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European Journal of Public Health, Vol. 25, No. 6, 1042–1046

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doi:10.1093/eurpub/ckv129 Advance Access published on 25 June 2015

Prenatal stress and childhood asthma in the offspring: role of age at onset

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Background: Asthma is a heterogeneous disorder with different phenotypes, and age at onset may define part of them. Little is known about possible association between prenatal stress and asthma phenotypes according to age at onset. We aim to investigate whether there is an association between prenatal stress and asthma, and if so, whether such an association differs according to age at asthma onset. **Methods:** We carried out a cohort study based on several national registers in Denmark, including all live singletons born during 1996–2007 in Denmark ($N=750\,058$). We identified children born to mothers who lost a close relative (a child, partner/spouse, a parent or a sibling) 1 year prior to or during pregnancy as the bereaved group. Using Cox proportional hazards regression model, we evaluated the hazard ratios (HRs) for asthma in children of bereaved mothers, compared with children of non-bereaved mothers. **Results:** Prenatal stress following maternal bereavement was associated with a marginally increased risk of asthma events in children aged 0–3 years [HR = 1.04, 95% confidence interval (CI): 1.00–1.07], while unexpected bereavement was associated with a higher risk (HR = 1.13, 95% CI: 1.02–1.24). There was no association between prenatal bereavement and asthma in children aged 4–15 years (HR = 1.02, 95% CI: 0.96–1.09). **Conclusions:** Prenatal stress is possibly associated with asthma events in children aged 0–3 years, but not with asthma in children aged 4–15 years irrespective of age at asthma onset.

Introduction

Asthma is one of the most common chronic diseases in childhood, with a lifetime prevalence of 2.6–30.5% in children aged 13–14 years.¹ It causes profound healthcare costs and is one of the leading causes of school absenteeism.² The underlying mechanisms for asthma remain to be elucidated.

Asthma may have foetal origins related to stress. Prenatal stress may affect cytokine profiles,³ influence the maturation process of dendritic cells,⁴ and alter the development of immunocompetence,⁵ modifying the balance between T-helper (Th)1/Th2 response in favour of Th2 profile, consequently predisposing the offspring to asthma. Epidemiologic data on the potential effect of prenatal stress on development of asthma are inconclusive, perhaps due to differences in study populations or mixing incidence with prevalence of asthma. Asthma cases with different age at onset may have different allergic sensitisation and clinical response to external triggers,⁶ and may well have different etiology. Previous studies that examined the association between prenatal stress and the

incidence of asthma have addressed younger children,⁷ while studies in older children often focus on the prevalence of asthma.^{7,8} To date, few studies have studied the incidence of asthma in different age groups.

By using the Danish National Patient Register⁹ and the Danish National Prescription Registry,¹⁰ we were able to identify a large part of asthma cases with the information on age at asthma onset. We postulated that maternal bereavement following the death of a close relative 1 year prior to or during pregnancy could increase the risk for asthma in the offspring, and such an association may differ according to age at asthma onset.

Methods

Study population

All live-born children and new residents in Denmark are assigned a unique personal identification number, which can be used to accurately link information at the individual level in all national

registers. All singleton live births were recorded in a computerized form in the Danish Medical Birth Registry (DMBR) since 1973.¹¹ We identified all live singletons born during 1996–2007 recorded in the DMBR, and 755 358 births were recorded during the study period in the birth registries. We excluded 85 infants whose mothers' data on parity were missing, 5215 (0.7%) infants who had missing gestational age or a gestational age <154 or >315 days. A total of 750 058 children were included in the analysis. The DMBR was linked to the Danish Civil Registration System,¹² the Danish National Patient Register, the Danish National Prescription Registry, the Danish Registers of Causes of Death¹³ and the Danish Integrated Database for Longitudinal Labour Market Research.¹⁴

Bereavement

Death of a close relative (a child, partner/spouse, a parent or a sibling) is considered to be one of the most stressful life events.¹⁵ We identified children born to mothers who lost a child, partner/spouse, a parent or a sibling 1 year prior to or during pregnancy as the bereaved group. The starting date of pregnancy was estimated by using date of birth and gestational age. Information on bereavement was obtained from the Danish Registers of Causes of Death. Causes of death were coded according to the International Classification of Diseases (ICDs), 10th revision (ICD-10). When multiple losses happened, the first bereavement was used to classify the exposure status of the children.

