2010, Brown et al., 2000, Khashan et al., 2008a, Kinney et al., 2008a), as well as increased risk for bipolar disorder and attempted and completed suicide, but not ASD (Li et al., 2009, Rai et al., 2012). Finally, we hypothesized that postnatal bereavement stress would be associated with increased risk for offspring ASD, ADHD (Epstein et al., 2008, Guinchat et al., 2012, Landau et al., 2010, Rai et al., 2012) and attempted and completed suicide (Williams and Pollock, 2000). We also performed sensitivity analyses to rule out moderation by offspring sex, test the robustness of associations by birth outcomes and parental psychopathology, and explore outcome specificity (Khashan et al., 2008b, Smith et al., 2003, Gluckman and Hanson, 2004, Mittendorfer-Rutz et al., 2004, Lindstrom et al., 2011, Abel et al., 2010, Moster et al., 2008, Hultman et al., 2007, Losh et al., 2011).

Methods

Study population

After approval from the Institutional Review Board and ethical committees at Karolinska Institutet and Indiana University, we constructed a population-based sample by linking Swedish nationwide, longitudinal population registries via unique personal identification numbers. The Medical Birth Registry (Centre for Epidemiology, Cnattingius et al., 1990) included data on over 99% of all births in Sweden from 1973 to 2008 and was used to obtain information on gestational length and birth complications. First degree biological relatives of the mother (parents, full siblings, already born children) were identified using the Multi-Generation Registry (Statistics Sweden, 2006). The Cause of Death Registry was used to identify family member dates of death for bereavement stress exposure indication. The National Patient Register provided diagnosis for all inpatient hospital admissions since 1973 and outpatient since 2001. The Education Register (Statistics Sweden) provided information on parental highest level of completed formal education, and the National Crime Register (Fazel and Grann, 2006) provided data on parental criminal convictions since the age of 15,

the Swedish age of criminal responsibility, from 1973 onward. Finally, the Migration Register provided information on dates of migration in or out of Sweden.

Figure 1 presents the sample flow across child and adult specific samples. The dataset began with 2,842,683 individuals born from 1973 to 2000. We removed multiple births because rates of adverse birth outcomes in multiples differs from singletons (Matthews and Rodin, 1992), and offspring with missing mother, grandmother, and father identification numbers for complete identification of family members that may have died during the exposure window. We also removed offspring with missing gestational age and possible erroneous gestational age values of greater than 42 weeks and 6 days because timing of stress exposure was determined by gestational age at birth. A total of 2,411,725 (84.8%) singleton offspring remained before separating by year of birth for child and adult outcome samples.

Valid and reliable childhood outcomes from the National Patient Register were available for offspring born from 1992 to 2000 ($n=742,947$). Children had to be at least 2 years old to receive a diagnosis of ASD or ADHD. We removed children that had died, emigrated, or were diagnosed before their second birthday and or were missing a diagnosis date. Thus, our final child sample contained 738,144 offspring. No offspring were diagnosed with ASD or ADHD before exposure to stress in the second postnatal year. Adult outcomes were limited to a cohort of offspring born between 1973 and 1997 ($n=2,197,707$) to allow offspring to reach 12 years of age to receive a valid diagnosis age. Similar to the child outcome sample, we removed adults who died, emigrated, presented with an adult-onset outcome before their twelfth birthday, or were missing their date of diagnosis resulting in a final sample of 2,155,221 adults. Both cohorts were followed through 2009.

Exposure

Death of a first degree relative was chosen to provide an insult that resulted in substantial psychological stress (Arbuckle and de Vries, 1995) with precise timing. For preconception bereavement stress, this included death of her biological parents, siblings, or already born children; for prenatal and postnatal bereavement stress, this definition was extended to include death of the biological father of the index child.

Exposure periods were divided into preconception (6-0 months prior to conception) and was further subdivided into 0–3 months and 4–6 months preconception windows; prenatal (conception to birth) and further subdivided into trimesters (1st trimester 0–12 weeks; 2nd trimester 13–24 weeks; and 3rd trimester 25 weeks to birth); and postnatal (0–2 years) which was subdivided into first year and second year windows. See Table 1 for details concerning the number of exposed individuals across the risk periods. For the few mothers (32 preconception, 25 prenatal, 34 first postnatal year, and 66 second postnatal year) that experienced more than one stressor within the same exposure window, the timing of the first stress exposure was used. Less than 0.01% of the sample experienced a stressor during more than one exposure windows. Sample size restricted further investigation of possible stress exposure dosage effects.

