ORIGINAL ARTICLE

Higher Risk of Offspring Schizophrenia Following Antenatal Maternal Exposure to Severe Adverse Life Events

Ali S. Khashan, MSc; Kathryn M. Abel, MRCP, MRCPsych, PhD; Roseanne McNamee, PhD; Marianne G. Pedersen, MSc; Roger T. Webb, PhD; Philip N. Baker, DM, FRCOG; Louise C. Kenny, PhD, MRCOG; Preben Bo Mortensen, MD, DMSc

Context: Most societies believe that a mother's psychological state can influence her unborn baby. Severe adverse life events during pregnancy have been consistently associated with an elevated risk of low birth weight and prematurity. Such events during the first trimester have also been associated with risk of congenital malformations.

Objective: To assess the effect in offspring of antenatal maternal exposure to an objective measure of stress on risk of adverse neurodevelopment, specifically schizophrenia. We hypothesized that the strongest relationship would be to maternal exposures during the first trimester.

Design: Population-based study.

Setting: Denmark.

Participants: In a cohort of 1.38 million Danish births from 1973 to 1995, mothers were considered exposed if 1 (or more) of their close relatives died or was diagnosed with cancer, acute myocardial infarction, or stroke syndrome up to 6 months before conception or during pregnancy. Offspring were followed up from their 10th birthday until their death, migration, onset of schizophrenia, or June 30, 2005; admissions were identified by linkage to the Central Psychiatric Register.

Main Outcome Measure: Schizophrenia.

Results: The risk of schizophrenia and related disorders was raised in offspring whose mothers were exposed to death of a relative during the first trimester (adjusted relative risk, 1.67 [95% confidence interval, 1.02-2.73]). Death of a relative during other trimesters or up to 6 months before pregnancy were not linked with a higher risk of schizophrenia.

Conclusions: Our population-based study suggests that severe stress to a mother during the first trimester may alter the risk of schizophrenia in offspring. This finding is consistent with ecological evidence from whole populations exposed to severe stressors and suggests that environment may influence neurodevelopment at the feto-placental-maternal interface.

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Author Affiliations: Centre for Women's Mental Health Research (Mr Khashan and Drs Abel and Webb), Biostatistics Group (Dr McNamee), and Maternal and Fetal Health Research Group (Mr Khashan, Prof Baker, and Dr Kenny), University of Manchester, Manchester, England; National Centre for Register-based Research, University of Aarhus, Aarhus, Denmark (Ms Pedersen and Prof Mortensen); and BUPA Ireland Research Center, Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, Cork, Ireland (Dr Kenny).

THE COMMON CONCEPTION that a mother's psychological state can influence her unborn baby is to some extent substantiated by the literature.[1] Severe life events during pregnancy are consistently associated with an elevated risk of low birth weight[2] and prematurity.[3] Recently, Hansen et al[4] reported specific effects of severe life events on neurodevelopment in exposed offspring. They found an increased risk of cranial neural crest malformations in offspring of mothers exposed to death of an older child during the first trimester. Other studies have also attempted to find evidence of a positive association between antenatal maternal stress and an increased risk of adult schizophrenia in exposed offspring.[5,6]

Schizophrenia is a serious, potentially lifelong, and disabling condition that is associated with abnormalities of brain structure and function. A large body of evidence from "natural experiments," such as twin studies, suggests that it is highly heritable (up to 85%).[7] Increasingly, schizophrenia is believed to be a disorder of early brain development influenced by environmental risk factors that interact with the combined effects of multiple (small-effect) susceptibility genes.[8,9]

War,[6,10] famine,[11-13] A-bomb radiation,[14] and unwanted pregnancy[5] have all been studied in relation to stress and offspring schizophrenia risk. Most of these studies reported a positive association between exposure of a population to a severe life event and schizophrenia risk in subsequent offspring cohorts. However, apart from Myhrman et al,[5] they have been unable to examine exposure of individual subjects to risk factors/stressors. Furthermore, exposures like famine, the

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A-bomb, and war are complex and may combine several risk factors other than emotional stress, including malnutrition, ionizing radiation, and infectious disease. In addition, most of these studies have failed to control for potential confounders such as family history of mental illness and urbanicity.

