Risk of affective disorders following prenatal exposure to severe life events: A Danish population-based cohort study

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A B S T R A C T

Objective: To examine the effect of prenatal exposure to severe life events on risk of affective disorders in the offspring.

Methods: In a cohort of 1.1 million Danish births from May 1978 until December 1997, mothers were considered exposed if one (or more) of their close relatives died or was diagnosed with serious illness up to 6 months before conception or during pregnancy. Offspring were followed up from their 10th birthday until their death, migration, onset of affective disorder or 31 December 2007; hospital admissions were identified by linkage to the Central Psychiatric Register. Log-linear Poisson regression was used for data analysis.

Results: The risk of affective disorders was increased in male offspring whose mothers were exposed to severe life events during the second trimester (adjusted RR 1.55 [95% CI 1.05–2.28]). There was an increased risk of male offspring affective disorders in relation to maternal exposure to death of a relative in the second trimester (adjusted RR 1.74 [95% CI 1.06–2.84]) or serious illness in a relative before pregnancy (adjusted RR 1.44 [95% CI 1.02–2.05]). There was no evidence for an association between prenatal exposure to severe life events and risk of female offspring affective disorders.

Conclusions: Our population-based study suggests that prenatal maternal exposure to severe life events may increase the risk of affective disorders in male offspring. These findings are consistent with studies of populations exposed to famine and earthquake disasters which indicate that prenatal environment may influence the neurodevelopment of the unborn child.

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1. Introduction

The prenatal environment can have a major impact on the children’s short and long term future health and intrauterine exposures have been associated with an increased likelihood of developing a range of adult onset disorders such as hypertension, cardiovascular diseases and diabetes (Barker, 1997; Barker et al., 1993). Prenatal maternal stress has come under recent scrutiny with respect to a hypothesized fetal programming effect. Evidence suggests that prenatal stress may influence fetal and offspring neurodevelopment, which could explain potential pathways between prenatal stress and childhood and adulthood neurological and psychiatric disorders (Welberg et al., 2001; Wadhwa, 2005).

Maternal exposure to major life events, such as famine, war and severe life events (death or serious illness in close relatives), during or before pregnancy has been reported to adversely influence obstetric outcomes and offspring psychiatric morbidity (Khashan et al., 2008, 2009; Susser et al., 1996; Van Os and Selten, 1998). Furthermore, there is evidence to suggest that the association between prenatal exposure to major life events and risk of affective disorders in the offspring may be gender specific (Brown et al., 1995, 2000; Watson et al., 1999). Prenatal exposure to the Dutch famine was associated with a higher risk of affective disorders (Brown et al., 1995; Brown et al., 2000). Brown et al. (1995) performed two studies to investigate the effect prenatal exposure to the Dutch Famine (1944–1945) on the risk of affective disorders in...
the offspring. The authors used inpatient data from the Dutch Psychiatric Registry to identify affective disorder diagnoses between 1978 and 1991 in the offspring who were born between 1944 and 1946 and survived to at least 18 years. They found more than two fold increased risk of affective disorder in male offspring who were prenatally exposed to the famine in the second trimester but not in females. Few years later, the authors repeated the investigation by including all affective disorder cases between 1970 and 1996. They reported about 70% increase in risk of affective disorder in male offspring and about 30% increase in female offspring in the second and third trimesters but not the first (Brown et al., 2000). Watson et al. compared the risk of affective disorder in 18-year old high school students who were exposed in utero to the Tangshan earthquake in China in 1976 with 18-year old students who were not exposed. The authors reported an increased risk of severe depression in all trimesters in male offspring but not females (Watson et al., 1999). Most recently, Li et al. reported an association between prenatal bereavement and risk of attention deficit/hyperactivity disorder (ADHD) in male offspring but not females (Li et al., 2010) using data from the Danish national registers. In contrast, recent studies found no association between prenatal exposure to severe life events and risk of epilepsy (Li et al., 2008) or autism (Li et al., 2008) in the offspring.