Outcome Variables

The National Patient Register provided discharge date and primary diagnosis using WHO's International Classification of Diseases (ICD-8, -9, and -10).

Childhood psychiatric outcomes—Children receiving an ASD diagnosis included inpatient and outpatient diagnoses of ASD and Asperger's syndrome (ICD-10: F84). Children receiving an ADHD diagnosis included inpatient or outpatient diagnosis of hyperkinetic disorder (ICD-10: F90).

Adult psychiatric outcomes—We identified bipolar disorder (ICD-8: 296 excluding 296.20, 296.4–296.7; ICD-9: 296A, C, D, E, W; ICD-10: F30, 31) and strictly defined schizophrenia (ICD-8: 295 excluding 295.40, 295.50, 295.70; ICD-9: 295 excluding 295E, 295F, 295H; ICD-10: F20; Lichtenstein et al., 2009). We also identified suicide attempt that resulted in inpatient hospitalisation and completed suicide (ICD-8: E950-959, E980-989; ICD-9: E950-959, E980-989; ICD-10: X60-84, Y10-34, Y870, Y872; Tidemalm et al., 2008). For individuals presenting with multiple suicide attempts, only the first occasion was counted. We chose not to examine broadly defined affective disorder because hospitalisation for that diagnosis may indicate suicidality or psychosis and be better examined when categorised as such.

Analyses

We used Cox proportional survival analyses to estimate the association of early bereavement stress on right-censored psychiatric outcomes using SAS 9.2. Information on migration and death were used to calculate person-years at risk for receiving a diagnosis; if offspring did not receive a diagnosis within the study period, they contributed person-time at risk until death, emigration, or the end date of follow-up (December 31, 2009), whichever came first. For each outcome, unadjusted and adjusted estimates were fitted using dichotomous predictors for each preconception, prenatal, and postnatal stress exposure. Robust standard errors were utilized in baseline and adjusted models to account for the nested nature of the data (the possibility of one mother having multiple children within the dataset).

Adjusted models controlled for the following potential confounders: offspring sex, birth order (first [referent], second, third, fourth born and higher), offspring birth weight, (missing, 500–2499, and 2500–6000 [referent] g), gestational age (23–32.6, 33–36.6, 37–41.6 [referent], and 42+ weeks), maternal and paternal age (< 20, 20–24, 25–29 [referent], 30–34, and > 34 years), maternal and paternal country of birth (Swedish [referent], non-Swedish, or missing), maternal and paternal highest education (primary or lower secondary education of 9 or fewer years, 1–3 years of upper secondary school [referent], post-secondary education, and missing), a binary indicator of maternal and paternal history of any criminal conviction, a binary indicator of both maternal and paternal history of severe mental illness (including bipolar disorder, broadly defined schizophrenia, and suicide attempt resulting in inpatient care), and a binary indicator of both maternal and paternal death by suicide.

Sensitivity analyses—First, we tested whether offspring sex moderated the association between bereavement stress and outcome by including an offspring sex by exposure interaction term because previous research has indicated that sex differences may exist in some of these associations (Khashan et al., 2011, Li et al., 2010). Second, we included only offspring whose parents did not have a history of severe psychopathology, including bipolar disorder, broadly defined schizophrenia, suicide attempt, or completed suicide, to control more rigorously for familial risk of psychopathology. Third, we restricted the analysis to full term (> 37 and < 43 weeks gestation) and normal birth weight (> 2500g) because these obstetric factors are associated with both maternal exposure to stressors and excess risk of later psychopathology (Losh et al., 2011, Lindstrom et al., 2009, Abel et al., 2010, Class et al., 2011, Khashan et al., 2008b, Khashan et al., 2009). Fourth, we predicted broadly defined schizophrenia, including schizoaffective disorder and non-affective psychosis (ICD-8: 295, 297, 298.20–298.99, 299.99; ICD-9: 295, 297, 298C-X; ICD-10: F20-29), in order more precisely replicate or refute previous research (Khashan et al., 2008a). Finally, we combined bipolar disorder and strictly defined schizophrenia into severe mental illness because of the shared genetic aetiology of these disorders (Lichtenstein et al., 2009). This test explored if associations were outcome-specific or if early stress constitutes a shared risk factor.