Huttunen and Niskanen[15] reported that death of the mothers' partner/spouse during months 3 to 5 and 9 and 10 of pregnancy was associated with an increased risk of psychiatric admission in offspring. To our knowledge, no study has been able to examine schizophrenia risk using this exposure measured at an individual level. In this study, we used the Danish population registers to examine rates of schizophrenia in a cohort of offspring whose mothers had been exposed antenatally to an objective and incontrovertible measure of stress that would be independent of the psychological characteristics of the mother: death or illness in a first-degree relative (mother, father, spouse/partner, sibling, or older child). Based on findings reported by Hansen et al,[4] we hypothesized that the strongest association would be to stressors affecting the mother during the first trimester.

METHODS

All women who gave birth in Denmark between January 1, 1973, and June 30, 1995, were identified using the Medical Birth Registry,[16] which includes information on gestational age. These women were linked to their close relatives (older children, spouses, fathers, mothers, and siblings) using the Civil Registration Number. This number is unique and enables linkage between all national registers in Denmark. Spouse was defined as the legal father of the child. The close relatives were linked to the Civil Registration System[17] to determine if and when they had died. Linkage was also made to the National Hospital Register[18] to identify any diagnoses of cancer, acute myocardial infarction, or stroke syndrome among first-degree relatives.

Exposure was defined by first diagnosis of cancer (*International Classification of Diseases, Eighth Revision [ICD-8]* codes 140-207 and *International Statistical Classification of Diseases, 10th Revision [ICD-10]* codes C00-C97), acute myocardial infarction (*ICD-8* code 410 and *ICD-10* codes I21 and I22), stroke syndrome (*ICD-8* codes 431, 433, or 434 and *ICD-10* codes I61, I63, or I64), or death of the father, mother, sibling, child, or spouse of the pregnant mother. The date of exposure was defined as the date of death or the first hospital admission leading to illness diagnosis. The first day of the last menstrual period (date of pregnancy) was defined using the date of birth and gestational age. Exposure during pregnancy or 6 months before pregnancy was classified by timing: up to 6 months before pregnancy, first trimester (0-12 weeks), second trimester (13-24 weeks), and third trimester (25 weeks to birth). Pregnant women were considered exposed if at least 1 relative died or was diagnosed with illness during the exposure period, regardless of the links to the other relatives. They were considered unexposed if they had links to all relatives and none of them had an event during the exposure period. During the period 1973 to 1995, mothers of 36 193 offspring were exposed to illness or death of a close relative. If more than 1 exposure occurred during the same pregnancy, priority was given to first trimester, before pregnancy, second trimester, and, finally, third trimester (ie, if a woman was exposed to death of her spouse in the first trimester and death of her father in the second trimester, she was considered exposed in the first trimester). In separate analyses, priority was instead given to the second trimester, then to the third, then to "up to 6 months before pregnancy."

