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Attention-deficit /hyperactivity Disorder (ADHD) in the offspring following prenatal maternal bereavement: a nationwide follow-up study in Denmark

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Abstract

Severe prenatal stress exposure has been found to increase the risk of neuropsychiatric conditions like schizophrenia. We examined the risk of Attention-deficit/hyperactivity disorder (ADHD) in the offspring following prenatal maternal bereavement, as a potential source of stress exposure. We conducted a nationwide population-based cohort study including all 1 015 912 singletons born in Denmark from 1987 to 2001. A total of 29 094 children were born to women who lost a close relative during pregnancy or up to one year before pregnancy. These children were included in the exposed cohort and other children were in the unexposed cohort. We used Cox regression to estimate hazard ratios for ADHD, defined as the first-time ADHD hospitalization or first-time ADHD medication after 3 years of age. Boys born to mothers who were bereaved by unexpected death of a child or a spouse, had a 72% increased risk of ADHD (Hazard ratio [HR]=1.72, 95% confidence interval [CI]=1.09-2.73). Boys born to mothers who lost a child or a spouse during 0-6 months before pregnancy and during pregnancy had a HR of 1.47 (95%CI=1.00-2.16) and 2.10 (95% CI =1.16-3.80), respectively. Our findings suggest that prenatal maternal exposure to severe stress may increase the risk of ADHD in the offspring.

Key words Attention-deficit/hyperactivity Disorder (ADHD); stress; bereavement; fetal programming; child psychiatry.

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders (1;2). This disease causes a number of adverse academic and vocational conditions in children, and exerts stress to the affected families and economic burden on society (3). The disorder has a substantial genetic component but epidemiological studies suggest that environmental factors operating in early life most likely contribute to the disease risk (3-5). Evidence from animal studies suggests that maternal stress during pregnancy may affect fetal neurodevelopment (6;7). One of the underlying mechanisms is termed as 'fetal programming', which occurs when the normal pattern of fetal development is disrupted by an abnormal stimulus or insult at critical time points (6;8). Excessive glucocorticoids following stress in pregnant mothers may have such a programming effect on brain development (6-9). In epidemiological studies, prenatal stress has been linked to congenital malformations (10), cerebral palsy (11), and psychiatric disorders including schizophrenia(12;13). Anxiety during pregnancy has been associated with ADHD phenotypical behavior in the offspring (14;15) but no published studies have evaluated the association between prenatal stress and the risk of ADHD.

We hypothesized that prenatal stress had a programming effect on brain development (16-18) and could increase the risk of ADHD in childhood. We examined this hypothesis in a cohort study based on data from several nationwide registers in Denmark.

Bereavement is a severe life event known to induce stress (19;20) and death of a child is rated as the most severe type of bereavement (21;22). We thus expected the children born to mothers who lost a child during the prenatal period had a higher risk of ADHD than

other children. We also anticipated the effect of prenatal stress to be modified by the timing (10;12;13) and other characteristics of bereavement like cause of death (19;20;23).

Method

We conducted a nationwide cohort study based on data from 6 Danish national registers, namely, the Civil Registration System (24), the Medical Birth Register (25), the Psychiatric Central Register (26), the Hospital Discharge register (27), Register of Medicinal Product Statistics (28), and the Integrated Database for Longitudinal Labour Market Research (IDA) (29). The national board of Health and the Danish Data Protection Agency approved the project.

Study population, exposure, and follow up

We used data from the Danish Civil Registration System (24) to identify all singletons born in Denmark between January 1, 1987 and December 31, 2001, and their next of kin (mother, father, siblings, mother's siblings, and mother's parents). All live-born children and new residents in Denmark are assigned a unique civil personal registration number (CPR number), which is stored in the Danish Civil Registration System together with information on vital status, emigration, disappearance, address, and CPR numbers of family members. The CPR number is used as the key to individual information in all national registries.

Among the 1 015 912 singletons, 29 094 children were included in the exposed cohort as they were born to mothers who lost a child, or a spouse, or a sibling, or a parent during the pregnancy or up to one year before the pregnancy. The remaining children (986 816) were included in the unexposed cohort. All children were followed from 3 years of age

until the first diagnosis of ADHD, first use of ADHD medication, or death, or emigration, or December 31, 2006, whichever came first.

Attention-deficit/hyperactivity Disorder (ADHD)

A child was defined as an ADHD case if the child, for the first time after her/his third birthday, had a hospital diagnosis of ADHD (ICD 10 code F90), or redeemed ADHD medication. According to the diagnostic criteria, we excluded children with autism (ICD 10 codes F84.0, F84.1) and with mental retardation (ICD 10 codes F70-79). We also examined ADHD hospital diagnoses and ADHD medication as separate outcomes.