Results

We identified a total of 6,430 children with ASD [Kaplan-Meier estimate (K-M est) = 1.2% by the age 17.9 years; 72.4% male] and 14,313 children with ADHD (K-M est = 2.7% by age 17.9 years; 75.8% male) within the child sample. We identified 8,001 individuals with bipolar disorder (K-M est = 0.9% by age 35 years; 68.5% male), 8,063 with non-affective psychoses (K-M est = 0.8% by age 35 years; 57.9% male), 2,400 individuals with schizophrenia (K-M est = 0.3% by age 35 years; 66.5% male), 25,855 cases of attempted suicide that resulted in inpatient hospital care (K-M est = 1.9% by age 35 years; 34.0% male), and 1,751 cases of completed suicide (K-M est = 0.2% by age 35 years) in the adult sample.

Preconception maternal stress

Table 2 presents the results from the survival analyses. We found no significant associations between preconception bereavement stress and offspring child or adult disorders. The magnitude of association with bipolar disorder and schizophrenia remained marginally elevated in adjusted models, but not statistically significantly elevated. In spite of the size of our sample, lack of a statistically significant estimate in a low number of exposed cases ($n_{\text{bipolar}}=73$, $n_{\text{schizophrenia}}=24$) may suggest that the association is too weak to be found in small numbers. Separating the preconception period into two 3-month windows (0–3 mo and 4–6 mo preconception) echoed the null associations seen across the entire six month window.

Prenatal maternal stress

Table 3 shows associations with exposure to prenatal maternal stress. A statistically significant association was found for offspring ASD (adjusted HR = 1.30, 95% CI: 1.04–1.62). No other significant associations were found for the analysis across the entire prenatal period.

Analyses by trimester (Table 3) suggested that the association between prenatal maternal exposure to stress and increased risk for offspring ASD may be driven by risk incurred from third trimester exposure (adjusted HR = 1.58, 95% CI: 1.15–2.17). An elevated risk, however, was also noted following first trimester stress exposure, although the confidence interval around the association was large (adjusted HR = 1.25, 95% CI: 0.82–1.91). Risk for ADHD was significantly increased following third trimester stress exposure (adjusted HR = 1.31, 95% CI: 1.04–1.66). No other significant associations by trimester were found.

Postnatal maternal stress

Table 4 presents associations with postnatal maternal stress. Over the first two postnatal years, maternal exposure to bereavement stress marginally increased risk of offspring ASD (adjusted HR = 1.15, 95% CI: 1.00–1.32) and suicide attempt (adjusted HR = 1.10, 95% CI: 1.03–1.18). When separated by postnatal year of exposure, offspring of women who experienced stress in the first postnatal year were at increased risk of suicide attempt (adjusted HR = 1.13, 95% CI: 1.02–1.25) and completed suicide (adjusted HR = 1.51, 95% CI: 1.08–2.11). Maternal stress during the second postpartum year was associated with a significant increased risk of ASD (adjusted HR = 1.30, 95% CI: 1.09–1.55). No other significant associations between postnatal maternal stress and offspring psychiatric outcomes were found.

Sensitivity analyses

First, no sex interaction was statistically significant (all results available upon request). Results from the second and third sensitivity analyses, restricting the sample to offspring

whose parents had no history of severe mental illness or completed suicide and restricting the sample to offspring to full term and normal birth weight respectively, paralleled findings from original models. Fourth, no notable or significant associations with broadly defined schizophrenia were found across any exposure period. Finally, results predicting combined severe mental illness revealed that preconception estimates remained elevated and the association trended towards statistical significance (adjusted HR = 1.18, 95% CI: 0.96–1.45, N=92).

Discussion

Using one of the largest population databases currently available, we examined the effect of preconception, prenatal, and early postnatal maternal bereavement stress on risk of child and adult psychopathology. Our data point to three key findings: First, in contrast with some previous studies (Khashan et al., 2008a, Khashan et al., 2011, Huttunen and Niskanen, 1978, Beydoun and Saftlas, 2008), we found few associations between a well-characterised, objective measure of early maternal exposure to psychological stress and odds of later severe psychiatric problems. Second, associations reported are dependent on the timing of the exposure and on the particular outcome assessed. Third, in line with previous findings (Ward, 1990, Kinney et al., 2008a, Beversdorf et al., 2005, Ronald et al., 2011), excess risk following maternal prenatal bereavement stress was identified for childhood onset developmental disorders, namely ASD and ADHD. We also identified novel associations between postnatal maternal bereavement exposure and offspring attempted and completed suicide and ASD. Generally, these findings suggest that previous research may have overestimated the magnitude of associations identified.

We report no statistically significant effect of preconception stress on any of the studied outcomes. However, the effect sizes and parallel findings from sensitivity analyses suggest that marginal associations may be present for severe mental illness (i.e. bipolar disorder and schizophrenia combined; Lichtenstein et al., 2009). Increased numbers of exposed cases would allow for better precision in estimating effects. Our preconception null results are consistent with previous findings for ASD (Li et al., 2009), but inconsistent with a previous study predicting ADHD (Li et al., 2010). These authors defined ADHD by diagnosis and/or medication, found significant association only in male offspring, and only following the unexpected death of a spouse or already born child.

