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Chernobyl exposure as stressor during pregnancy and behavior in adolescent offspring

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Abstract

Objective—To study the potential harmful effect of in utero exposure to the Chernobyl disaster in April 1986, and maternal anxiety associated with that exposure, on symptoms of behavior disorder observed at age 14.

Method—The sample included 419 Finnish twin pairs, born in 1985–1987. Prenatal exposure to Chernobyl was determined, and a group of exposed twins (n=232) were compared with a non-exposed reference group of twins (n= 572). The exposed group was further subdivided into three trimesters of pregnancy in which exposure occurred. The Finnish translation of the adolescent Semi-Structured Assessment of Genetics of Alcoholism (C-SSAGA-A) interview was used to assess symptoms of common psychiatric disorders based on DSM-III-R criteria when the twins were age 14. The number of lifetime symptoms of depression, generalized anxiety disorder, attention deficit hyperactivity disorder, conduct disorder and oppositional defiant disorder symptoms were compared by means of Poisson regression analyses, adjusted for SES, sex, age and clustering of data.

Results—Adolescents who were exposed from the second trimester in pregnancy onwards, had a 2.32-fold risk (95 % CI: 1.13 – 4.72) of having lifetime depression symptoms, an increased risk of fulfilling DSM-III-R criteria of a Major Depressive Disorder (OR = 2.48, 95 % CI: 1.06 – 5.7) , and a 2.01-fold risk (95 % CI: 1.14 – 3.52) of having ADHD symptoms. No associations with anxiety, CD or ODD symptoms were found.

Conclusions—Perturbations in fetal brain development may result in the increased prevalence of depressive and AHDH symptoms after prenatal stress exposure from second trimester onwards.

Keywords

Prenatal stress; Disaster; Chernobyl; Behavior; Depression; Adolescents

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Introduction

Research in animals has shown fairly consistent evidence that exposure to a variety of stressors during pregnancy is associated with increased emotionality, decreased exploratory behavior, and reduced attention in offspring (1–3). Recently, similar associations have been found in prospective human studies, which showed that prenatal maternal anxiety was related to hyperactivity, emotional and inattention problems in infants and children (4–9).

These prospective human studies were based on maternal report of exposure to prenatal stressors, such as high levels of anxiety assessed with self-rating inventories (5–7;9), or high levels of perceived stress and pregnancy-related anxieties (4;8). In contrast, all animal studies used a circumscribed and well-defined form of stress, such as restraint, noise, or tail shocks, which was inflicted on the pregnant dam. Thus, the exposure measures in human and animal studies are not easily comparable.

In humans, a general distinction should be made between exposure to self-reported stressors and naturally occurring stressors (10). The former reflect subjective feelings of stress or anxiety of pregnant women, whereas the latter reflect exposure to a disaster or a severe traumatic event, which may be more comparable with the experimental stressors in animal studies. An advantage of naturally occurring stressors is that the timing of occurrence is often known, whereas for most self-reported stressors, the timing of exposure during pregnancy is not exactly known. Thus, for self-reported stressors, it is often difficult to make claims about the timing of risk exposure. A further disadvantage of maternal self-reported stressors is that relations found between exposure to self-reported stressors and adolescent offspring behavior might also be indicative of a shared predisposition towards behavioral or emotional problems. A few human studies have taken advantage of naturally occurring stressors during pregnancy to examine the relationship with offspring behavioral outcomes retrospectively. Meijer (11) showed that the threat of and exposure to the 6-day Arab-Israeli war of 1967 was associated with increased behavioral problems, such as excessive clinging, crying, hyperactivity and antisocial behavior at age 2–10 years. A relatively high incidence of psychiatric disorders, including schizophrenic episodes, depressive and neurotic symptoms, alcoholism, and antisocial behavior, was found in children up to age 15 born to mothers who experienced the death of their spouse during pregnancy (12). Prenatal stress exposure in the first trimester of pregnancy caused by the German invasion during the World War II in the Netherlands was found to be associated with a small but significantly elevated risk for schizophrenia (13). Similar results were found after exposure to a tornado during the second trimester of pregnancy (14). The stress of a prenatal exposure to a severe earthquake in China was related to more self-reported depressive symptoms and more signs of severe depression in 18-year-old students when compared with non-exposed peers (15). These retrospective studies have shed some light on potential relationships between prenatal maternal stress and adult psychopathology.

