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ORIGINAL ARTICLE

Offspring psychopathology following preconception, prenatal and postnatal maternal bereavement stress

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Background. Preconception, prenatal and postnatal maternal stress is 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.

Method. 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 to 2009. Maternal stress was defined as death of a first-degree relative during (*a*) the 6 months before conception, (*b*) pregnancy or (*c*) the first two postnatal years. Cox proportional survival analyses were used to obtain hazard ratios (HRs) 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 the risk of ASD [adjusted HR (aHR) 1.58, 95% confidence interval (CI) 1.15–2.17] and ADHD (aHR 1.31, 95% CI 1.04–1.66). First postnatal year stress increased the risk of offspring suicide attempt (aHR 1.13, 95% CI 1.02–1.25) and completed suicide (aHR 1.51, 95% CI 1.08–2.11). Bereavement stress during the second postnatal year increased the risk of ASD (aHR 1.30, 95% CI 1.09–1.55).

Conclusions. Further research is needed regarding associations between preconception stress and psychopathological outcomes. Prenatal bereavement stress increases the risk of offspring ASD and ADHD. Postnatal bereavement stress moderately increases the 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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Key words: Attention deficit hyperactivity disorder, autism, postnatal, preconception, prenatal, psychiatric, psychopathology, schizophrenia, stress, suicide.

Introduction

In support of the developmental origins of disease hypothesis (Barker, 1998), accumulating evidence links maternal stress to increased risk of psychopathological morbidity in offspring (Huttunen & Niskanen, 1978; van Os & Selten, 1998; Rodriguez & Bohlin, 2005; Khashan *et al.* 2008*a*, 2011; Li *et al.* 2010; Ronald *et al.* 2011). Studies have identified associations with severe, impairing and costly psychiatric disorders, including autism spectrum disorder (ASD; Beversdorf *et al.* 2005; Ganz, 2007), attention deficit hyperactivity disorder (ADHD; Rodriguez & Bohlin, 2005; Pelham *et al.* 2007; Polanczyk *et al.* 2007) and schizophrenia (Jablensky, 2000; Khashan *et al.* 2008*a*). Associations with adverse psychopathological outcomes have been reported following maternal exposure to physical stressors, such as famine (Brown *et al.* 1995, 2000), and psychological stressors, such as bereavement (Khashan *et al.* 2008*a*, 2011; Li *et al.* 2010), trauma (Brand *et al.* 2006), war (van Os & Selten, 1998) and natural disaster (Glynn *et al.* 2001; King & Laplante, 2005; Kinney *et al.* 2008*a*). 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).

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Previous research suggests that exposure during sensitive crucial 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 (Huttunen & Niskanen, 1978; van Os & Selten, 1998; O'Connor *et al.* 2003; Beversdorf *et al.* 2005; Rodriguez & Bohlin, 2005; Talge *et al.* 2007; Beydoun & Saftlas, 2008; Khashan *et al.* 2008*a*, 2011; Kinney *et al.* 2008*a*; Bale *et al.* 2010; Li *et al.* 2010; Ronald *et al.* 2011). Additionally, postnatal stress exposure is associated with increased risk of offspring psychiatric outcomes (Mortensen *et al.* 2003; Brent & Mann, 2006; Rosenberg *et al.* 2007; Epstein *et al.* 2008; Heim *et al.* 2008; Landau *et al.* 2010; Guinchat *et al.* 2012; Rai *et al.* 2012).

Although associations between early stress exposure and perinatal outcomes show relative consistency (Beydoun & 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 this does exist, effect sizes are modest at best (Khashan *et al.* 2008*a*, 2011). Second, replication is needed for several reported effects. For example, a meta-analysis did not support an association between prenatal stress and schizophrenia (Selten *et al.* 2003), and studies predicting ASD from prenatal stress have been inconsistent (Beversdorf *et al.* 2005; Li *et al.* 2009; Ronald *et al.* 2011; Rai *et al.* 2012). Third, 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 and nutritional stressors, and women who conceive and complete pregnancy during famine may represent an unusual group (Brown *et al.* 2000; St Clair *et al.* 2005; Rodriguez & Bohlin, 2005; Dunkel-Schetter & Glynn, 2011). 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. Use of 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 made use of 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 controlling statistically for measured covariates to help account for alternative explanations.