We found evidence for an association between prenatal bereavement stress and offspring ASD and ADHD only. Estimates were highest following third trimester exposure. The associations with ASD remained significant after adjustment for potential confounders and in all of the sensitivity analyses. Similar positive associations with ASD have been reported in studies measuring potentially less severe but more chronic stress exposure from family discord (Ward, 1990), after hurricanes and tropical storm exposure (Kinney et al., 2008a), and retrospectively recalled (Beversdorf et al., 2005) and prospectively measured (Ronald et al., 2011) stressful life events. In contrast, others have not identified increased odds of ASD following stress exposure in a large Danish cohort (Li et al., 2009) and in a somewhat smaller study using a broader definition of stress (Rai et al., 2012). Unlike previous studies (Li et al., 2010, Rodriguez and Bohlin, 2005), we did not identify moderation by offspring sex. More research is needed to clarify this.

Our findings are not consistent with previous studies reporting associations between maternal anxiety, prenatal stress exposure or potentially non-independent life events, and subsequent neurodevelopmental or behavioural problems in infants and children (Beydoun and Saftlas, 2008). Many of these associations may be confounded by genetic transmission of temperament from mother to child (King *et al.* 2005), although some have taken these

effects into account (Charil et al., 2010). It may be that specific symptoms, such as cognitive and language deficits, are more likely to have a positive association with prenatal stress exposures than the disorders we examined (e.g., Buss et al., 2012, King and Laplante, 2005, Charil et al., 2010, Talge et al., 2007). However, this would imply more discontinuity between child neurodevelopment or behaviour and mental health outcomes than might be expected (Caspi et al., 1996, Rutter et al., 2006).

ASD and ADHD are comorbid conditions (Simonoff et al., 2008), and prenatal stress may act as a shared risk factor for abnormal neurodevelopment (Wadhwa, 2005). This notion, however, is inconsistent with our lack of association with adult neurodevelopmental outcomes. In our larger sample, we do not replicate the first trimester association with broadly defined schizophrenia (Khashan et al., 2008a). Our findings on bipolar disorder are consistent with a null finding between prenatal stress and affective disorder, including bipolar disorder (Van Os and Selten, 1998). To our knowledge, this is the first study to have examined the association between prenatal bereavement stress and offspring suicidal behaviour. Overall, our findings do not support even moderate effects of prenatal bereavement stress on risk of adult psychiatric outcomes.

Postnatal maternal bereavement stress increased the risk for offspring suicide attempt and completed suicide, in line with previous research on childhood trauma and later suicidal behaviour (Brent and Mann, 2006, Heim et al., 2008). Maternal exposure to bereavement stress in the second postnatal year was also associated with increased odds of ASD and the association was robust in offspring without parental history of severe mental illness or adverse birth outcome (Rai et al., 2012). Unlike the shared ASD/ADHD patterns identified following prenatal stress, associations between postnatal stress and ADHD were not consistently statistically significant. Thus, different mechanisms may be responsible for the postnatal and prenatal associations with ASD.

Determining if outcomes are associated with particular sensitive periods of development may offer insight into aetiological mechanisms (Jirtle and Skinner, 2007, Meaney, 2010, Smits and Essed, 2001, Van den Bergh et al., 2008, Wadhwa, 2005, Buss et al., 2010, Van den Bergh et al., 2005, Brent and Mann, 2006). If prenatal associations with ASD are replicated, future research should examine mechanisms specific to late pregnancy relevant to the risk of psychopathology, including development of olivary neurons and Purkinje cells in the cerebellum (Bauman and Kemper, 2005, Bauman and Kemper, 1994, Bailey et al., 1998) or oestradiol-sensitive gene expression (Kinney et al., 2008b). Postnatal developmental changes in the prefrontal cortex (Liu et al., 2012) or susceptibility to diminished parenting resources, sensitivity, and/or stimulation as a consequence of maternal stress (Bagner et al., 2010, Goodman and Gotlib, 1999) may be particularly critical for ASD risk during the second postnatal year of development (Mantymaa et al., 2012). Future research may also consider differential susceptibility to stressors given that family members of individuals with ASD show elevated rates of anxiety (Piven and Palmer, 1999), which may be related to stress reactivity. General mechanisms linking prenatal stress exposure and ADHD may include a disruption in stress-response systems (Wadhwa, 2005, Van den Bergh et al., 2008), prefrontal cortex development (Van den Bergh et al., 2005), gray matter density development (Buss et al., 2010), or confounding inherited factors that are associated both with the odds of stress exposure and offspring psychopathology (Rice et al., 2010). Postnatally, exposure to trauma, stress and maternal depression (Whiffen and Gotlib, 1989, Bagner et al., 2010) may adversely affect offspring problem-solving abilities, cognitive ability, attachment, and/or compound genetic vulnerability to suicide (Williams and Pollock, 2000, Mann, 2003, Brent and Mann, 2005, Goodman and Gotlib, 1999).