In the present study, we have the unique possibility to test the association of prenatal exposure to a naturally occurring stressor with behavior followed-up in early adolescence. In an ongoing genetic epidemiological study in Finland, several consecutive birth cohorts of twins were invited to participate. One of these cohorts included twins that were exposed in utero to the Chernobyl disaster of April 1986. Although the Chernobyl disaster resulted in the release of radioactivity into the direct and surrounding environment, test results in Finland showed that during the Chernobyl accident in 1986, the highest momentary dose rate measured in Finland was 5 μSv/h, a small fraction of the dose rate (>100 μSv/h) at which the Nuclear and Radiation Safety Authority of Finland advises seeking shelter indoors (http://www.stuk.fi/sateilytietoa/sateilyvalvonta/en_GB/ulk_sateily). Auvinen et al. (16) examined the relationship between the Chernobyl fallout and birth outcomes in Finland and found no evidence for an association.

Thus, most likely, exposure to radiation in utero within Finland was too limited to directly influence the development of the fetus. Nonetheless, the threat of radiation exposure while pregnant and the overall effects of such a disaster in a nearby environment may have caused significant prenatal maternal stress.

The aim of the present study was to study the potential harmful effect of in utero exposure to the Chernobyl disaster in April 1986, and maternal anxiety associated with that exposure, on symptoms of behavior disorder observed at age 14. Groups of 14-year-old adolescents that were exposed from early, mid or late pregnancy onwards were compared with reference groups, on internalizing (anxiety and depression) and externalizing (attention deficit hyperactivity disorder (ADHD), conduct disorder (CD) and oppositional defiant disorder (ODD)) problem behavior.

METHODS

Sample

The sample included 419 twin pairs, 447 boys and 391 girls, born in Finland in 1985, 1986 and 1987. These twins were members of the three youngest of five consecutive birth cohorts of Finnish twins that comprise a population-based twin-family study called FinnTwin12 (17). The full FinnTwin12 sample consists of 2724 twin pairs and their parents, representing nearly 90% of all twins born in the five birth cohorts, alive, resident in Finland, living with one or both biological parents and eligible for study (17). Nested within this population-based sample, 1035 families of twins were selected for intensive study (see 18, for details). This intensive study‘s main goal was to focus on risk factors associated with alcoholism. Therefore, the intensive study included a randomly selected subsample from the total FinnTwin12 population, enriched with twins at elevated familial risk for alcoholism. The intensive sample consists of a pilot sample drawn from the 1983 cohort (13%), which was randomly selected from a geographically limited region of the main population areas in Finland, a random sample selected from all eligible twin pairs in the remaining four birth cohorts (59%), and an enriched sample (28%), which added twin families in which one or both of the twin parents exceeded a cut-off (≥ 6 of 11 items) of the lifetime version of the Malmö-modified Michigan Alcohol Screening Test (Mm-MAST; 19), an 11-item diagnostic screen for alcohol-related problems, included in both parents’ questionnaires administered at baseline. Data collection was approved by the Institutional Review Board of Indiana University, Bloomington, Indiana, and the ethical committee of the Hospital District of Helsinki and Uusimaa, Helsinki, Finland.

For the present study, we selected twins that were prenatally exposed to Chernobyl from the last three birth cohorts of the intensive study of FinnTwin12. Seventeen twin pairs were excluded due to a very low birth weight (< 1500 gram) of one or both of the twins, and/or a gestational age shorter than 31 weeks. Prenatal exposure to Chernobyl was determined by subtraction of gestational age from birth date, yielding a group of twins (n=232) who were born between April 27, 1986 and January 26, 1987. All twins (n= 572) born a year before (n= 222) or a year after this period (n= 350) were selected to form the non-exposed reference group.

The exposed group was further subdivided into three periods of pregnancy in which the Chernobyl disaster occurred; (1) first trimester (weeks 1–13 of gestation), (2) second trimester (weeks 14–27 of gestation), and (3) third trimester (>28 weeks gestation). Although the actual starting point of the exposure is known (April 26th, 1986), the endpoint of the exposure period of maternal stress associated with the disaster is unknown, and likely varied across individuals. We therefore use the terms ‘exposure from first, or second trimester onwards’, to refer to exposure that started in the first or second trimester, respectively. Since the third trimester reflects the final part of pregnancy, exposure in this period is referred to as ‘exposure in the third trimester’. The reference group was also further divided into three groups, with similar

months of birth as compared to the three exposed groups, in order to control for potential confounding due to season of birth.