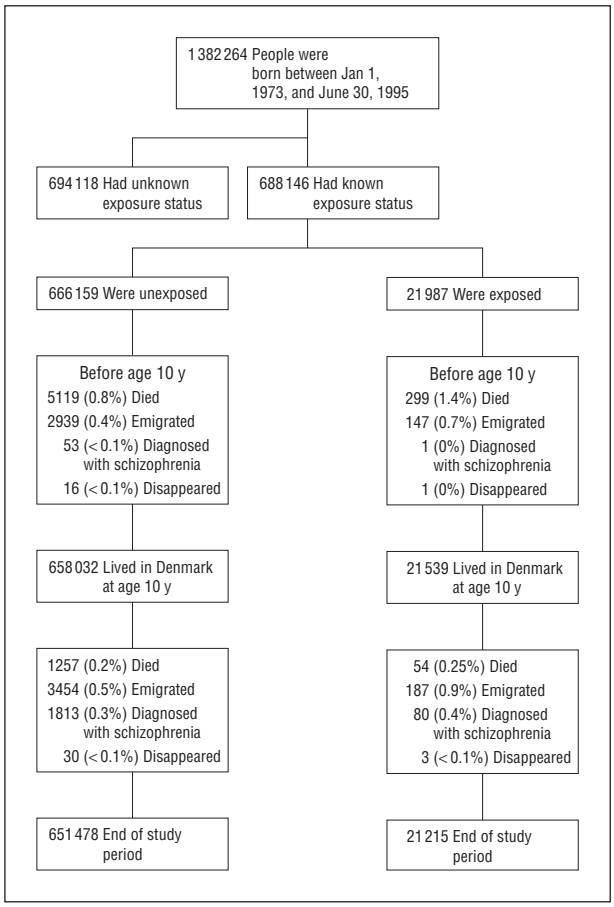

Figure. Data for maternal exposure status, offspring who were not living in Denmark on their 10th birthday, and offspring who were lost to follow-up. These data are related to death of a close relative. Mothers of 21 987 offspring were exposed during pregnancy and up to 6 months before pregnancy. Of those, 11 715 were exposed up to 6 months before pregnancy; 3096, in the first trimester; 3052, in the second trimester; and 4124, in the third trimester.

The initial cohort consisted of 1.38 million births and was linked to the Danish Psychiatric Central Register.[19] This contains records on all admissions to Danish psychiatric inpatient facilities since 1969 and outpatient visits to psychiatric departments since 1995. *ICD-8*[20] was used from April 1969 to December 1993. *ICD-10*[21] was used from January 1994. To maximize statistical power, a broad definition of schizophrenia and related disorders was used (*ICD-8* code 295, 296.8, 297, 298.39, or 301.83 or *ICD-10* codes F20-F29), where cases were diagnosed following admission to a psychiatric hospital or in receipt of outpatient care. Schizophrenia onset was defined as the date of the first contact that led to this diagnosis. The cohort was followed up from the 10th birthday of the offspring until onset of schizophrenia, death, migration, disappearance, or June 30, 2005 (end of study period), whichever came first. As depicted in the **Figure**, the "censoring mechanism" because of death, disappearance, migration, or end of study period was independent of an exposure event (ie, the percentages of censored data are trivial and comparable between exposed and unexposed groups). Schizophrenia diagnoses before age 10 years are likely to have been due to reporting errors.

STATISTICAL ANALYSIS

Log-linear Poisson regression of aggregated person-years data[22] in Stata software[23] was used to estimate the relative risk (RR) of schizophrenia. Cox regression is too computationally intensive

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Table 1. Distribution of 7331 Cases of Schizophrenia and 15.1 Million Person-years of Follow-up in a Cohort of 1.38 Million Danish People

Variable	No. of Cases	Incidence per 100 000 Person-years
Sex		
M	4287	55.4
F	3044	41.3
Place of birth		
Capital	1686	85.6
Suburb of capital	1065	61.5
Provincial city	911	46.3
Provincial town	2307	41.8
Rural area	1362	34.7
Family history (all psychiatric admissions)		
Admitted, not schizophrenia	1996	110.6
Admitted, schizophrenia	758	272.5
Not admitted	4577	35.1
Maternal age, y		
12-19	629	80.5
20-25	2903	48.6
26-29	1979	43.3
30-34	1301	45.4
≥ 35	519	56.2

Table 2. RR Estimates for Offspring Schizophrenia Risk According to Timing of Exposure (Severe Life Events in Mother's Close Relatives) During the Antenatal Period

Variable: Death or Illness in Any Relative	No. of Cases	Partially Adjusted RR[a] (95% CI)	Adjusted RR[b] (95% CI)
Unexposed	1775	1 [Reference]	1 [Reference]
Exposed before pregnancy	56	0.96 (0.73-1.25)	0.96 (0.74-1.26)
Exposed first trimester	24	1.44 (0.96-2.15)	1.44 (0.96-2.16)
Exposed second trimester	20	1.37 (0.88-2.13)	1.35 (0.87-2.11)
Exposed third trimester	22	1.11 (0.73-1.69)	1.12 (0.74-1.71)