Recently, we reported an association between prenatal exposure to death of a close relative in the first trimester and risk of schizophrenia in the offspring (Khashan et al., 2008). However, in that study we were unable to explore the gender difference in the association due to lack of adequate statistical power. In the present study we aimed to investigate the effect of prenatal exposure to severe life events, defined as death or serious illness in close relatives, during or before pregnancy on the risk of affective disorders. Based on our previous study (Khashan et al., 2008) and others (Brown et al., 2000), we hypothesised that prenatal exposure to severe life events in the first, second or third trimesters would increase the risk of affective disorders. We also aimed to explore whether there would be gender difference in the effect of prenatal exposure to severe life events on affective disorders.

2. Methods

All women who delivered singleton live babies in Denmark between May 1, 1978 and December 31, 1997 were identified using the Danish Medical Birth Register (Knudsen and Olsen, 1998) which contains maternal and obstetric information such as gestational age and date of delivery. Data on these women were linked to data related to their close relatives (parents, siblings, partners and children) using the Civil Person Registration (CPR) number (Pedersen and Gøtzsche, 2006). The CPR is a unique number used uniformly across all services in Denmark and enables linkage of data from several Danish national registers. We defined partner as the legal father of the child. Using the CPR number, close relatives were linked to the Civil Registration System (Pedersen and Gøtzsche, 2006) to identify if and when they died. They were also linked to the Danish National Hospital Register (Andersen et al., 1999) to identify if and when they were diagnosed with serious illness (cancer, acute myocardial infarction, cerebrovascular accident). The index women, their partners and children were linked to the Danish Psychiatric Central Register (Munk-Jørgensen and Mortensen, 1997) to identify index children with family history of mental illness.

The index children were linked to data from the Danish Central Psychiatric Register, which contains records of all admissions to Danish psychiatric inpatient facilities since 1969 and on outpatient visits to psychiatric departments since 1995. This enabled us to identify index children with diagnoses of affective disorders. Affective disorders were defined according to ICD-8 (WHO, 1967) (296.09, 296.19, 296.29, 296.39, 296.99, 298.09, 298.19, 300.49, 301.19) and ICD-10 (F30-F34, F38-F39). ICD-8 codes were used from April 1969 until December 1993 and ICD-10 (WHO, 1992) codes were used from January 1994 onwards. Date of onset was defined as the first day of the first contact (in- or outpatient) with a diagnosis of an affective disorder. Kessing (1998) investigated the influence of the introduction of ICD-10 on the diagnostic borders on affective disorders using data from the Danish Psychiatric Central Register. The author concluded that the differences between ICD-8 and ICD-10 within major affective disorders were minor and that ICD-10 was broader and more comprehensive. The index children were followed from their 10th birthday until their diagnosis with affective disorder, death, migration from Denmark or December 31, 2007 (end of follow-up), whichever came first.

Exposure was defined as death and/or diagnosis of cancer (ICD-8 codes 140 to 207 and ICD-10 C00 to C97), acute myocardial infarction (ICD-8 I21, I22), and cerebrovascular accident (ICD-8 I61, I63, I64) in the father, mother, sibling, child or spouse of the index woman during or in the six months before pregnancy. Date of first exposure was defined as the date of death or the first date of the first contact (in- or outpatient) with a diagnosis of cancer, acute myocardial infarction or cerebrovascular disease in a family member. Date of pregnancy was calculated using date of birth of the index child and gestational age. We classified exposure according to the timing of the exposure event in relation to pregnancy: six months before pregnancy; first trimester (0–12 gestation weeks); second trimester (13–24 gestation weeks) and third trimester (25 gestation weeks until birth). Women were considered exposed if they had links to all their close relatives and at least one of them died or was diagnosed for the first time with a relevant illness during the exposure period. They were considered unexposed if they had links to all their close relatives and none of them died or were diagnosed with a relevant illness. We considered exposure status to be unknown if the pregnant woman had missing links to at least one relative. If the index woman was exposed to more than one exposure during the same pregnancy priority was given to the earliest.