Information on ADHD diagnosis (both as inpatients and as outpatients) was obtained from the Danish Psychiatric Central Register (26) and Danish National Hospital Register (27). Diagnostic information is based on the Danish version of the International Classification of Diseases, 10th revision (ICD-10) from 1994 and onwards. From 1995 outpatient contacts are also registered.

Information on ADHD medication was obtained from the Register of Medicinal Product Statistics for 1996-2006 (28). All Danish residents are provided tax-supported health care by the National Health Service, which refunds the costs of most physician-prescribed drugs, including ADHD medication with N06BA04 (central stimulating drug only methylphenidate), or N06BA09 (Noradrenalin reuptake inhibitors, atomoxetine), or N06BA07 (modafinil).

Other variables

Perinatal factors were retrieved from the Medical Birth Register (25), which was established in 1968 and has been computerized since 1973. It holds data on characteristics of mothers and newborns, such as gestational age, birth weight, Apgar score at 5 minutes, maternal age, and maternal smoking status during pregnancy. Apgar scores evaluate the clinical state of the newborns during first minutes of life and a total score of 10 indicates that the baby is 'in its best possible condition' (25). Maternal smoking status was available for the period of 1991-2001, which was a categorical variable (yes, no) (25). We defined small for gestational age (SGA) as a birth weight below the 10th percentile for gestational age, sex, and parity, based on the distribution within all newborn singletons in Denmark between 1978 and 2004.

Socio-demographic factors for mothers (residential place, education, income, and cohabitation status) were obtained from the Intergrated Database for Longitudinal Labour Market Research (IDA), which contains longitudinal information on demographic variables and socioeconomic data from 1980 and onwards (29).

Data on maternal psychiatric hospital admission (ICD 8 codes 290-299, ICD 10 codes F00-F99) was retrieved from the Central Psychiatric Register (26).

Statistical analysis

We used Cox regression model (SAS Proc Phreg procedure, version 9.1) to estimate hazard ratios (HRs) (30). To examine whether the associations varied by nature of the

bereavement, we first categorized the exposed children into two groups: a) children of mothers who lost a child or a spouse, and b) children of mothers who lost a parent, or a sibling, since we assumed that loss of a child or a spouse was more severe than loss of a parent or a sibling (21;23). We further categorized the cause of death into 2 groups: unexpected death (unexpected causes, ICD8 codes 7950 to 7959, ICD 10 codes R95 to R97, motor vehicle accidents, ICD8 codes 8100-8230, ICD10 codes V01 to V89, suicide, ICD8 codes 950 to 959, ICD10 codes X60 to X84, other accidents and violence, ICD8 codes 800 to 807, 825 to 949, 960 to 999, ICD10 codes V90 to V99, W00 to X59, X85 to Y89), and death by other causes. In order to examine whether a potential effect of prenatal stress on ADHD differed across different prenatal periods, the exposure window was divided into 3 periods (12 to 7 months before pregnancy, 6 to 0 months before pregnancy, and pregnancy). The pregnancy period was further divided into 3 trimesters (0-12 weeks, 13-24 weeks, >24 weeks).

We adjusted for the following potential confounders: gender (male, female), birth year (1987 to 1994, 1994 to 1997, 1998 to 2001), maternal age (<27 years, 27 to 30 years, 31 years and over), maternal residential area (capital city of Copenhagen area, cities with over 100,000 inhabitants, other places), maternal education (0 to 9 years, 10 to 11 years, 12+ years), maternal income (lowest quartile, 2nd quartile, 3rd quartile, highest quartile in the calendar year), maternal cohabitation status (yes, no), maternal history of psychiatric diseases (yes, no), maternal smoking status at pregnancy (yes, no). Gestational age (<37 weeks, >=37 weeks), Apgar score at 5 minutes (0 to 7, 8 to 9, 10), SGA (yes, no) were

added into the models to examine whether the associations were affected by these potential intermediate variables.

The above analyses were performed for boys and girls separately to examine whether gender interacted significantly with the exposure. We further analyzed data after excluding those with low birth weight (<2500g), low gestational age at birth (<37 weeks), low Apgar scores at 5 minutes (<10) to examine whether a possible effect of stress was seen for children born without those complications. The analyses were also performed restricting the birth years from 1991 to 2001 when maternal smoking status was available.

Results

The baseline characteristics of exposed children and unexposed children are presented in Table 1.