Abbreviations: CI, confidence interval; RR, relative risk.
[a] Adjusted for calendar year and statistical interaction between offspring age and sex.
[b] Adjusted for offspring age, sex, place of birth, family history, maternal age, calendar year, unknown father, and statistical interaction between offspring age and sex.

for studies of this size; therefore, we used Poisson regression as an approximation.[24] Negative binomial regression models suggested that the Poisson models were not subject to overdispersion.[25] Relative risks were adjusted for place of birth (capital, capital suburb, provincial city, provincial town, and rural area); offspring age (10-11, 12-13, 14, 15, 16, 17, 18, 19, 20-21, 22-23, 24-25, 26-27, 28-29, and 30-32 years), offspring sex (and an interaction between offspring age and sex), maternal age, calendar year (1983-1987, 1988-1989, and 1-year categories thereafter until 2005), and unknown spouse. The models also controlled for family history of schizophrenia and other mental illnesses (parents and siblings of index offspring). Calendar year, family history of schizophrenia, and other mental illness and offspring age were generated as time-dependent variables; all other explanatory variables were time fixed.[26]

Analyses were carried out separately for (1) illness in any close relative, (2) death of any close relative, and (3) illness and/or death (events) of any close relative during pregnancy or up to 6 months before pregnancy. All analyses considered the timing of the event to assess variation by trimester in the effect on schizophrenia risk.

ATTRIBUTABLE RISK

The population attributable risk of schizophrenia is an estimate of the fraction of the total number of cases of schizophrenia in the population that can be attributed to a particular exposure. The estimation was carried out as described by Last[27] using the formula

$$P \times (RR-1)/1 + P \times (RR-1),$$

where P is the proportion of the total population exposed to death of a close relative during the first trimester. The adjusted RR of schizophrenia in relation to maternal exposure to death of a close relative during the first trimester was used.

MISSING DATA

The main sources of missing information were gestational age and links between mothers and their relatives. During the study period, there were 60 438 births (4.4%) with missing gestational age. Mothers of 11 629 offspring (0.8%) had no links to the child's father. Mothers who were not living at the same address as their parents when the Danish Civil Registration System was established in 1968 had no links to them in this data source and subsequently had no links to their siblings either. In total, mothers of 680 250 offspring (49.2%) had at least 1 missing link to their father, mother, siblings, or father of their offspring. All children registered in the Medical Birth Registry have complete linkage to their mothers. For the purpose of sensitivity analysis, subjects with missing data were grouped in 3 categories: unknown relative and unknown gestational age; unknown relative and known gestational age; and known relative and unknown gestational age.

RESULTS

During the study follow-up period (15.1 million person-years), 7331 people (4287 males and 3044 females) were diagnosed with schizophrenia. Mothers of 21 987 children were exposed to death and 14 206, to serious illness in close relatives. One hundred twenty-two children whose mothers were exposed antenatally to severe life events (80 of whom were exposed to death of relatives) developed schizophrenia in later life. **Table 1** presents the number of cases and rates of schizophrenia by sex, place of birth, family history of mental illness, and maternal age.

EXPOSURE TO ALL EVENTS COMBINED (DEATH AND/OR ILLNESS) IN CLOSE RELATIVES

The RRs (partially adjusted and fully adjusted) of developing schizophrenia in relation to maternal exposure to severe life events (illness or death) in any close relative are presented in **Table 2**. The estimates do not support an association between maternal exposure to severe life events during any exposure period and risk of developing schizophrenia in the offspring. The estimated RR of schizophrenia, however, was elevated during the first (adjusted RR, 1.44 [95% confidence interval (CI), 0.96-2.16]) and second (adjusted RR, 1.35 [95% CI, 0.87-2.11]) trimesters, but not significantly.