2.1. Statistical analysis

The statistical analyses were performed in Stata Software 9.0. Log-linear Poisson regression (Breslow and Day, 1987) with aggregated person-years data was used to estimate the relative risk (RR) of affective disorders in relation to the exposure. Cox regression is too computationally intensive for cohorts of this size; therefore we used Poisson regression as an approximation (Andersen et al., 1995). The models were adjusted for calendar year (1988–1989 and in one year categories thereafter until 2007), offspring age (10–11 years, 12–13, 14, and in one year categories until 19, 20–21, and in 2 years categories until 29 and 30–32) and sex and a statistical interaction between offspring age and sex (Model I). These covariates allow for variation in incidence over calendar time and differential age pattern for males and females. To estimate the relative risk of affective disorders in males and females separately we created a model with the same variables as above and added a statistical interaction term between the exposure variable and offspring sex (Model II). Negative binomial models suggested that the Poisson models (models I and II) were not subject to overdispersion (Gardner et al., 1995).

2.2. Further analyses

We fitted Model II again after excluding index children who had family history of mental illness and after restricting the analysis to term babies of normal birthweight (gestational age ≥37 weeks and
Adjusted relative risk estimates for offspring affective disorders risk according to timing of prenatal exposure (events mother palace birth | maternal and paternal age at the time of birth, maternal and paternal ethnicity (born in Denmark or abroad), birthweight (<1500 g, 1500 < 2500 and ≥2500) and gestational age (23–32, 33–36, 37–41 and 42+ weeks). Offspring age, calendar year and family history of mental illness were generated as time-dependent variables while the other variables were time fixed. In another analysis, we started follow-up from the children’s 18th birthday, since childhood onset disorder might have a different relationship to prenatal maternal exposures compared to adult onset. We also examined the association between prenatal exposure to severe life events and affective disorders excluding bipolar disorder due to small number of bipolar disorder cases in the study cohort.

We performed the analyses separately for 1) death and/or illness in any relative (events); 2) death of any relative; 3) illness in any relative. These comparisons were performed once by combining all the relevant events in one category and then according to the timing of the exposure to assess the effect of the exposure on the risk of affective disorders.

3. Unknown exposure status

Women who had no links to at least one close relative and/or had missing gestational age were considered as having unknown exposure status. Women who were not living at their parents’ home when the Danish Civil Registration System was established in 1968 had no links to their parents and subsequently to their siblings in this cohort. The great majority of missing links to relatives were to parents of the pregnant women. Mothers had complete linkage to parents of the pregnant women. Mothers had complete linkage to their children who are registered in the Medical Birth Registry and to more than 99% of their partners. Women with unknown exposure status were grouped in three categories according to the source of missingness: missing link to at least one relative and known gestational age; missing gestational age and known links to all relatives; and missing link to at least one relative and missing gestational age.

The study was approved by the Danish Data Protection Agency and the Danish National Board of Health.

4. Results

There were 1,133,694 singleton live births in Denmark between May 1, 1978 and December 31, 1997. During the study follow-up period, 13,699 offspring (9476 females and 4223 males) were diagnosed with affective disorders. Mothers of 34,405 (3.03%, 17571 males) offspring were exposed to death or serious illness in close relatives; 19144 (1.69%, 9708 males) were exposed to death, while 19603 (1.73%, 10016 males) were exposed to serious illness in close relatives. Mothers of 4342 (2153 males) offspring had multiple exposures during the same pregnancy and 54 (18 males) of them were diagnosed with affective disorders. The risk of affective disorders appeared to be greater in females and in persons with family history of mental illness. The risk appeared to increase with age but was almost constant from early to late 20s (Table 1).

4.1. Exposure to all events (death or serious illness) in close relatives

The RRs of offspring affective disorders in relation to prenatal exposure to severe life events are presented in Table 2. Overall, there was no association between maternal exposure to severe life events during or before pregnancy and affective disorders in the offspring. When an interaction term between the exposure variable and offspring sex was added to the model, the RR of affective disorders was increased in males (adjusted RR = 1.20, [95% CI: 1.00,