Table 2 shows that a total of 10 278 children who either received an ADHD diagnosis (6274) or redeemed ADHD medication (7641) during the follow up. There were 3637 children who received both a diagnosis and medication. There were, as expected, more cases in boys (8477) than in girls (1831).

Table 3 presents the hazard ratios (HRs) for ADHD according to maternal bereavement during the prenatal period by gender, type of deceased relatives, and cause of death.

Prenatal maternal bereavement by death of a child or spouse was associated with a 37% increased risk of ADHD (HR=1.37, 95% CI=1.03-1.79) in male offspring. Boys born to mothers who lost a child or spouse due to unexpected death had a HR of 1.72 (95% CI = 1.09-2.73). Exposed girls, however, had a similar risk of ADHD as unexposed girls.

Table 4 shows the HRs when diagnosis and medication were treated as separate outcomes in boys. Similar findings were seen as in Table 3, although the associations were not statistically significant. Data for girls only are sparse and not presented.

Table 5 presents the results according to timing of exposure in boys. Maternal bereavement by loss of a child or spouse during pregnancy had a HR of 2.10 (95% CI= 1.16-3.80), higher than those HRs in previous periods (HR=1.47, 95% CI=1.00-2.16 for

6-0 months before pregnancy, and HR= 0.95, 95% CI= 0.57-1.61 for 12 to 7 months before pregnancy). The HRs tended to be the highest when bereavement occurred in third trimester, but the confidence intervals were wide because of limited cases in the exposed group. Data for girls only are sparse and not presented.

We observed similar gender-specific and timing-specific results as described above when ADHD diagnosis and ADHD medication were treated as separate outcomes (data not shown). Similar results were also observed when analyses were restricted in children with birth weight>2500g, gestational age>37 weeks, or Apgar score at 5 minutes of 10 (data not shown). Similar results were also seen when birth year was restricted to the period of 1991-2001.

Discussion

We found that boys born to mothers who lost a child or a spouse during the pregnancy had a higher risk of receiving a hospital diagnosis of ADHD or receiving ADHD medication. No such associations were seen for girls, nor for the bereavement by death of other types of relatives.

As early as in 1978 Huttunen et al. introduced the idea of using the loss of a close relative to test the effect of prenatal stress on fetal brain development (12). Other have shown that maternal anxiety or depression during pregnancy was associated with behavioural/emotional problems in the offspring (14;15). To our knowledge, this is the first population-based study to investigate the association between prenatal stress and the risk of ADHD in childhood. As expected (19;20;23), maternal bereavement by death of a child and death by unexpected causes were associated with higher risks than other types of death. Our data suggest that only the most severe type of prenatal stress may contribute to future risk of ADHD.

Our study has a number of important methodological strengths. First, the study was based on a large population-based cohort of all singletons born in Denmark with up to 17 years follow up with minimal loss (24). Thus the study is not biased by selection of study participants or loss to follow up. Second, studies on stress are often limited by too small exposure contrast between the compared groups, or recall bias, which rendered difficulties in interpretation and comparison between studies (31-34). Our data on bereavement from the Danish Civil Registration System are valid and complete (close to

100%), thus yielding accurate information exposure (24). Third, in contrast to previous studies we were able to adjust for birth outcomes and several maternal factors (smoking status during pregnancy, socio-demographic factors, history of psychiatric illnesses), which were potential confounders (3-5).

A limitation of the study is that not all children with ADHD received a hospital diagnosis in the register system. The majority of children with ADHD are treated as outpatients, which we were able to register but others are treated by child psychiatrists working outside the hospital system and thus not included in registers. By using the prescription data we were able to include most of ADHD cases who were not hospitalized. The primary medication of ADHD is methylphenidate, which only has one other rare indication (narcolepsy). The outcome has therefore a high specificity but a low sensitivity. However, such a low sensitivity is non-differential and will not bias relative estimates of the association.

It has been suggested that the effect of prenatal stress on neurodevelopment may vary by the timing of exposure. Studies on schizophrenia (13) indicated that the first trimester was the most vulnerable period, but studies on other endpoints suggested that the time window of susceptibility was in late pregnancy (12;35). Our findings suggest that exposure to severe stress during late pregnancy may have a greater influence on fetal brain development. ADHD is a less severe and pervasive disorder than schizophrenia and it is expected that later exposure in pregnancy may be more important in relation to ADHD in view of the more matured brain in late pregnancy.