Asthma

We extracted information on asthma hospital contact and asthma treatment from the Danish National Patient Register and the Danish National Prescription Registry. The Danish National Patient Register has collected data on all inpatient contacts since 1977, and from 1995 also for all emergency room visit and outpatient contacts. The Danish National Prescription Registry covers all redeemed prescriptions in Denmark since 1995, and drugs prescribed for children under their own ID-numbers since 1 January 1996. Asthma cases were defined as at least one hospital contact for asthma or two prescriptions for asthma medication during 1996–2010. Hospital contact for asthma was identified based on the following ICD-10 codes: J45 and J46. The anatomical therapeutic chemical (ATC) codes for inhaled asthma drugs were: inhaled β_2 -agonists (R03AC02, R03AC03, R03AC04, R03AC12 and R03AC13), inhaled glucocorticoids (R03BA01, R03BA02 and R03BA05), fixed-dose combination of inhaled β_2 -agonists and glucocorticoids (R03AK06 and R03AK07) and leukotriene receptor antagonists (R03DC03). Prescriptions redeemed on the same day were considered to be one prescription. Since a definitive diagnosis of asthma cannot be made before 3 years of age,¹⁶ we used the term of 'asthma event' for asthma and asthma-like events in children aged 0–3 years. The term 'asthma' was used for the whole study population and for children aged >3 years.

Follow-up

The children were followed from birth to the first asthma diagnosis (i.e. the first admission, emergency room visit or outpatient contact for asthma or first anti-asthmatic drugs redeemed in the registers), emigration, death, or the end of 2010, whichever came first.

Statistical analysis

Cox proportional hazards regression model was used to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) for asthma in children whose mothers lost a close relative 1 year prior to or during pregnancy. We used robust standard errors to adjust for dependency between siblings in the analysis. We adjusted for the following potential factors: sex of the child (boy, girl), calendar year of birth (1996–98, 1999–2001, 2002–04 and 2005–07),

maternal age at delivery (<25, 25–29, 30–34 and ≥ 35 years), maternal parity (first, second and higher), mother's country of origin (Nordic countries, other countries), maternal social status at birth (not in labour market, unskilled workers, skilled workers and white collar workers, and top level status), maternal smoking during pregnancy (yes, no), mode of delivery (delivered vaginally, delivered by caesarean section) and family history of asthma (in father or mother). Information on sex of the child, calendar year of birth, maternal parity, and maternal age at delivery, maternal smoking during pregnancy and mode of delivery was obtained from the DMBR. Information on maternal social status and mother's country of origin was obtained from the Danish Integrated Database for Longitudinal Labour Market Research. Information on a family history of asthma was obtained from the Danish National Patient Register and the Danish National Prescription Registry.

To examine whether the association between prenatal bereavement and asthma depended on the type of loss, we categorized prenatal bereavement into four groups according to the mother's relationship to the deceased (a child, partner/spouse, a parent or a sibling). We also categorized the exposure window into five periods (7–12 months before pregnancy, 0–6 months before pregnancy, first trimester, second trimester and third trimester). We further categorized the cause of death into two groups: (i) unexpected death (ICD-10: sudden death without a cause, R96–R98; death from motor vehicle accidents, V01–V89; suicide, X60–X84; other accidental and violent death, V90–V99, W00–X59, X85–Y89; supplementary factors related to causes of mortality classified elsewhere Y90–Y98), and (ii) other causes of death.

To investigate whether the associations differed according to age at asthma onset, we investigated the associations in children aged 0–3 and 4–15 years separately. We also investigate whether the associations varied with different age at onset in four different age groups (0–3, 4–6, 7–12 and 13–15 years).

In order to account for confounding by maternal pre-pregnancy body mass index (BMI), we also did a sub-analysis by further adjustment for maternal pre-pregnancy BMI (<18.5, 18.5–24.9, 25–29.9 and ≥ 30) in the subset of data included in the Danish National Birth Cohort.¹⁷

All the data were analyzed in STATA 11.1 (Stata Corp, College Station, TX).