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n)</th>
<th>Incidence per 100,000 person yrs</th>
</tr>
</thead>
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<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>9476</td>
<td>4223</td>
</tr>
<tr>
<td>Place of birth</td>
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<td></td>
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<tr>
<td>Capital</td>
<td>1522</td>
<td>132.7</td>
</tr>
<tr>
<td>Suburb of capital</td>
<td>1894</td>
<td>132.9</td>
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<tr>
<td>Provincial cities</td>
<td>1665</td>
<td>136.4</td>
</tr>
<tr>
<td>Provincial towns</td>
<td>4019</td>
<td>138.1</td>
</tr>
<tr>
<td>Rural areas</td>
<td>4599</td>
<td>119.5</td>
</tr>
<tr>
<td>Family history of mental illness (all psychiatric admissions)</td>
<td>Yes</td>
<td>4732</td>
</tr>
<tr>
<td>No</td>
<td>8967</td>
<td>100.6</td>
</tr>
<tr>
<td>Maternal age (in years)</td>
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<td></td>
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<tr>
<td>12–19</td>
<td>804</td>
<td>191.0</td>
</tr>
<tr>
<td>20–25</td>
<td>5134</td>
<td>136.1</td>
</tr>
<tr>
<td>26–29</td>
<td>3937</td>
<td>119.8</td>
</tr>
<tr>
<td>30–34</td>
<td>2809</td>
<td>122.7</td>
</tr>
<tr>
<td>35+</td>
<td>1015</td>
<td>129.7</td>
</tr>
<tr>
<td>Offspring age</td>
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<td></td>
</tr>
<tr>
<td>10–11</td>
<td>190</td>
<td>8.9</td>
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<tr>
<td>12–13</td>
<td>536</td>
<td>28.5</td>
</tr>
<tr>
<td>14–15</td>
<td>1436</td>
<td>88.6</td>
</tr>
<tr>
<td>16–17</td>
<td>1973</td>
<td>145.1</td>
</tr>
<tr>
<td>18–19</td>
<td>2388</td>
<td>213.2</td>
</tr>
<tr>
<td>20–25</td>
<td>6057</td>
<td>279.1</td>
</tr>
<tr>
<td>26–30</td>
<td>1137</td>
<td>307.3</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of cases (males)</th>
<th>Adjusted RR&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; in males (95% CI)</th>
<th>Adjusted RR&lt;sup&gt;b&lt;/sup&gt; in females (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or illness in any relative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>7144 (2179)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Exposed during any period</td>
<td>347 (123)</td>
<td>1.03 (0.93, 1.15)</td>
<td>1.20 (1.00, 1.44)</td>
<td>0.96 (0.84, 1.10)</td>
</tr>
<tr>
<td>Exposed before pregnancy</td>
<td>151 (45)</td>
<td>1.01 (0.86, 1.19)</td>
<td>1.00 (0.75, 1.35)</td>
<td>1.02 (0.84, 1.23)</td>
</tr>
<tr>
<td>Exposed 1st trimester</td>
<td>60 (24)</td>
<td>1.00 (0.76, 1.29)</td>
<td>1.26 (0.85, 1.89)</td>
<td>0.88 (0.64, 1.23)</td>
</tr>
<tr>
<td>Exposed 2nd trimester</td>
<td>64 (26)</td>
<td>1.18 (0.93, 1.51)</td>
<td>1.55 (1.05, 2.28)</td>
<td>1.02 (0.74, 1.40)</td>
</tr>
<tr>
<td>Exposed 3rd trimester</td>
<td>72 (28)</td>
<td>0.99 (0.79, 1.25)</td>
<td>1.27 (0.88, 1.85)</td>
<td>0.87 (0.65, 1.17)</td>
</tr>
<tr>
<td>Unknown relative</td>
<td>5104 (1539)</td>
<td>0.98 (0.94, 1.02)</td>
<td>0.96 (0.90, 1.03)</td>
<td>0.98 (0.94, 1.03)</td>
</tr>
<tr>
<td>Unknown GA</td>
<td>376 (119)</td>
<td>1.06 (0.95, 1.17)</td>
<td>1.07 (0.89, 1.29)</td>
<td>1.05 (0.92, 1.19)</td>
</tr>
<tr>
<td>Unknown relative and GA</td>
<td>728 (263)</td>
<td>0.93 (0.85, 1.01)</td>
<td>1.07 (0.93, 1.22)</td>
<td>0.86 (0.78, 0.96)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Variables included in the model were: calendar year and statistical interaction between offspring age and sex.

<sup>b</sup> Variables included in the model were: calendar year, statistical interaction between exposure and offspring sex, and statistical interaction between offspring age and sex.