Procedure

The intensive study entailed nationwide interview assessments of the twins, who were interviewed in person at age 14 at the twins' schools by trained staff. For the smaller subset of twins whose school was very distant from any of the research staff, appointments were made for home interviews on non-school days. Data were collected throughout most weeks of the year as soon as possible after each subject's 14th birthday, such that 90% of interviews were completed before the subject was 14 years,6 months old. The staff of Finnish interviewers was trained in standard techniques used by the Collaborative Study of the Genetics of Alcoholism (COGA). Intensive training of the initial interviewers was conducted at the Institute of Psychiatric Research at Indiana University Medical School and continued in Finland under supervision of Finnish psychiatrists. Details on interviewer training and procedures are reported elsewhere (18).

Interview content—The Finnish translation of the adolescent Semi-Structured Assessment of Genetics of Alcoholism (C-SSAGA-A) was used. The C-SSAGA-A is a polydiagnostic instrument that was developed by the Collaborative Study on the Genetics of Alcoholism (COGA) group for use in adolescence (20). Lifetime diagnoses are made by the C-SSAGA-A for most major psychiatric disorders. The version of the C-SSAGA-A used at the time that FinnTwin12 was initiated provides DSM-III-R diagnosis. The C-SSAGA-A operationalizes each of the symptoms that comprise a diagnostic criteria for the various disorders into questions for the interview. Positive symptoms are defined by responses to one or more key questions. In the analyses, we focused on symptom counts and the presence of at least one symptom rather than diagnoses because the relatively low prevalence (as shown below, Table 2) of diagnosable disorders in a nonclinical sample at the age of 14 decreases the power of the analyses in which an exposed group is compared with non-exposed reference groups. One exception was made for the DSM-III-R diagnosis of Major Depressive Disorder.

Statistical analyses

Background information on birth outcome was compared by means of T-tests for the exposed and the non-exposed groups. Next, we studied the relationship between prenatal exposure to Chernobyl and the number of symptoms of depression, of generalized anxiety disorder, and of ADHD, CD and ODD. Because the distribution of symptom counts was skewed, we used Poisson regression analyses, yielding an Incidence Rate Ratio (IRR) and its 95% Confidence Interval (CI). First, an overall test for each outcome variable was performed in which exposed groups were compared with non-exposed reference groups. Second, the relation of exposure in each part of pregnancy with outcome measures was examined. All associations were corrected for clustering of data due to twins' relatedness, by using a random effects model, and we adjusted for SES, sex, and age. Descriptive analyses were carried out in SPSS version 12.0, and Poisson and logistic regression analyses were done in STATA/SE 8.0 for Windows, and $p < .05$ (two-tailed) was used to determine statistical significance.

RESULTS

Descriptive analyses

Twins born following in utero exposure had slightly higher birth weights than those not exposed, and were slightly younger on average when interviewed at age 14 (Table 1). Moreover, in the exposed group fewer parents were of high SES.

Table 2 provides descriptive information on the prevalence of each of the traits studied in the exposed and unexposed groups. These differences were tested formally by means of Poisson regression analyses and are presented in Table 3.

Poisson and logistic regression analyses

When those exposed to Chernobyl in utero were compared with those not exposed and when all periods of pregnancy were taken together, a higher incidence was found for lifetime depression symptoms in the exposed group (Table 3); no differences were found with regard to symptoms of other disorders, when those exposed to Chernobyl in utero were compared with those not exposed. Because Table 2 showed that a difference in the prevalence of a Major Depression Disorder Diagnosis may also be expected, we further tested whether a DSM-III-R diagnosis for major depression was found more frequently in the exposed group than the unexposed group, by means of logistic regression analysis, adjusted for SES, sex, age and clustering of data. It was found that exposed adolescents had an increased risk of having a MDD according to the DSM-III-R diagnostic criteria (OR = 2.48, 95 % CI: 1.06 – 5.79, p = 0.036). For exposure from first trimester onwards, no significant differences were found for life time depression symptoms, anxiety, ADHD, CD or ODD symptoms, when those exposed to Chernobyl from the first trimester of pregnancy onwards were compared with those not exposed (Table 3).

Adolescents who were exposed from the second trimester in pregnancy onwards had a 2.32-fold (95 % CI:1.13 to 4.72, p = 0.02) risk of having lifetime depression symptoms (21.1% of exposed adolescents, versus 10.7% non-exposed adolescents). Furthermore, exposed adolescents showed a significant elevated risk (IRR = 2.01, 95 % CI:1.14 – 3.52, p = .02) for having ADHD symptoms (31.6% of exposed adolescents, versus 21.5% non-exposed adolescents).