Ethics

The study was approved by the Danish Data Protection Agency and the Science Ethics Committee of Central Region Jutland in Denmark. No informed consent is needed for a register-based study based on encrypted data according to the legislation in Denmark.

Results

Table 1 shows the demographic characteristics of population in two groups. Compared with children of non-bereaved mothers, children of bereaved mothers were born in earlier calendar years, and their mothers tended to smoke during pregnancy and to have caesarean section, were older at delivery, and had a higher parity and a better social status. Children born to bereaved and non-bereaved mothers were comparable on their mother's country of origin, family history of asthma, and their gender.

There were 149 261 asthma cases observed during the study period, of which 115 471 and 33 790 cases diagnosed before and after 3 years of age, respectively. The overall HR of asthma for prenatal bereavement was 1.03 (95% CI: 1.00–1.06). Children of bereaved mothers had a marginally higher risk for asthma events before 3 years of age compared with non-bereaved children (HR = 1.04, 95% CI: 1.00–1.07). A stronger association was observed in children whose mothers lost a close relative unexpectedly (HR = 1.13, 95% CI: 1.02–1.24). The timing of bereavement was

Table 1 Demographic characteristics of study population

Characteristics	Bereaved (N = 19 939)	Non-bereaved (N = 730 119)
Mother's country of origin		
Nordic countries	99.2	99.0
Other countries	0.8	1.0
Maternal age at delivery (years)		
<25	10.1	14.2
25–29	28.1	35.6
30–34	37.7	34.8
≥35	24.1	15.4
Maternal parity		
1	33.6	43.3
≥2	66.4	56.7
Maternal social status		
Not in labour market	0.4	1.3
Unskilled workers	32.1	35.8
Skilled workers and white collar workers	40.5	38.1
Top level status	26.9	24.5
Unknown	0.1	0.3
Maternal smoking during pregnancy		
Yes	25.0	19.7
No	71.1	76.9
Unknown	3.9	3.4
Mode of delivery		
Delivered vaginally	89.1	91.8
Delivered by caesarean section	10.4	7.7
Unknown	0.5	0.5
Family history of asthma		
Yes	24.9	24.2
No	75.1	75.8
Sex of the child		
Boy	51.0	51.3
Girl	49.0	48.7
Calendar year of birth		
1996–98	29.2	25.5
1999–2001	26.0	25.2
2002–04	23.8	24.6
2005–07	21.0	24.7

Table 2 HRs for asthma events in the offspring aged 0–3 years according to bereavement stratified on the timing of bereavement, mother's relationship to the deceased and causes of death

Bereavement	Asthma events	N	Crude HRs	Adjusted HRs (95% CI) ^a
Non-bereaved	112 297	730 119	1	1 (ref)
Bereaved	3 174	19 939	1.04	1.04 (1.00–1.07)
Timing of bereavement				
7–12 months before pregnancy	952	5 769	1.08	1.08 (1.01–1.15)
0–6 months before pregnancy	950	6 148	1.00	0.99 (0.93–1.06)
First trimester	422	2 567	1.07	1.05 (0.95–1.15)
Second trimester	498	3 262	0.99	0.99 (0.91–1.08)
Third trimester	352	2 193	1.04	1.06 (0.96–1.17)
Mother's relationship to the deceased				
Death of the partner	31	163	1.29	1.20 (0.84–1.70)
Death of a child	331	1 937	1.13	1.05 (0.95–1.17)
Death of a parent	2 558	16 483	1.01	1.01 (0.98–1.05)
Death of a sibling	254	1 356	1.23	1.19 (1.00–1.34)
Deaths by cause				
Unexpected death	408	2 288	1.17	1.13 (1.02–1.24)
Other causes of death	2 727	17 426	1.02	1.02 (0.98–1.06)
Unknown	39	225	1.17	1.20 (0.88–1.65)

a: Adjusted for mother's country of origin, maternal age at delivery, parity, maternal social status, maternal smoking during pregnancy, mode of delivery, family history of asthma, sex of the child and calendar year of birth

not systematically associated with asthma events in the offspring (table 2).