GA = gestational age.
An association between maternal exposure to serious illness in any trimester or before pregnancy and affective disorders in female offspring. The risk of affective disorders in male offspring was elevated in relation to serious illness in close relatives in the overall exposure period (adjusted RR = 1.33, [95% CI: 1.06, 1.66]). There was no evidence to support an association between maternal exposure to serious illness in close relatives during the second trimester and affective disorders in male offspring was significantly increased RR = 1.74, [95% CI: 1.06, 2.84]). An increased RR was also observed in the first trimester, although not significantly adjusted (RR = 1.53, [0.91, 2.59]). When we combined 1st and 2nd trimester exposures, the adjusted RR of affective disorders in males was 1.64(1.14, 2.34). We found no association between death of close relatives in the 3rd trimester or before pregnancy and affective disorders in male offspring. There was no association between maternal exposure to death of close relatives in any exposure period and risk of affective disorders in female offspring.

### 4.2. Exposure to death of close relatives

Overall, there was no association between maternal exposure to death of a close relative during any exposure period and risk of affective disorders in the offspring (Table 3). However, male offspring of women who experienced the death of a close relative during the second trimester had an increased risk of affective disorders (adjusted RR = 1.74, [95% CI: 1.06, 2.84]). An increased RR was also observed in the first trimester, although not significantly adjusted (RR = 1.53, [0.91, 2.59]). When we combined 1st and 2nd trimester exposures, the adjusted RR of affective disorders in males was 1.64(1.14, 2.34). We found no association between death of close relatives in the 3rd trimester or before pregnancy and affective disorders in male offspring. There was no association between maternal exposure to death of close relatives in any exposure period and risk of affective disorders in female offspring.

### 4.3. Exposure to serious illness in close relatives

Overall, there was no association between offspring affective disorders and maternal exposure to serious illness in close relatives or in any specific exposure period (Table 4). The risk of affective disorders in male offspring was elevated in relation to serious illness in close relatives in the overall exposure period (adjusted RR = 1.33, [1.06, 1.66]) and in the six months before pregnancy (adjusted RR = 1.44, [95% CI: 1.02, 2.05]). There was no evidence to support an association between maternal exposure to serious illness in any exposure period and risk of affective disorders in female offspring.

### 4.4. Further analyses results

In separate analyses we adjusted the Poisson models for place of birth, paternal and maternal age, paternal and maternal ethnic background (parent born in Denmark or abroad) and family history of mental illness (parents and siblings of the index child), birthweight and gestational age but they did not change the estimates materially. We also restricted the analyses to term babies of normal birthweight and again the results were not changed. Furthermore, we restricted the analysis to children with no family history of mental illness but that did not change the conclusions materially: for example, the RRs of affective disorders in male offspring were 1.41(0.70, 2.83) and 1.80(0.96, 3.35) in relation to maternal exposure to death of a close relative in the first and second trimesters compared with 1.53 and 1.74, respectively without this restriction. The restricted analyses were based on only 8 exposed offspring in the first trimester and 10 in the second trimester which may explain the lack of statistical significance.

When we started follow-up from the children’s 18th birthday the RR estimates did not change materially. This analysis effectively included diagnoses of affective disorders from 1995 onwards i.e. when outpatients were included and ICD-10 only. Also, we excluded offspring of all mothers who were exposed to serious illness in one exposure period and death in another and performed the analyses again but that had little effect on the estimates.

### 4.4.1. Bipolar disorder

We attempted to investigate the effect of maternal exposure to severe life events on the risk of bipolar disorder but the number of exposed cases was too limited, due to rarity of the condition (Laursen et al., 2007), for meaningful analyses (7 exposed before pregnancy and 3 in each trimester). In a separate analysis children were followed for development of any affective disorder except bipolar disorder from their 10th birthday until their first diagnosis with affective disorder, death, migration from Denmark or December 31, 2007 (end of follow-up), whichever came first. The exclusion of bipolar disorder from the outcome did not change the results.