No significant differences were found for any symptoms when those exposed to Chernobyl in the third trimester of pregnancy were compared with those not exposed (Table 3).

DISCUSSION

An ongoing genetic epidemiological study in Finland afforded us the unique possibility to test the association of prenatal exposure to a naturally occurring stressor with behavior outcomes in early adolescence. Large groups of 14-year-old adolescents that were exposed from early or mid pregnancy onwards, or during the third trimester of pregnancy, were compared with reference groups. Our results show that adolescents who were exposed from second trimester in pregnancy onwards had more than a two-fold risk of exhibiting lifetime depression symptoms and ADHD symptoms in structured interviews. This effect was found only among those exposed from the second trimester onwards and not after exposure from first trimester onwards or during third trimester; that contrast may suggest that this period in fetal brain development is sensitive to perturbations. We also showed that exposure during pregnancy resulted in a more than 2-fold risk of fulfilling DSM-III-R criteria for Major Depressive Disorder. The twins' mothers had been interviewed with the adult SSAGA on average two years before the twin's own interview; using those data, we performed an additional adjustment for maternal depressive symptoms and found that adjustment did not change these findings (data not shown).

Similar results have been found in several other studies. A relatively high incidence of psychiatric disorders, including depressive and neurotic symptoms was found in children up to age 15 born to mothers who faced the death of their spouse during pregnancy (12). Watson et al. (15) reported more depressive symptoms and more signs of severe depression in 18-year-old students that were prenatally exposed to a severe earthquake in China when compared with

non-exposed peers. The latter study found that males exposed in the second trimester differed most from controls on rates of severe depression (19.0% versus 6.8%). No such timing effect was found for prenatally exposed females.

Our findings with regard to ADHD symptoms are also consistent with other studies. Most previous studies that focused on ADHD symptoms after exposure to prenatal stress, were conducted with younger children up to the age of 9 (4–7). Van den Bergh and Marcoen (5) found that high antenatal maternal anxiety, especially in the second trimester, was related to ADHD symptoms and anxiety in 8-to-9-year-olds: this report used a prospective design with its methodological strengths, but the study sample was relatively small (n=52). Nonetheless, it is interesting that the strongest effects in this study were also found for second trimester exposure.

The fetal central nervous system is undergoing development, including rapid proliferation, migration and differentiation, of many critical areas (21) during the second trimester of pregnancy and many neurons are still immature (22). Of interest, the limbic system, including the hippocampus and the amygdala, starts differentiating from the third month of gestation onwards (23). The limbic system is involved in affective disorders. Moreover, the fetal hippocampus exhibits a prenatal peak from week 16–22 in the density of serotonin receptors (24). Thus, perturbations in this period of fetal brain development may affect serotonin receptor functioning, which may explain the increased prevalence of depressive symptoms after prenatal stress exposure from the second trimester onwards in our study and the study of Watson et al. (15).

In contrast, we found no differences in anxiety, CD or ODD symptoms between prenatally exposed and non-exposed adolescents. Apparently, the prenatal exposure may have resulted in more specific behavioral outcomes, i.e. depression and ADHD, rather than resulting in a general increased risk of internalizing or externalizing psychopathology.

We emphasize that the differences in outcome observed here appear to be related to maternal stress associated with the threat of being exposed to radiation, and the overall effects of the Chernobyl disaster in a nearby environment, rather than being due to prenatal fetal exposure to radiation. Auvinen et al. (16) examined the relationship between the Chernobyl fallout and birth outcomes, such as rate of live births and stillbirths, pregnancy loss, and induced abortions in Finland and found no association. In the present study, no adverse effects on birth outcome of in utero exposure to Chernobyl was found. Rather, twins born after in utero exposure had marginally increased gestational ages and higher birth weights than those not exposed. Thus, if present, exposure to radiation in utero has not resulted in adverse birth outcomes. Moreover, the mothers of the twins in the present study lived in all areas throughout Finland, so that the exposure to actual and perceived radiation levels likely show high variability within our sample. However, because the highest momentary dose rate measured in Finland was only 5 μSv/h it is highly unlikely that exposure to radiation in utero has directly influenced the development of the twins in this study. Fetuses may be exposed to excess glucocorticoids when the mother is stressed (e.g. 25–28). Unfortunately we did not, even retrospectively, have individual-level assessments of perceived stress in the mothers of the present study.