This study has several methodological strengths. We describe the associations between preconception, prenatal, and postnatal maternal stress exposures and offspring risk for later psychiatric morbidity in the largest population cohort to date. We use a precise measurement of severe psychological stress, include validated measures of psychopathological outcomes, and control for important child, family, and parental confounds. Notwithstanding, several limitations need to be considered and addressed in future research. For example, death of a relative causes a subjective level of stress that varies by individual and circumstance. Therefore, such stress may endure over a variable length of time and we are making assumptions about the relevant period of stress. It is possible that death of a relative provides psychological relief in cases of death due to a long-term illness (Schulz et al., 2003). Mothers who are bereaved might also experience other unmeasured stressors (e.g. economic or social) or modify relevant aspects of their behaviour (e.g. increase alcohol intake) in response to the bereavement, which may influence the associations (Monk et al., 2012). Studies that can reliably measure a mother's subjective experience of stress may be invaluable for understanding potential mechanisms through which early life experiences influence later outcomes. Although we utilised the largest sample to date, relatively low numbers of exposed cases resulted in some wide confidence intervals. Given that we performed a high number of analyses, the likelihood of identifying a significant association by chance is high. Future research predicting symptom counts and neuropsychiatric or neurocognitive outcomes rather than diagnostic categories may help to compare the findings to previous research, improve statistical power, and enhance generalizability. Finally, while we identified statistically significant associations, such epidemiological associations cannot be said to be causal, given the complexity of unmeasured factors. Other quasi-experimental designs, such as sibling comparisons, could be used in future research to strengthen causal inferences (Rutter, 2007, Smith, 2008).

Overall, we report little influence of preconception, prenatal, and postnatal maternal stress exposure on risk of major psychiatric outcomes. This contrasts with reports from previous, less robust evidence. Only a moderately increased risk was found for childhood developmental disorders, namely ASD and ADHD, following prenatal third trimester exposure, and, for ASD, suicide attempt, and completed suicide following early postnatal exposure. Future research should attempt to replicate these findings, explore the underlying mechanisms, and examine the specificity of the type, timing, and severity of maternal stressors.

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Figure 1.

Participant selection flow from the Swedish birth cohort through child and adult outcomes samples that were restricted by birth years and quality of neuropsychiatric outcomes.

Note: ^aChild outcomes include ADHD and ASD. ^bTable 1 (A) provides demographic information on child outcome sample. ^cAdult outcomes include bipolar disorder, schizophrenia, suicide attempt, and completed suicide. ^dTable 1 (B) provides demographic information on adult outcome sample.

Table 1

Descriptive characteristics of all Swedish, live-born, singleton offspring across child (A) and adult (B) outcome samples by maternal stress exposure status.