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Table 3. RR Estimates for Offspring Schizophrenia Risk According to Timing of Exposure (Illness in Mother's Close Relatives) During the Antenatal Period

Variable: Illness in Any Relative	No. of Cases	Partially Adjusted RR[a] (95% CI)	Adjusted RR[b] (95% CI)
Unexposed	1813	1 [Reference]	1 [Reference]
Exposed before pregnancy	15	0.85 (0.51-1.41)	0.87 (0.52-1.44)
Exposed first trimester	9	1.05 (0.55-2.02)	1.07 (0.56-2.06)
Exposed second trimester	13	1.56 (0.90-2.69)	1.58 (0.91-2.72)
Exposed third trimester	14	1.20 (0.71-2.03)	1.22 (0.72-2.06)

Abbreviations: See Table 2.
[a] Adjusted for calendar year and statistical interaction between offspring age and sex.
[b] Adjusted for offspring age, sex, place of birth, family history, maternal age, calendar year, unknown father, and statistical interaction between offspring age and sex.

Table 4. RR Estimates for Offspring Schizophrenia Risk According to Timing of Exposure (Death of Mother's Close Relatives) During the Antenatal Period

Variable: Death of Any Relative	No. of Cases	Partially Adjusted RR[a] (95% CI)	Adjusted RR[b] (95% CI)
Unexposed	1813	1 [Reference]	1 [Reference]
Exposed before pregnancy	46	1.01 (0.75-1.36)	1.01 (0.75-1.35)
Exposed first trimester	16	1.74 (1.06-2.85)	1.67 (1.02-2.73)
Exposed second trimester	9	1.04 (0.54-1.99)	0.97 (0.50-1.87)
Exposed third trimester	9	0.76 (0.39-1.46)	0.74 (0.38-1.43)
Unknown relative and unknown GA	323	0.87 (0.77-0.98)	0.99 (0.87-1.12)
Unknown relative and known GA	4994	1.05 (0.99-1.12)	1.05 (0.98-1.13)
Known relative and unknown GA	121	0.97 (0.81-1.18)	1.01 (0.84-1.21)

Abbreviations: CI, confidence interval; GA, gestational age; RR, relative risk.
[a] Adjusted for calendar year and statistical interaction between offspring age and sex.
[b] Adjusted for offspring age, sex, place of birth, family history, maternal age, calendar year, unknown father, and statistical interaction between offspring age and sex.

EXPOSURE TO ILLNESS IN ANY CLOSE RELATIVE

We also examined the effect of maternal exposure to serious illness diagnosis (cancer, acute myocardial infarction, and stroke syndrome) in close relatives on risk of schizophrenia in the offspring. The estimates (**Table 3**) do not support an association between maternal exposure to illness diagnosis in close relatives during any exposure period and risk of schizophrenia in the offspring. However, the estimated RR was elevated, but not significantly, during the second trimester (adjusted RR, 1.58 [95% CI, 0.91-2.72]).

EXPOSURE TO DEATH OF ANY CLOSE RELATIVE

We examined the effect of maternal exposure to death of a close relative on risk of schizophrenia in the offspring. The estimates (**Table 4**) suggest that maternal exposure to death of a close relative during the first trimester increases the risk of developing schizophrenia in the offspring (partially adjusted RR, 1.74 [95% CI, 1.06-2.85]; fully adjusted RR, 1.67 [95% CI, 1.02-2.73]). There were 16 mothers who were exposed to death of a close relative during the first trimester whose offspring subsequently developed schizophrenia. We explored the causes of death of the 16 relatives who died and only 1 of them was registered as suicide. The estimates, however, do not support an association between risk of schizophrenia and maternal exposure to death of a relative during other trimesters or up to 6 months before pregnancy. When exposure priority was given to the second trimester, then to the third, then to "up to 6 months before pregnancy," the results did not change. Furthermore, none of the offspring who developed schizophrenia had mothers exposed to more than 1 relative's death during the same pregnancy.

We also adjusted the RRs for paternal age, maternal ethnicity (mother born in Denmark or abroad), and paternal ethnicity (father born in Denmark or abroad). These factors did not change the estimates and they were omitted from the models.