Despite this limitation, the results of our study provide evidence for the fetal programming hypothesis, which reflects the action of a disturbing factor during sensitive developmental periods to affect the development and organization of specific tissues, producing effects that persist throughout life (29). More specifically, the present study of a large sample of adolescents shows that prenatal exposure to stress or anxiety may be related to increased risk of depressive symptoms and ADHD symptoms in adolescence. We do not know whether these are transient effects manifesting themselves during puberty or are more permanent and persist into

adulthood. These results warrant future studies into the mechanisms related to prenatal perturbations in fetal brain development.

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Table 1

Birth outcome and SES comparisons between exposed and non-exposed groups

	Exposed	Non-exposed	Significance
	Mean (SD)	**Mean (SD)**	**T-test**
Gestational age at birth in weeks	37.2 (2.0)	37.0 (1.8)	p = .22
Birthweight twin A in grams	2824 (468)	2724 (448)	p = .005
Birthweight twin B in grams	2768 (475)	2691 (441)	p = .028
Age at interview	14.18 (0.13)	14.20 (0.14)	p = .025
	Prevalence	**Prevalence**	**Chi-square test**
Sex			p = .82
Male	54.3 %	53.3 %	
Female	45.7 %	46.7 %	
Socioeconomic status (SES)[a]			p = .002
Low-moderate level	62.5 %	50.2 %	
High level	37.5 %	49.8 %	

SD = standard deviation;

[a] high level SES was defined as having at least one parent with an upper level salary or working at one's own company; low-moderate SES was defined as having both parents with either a lower level salary, a job as worker, a student or pensioners' status.

Table 2

Prevalence of ≥ 1 symptom for each outcome measure and prevalence of diagnoses

Outcome measure	Exposed (N = 232)	Non-exposed (N = 572)
Number of depressive symptoms		
Prevalence of ≥ 1 symptom	14.7% (n = 34)	12.2% (n = 70)
Major Depression DSM-III-R	6.5 % (n= 15)	3.3 % (n = 19)
Number of anxiety symptoms		
Prevalence of ≥ 1 symptom	13.8% (n = 32)	13.8% (n = 79)
General Anxiety Disorder	1.7 % (n = 4)	1.7 % (n= 10)
Number of ADHD symptoms		
Prevalence of ≥ 1 symptom	28.4% (n = 66)	23.3% (n = 133)
ADHD diagnosis	0 % (n= 0)	0.3 % (n= 3)
Number of CD symptoms		
Prevalence of ≥ 1 symptom	42.7 % (n = 99)	40.2 % (n = 230)
CD diagnosis	13.7% (n=32)	10.5% (n=60)
Number of ODD symptoms		
Prevalence of ≥ 1 symptom	10.8 % (n = 25)	8.4 % (n = 48)
ODD diagnosis	2.2 % (n = 5)	0.7 % (n = 4)

ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder

Table 3

Poisson regression analyses for risk symptom counts of depression, anxiety, ADHD, CD and ODD among exposed versus non-exposed during pregnancy (overall) and for each period of pregnancy separately.

Behavior	Overall	First trimester onwards	Second trimester onwards	Third Trimester onwards
Depression				
IRR	1.83	1.47	2.32	0.78
95% CI	1.11 – 3.00	0.52 – 4.16	1.13 – 4.72	0.18 – 3.33
p-value	0.02	0.47	0.02	0.73
Anxiety				
IRR	1.11	1.32	1.31	0.62
95% CI	0.63 – 1.95	0.45 – 3.93	0.67 – 2.54	0.17 – 2.17
p-value	0.72	0.61	0.43	0.45
ADHD				
IRR	1.30	1.06	2.01	0.98
95% CI	0.85 – 1.99	0.59 – 1.91	1.14 – 3.52	0.46 – 2.11
p-value	0.22	0.85	0.02	0.96
CD				
IRR	1.14	1.18	1.27	0.96
95% CI	0.83 – 1.56	0.74 – 1.86	0.82 – 1.97	0.44 – 2.11
p-value	0.41	0.49	0.29	0.92
ODD				
IRR	1.45	1.06	1.36	0.74
95% CI	0.81 – 2.61	0.51 – 2.20	0.66 – 2.80	0.28 – 1.95
p-value	0.21	0.87	0.41	0.53

ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder: IRR: Incidence Rate Ratio: CI: confidence interval.