Characteristic (n, %)	A. Child Outcomes Sample: born 1992–2000 (n=738,144)				B. Adult Outcomes Sample: born 1973–1997 (n=2,155,221)			
	Stress Exposure Period				Stress Exposure Period			
	None	Preconception	Prenatal	Postnatal	None	Preconception	Prenatal	Postnatal
N	707361	4944	6625	19592	2060313	15799	19903	60223
Female Offspring	344779 (48.7)	2417 (48.9)	3249 (49.0)	9488 (48.4)	1002197 (48.6)	7706 (48.8)	9710 (48.8)	29457 (48.9)
Birth Order								
First ^a	295710 (41.8)	1320 (26.7)	2232 (33.7)	6669 (34.0)	871133 (42.3)	4163 (26.4)	6600 (33.2)	20722 (34.4)
Second	264985 (37.5)	1899 (38.4)	2387 (36.03)	7162 (36.6)	764177 (37.1)	6108 (38.7)	7438 (37.4)	22417 (37.2)
Third	104759 (14.8)	1124 (22.7)	1301 (19.6)	3669 (18.7)	311043 (15.1)	3766 (23.8)	4020 (20.2)	11519 (19.1)
Fourth or more	41907 (5.9)	601 (12.2)	705 (10.7)	2092 (10.7)	113959 (5.5)	1762 (11.0)	1845 (9.3)	5565 (9.2)
Gestational length (weeks)								
22–27.6	926 (0.1)	10 (0.2)	10 (0.2)	34 (0.2)	2005 (0.1)	17 (0.1)	16 (0.1)	75 (0.1)
28–30.6	1891 (0.3)	23 (0.5)	19 (0.3)	81 (0.4)	5014 (0.2)	57 (0.4)	43 (0.2)	198 (0.3)
31–33.6	5105 (0.7)	47 (1.0)	38 (0.6)	161 (0.8)	14522 (0.7)	136 (0.9)	137 (0.7)	522 (0.9)
34–36.6	25959 (3.7)	235 (4.8)	232 (3.5)	768 (3.9)	76801 (3.7)	691 (4.4)	762 (3.8)	2483 (4.1)
37–42.6 ^a	673480 (95.2)	4629 (93.6)	6326 (95.5)	18548 (94.7)	1961971 (95.2)	14898 (94.3)	18945 (95.2)	56945 (94.6)
Birth weight (g)								
missing	2086 (0.3)	12 (0.2)	16 (0.2)	60 (0.3)	4981 (0.2)	27 (0.2)	49 (0.3)	158 (0.3)
500 – 2499	21174 (3.0)	195 (3.9)	207 (3.1)	686 (3.5)	67819 (3.3)	638 (4.0)	702 (3.5)	2327 (3.9)
2500 – 4499 ^a	684101 (96.7)	4737 (95.8)	6402 (96.6)	18846 (96.2)	1987513 (96.5)	15134 (95.8)	19152 (96.2)	57738 (95.9)
Maternal Age (years)								
< 20	14448 (2.0)	50 (1.0)	83 (1.3)	260 (1.3)	79241 (3.9)	324 (2.1)	453 (2.3)	1363 (2.3)
20–24	123749 (17.5)	551 (11.1)	719 (10.9)	2007 (10.2)	515551 (25.0)	2751 (17.4)	3146 (15.8)	9600 (15.9)
25–29 ^a	268893 (38.0)	1431 (28.9)	1859 (28.1)	5574 (28.5)	785665 (38.1)	5310 (33.6)	6527 (32.8)	19993 (33.2)
30–34	209476 (29.6)	1669 (33.8)	2261 (34.1)	6762 (34.5)	488889 (23.7)	4674 (29.6)	5991 (30.1)	18224 (30.3)
35	90795 (12.8)	1243 (25.1)	1703 (25.7)	4989 (25.5)	190967 (9.3)	2740 (17.3)	3786 (19.0)	11043 (18.3)
Paternal Age (years)								

