



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

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ABSTRACT

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

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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., 2009) 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 (Anderson 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-8410 and ICD-10 I21, I22), and cerebrovascular accident (ICD-8431, 433, 434 and ICD-10 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

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