We hypothesized that the findings would support prior positive findings by timing of exposure, and also 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 (Khashan *et al.* 2008*a*; Li *et al.* 2009, 2010). We hypothesized that prenatal bereavement stress would be associated with increased risk for ADHD and schizophrenia (Brown *et al.* 2000; Kinney *et al.* 2008*a*,*b*; Li *et al.* 2010; Ronald *et al.* 2011), and also 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; Landau *et al.* 2010; Guinchat *et al.* 2012; Rai *et al.* 2012) and attempted and completed suicide (Williams & 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 (Smith *et al.* 2003; Gluckman & Hanson, 2004; Mittendorfer-Rutz *et al.* 2004; Hultman *et al.* 2007; Khashan *et al.* 2008*b*; Moster *et al.* 2008; Abel *et al.* 2010; Lindstrom *et al.* 2011; Losh *et al.* 2011).

Method

Study population

After approval from the Institutional Review Board and ethical committees at Karolinska Institutet and Indiana University, we constructed a population-based

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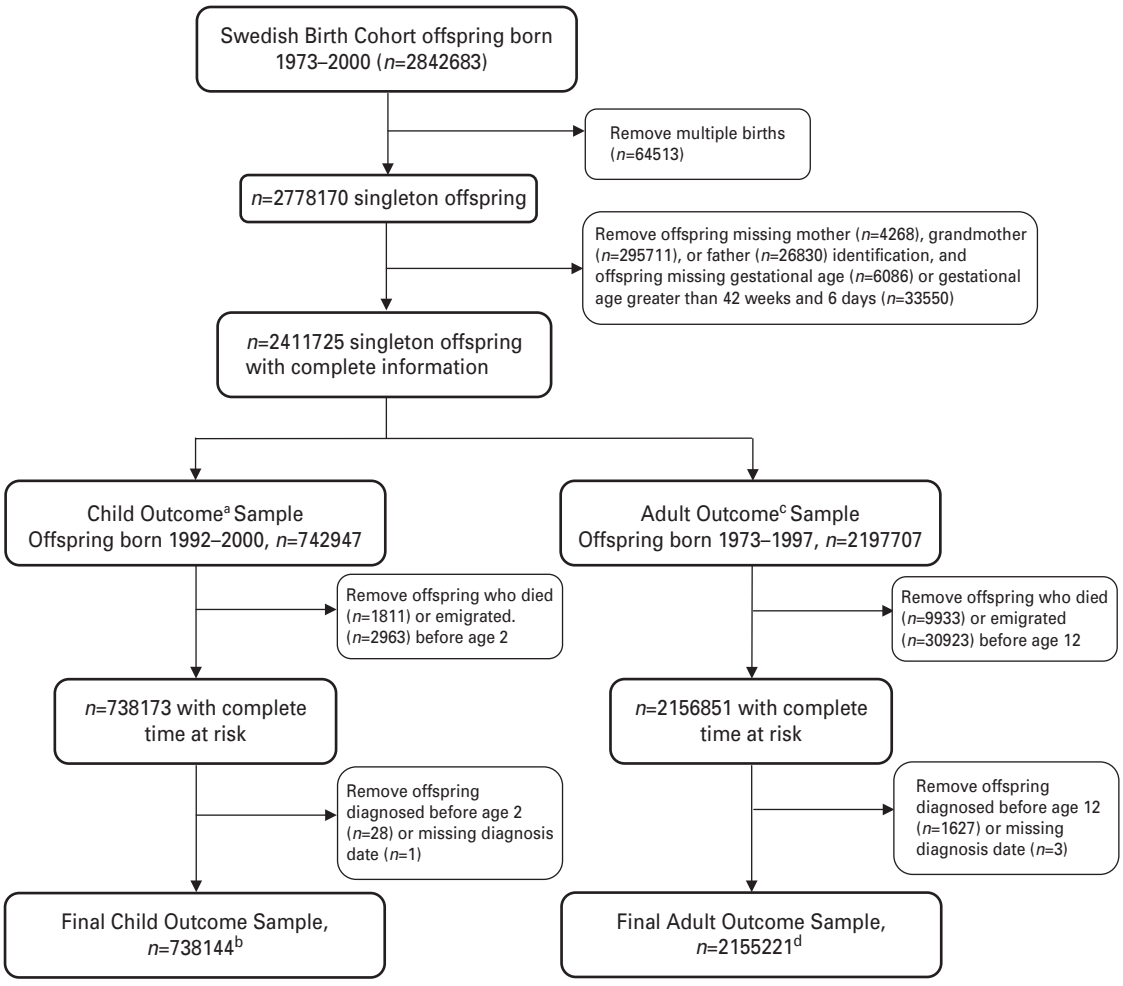