ADHD is found more often in boys than in girls and evidence from animal studies suggest that the sensitivity to neuro-toxic exposures may depend on gender (36). Furthermore, it has been indicated that the central dopamine system matures slower in males than in females, thus increasing the period of vulnerability in the dopamine transmitter system (37). Our findings in male offspring may be a chance finding due to the fact that we did not have enough cases in girls. ADHD behaviors, as currently defined, are more likely to be identified in boys than girls. The effects of bereavement may also hold for girls, but girls are less often identified by teachers and parents as exhibiting ADHD symptoms-even though they may have the inattentive characteristics (38). Alternatively, bereavement may result in different emotional problems in girls, which needs to be examined in future studies.

In conclusion, the most severe types of prenatal stress during pregnancy may play a role in the development of ADHD in the offspring.

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Table 1. Baseline characteristics of the study population ^a

Variables	Exposed cohort	Unexposed cohort	P value
Gender			0.92
Boys	14 929 (51)	506 666 (51)	
Girls	14 165 (49)	480 150 (49)	
Birth year			<0.05
1987-1994	10 356 (36)	455 375 (46)	
1995-1998	8944 (31)	274 539 (28)	
1999-2003	9794 (34)	256 904 (26)	
Apgar score at 5 minutes			0.90
0-7	393 (1)	12 844 (1)	
8-9	1623 (6)	52 357 (5)	
10	26 193 (90)	844 976(86)	
Unknown	885 (3)	76 639 (8)	
Parity			0.89
1	11 222 (39)	408 279 (41)	
2	11 012 (38)	341 933 (35)	
>2	6089 (21)	164 660 (17)	
Unknown	721 (2)	71 939 (7)	
Gestational age			<0.05
<37 weeks	1798 (6)	50 659 (5)	
>=37 weeks	26 575 (91)	864 217(88)	

Unknown	721 (2)	71 939 (7)	
SGA^b			0.02
Yes	3089 (11)	103 827 (11)	
No	25 284 (87)	811 050(82)	
Unknown	721 (2)	71 939 (7)	
Maternal age			0.60
13-26	4758(16)	176 971(18)	
27-30	15 956(55)	518 406(53)	
>30	8380 (29)	288 515(29)	
Unknown	0	2924 (>1)	
Maternal smoking at pregnancy			<0.05
Yes	6196(21)	172 964(18)	
No	16 148(56)	485 052(49)	
Unknown	6750 (23)	328 800(33)	
Maternal history of psychiatric illness			<0.05
Yes	1092 (4)	31 469 (3)	
No	28 002(96)	955 347 (97)	
Maternal education			<0.05
Primary	11 172 (38)	374 415 (38)	
Secondary	10 114 (35)	319 230(32)	
High	7 597 (26)	245 383 (25)	

Unknown	211 (1)	47 789 (5)	
Maternal income			0.19
1 st quartile	9 388(32)	311 828 (32)	
2 nd quartile	12 105 (42)	376 823 (38)	
3 rd quartile	5563 (19)	187 974 (19)	
4 th quartile	1827 (6)	62 403 (6)	
Unknown	211 (1)	47 789 (5)	
Maternal marital status			<0.05
Yes	11 137 (38)	338 946 (34)	
No	17 746 (61)	600 081 (61)	
Unknown	211 (1)	47 789 (5)	
Maternal residence			<0.05
Copenhagen	6709(23)	242 431 (26)	
Cities ^c	3367 (12)	112 340 (11)	
Other	18 807 (65)	584 256 (59)	
Unknown	211 (1)	47 789 (5)	

^a Value is n (%).

^b Small for gestational age.

^c Cities with over 100 000 inhabitants.

Table 2 ADHD cases defined by hospitalisation or medication

	Medication		Total cases
	Hospitalisation		
Boys and Girls	No	Yes	
	No	1 005 632	4004
	Yes	2637	3637
			10 278
Boys			
	No	513 148	3249
	Yes	2152	3076
			8477
Girls			
	No	492 484	785
	Yes	485	561
			1831

Table 3. The hazard ratio (HR) for ADHD in the offspring according to maternal bereavement during prenatal period, by gender, type of relatives, and cause of death