### Table 3

Adjusted relative risk estimates for offspring affective disorders according to timing of prenatal exposure (death of mother’s close relatives).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of cases (males)</th>
<th>Adjusted RR(^a) (95% CI)</th>
<th>Adjusted RR(^b) in males (95% CI)</th>
<th>Adjusted RR(^c) in females (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death of any relative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>7295 (2238)</td>
<td>1[Reference]</td>
<td>1[Reference]</td>
<td>1[Reference]</td>
</tr>
<tr>
<td>Exposed during any period</td>
<td>196(64)</td>
<td>1.01(0.87, 1.16)</td>
<td>1.09(0.85, 1.40)</td>
<td>0.97(0.82, 1.15)</td>
</tr>
<tr>
<td>Exposed before pregnancy</td>
<td>81(20)</td>
<td>0.87(0.70, 1.08)</td>
<td>0.71(0.46, 1.10)</td>
<td>0.93(0.73, 1.20)</td>
</tr>
<tr>
<td>Exposed 1st trimester</td>
<td>34(14)</td>
<td>1.14(0.82, 1.60)</td>
<td>1.53(0.91, 2.59)</td>
<td>0.97(0.62, 1.50)</td>
</tr>
<tr>
<td>Exposed 2nd trimester</td>
<td>37(16)</td>
<td>1.23(0.89, 1.70)</td>
<td>1.74(1.06, 2.84)</td>
<td>1.01(0.66, 1.55)</td>
</tr>
<tr>
<td>Exposed 3rd trimester</td>
<td>44(14)</td>
<td>1.06(0.79, 1.43)</td>
<td>1.15(0.68, 1.94)</td>
<td>1.02(0.71, 1.47)</td>
</tr>
</tbody>
</table>

\(^a\) Variables included in the model were: calendar year, statistical interaction between exposure and offspring sex, and statistical interaction between offspring age and sex.

\(^b\) Variables included in the model were: calendar year, statistical interaction between exposure and offspring sex, and statistical interaction between offspring age and sex.

\(^c\) Variables included in the model were: calendar year, statistical interaction between exposure and offspring sex.

### Table 4

Adjusted relative risk estimates for offspring affective disorders according to timing of prenatal exposure (illness in mother’s close relatives).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of cases (males)</th>
<th>Adjusted RR(^a) (95% CI)</th>
<th>Adjusted RR(^b) in males (95% CI)</th>
<th>Adjusted RR(^c) in females (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness in any relative</td>
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</tr>
<tr>
<td>Unexposed</td>
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<td>1[Reference]</td>
<td>1[Reference]</td>
</tr>
<tr>
<td>Exposed during any period</td>
<td>205(77)</td>
<td>1.10(0.96, 1.26)</td>
<td>1.33(1.06, 1.66)</td>
<td>1.00(0.84, 1.19)</td>
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<tr>
<td>Exposed before pregnancy</td>
<td>89(32)</td>
<td>1.21(0.98, 1.49)</td>
<td>1.44(1.02, 2.05)</td>
<td>1.11(0.86, 1.45)</td>
</tr>
<tr>
<td>Exposed 1st trimester</td>
<td>27(11)</td>
<td>0.80(0.55, 1.16)</td>
<td>0.98(0.54, 1.77)</td>
<td>0.71(0.43, 1.16)</td>
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<tr>
<td>Exposed 2nd trimester</td>
<td>41(14)</td>
<td>1.21(0.89, 1.64)</td>
<td>1.32(0.78, 2.23)</td>
<td>1.16(0.79, 1.69)</td>
</tr>
<tr>
<td>Exposed 3rd trimester</td>
<td>48(20)</td>
<td>1.06(0.80, 1.41)</td>
<td>1.42(0.91, 2.21)</td>
<td>0.90(0.62, 1.30)</td>
</tr>
</tbody>
</table>

\(^a\) Variables included in the model were: calendar year and statistical interaction between exposure and sex.

\(^b\) Variables included in the model were: calendar year, statistical interaction between exposure and offspring sex, and statistical interaction between offspring age and sex.
4.4.2. Unknown exposure status

Mothers of 694,178 (61.23%) offspring were unexposed to severe life events during pregnancy or in the 6 months before pregnancy. Mothers of 405,111 (35.73%) offspring had unknown exposure: 290,833 (25.65%) had missing links to at least 1 relative, 73,995 (6.53%) had missing gestational age and 40,283 (3.55%) had missing gestational age and missing links to relatives. The risk of affective disorders in the offspring of these women was similar to that of the unexposed population. The RR’s of affective disorders in the unknown exposure status categories were generally close to one and not significant with one exception (Table 2). Excluding all persons with unknown exposure status from the analyses did not change the estimates.