Fig. 1. Participant selection flow from the Swedish birth cohort through child and adult outcomes samples that were restricted by birth years and quality of neuropsychiatric outcomes. [a]Child outcomes include attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). [b]Table 1*a* provides demographic information on child outcome sample. [c]Adult outcomes include bipolar disorder, schizophrenia, suicide attempt and completed suicide. [d]Table 1*b* provides demographic information on adult outcome sample.

sample by linking Swedish nationwide, longitudinal population registries through unique personal identification numbers. The Medical Birth Registry (Centre for Epidemiology, 2003; Cnattingius *et al.* 1990) included data on more than 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, children already born) 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 indication of bereavement stress exposure. The National Patient Register provided diagnoses for all in-patient hospital admissions since 1973 and for out-patient hospital visits since 2001. The Education Register (Statistics Sweden, 2011) provided information on parental level (highest) of formal education completed, and the National Crime Register (Fazel & Grann, 2006) provided data on parental criminal convictions since the age of 15, the Swedish age of criminal responsibility, from 1973 onwards. Finally, the Migration Register provided information on dates of migration in or out of Sweden.

Fig. 1 presents the sample flow across child and adult samples. The data set began with 2842683 individuals born from 1973 to 2000. We removed multiple births because rates of adverse birth outcomes in multiples differ from those in singletons (Matthews & Rodin, 1992), and we also removed offspring with missing mother, grandmother and father identification numbers for complete identification of family members who may have died during the exposure window. We removed offspring with missing gestational age and possible erroneous gestational age values greater than 42 weeks and 6 days because timing of stress exposure was determined by gestational age at birth.

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Table 1. *Descriptive characteristics of all Swedish, live-born, singleton offspring across (a) child and (b) adult outcome samples by maternal stress exposure status (none, preconception, prenatal and postnatal)*

	(*a*) Child outcome sample: born 1992–2000 (*n*=738144)				(*b*) Adult outcome sample: born 1973–1997 (*n*=2155221)			
Characteristic	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)
Birthweight (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)								
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[a]	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[a]	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[a]	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)

[a] Reference.

Pregestational stress period is from 6 to 0 months before conception, prenatal period is from conception to birth, postnatal period is from birth to second birthday.

A total of 2411725 (84.8%) singleton offspring remained before separation 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=742947). Children had to be at least 2 years old to receive a diagnosis of ASD or ADHD. We removed children who had died, emigrated or were diagnosed before their second birthday and or were missing a diagnosis date. Thus, our final child sample contained 738144 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=2197707) 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 had died, emigrated, presented with an adult-onset outcome before their 12th birthday or were missing their date of diagnosis, resulting in a final sample of 2155221 adults. Both cohorts were followed to 2009.

Exposure

Death of a first-degree relative was chosen to provide an insult that resulted in substantial psychological stress (Arbuckle & de Vries, 1995) with precise timing. For preconception bereavement stress, this included death of the 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; subdivided into preconception windows of 0–3 and 4–6 months), prenatal [conception to birth; subdivided into trimesters (first trimester 0–12 weeks; second trimester 13–24 weeks; and third trimester 25 weeks to birth] and postnatal periods (0–2 years; subdivided into first- and second-year windows). Table 1 presents details of 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) who 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. The sample size restricted further investigation of possible stress exposure dosage effects.