Maternal stress was not associated with asthma in children aged 4–15 years (HR = 1.02, 95% CI: 0.96–1.09). However, an association

Table 3 HRs for asthma in the offspring aged 4–15 years according to bereavement stratified on the timing of bereavement, mother's relationship to the deceased and causes of death

Bereavement	Asthma cases	N	Crude HRs	Adjusted HRs (95% CI) ^a
Non-bereaved	32 843	602 683	1	1 (ref)
Bereaved	947	16 467	1.00	1.02 (0.96–1.09)
Timing of bereavement				
7–12 months before pregnancy	279	4 716	1.03	1.05 (0.94–1.19)
0–6 months before pregnancy	313	5 111	1.05	1.07 (0.96–1.20)
First trimester	122	2 106	1.04	1.06 (0.89–1.27)
Second trimester	137	2 724	0.88	0.88 (0.74–1.04)
Third trimester	96	1 810	0.93	0.95 (0.77–1.16)
Mother's relationship to the deceased				
Death of the partner	9	129	1.20	1.25 (0.65–2.40)
Death of a child	119	1 553	1.23	1.34 (1.12–1.61)
Death of a parent	762	13 700	0.98	0.99 (0.92–1.06)
Death of a sibling	57	1 085	0.91	0.92 (0.71–1.20)
Deaths by cause				
Unexpected death	100	1 845	0.88	0.87 (0.72–1.06)
Other causes of death	832	14 444	1.01	1.03 (0.97–1.11)
Unknown	15	178	1.32	1.34 (0.81–2.23)

a: Adjusted for mother's country of origin, maternal age at delivery, parity, maternal social status, maternal smoking during pregnancy, mode of delivery, family history of asthma, sex of the child and calendar year of birth

was observed in children whose mothers lost a child (HR = 1.34, 95% CI: 1.12–1.61). We did not observe any association to be modified by cause of death as seen in table 2 (table 3).

Prenatal stress was not significantly associated with incident asthma in children aged 4–6, 7–12 and 13–15 years (Data available on request). The associations between prenatal bereavement and asthma remained similar after further adjustment for maternal pre-pregnancy BMI (Data not shown). When stratifying on family history of asthma, the HRs for asthma were 1.01 (95% CI: 0.96–1.06) and 1.04 (95% CI: 0.99–1.08) in children of bereaved mothers with and without a family history of asthma, respectively. There was no evidence of any significant interaction between prenatal bereavement and family history of asthma in the association with asthma (*P* for interaction = 0.506).

Discussion

In this population-based study, the association between prenatal stress and childhood asthma differed according to age at asthma onset. Prenatal stress was not associated with asthma in children aged 4–15 years, but asthma events was slightly more frequent in bereaved children aged 0–3 years.

Asthma diagnosed before and after 3 years of age may reflect different phenotypes or different diagnostic practice and etiologic conditions.¹⁶ Pathogens associated with asthma by age may also be different. Respiratory syncytial virus is an important pathogen in asthma among children before 3 years of age, whereas rhinovirus and atopy play a more prominent role after the age of 3 years.¹⁸ Two previous cohort studies have been done on incident asthma in older age groups; one reported an increased lifetime risk of asthma in children aged 12 years following prenatal stress,¹⁹ and the other reported an increased risk of asthma hospitalization in subjects aged 0–33 years.²⁰ It is not known whether the observed overall association was mainly due to an association in children aged 0–3 years. To our knowledge, our study is the first longitudinal study on the association of prenatal bereavement and incident asthma according to age of onset.