Characteristic (n, %)	A. Child Outcomes Sample: born 1992–2000 (n=738,144)				B. Adult Outcomes Sample: born 1973–1997 (n=2,155,221)			
	Stress Exposure Period				Stress Exposure Period			
	None	Preconception	Prenatal	Postnatal	None	Preconception	Prenatal	Postnatal
missing	584 (0.1)	2 (0.0)	6 (0.1)	29 (0.2)	1884 (0.1)	17 (0.1)	17 (0.1)	80 (0.1)
< 20	4188 (0.6)	17 (0.3)	24 (0.4)	82 (0.4)	17281 (0.8)	73 (0.5)	97 (0.5)	312 (0.5)
20–24	64025 (9.1)	295 (6.0)	405 (6.1)	1126 (5.8)	278453 (13.5)	1442 (9.1)	1680 (8.4)	5295 (8.8)
25–29*	221051 (31.3)	1164 (23.5)	1471 (22.2)	4448 (22.7)	714983 (34.7)	4489 (28.4)	5394 (27.1)	16424 (27.3)
30–34	235552 (33.3)	1648 (33.3)	2081 (31.4)	6488 (33.1)	624736 (30.3)	5079 (32.2)	6350 (31.9)	19391 (32.2)
35	182545 (25.8)	1820 (36.8)	2644 (39.9)	7448 (38.0)	422976 (20.5)	4699 (29.9)	6365 (32.0)	18721 (31.1)
Maternal highest education								
missing	281 (0.0)	4 (0.1)	7 (0.1)	12 (0.1)	1756 (0.1)	10 (0.1)	14 (0.1)	200 (0.3)
9 years	54342 (7.7)	475 (9.6)	664 (10.0)	2053 (10.5)	272846 (13.2)	2490 (15.8)	3185 (16.0)	9602 (15.9)
1–3 years upper secondary*	178733 (25.3)	2576 (52.1)	3410 (51.5)	10054 (51.3)	1060344 (51.5)	7874 (49.8)	9900 (49.7)	29978 (49.8)
Post secondary	285652 (40.4)	1889 (38.2)	2544 (38.4)	7473 (38.1)	725367 (35.2)	5425 (34.3)	6804 (34.2)	20443 (34.0)
Paternal highest education								
missing	1614 (0.2)	11 (0.2)	20 (0.3)	69 (0.4)	9032 (0.4)	68 (0.4)	235 (1.2)	671 (1.1)
9 years	95271 (13.5)	741 (15.0)	1043 (15.7)	3204 (16.4)	453530 (22.0)	3699 (23.4)	4751 (23.9)	14580 (24.2)
1–3 years upper secondary*	387182 (54.7)	2725 (55.1)	3512 (53.0)	10283 (52.5)	1020115 (49.5)	7579 (48.0)	9406 (47.3)	28288 (47.0)
Post secondary	223294 (31.6)	1467 (29.7)	2050 (30.9)	6036 (30.8)	577636 (28.0)	4453 (28.2)	5511 (27.7)	16684 (27.7)
Maternal Swedish Nationality	675121 (95.4)	4773 (96.5)	6372 (96.2)	18841 (96.2)	1985462 (96.4)	15342 (97.1)	19325 (97.1)	58549 (97.2)
Paternal Swedish Nationality	643012 (91.0)	4479 (90.6)	6023 (91.0)	17740 (90.7)	1909901 (92.8)	14619 (92.6)	18394 (12.6)	55630 (92.5)
missing	584 (0.1)	2 (0.0)	6 (0.1)	29 (0.2)	1884 (0.0)	17 (0.1)	17 (0.1)	80 (0.1)
Maternal criminal history	82974 (11.7)	693 (14.0)	964 (14.6)	2764 (14.1)	229640 (11.2)	1904 (12.1)	2501 (12.3)	7465 (12.4)
Paternal criminal history	293483 (41.5)	2145 (43.4)	2895 (43.7)	8515 (43.5)	797719 (38.7)	6029 (38.2)	7714 (38.8)	23449 (38.9)
Maternal psychopathology	23874 (3.4)	182 (3.7)	307 (4.6)	840 (4.3)	76420 (3.7)	619 (3.9)	889 (4.5)	2569 (4.3)
Paternal psychopathology	17044 (2.4)	142 (2.9)	218 (3.3)	627 (3.2)	60781 (3.0)	486 (3.1)	644 (3.2)	2114 (3.5)
Maternal completed suicide	399 (0.1)	4 (0.1)	11 (0.2)	52 (0.3)	3231 (0.2)	30 (0.2)	30 (0.2)	173 (0.3)
Paternal completed suicide	1326 (0.2)	16 (0.3)	60 (0.9)	226 (1.2)	9737 (0.5)	74 (0.5)	172 (0.9)	622 (1.0)

Note:

* Reference. Pregestational stress period is from 6-0 mo before conception, prenatal period is from conception to birth, postnatal period is from birth to second birthday.

Table 2

Risk for child and adult neuropsychiatric outcomes associated with preconception maternal stress exposure within the six months prior to conception.

Outcome	Across 6-0 mo preconception						6-4 mo preconception						3-0 mo preconception					
	Unadjusted			Adjusted*			Unadjusted			Adjusted*			Unadjusted			Adjusted*		
	N exposed	HR	95% CI	HR	95% CI		N exposed	HR	95% CI	HR	95% CI		N exposed	HR	95% CI	HR	95% CI	
ASD	40	0.91	0.67–1.24	0.88	0.64–1.19		17	0.76	0.47–1.22	0.72	0.45–1.16		23	1.07	0.71–1.61	1.04	0.69–1.56	
ADHD	91	0.93	0.76–1.14	0.9	0.73–1.10		45	0.90	0.67–1.21	0.86	0.64–1.16		46	0.96	0.72–1.28	0.93	0.70–1.24	
Bipolar	73	1.24	0.98–1.56	1.20	0.95–1.51		36	1.18	0.85–1.64	1.14	0.82–1.58		37	1.30	0.94–1.80	1.26	0.91–1.74	
Schizophrenia	24	1.36	0.91–2.03	1.32	0.88–1.97		13	1.42	0.83–2.45	1.39	0.81–2.40		11	1.29	0.71–2.33	1.24	0.69–2.25	
Suicide Attempt	175	0.92	0.79–1.06	0.88	0.76–1.02		98	1.00	0.82–1.21	0.95	0.78–1.16		77	0.83	0.66–1.03	0.80	0.64–1.01	
Completed Suicide	8	0.62	0.31–1.23	0.61	0.30–1.21		5	0.74	0.31–1.79	0.73	0.30–1.76		3	0.48	0.15–1.48	0.47	0.15–1.46	

* Adjusted for offspring sex, birth order, birth weight, gestational age, maternal and paternal age, highest education, nationality, criminality, severe psychopathology, and completed suicide.