Outcome variables

The National Patient Register provided discharge dates and primary diagnoses using ICD-8, -9 and -10.

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Childhood psychiatric outcomes

Children receiving an ASD diagnosis included in-patient and out-patient diagnoses of ASD and Asperger's syndrome (ICD-10: F84). Children receiving an ADHD diagnosis included an in-patient or out-patient 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 in-patient hospitalization 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 hospitalization for that diagnosis may indicate suicidality or psychosis and may be better examined when categorized as such.

Analyses

We used Cox proportional survival analyses to estimate the association of early bereavement stress with right-censored psychiatric outcomes using SAS version 9.2 (SAS Institute Inc., USA). Information on migration and death was used to calculate the number of 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 (31 December 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 used in baseline and adjusted models to account for the nested nature of the data (the possibility of one mother having multiple children within the data set).

Adjusted models controlled for the following potential confounders: offspring sex, birth order [first (referent), second, third, fourth born and higher], offspring birthweight [missing, 500–2499 g 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 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 in-patient 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 (Li *et al.* 2010; Khashan *et al.* 2011). 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 birthweight (⩾2500 g) because these obstetric factors are associated with both maternal exposure to stressors and excess risk of later psychopathology (Khashan *et al.* 2008*b*, 2009; Lindstrom *et al.* 2009; Abel *et al.* 2010; Class *et al.* 2011; Losh *et al.* 2011). Fourth, we predicted broadly defined schizophrenia, including schizo-affective 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), to more precisely replicate or refute previous research (Khashan *et al.* 2008*a*). Fifth, 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 whether associations were outcome specific or whether early stress constitutes a shared risk factor.

Results

We identified 6430 children with ASD [Kaplan–Meier estimate (KM_{est})=1.2% by the age 17.9 years; 72.4% male] and 14313 children with ADHD (KM_{est}=2.7% by age 17.9 years; 75.8% male) within the child sample. We identified 8001 individuals with bipolar disorder (KM_{est}=0.9% by age 35 years; 68.5% male), 8063 with non-affective psychoses (KM_{est}=0.8% by age 35 years; 57.9% male), 2400 individuals with schizophrenia (KM_{est}=0.3% by age 35 years; 66.5% male), 25855 cases of attempted suicide that resulted in in-patient hospital care (KM_{est}=1.9% by age 35 years; 34.0% male), and 1751 cases of completed

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Table 2. *Risk for child and adult psychopathological outcomes associated with preconception maternal stress exposure within the 6 months prior to conception*

	6–0 months preconception			6–4 months preconception			3–0 months preconception		
Outcome	*n* exposed	HR (95% CI)	aHR (95% CI)	*n* exposed	HR (95% CI)	aHR (95% CI)	*n* exposed	HR (95% CI)	aHR (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 disorder	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)

ASD, Autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; HR, hazard ratio; aHR, adjusted HR (adjusted for offspring sex, birth order, birthweight, gestational age, maternal and paternal age, highest education, nationality, criminality, severe psychopathology and completed suicide); CI confidence interval.

suicide (KM_{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. Despite the size of our sample, lack of a statistically significant estimate in a low number of exposed cases ($n_{bipolar}$=73, $n_{schizophrenia}$=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 and 4–6 months preconception) echoed the null associations seen across the entire 6-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 hazard ratio (aHR) 1.30, 95% confidence interval (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 (aHR 1.58, 95% CI 1.15–2.17). An elevated risk, however, was also noted following first-trimester stress exposure, although the CI around the association was large (aHR 1.25, 95% CI 0.82–1.91). Risk for ADHD was significantly increased following third-trimester stress exposure (aHR 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 (aHR 1.15, 95% CI 1.00–1.32) and suicide attempt (aHR 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 (aHR 1.13, 95% CI 1.02–1.25) and completed suicide (aHR 1.51, 95% CI 1.08–2.11). Maternal stress during the second postpartum year was associated with a significant increased risk of ASD (aHR 1.30, 95% CI 1.09–1.55). No other significant associations between