Wheezing before 3 years of age is often transient,²¹ and it is not in general associated with asthma later in life.¹⁶ We found prenatal bereavement was associated with an increased risk of asthma

events in children aged 0–3 years, which is in line with previous studies.^{7,22,23} The overall association we found is weak, and timing of bereavement and mother's relationship to the deceased were not systematically associated with asthma events in the offspring. This may indicate that the effect of prenatal bereavement is small, or the association may be attributed to chance or residual confounding. The increased risk in children born to bereaved mothers could also be due to smaller airways,²⁴ as a result of diminished growth.²⁵ With pre-existent smaller airways, marginally additional narrowing can cause further flow limitation and a subsequent asthma. As the airways grow in absolute size and the prevalence of viral infections declined with age,¹⁸ children with smaller airways have fewer symptoms in the older age, which would explain the transient nature of the association between prenatal stress and childhood asthma events in younger age. Prenatal stress may also operate through dysregulation of the fetal epigenome. It has been implicated that alterations in DNA methylation may underlie stress-induced phenotypic plasticity related to respiratory outcomes.²⁶ Prenatal stress may as well act indirectly through its effects on maternal behaviours, such as reduced breastfeeding,²⁷ which has a protective effect on asthma until the age of 2 years.²⁸ Bereaved mother may be more likely to smoke cigarette,²⁹ which may increase the risk of childhood asthma in early life.³⁰ It is also possible that mothers experiencing higher levels of stress during pregnancy may have a lower threshold for seeking medical contact in case of asthma symptoms.

To our knowledge, no study has been done on the association of prenatal stress and incident asthma in children older than 3 years. Our data did not support an association in children aged 4–15 years irrespective of the age at onset, except for the loss of a child. Mothers who lost a child may be more anxious and tend to seek hospital contact or prescription for their children. The overall non-significant association may indicate that a possible effect of prenatal stress on asthma may not be mediated through allergic mechanisms as asthma after 3 years has striking atopic characteristics.¹⁸ Several studies have demonstrated a higher prevalence of asthma in children exposed to prenatal stress.^{7,8} Women with depression during pregnancy may remain depressed after giving birth,³¹ and maternal depressive symptoms were associated with decreased adherence to asthma medications and illness management.³² Taken together, these findings indicate that prenatal stress may be not associated with asthma onset but with recurrence or persistence of childhood asthma, and thus the prevalence of asthma.

Our study has several strengths. Our data are based on medical records and prescription data. There is a substantial non-overlap between the cases ascertained by the two registers ($\kappa=0.21$). The patient register will capture more severe cases, while the prescription registry identify a heterogeneous mix of cases, ranging from suspected asthma cases to more severe cases.³³ The using of prescription and patient registers probably enables us to identify more asthma cases than the using of one register only. The population-based nature of our study allows for almost complete follow-up. Furthermore, the large sample size in our study presented a unique opportunity to detect even small differences between the groups if exist. The availability of population-based data on potential confounding variables provides some options for confounder control when studying the relationship between prenatal stress and childhood asthma.

Our study findings should be interpreted with caution in the light of limitations. We could not investigate residual confounding from other stressors, such as divorce and unemployment. This may lead to underestimate the associations in our study although both exposed and unexposed group will be subject to these stress exposures. Second, asthma is a clinical diagnosis that is not easily captured in population-based studies and there is no 'gold standard' for identifying asthma cases in epidemiology. We used first hospital contact or first prescription for asthma as the

outcome, and thereby, we did not identify asthma cases with mild symptoms not seeking medical contacts. Our findings may therefore not necessarily be generalizable to asthma cases with mild symptoms. On the other hand, anti-asthma medication or hospitalization does not always reflect an asthma diagnosis,^{34,35} and we may misclassify non-asthma patients, such as children with respiratory tract infections, as asthma patients, especially in the younger age group. Third, age at asthma onset was determined by the date of first prescription or hospital contact. It is possible that anxious parents are more willing to seek hospital contact for their children earlier, especially in the first few years after bereavement, as we observed. This misclassification is differential and may lead to overestimation of the association. Fourth, since we performed several comparisons, the potential for Type I error and chance findings should be considered.

Funding

The study was supported by the European Research Council (ERC-2010-StG-260242-PROGEURO) and the Danish Medical Research Council (Project no. 09-072986). Xiaoqin Liu is supported by a Mobility PhD fellowship from Aarhus University.

Conflict of Interests: None declared.

Key points

- Prenatal stress is possibly associated with asthma in children aged 0–3 years.
- Prenatal stress is not related to asthma in children aged 4–15 years.
- Prenatal stress may be not associated with asthma onset but with recurrence or persistence of asthma, and thus the prevalence of asthma.

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