5. Discussion

This study suggests that prenatal exposure to severe life events related to close relatives illness or death increases the risk of affective disorders in male offspring. The association appeared to be dependent on timing and type of the exposure. Bereavement due to the loss of a close relative during the first two trimesters, but not before pregnancy or during the third trimester, of pregnancy appeared to increase the risk of male affective disorders. On the other hand, severe illness in close relatives before pregnancy appeared to increase the risk of male affective disorders. We found no evidence to suggest an association between prenatal exposure to severe life events, whether death or serious illness, and risk of female offspring affective disorders.

The present study was a large population-based cohort of all children born in Denmark between May 1978 and December 1997. To our knowledge, this is the first study to investigate the association between risk of affective disorders and prenatal exposure to individual level severe life events. We used a standardised and objective measure of stress (death or serious illness) on the individual level of an entire population which is thought to induce the most severe stress (APA, 1987; Osterweis et al., 1984). By using data from the registers we avoided the problem of selection bias and loss to follow-up from which cohort studies often suffer. Although both the exposure and outcome variables were rare we were able to explore the effect of maternal stress on risk of affective disorders in males and females separately. We were also able to explore the effect of timing of the exposure on the risk of affective disorders. We restricted the exposure to death or serious illness in close relatives to secure a robust definition of stress. However, we cannot rule out that less catastrophic events such as family, financial or work-related events may also cause stress and be associated with an increased risk of affective disorders in the offspring.

Although the study was large and population-based there was a lack of adequate statistical power to investigate the effect of prenatal stress on risk of bipolar disorder in offspring therefore the results are mainly interpretable for depression. Furthermore, some of the subgroup analyses did not reach statistical significance probably because of inadequate statistical power. The main reasons for lack of statistical power were the rarity of the exposure and outcome and missing links to relatives. It is unlikely that missing data relating to the national registration system should bias the reported results; however, having an unknown parent could be related to mental illness i.e. there could be an independent effect of having an unknown parent on risk of affective disorders.

Furthermore, we were unable to adjust the statistical models for the potential confounding effect of parental socio-economic status (SES). It is possible that low SES mothers have larger families with higher rates of morbidity and mortality, and therefore are more likely to be exposed (Wagner et al., 1985); for example McFadden et al. reported an increased risk of all-cause mortality, mortality from cardiovascular disease and mortality from cancer with decreasing social class (McFadden et al., 2008), and Blakely et al. found an association between low SES and child mortality (Blakely et al., 2003). Furthermore, previous research suggested an association between parental SES and risk of bipolar disorders (Tsuchiya et al., 2004) and an association between low SES in early childhood and major depression in adulthood (Gilman et al., 2003).

Finally, the data sources we used do not include self-reported data about the psychological stress caused by the death or illness in a close relative. It is possible that some of the women were not close to their parents or siblings and in some cases may have not known about the illness. On the other hand, one could argue that great majority of the women would have known about the death or life threatening illness of their relatives.

Brown et al. reported an increased risk of major affective disorders in male, but not female, offspring in relation to maternal prenatal exposure to famine. In their repeat study (Brown et al., 2000), they reported an increased risk of affective disorders in male offspring and some evidence for a higher risk of female offspring affective disorders. However, excess risk was only in relation to second and third trimester exposures (Brown et al., 2000). Watson et al. (1999) reported that the highest risk of depressive symptoms in male offspring of women who were exposed to the Tangshan earthquake during the second trimester, although the risk was also high in the first and third trimesters compared to controls. Unlike previous studies of ecological level stressors, in our study, we had the advantage of using a clearly defined measure of severe stress occurring at an individual maternal level and specifically timed during pregnancy. When population measures of exposure are used, it is less clear what aspects of famine or war, e.g. malnutrition, infectious diseases or psychological stress, might be responsible for any observed effects. Interestingly, Li et al. reported an association between prenatal exposure death of a child or unexpected death of a spouse and risk of ADHD in male offspring but not females (Li et al., 2010).