Table 3

Risk for child and adult neuropsychiatric outcomes associated with prenatal maternal stress exposure across pregnancy and by trimester.

Outcome	Across Pregnancy						Trimester 1						Trimester 2						Trimester 3									
	N exposed	Unadjusted			Adjusted*			N exposed	Unadjusted			Adjusted*			N exposed	Unadjusted			Adjusted*			N exposed	Unadjusted			Adjusted*		
		HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI
ASD	79	1.36	1.09–1.70	1.30	1.04–1.62		22	1.32	0.87–2.00	1.25	0.82–1.91		18	1.00	0.63–1.59	0.97	0.61–1.53		39	1.67	1.22–2.28	1.58	1.15–2.17					
ADHD	149	1.15	0.98–1.35	1.12	0.95–1.32		34	0.91	0.65–1.28	0.87	0.62–1.23		45	1.12	0.84–1.50	1.10	0.82–1.47		70	1.34	1.06–1.70	1.31	1.04–1.66					
Bipolar	73	1.00	0.79–1.25	0.96	0.76–1.21		16	0.79	0.48–1.29	0.76	0.46–1.24		27	1.20	0.82–1.74	1.14	0.78–1.66		30	0.98	0.69–1.41	0.95	0.67–1.37					
Schizophrenia	18	0.82	0.51–1.30	0.78	0.49–1.24		1	0.17	0.02–1.17	0.16	0.02–1.10		8	1.18	0.59–2.36	1.13	0.56–2.26		9	0.98	0.51–1.89	0.94	0.49–1.80					
Suicide Attempt	251	1.06	0.93–1.20	1.04	0.92–1.17		59	0.89	0.69–1.15	0.86	0.67–1.12		77	1.05	0.84–1.31	1.03	0.82–1.29		115	1.16	0.97–1.40	1.16	0.97–1.40					
Completed Suicide	15	0.93	0.56–1.55	0.92	0.56–1.54		4	0.90	0.34–2.40	0.88	0.33–2.35		4	0.81	0.30–2.15	0.80	0.30–2.14		7	1.05	0.50–2.20	1.04	0.50–2.19					

* Adjusted for offspring sex, birth order, birth weight, gestational age, maternal and paternal age, highest education, nationality, criminality, severe psychopathology, and completed suicide.

Table 4

Risk for child and adult neuropsychiatric outcomes associated with postnatal maternal stress exposure across the first two postnatal years and separated by year.

Outcome	Across first two years						First year						Second year								
	N exposed	Unadjusted			Adjusted*			N exposed	Unadjusted			Adjusted*			N exposed	Unadjusted			Adjusted*		
		HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI		
ASD	209	1.21	1.06–1.39	1.15	1.00–1.32		85	1.04	0.84–1.29	0.99	0.80–1.22		124	1.37	1.15–1.64	1.30	1.09–1.55				
ADHD	426	1.11	1.01–1.22	1.06	0.96–1.17		189	1.03	0.90–1.19	1.00	0.86–1.15		237	1.17	1.03–1.33	1.11	0.98–1.27				
Bipolar	214	0.97	0.85–1.11	0.93	0.81–1.07		109	1.03	0.86–1.25	1.00	0.83–1.21		105	0.91	0.75–1.11	0.87	0.72–1.06				
Schizophrenia	76	1.15	0.92–1.45	1.09	0.87–1.37		35	1.11	0.80–1.55	1.06	0.76–1.48		41	1.19	0.88–1.62	1.12	0.82–1.53				
Suicide Attempt	801	1.12	1.04–1.20	1.10	1.03–1.18		389	1.14	1.03–1.26	1.13	1.02–1.25		412	1.10	1.00–1.21	1.07	0.97–1.18				
Completed Suicide	55	1.14	0.87–1.49	1.12	0.86–1.47		35	1.52	1.09–2.12	1.51	1.08–2.11		20	0.79	0.51–1.23	0.77	0.50–1.20				

* Adjusted for offspring sex, birth order, birth weight, gestational age, maternal and paternal age, highest education, nationality, criminality, severe psychopathology, and completed suicide.