HISTORY OF MENTAL ILLNESS IN CLOSE RELATIVES

We, moreover, explored the confounding effect of history of mental illness in the family on the effect of exposure to death in the first trimester. For this purpose, we restricted the cohort to persons with full links to all relatives to the mother (children, spouse, mother, father, and siblings). Cohort members who were unexposed to death and had no history of mental illness in the family (mother, father, siblings, mother's mother, mother's father, and mother's siblings) were chosen as the reference category. Persons exposed to death in the first trimester and with no history of mental illness in the family (8 cases) had an RR of 2.64 (95% CI, 1.31-5.29). Persons not exposed to death of a family member and who had a history of mental illness in a family member (1008 cases) had an RR of 2.12 (95% CI, 1.93-2.33) compared with the reference category. Persons exposed to death of a family member in the first trimester and who had a history of mental illness in a family member (4 cases) had an RR of 1.87 (95% CI, 0.70-4.99) also compared with the reference category.

We also explored the effect of maternal exposure to death of a relative in the first trimester in persons who had a history of mental illness in a close relative. We restricted the cohort to persons with history of mental illness in the family and full links to all close relatives of the mother. Offspring of mothers who were not exposed to death of a close relative were chosen as the reference category. Persons who were exposed to death of a relative in the first trimester and had a history of mental illness in a family member had an RR of 0.93 (95% CI, 0.38-2.23) compared with persons who had a history of mental illness in a family member but were not exposed to death of a close relative. Relative risks were adjusted for calendar year, age and its interaction with sex, place of birth, and maternal age. In conclusion, among

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Table 5. RR Estimates for Offspring Schizophrenia Risk According to Timing of Exposure (Death of Mother's Close Relatives) With the Data Set Restricted to Subjects With Full Links to Mother's First-Degree Relatives and Known Gestational Age

Variable: Death of Any Relative	No. of Cases	Partially Adjusted RR[a] (95% CI)	Adjusted RR[b] (95% CI)
Unexposed	1813	1 [Reference]	1 [Reference]
Exposed before pregnancy	18	0.81 (0.51-1.29)	0.82 (0.51-1.30)
Exposed first trimester	12	1.63 (0.92-2.87)	1.61 (0.91-2.84)
Exposed second trimester	8	1.10 (0.55-2.20)	1.06 (0.53-2.13)
Exposed third trimester	7	0.72 (0.34-1.51)	0.74 (0.35-1.55)

Abbreviations: See Table 2.
[a] Adjusted for calendar year and statistical interaction between offspring age and sex.
[b] Adjusted for offspring age, sex, place of birth, family history, maternal age, calendar year, and statistical interaction between offspring age and sex.

people without family history of mental illness, exposure to death in the first trimester was a significant risk factor for schizophrenia. In addition, among people with a history of mental illness in a family member, there was no evidence that exposure to death in the first trimester increased the risk of schizophrenia. However, the latter finding was based on limited power.

MISSING DATA

We were unable to link mothers to their parents if they had left their parents' homes before 1968. As a result, 49% of mothers had missing links to at least 1 relative, mainly their parents. Mothers in the categories with missing links to relatives tended to be older and more likely to have been born in the capital. Offspring of those mothers tended to be older. Therefore, comparing risk of schizophrenia in offspring of exposed and unexposed mothers might be expected to be confounded by such factors since the exposed group, but not the unexposed, contained missing links.

In a crude analysis (not shown), the risk of schizophrenia was significantly higher in the 3 missing data categories compared with the unexposed group. However, after adjustment for calendar year and a statistical interaction between offspring age and sex, only 1 RR remained significant (Table 4). In the fully adjusted model, there was no evidence of differences between the missing categories and the unexposed group, suggesting that confounding would be controlled by the factors in the model.

As a further check for bias, we performed a further sensitivity analysis where only mothers with full links to relatives and information on gestational age were included in both exposed and unexposed groups (**Table 5**). Predictably, this approach provided a smaller exposed sample of only 12 cases of offspring schizophrenia of mothers exposed in the first trimester and risk was not significantly increased in any trimester. However, the adjusted RR was greater than 1 in the first trimester (1.61 [95% CI, 0.91-2.84]). The adjusted RRs in the other trimesters and before pregnancy were close to 1 and not significant.