Accumulating evidence suggests that prenatal environmental factors such as stress and anxiety may affect the development of the fetal brain and that the effect depends on gestation time point (Seckl, 2004). Prenatal stress is linked with impaired behavioural, neuro-developmental, cognitive and psychiatric outcomes in the offspring (Bergman et al., 2007; Davis et al., 2007; Laplante et al., 2004). Although the mechanism whereby prenatal stress influences the risk of disease in the offspring is unclear, fetal programming is often mentioned as a potential mechanism (Seckl, 2004, 2001; Owen and Matthews, 2007). Stress hormones such as glucocorticoids, produced by the adrenal cortex, are essential for normal fetal development and are related to alterations in most regions of the fetal central nervous system (Welberg et al., 2001; Wadhwa, 2005; Seckl, 2004). In animals prenatal stress has been demonstrated to alter brain development by reducing the placenta’s ability to protect the fetus against teratogens such as maternal cortisol. Maternal glucocorticoids may cross the placenta and disturb the fetal brain development (Watson et al., 1999; Laplante et al., 2004). Prenatal stress is also associated with the programming of neuroendocrine and behavioural effects in the offspring. Repeated restraint as a prenatal stressor in rats resulted in a decreased ability to inhibit stress-induced glucocorticoid secretion in the offspring (which was only present in adrenalectomized mothers with substitutive glucocorticoids treatment) [Barbazanges et al., 1996]. A range of disturbances of HPA regulation and brain monoamine levels are associated with affective disorders in humans (Welberg et al., 2001).

It is unclear why the effect of prenatal exposure to severe life events on affective disorders was confined to male offspring in the present study. However, HPA axis programming has been reported to differ between male and female offspring in animals although
the conclusions are inconsistent (Seckl, 2004; Owen and Matthews, 2007; McCormick et al., 1995; Mueller and Bale, 2007). The sex specificity of effects in animal models also provides evidence that whether females or males are affected depends on the nature and timing of the prenatal stressor (Tobe et al., 2005). McCormick et al. (1995) reported a significant effect of prenatal stress on HPA in female rats, but not males, showing increased plasma ACTH and β responses to restraint compared to controls. Owen and Matthews (2007) found that guinea pig behavior was affected by prenatal synthetic-glucocorticoids exposure. Exposed female offspring were hyperactive at 10 days of age while exposed males had decreased activity at 200 days of age. Testosterone is recognized to dampen reactivity of the HPA axis in healthy animals including man. It is also recognized that early stress exposures can alter programming not only of the HPA axis, but also of the HPG axis. This means that exposed male fetuses may no longer experience protective levels of testosterone around adolescence when the most prominent sex difference in incidence of affective disorder usually occurs (Gaskin and Kitay, 1971; Viau and Meaney, 2004). Such accumulating evidence of biological causes of sex differentiated responses to stress in animals means that it is tempting to invoke more biological models for the sex differentiated incidence of depressive disorder (excl. bipolar disorder). However, psychosocial differences in women’s experiences, such as abuse and violence, are likely to explain much of the differences usually seen in incidence of depressive illness in women and men during their reproductive years (Cutler and Nolen-Hoeksema, 1991; Garcia-Moreno et al., 2005). With outcomes that are linked to clearly identified exposures of large effects size, it is likely that other factors are ‘overwhelmed’. Thus, men exposed to antenatal maternal stress may become vulnerable to life events to which they would normally be resilient, whereas for women, other well recognized risk factors may overwhelm any relatively small additional effects. Indeed, in our previous study, we reported that antenatal maternal exposure to severe stress was associated with an excess risk of schizophrenia only in those offspring with no family psychiatric history (Khashan et al., 2008).

In conclusion, this study indicates that prenatal maternal stress influences the neurodevelopment of the unborn child. Furthermore, our findings indicate that male infants are uniquely vulnerable and that the effect is dependent upon the stage of embryonic fetal development.

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Contributors

All authors contributed to the study design, ASK and MGP performed the statistical analysis, ASK wrote the first draft of the manuscript, all authors contributed to the interpretation of the results and critically reviewed the manuscript, all authors have approved the final manuscript.

Conflict of interest

None declared.

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