	Cases in the exposed / cases in the unexposed	Crude hazard ratio (HR)	Adjusted HR (95% CI) ^a
Boys & girls			
<i>Death of a child or partner</i>	55/9982	1.19	1.18 (0.91 - 1.54)
Unexpected death	21/9982	1.67	1.62 (1.04 - 2.46)*
Other death	34/9982	1.03	1.01 (0.72 - 1.41)
<i>Death of other relatives</i>	245/7987	1.13	0.98 (0.86 - 1.13)
Unexpected death	76/7987	1.42	1.07 (0.85 - 1.33)
Other death	169/7987	1.04	0.95 (0.82 - 1.11)
Boys			
<i>Death of a child or partner</i>	51/8201	1.39	1.37 (1.03 - 1.79)*
Unexpected death	18/8201	1.77	1.72 (1.09 - 2.73)*
Other death	33/8201	1.24	1.21 (0.86 - 1.71)
<i>Death of other relatives</i>	199/6575	1.11	0.96 (0.83 - 1.10)
Unexpected death	62/6575	1.38	1.06 (0.83 - 1.36)
Other death	137/6575	1.00	0.92 (0.78 - 1.09)
Girls			
<i>Death of a child or partner</i>	4/1781	0.47	0.45 (0.17 - 1.20)
Unexpected death	3/1781	1.31	1.17 (0.38 - 3.64)

Other death	1/1781	0.16	0.16 (0.02 - 1.13)
<i>Death of other relatives</i>	46/1412	1.23	1.06 (0.79 - 1.42)
Unexpected death	14/1412	1.52	1.12 (0.66 - 1.42)
Other death	32/1412	1.13	1.04 (0.73 - 1.47)

^a Hazard ratio (HR) adjusted for birth year, gestational age, Apgar score at 5 minutes, parity, SGA, maternal variables (smoking during pregnancy, age, psychiatric history, income, school education, residence, cohabitation).

*P<0.05

Table 4. The hazard ratio (HR) for ADHD diagnosis or medication in male offspring following maternal bereavement during prenatal period, by type of deceased relatives

	Cases in the exposed / cases in the unexposed	Crude hazard ratio (HR)	Adjusted HR (95% CI)^a
Hospitalization			
<i>Death of a child or partner</i>	46/5073	1.41	1.37 (0.97 - 1.95)
Unexpected death	10/5073	1.61	1.53 (0.82 - 2.84)
Other death	22/5073	1.34	1.31 (0.86 - 2.00)
<i>Death of other relatives</i>	125/4085	1.11	0.96 (0.81 - 1.15)
Unexpected death	36/4085	1.24	0.95 (0.69 - 1.32)
Other death	89/4085	1.06	0.96 (0.78 - 1.19)
Medication			
<i>Death of a child or partner</i>	38/6109	1.37	1.35 (0.98 - 1.86)
Unexpected death	12/6109	1.77	1.53 (0.87 - 1.88)
Other death	26/6109	1.30	1.28 (0.87 - 2.67)
<i>Death of other relatives</i>	152/4900	1.16	1.00 (0.85 - 1.17)
Unexpected death	45/4900	1.43	1.06 (0.79 - 1.41)
Other death	107/4900	1.08	0.97 (0.80 - 1.18)

^a Hazard ratio (HR) adjusted for birth year, gestational age, Apgar score at 5 minutes, parity, SGA, maternal variables (smoking during pregnancy, age, psychiatric history, income, school education, residence, cohabitation).

Table 5. The hazard ratio (HR) for ADHD in male offspring following maternal bereavement during prenatal period, by type of relatives, timing of death

	Cases in the exposed / cases in the unexposed	Crude hazard ratio (HR)	Adjusted HR (95% CI)^a
Death of a child or spouse			
<i>During 12 to 7 months before conception</i>	14/8201	0.98	0.95 (0.57 - 1.61)
<i>During 6 - 0 months before conception</i>	26/8201	1.44	1.47 (1.00 - 2.16)*
<i>Death during pregnancy</i>	11/8201	2.43	2.10 (1.16 - 3.80)*
First trimester	2/8201	1.39	1.23 (0.31 - 4.94)
Second trimester	4/8201	2.66	2.07 (0.78 - 5.51)
Third trimester	5/8201	3.04	2.98 (1.24 - 7.16)*
Death of other relatives			
<i>During 12 to 7 months before conception</i>	53/6575	0.99	0.84 (0.64 - 1.10)
<i>During 6 - 0 months before conception</i>	67/6575	1.35	1.18 (0.94 - 1.51)
<i>Death during pregnancy</i>	79/6575	1.03	0.90 (0.72 - 1.13)
First trimester	23/6575	1.01	0.89 (0.59 - 1.34)

Second trimester	30/6575	1.09	0.96 (0.67 - 1.38)
Third trimester	26/6575	0.98	0.84 (0.57 - 1.24)

^a Hazard ratio (HR) adjusted for birth year, gestational age, Apgar score at 5 minutes, SGA, parity, maternal variables (smoking during pregnancy, age, psychiatric history, income, school education, residence, cohabitation).

*P<0.05