ATTRIBUTABLE RISK

The population attributable fraction associated with maternal exposure to death of a close relative during the first trimester in the total study population (with known exposure status) was 0.003. Therefore, maternal exposure to death of a close relative during the first trimester accounted for 0.3% of the schizophrenia cases in the population.

COMMENT

The offspring of women exposed to the stress of losing a close relative in the first trimester of pregnancy appear to be at a significantly increased risk of developing schizophrenia as adults. This effect is independent of a range of factors known to influence risk of schizophrenia, such as offspring sex, age, family history of mental illness, place of birth, and maternal age. Deaths occurring up to 6 months before pregnancy and after the first trimester did not have a significant effect on subsequent schizophrenia risk. Loss of a close relative during the first trimester appears to have a significant effect on risk of schizophrenia in the offspring who had no family history of mental illness, but not among those who did have a family history of mental illness in close relatives (parents, grandparents, and siblings of offspring). Risk of schizophrenia in relation to maternal exposure to serious illness in close relatives was elevated in the second trimester, but not significantly so.

Attributable risk is determined by the RR and frequency of exposure in the population; therefore, it is a measure of the impact that RR has on the population occurrence of disease. The population attributable fraction was small in this study. To secure a robust definition of stress, we restricted our exposure variable to severe and objective events (death, serious illness), which are relatively rare. We cannot exclude the possibility that less catastrophic, more common events may also increase the risk of schizophrenia in offspring and that maternal stress in a broader sense may have a greater population impact. However, other studies are needed to test this hypothesis.

This study has a number of novel features and findings. The rarity of reliable data on maternal exposure to individual-level, objective measures of severe stress during pregnancy, and the rarity of schizophrenia, means that it is the first epidemiological population study, to our knowledge, to report a positive association between maternal antenatal exposure to death or serious illness in a close relative and schizophrenia. These data represent, to our knowledge, the largest reported cohort where exposure to a clearly defined severe stress is linked to women at an individual level and to specific timing of the exposure in pregnancy. In a small sample, Huttunen and Niskanen[15] reported that antenatal maternal exposure to death of the mother's spouse (offspring's father) led to an increase in the risk of adult psychiatric admission in offspring and a higher number of admissions for schizophrenia (n=6) compared with the control group (n=1).

A number of other studies have reported a link between schizophrenia risk and the exposure of an entire

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population to different stressors. These include 3 epidemiological studies of famine,[11-13] which reported RRs of around 2 (female offspring only in Susser and Lin[11]) for offspring of women exposed during the first trimester of pregnancy. Maternal exposure to war during the first and second trimesters[6] and A-bomb radiation during the second trimester[14] have also been reported to increase risk of schizophrenia in adult offspring. However, Selten et al[10] reported a nonsignificant association between maternal exposure to war and risk of schizophrenia in the offspring. They also conducted a meta-analysis of 3 studies,[5,6,14] including their own, and found no significant association with prenatal maternal exposure to stress. Selten et al did not dismiss maternal stress as a risk factor for schizophrenia; they suggested that the unexposed populations (in their study) may have also been exposed to stress during the period when the controls were born (ie, 2 years prior and subsequent to the war). The Myhrman et al[5] study is the only previous study to measure individual-level maternal stress. They reported an approximately 2-fold risk of developing schizophrenia in adulthood in the offspring of women reporting unwanted pregnancies.