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Table 3. *Risk for child and adult psychopathological outcomes associated with prenatal maternal stress exposure across pregnancy and by trimester*

	Across pregnancy			Trimester 1			Trimester 2			Trimester 3		
Outcome	*n* exposed	HR (95% CI)	aHR (95% CI)	*n* exposed	HR (95% CI)	aHR (95% CI)	*n* exposed	HR (95% CI)	aHR (95% CI)	*n* exposed	HR (95% CI)	aHR (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 disorder	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)

ASD, Autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; HR, hazard ratio; aHR, adjusted HR (adjusted for offspring sex, birth order, birthweight, gestational age, maternal and paternal age, highest education, nationality, criminality, severe psychopathology and completed suicide); CI confidence interval.

Bold font indicates Wald χ^2 test statistic with estimated p value <0.05.

Table 4. *Risk for child and adult psychopathological outcomes associated with postnatal maternal stress exposure across the first two postnatal years and separated by year*

Outcome	Across first two years			Across first year			Across second year		
	n exposed	HR (95% CI)	aHR (95% CI)	*n* exposed	HR (95% CI)	aHR (95% CI)	*n* exposed	HR (95% CI)	aHR (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 disorder	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)

ASD, Autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; HR, hazard ratio; aHR, adjusted HR (adjusted for offspring sex, birth order, birthweight, gestational age, maternal and paternal age, highest education, nationality, criminality, severe psychopathology and completed suicide); CI confidence interval.

Bold font indicates Wald $\chi 2$ test statistic with estimated p value <0.05.

postnatal maternal stress and offspring psychiatric outcomes were found.

Sensitivity analyses

Sex interaction was not 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 birthweight respectively, paralleled findings from the original models. 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 (aHR 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 (Huttunen & Niskanen, 1978; Beydoun & Saftlas, 2008; Khashan *et al.* 2008*a*, 2011), we found few associations between a well-characterized, objective measure of early maternal exposure to psychological stress and odds of later severe psychiatric problems. Second, the associations reported are dependent on the timing of the exposure and on the particular outcome assessed. Third, in line with previous findings (Ward, 1990; Beversdorf *et al.* 2005; Kinney *et al.* 2008*a*; 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. In general, 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

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with a previous study predicting ADHD (Li *et al.* 2010). These authors defined ADHD by diagnosis and/or medication, and 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 adjusting 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.* 2008*a*), and retrospectively recalled (Beversdorf *et al.* 2005) and prospectively measured (Ronald *et al.* 2011) stressful life events. By 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 (Rodriguez & Bohlin, 2005; Li *et al.* 2010), 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 & Saftlas, 2008). Many of these associations may be confounded by genetic transmission of temperament from mother to child (King & Laplante, 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. King & Laplante, 2005; Talge *et al.* 2007; Charil *et al.* 2010; Buss *et al.* 2012). 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 co-morbid 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.* 2008*a*). Our findings on bipolar disorder are consistent with a null finding between prenatal stress and affective disorder, including bipolar disorder (van Os & 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 & 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 whether outcomes are associated with particular sensitive periods of development may offer insight into aetiological mechanisms (Smits & Essed, 2001; Van den Bergh *et al.* 2005, 2008; Wadhwa, 2005; Brent & Mann, 2006; Jirtle & Skinner, 2007; Buss *et al.* 2010; Meaney, 2010). 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 & Kemper, 1994, 2005; Bailey *et al.* 1998) or oestradiol-sensitive gene expression (Kinney *et al.* 2008*b*). 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 (Goodman & Gotlib, 1999; Bagner *et al.* 2010) may be particularly important 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 & 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), grey 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 & Gotlib, 1989; Bagner *et al.* 2010) may adversely affect offspring

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problem-solving abilities, cognitive ability, attachment and/or compound genetic vulnerability to suicide (Goodman & Gotlib, 1999; Williams & Pollock, 2000; Mann, 2003; Brent & Mann, 2005).

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.* 2013). 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 used the largest sample to date, relatively low numbers of exposed cases resulted in some wide CIs. Given that we performed a large 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, although 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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Declaration of Interest

None.

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