There are several limitations to our findings. Although the study was large and population based, we had insufficient statistical power to analyze sex differences in schizophrenia risk or the difference in the risk of schizophrenia in different periods (*ICD-8* and *ICD-10*).[20,21] Insufficient statistical power stems from rarity of exposure and rarity of outcome and from missing exposure data. We were unable to link mothers who had left their parents' home before 1968 to their parents and, as such, mothers of 49% of the offspring had missing links to at least 1 relative, mainly mothers' parents. It is unlikely that missing data relating to the national recording system should bias the reported estimates; however, losing a link to a parent could be because of mental illness (ie, there could be an independent effect of having an unknown parent/relative on offspring schizophrenia risk). In the interest of completeness, we have shown results of all trimesters but our a priori hypothesis concerned exposure in the first trimester. Thus, multiple testing is not a serious concern in our study. Finally, we have not examined risk of other mental health and neurodevelopmental outcomes following exposure to antenatal maternal stress. The specificity of this finding to risk of schizophrenia should be addressed in future studies.

Risk associated with exposure to a well-defined, objective stressful event confined to the first trimester of pregnancy suggests a number of possible mechanisms. To date, most studies have focused on changes in offspring hypothalamic-pituitary-adrenal axis responsivity as a result of antenatal stress.[28] By the seventh week of gestation, corticotrophin-releasing hormone (CRH) messenger RNA is expressed in the placenta[29] and active placental CRH, released into the maternal circulation.[30] Placental CRH is structurally identical to hypothalamic maternal CRH; however, glucocorticoids secreted in response to stress activate placental CRH gene expression, in contrast to their effects on hypothalamic CRH gene expression, which is inactivated by glucocorticoids.[31,32] Several systems have been described that form part of a "feto-placental barrier," which protects the immature brain against effects of maternal stress.[33] These include (1) 11β-hydroxysteroid hydrogenase, an enzyme that breaks down maternal plasma glucocorticoids and whose activity correlates with birth weight in rats and humans[28]; (2) as pregnancy progresses, increasing levels of maternal CRH-binding protein binds to maternal CRH and inactivates it[34]; and (3) in late, but not early, pregnancy, maternal hypothalamic-pituitary-adrenal axis responses are attenuated or blunted.[35] These factors suggest that very early in pregnancy, during a most critical phase of neurodevelopment, the fetal brain may be more vulnerable to the physiological effects of stress than later in pregnancy. Fetal programming by glucocorticoids is known to occur early in gestation,[36] but the long-term effects of maternal stress are not confined to changes in stress axis responsivity in offspring. Bateson et al[37] suggest that human development involves inducing particular patterns of development by cues that prepare the individual for the type of environment in which they are likely to live. Their hypothesis relates specifically to the prenatal stressor of famine inducing programming of fetal growth and nutritional expectation leading to increased risk of hypertension and type 2 diabetes mellitus. A common mechanism of stress-induced fetal hypothalamic-pituitary-adrenal axis programming through glucocorticoids may similarly program a trajectory of abnormal brain growth, from fetal brain development through puberty and into adulthood, as we have previously suggested.[38] In this way, an adaptive mechanism for fetal survival in a stressful environment may become maladaptive for long-term neurodevelopment.

Recent research in rats examined the effects of restraint stress imposed throughout pregnancy on hippocampal-dependent learning and hippocampal *N*-methyl-D-aspartate (NMDA) receptor expression.[39] Both control and "stressed" offspring had "normal" postnatal environments, but the adults whose mothers were stressed during gestation showed reduced hippocampal NMDA receptor expression. These data suggest that abnormalities of neurodevelopment and of specific receptor subpopulations, such as the NMDA receptor, which have both been proposed in the etiology of schizophrenia, could independently result from adverse antenatal stress. However, it is also plausible that the association between maternal emotional stress and risk of schizophrenia is mediated in part through increased risk of pregnancy complications.[6]

CONCLUSIONS

Our population-based study indicates that severe stress to a mother in the first trimester of pregnancy is associated with an increased risk of schizophrenia in the offspring. This finding is consistent with other evidence from whole populations exposed to severe stressors but requires replication in larger samples to allow examination of, for example, sex differences. Our findings suggest that environment may influence neurodevelopment at the feto-placental-maternal interface.

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Correspondence: Kathryn M. Abel, MRCP, MRCPsych, PhD, Centre for Women's Mental Health Research, University of Manchester, Williamson Building, Oxford Road, Manchester M13 9PL, England (kathryn.m.abel@manchester.ac.uk).
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