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Parental asthma occurrence, exacerbations and risk of attention-deficit/hyperactivity disorder

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Abstract

Objective: To investigate whether intrauterine exposure to maternal asthma or asthma exacerbations increases the risk of attention-deficit/hyperactivity disorder (ADHD).

Methods: Using Danish register data, this cohort study comprised of 961,202 live singletons born in Denmark during 1997–2012. Children were followed to a maximum of 20.0 years from birth until the first of ADHD-diagnosis/prescription, emigration, death, or 31 December 2016. Cox regression models were used to evaluate the association between maternal or paternal asthma, asthma exacerbations and offspring ADHD.

Results: During 11.4 million person-years of follow-up, 27,780 (2.9%) children were identified as having ADHD. ADHD risk was increased among offspring born to asthmatic mothers (hazard

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ratio (HR) 1.41, 95% CI: 1.36–1.46) or asthmatic fathers (HR 1.13, 95% CI: 1.08–1.18). Antenatal antiasthma medication treatment did not increase offspring ADHD. However, higher risks were observed among offspring of mothers with asthma exacerbations compared with children of asthmatic mothers with no exacerbations: HR 1.12 (95% CI: 1.00–1.25) for pre-pregnancy exacerbations; 1.21 (95% CI: 1.00–1.47) for exacerbations during pregnancy; and 1.25 (95% CI: 1.08–1.44) for exacerbations after delivery.

Conclusions: These results support theories regarding shared genetic and environmental risk factors having a role in the development of ADHD.

Keywords

Asthma; attention-deficit/hyperactivity disorder; cohort studies; registries

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable, neurodevelopmental condition characterized by inattention, hyperactivity, and impulsivity, with a worldwide prevalence of around 3.4% in children and adolescents (Polanczyk et al., 2015). ADHD often persists into adulthood (Riglin et al., 2016), and is associated with increased mortality rates for individuals with ADHD (Dalsgaard et al., 2015) and impairments across the lifespan both for affected individuals and their families (Harpin, 2005).

The etiology of ADHD has not been fully elucidated but is considered multifactorial. Genetic risk factors are important; twin studies demonstrate the heritability of ADHD and molecular genetic studies implicate several candidate genes in its development (Demontis et al., 2017; Faraone et al., 2005). In addition, associations with birth outcomes suggest prenatal exposures could play a role (Class et al., 2014; D'Onofrio et al., 2013; Gustafsson and Kallen, 2011; Halmoy et al., 2012; Indredavik et al., 2005; Indredavik et al., 2004; Lindstrom et al., 2011; Linnert et al., 2006; Nigg and Breslau, 2007; Pettersson et al., 2015; Sucksdorff et al., 2018; Sucksdorff et al., 2015). An association between maternal asthma and increased ADHD risk in offspring has been reported in three studies (Instanes et al., 2017; Liang et al., 2017; Cowell et al., 2019). One underlying assumption for the association with ADHD is that maternal asthma may impact fetal development via altered fetal immune responses in the central nervous system resulting in neuronal injury, thus predisposing children to ADHD (Strickland, 2014). If the immune dysfunction assumption holds true, we should expect that maternal asthma exacerbations during pregnancy, as a proxy of severity or poor control, are associated with higher risk of ADHD in offspring, compared to asthma with no exacerbations. Only one study examined maternal active asthma and risk of ADHD-like symptoms in the offspring (Cowell et al., 2019). However, this study was based on small sample size and reliance on maternal report of ADHD-like symptoms which is not able to explore the impact of medication use and vulnerable to information bias.

To address this important question, we carried out a longitudinal cohort study by defining ADHD cases according to hospital contact and medication treatment. We hypothesized that, when looking at parental asthma and ADHD risk in offspring, if an observed association between maternal asthma and ADHD was mainly due to exposure to intrauterine immune

dysregulation, an elevated risk would be seen among offspring of women with asthma exacerbations during pregnancy. Furthermore, the risk would be more pronounced with maternal than paternal asthma exposure. Alternatively, if an observed association was also due to shared genetic and environmental risk factors, we would expect that asthma exacerbations *before* pregnancy or after delivery in both mothers and fathers would be associated with offspring ADHD.

2. Materials and methods

We conducted a population-based cohort study, linking data from Danish population registers. All children and residents in Denmark are assigned a unique personal identity number, which enables individual-level data linkage between registers. Using the Danish Medical Birth Registry (Bliddal et al., 2018), we identified all liveborn singletons in Denmark during 1997–2012 (N=988,720). We excluded 7,289 children who had missing or extreme gestational age (<154 or >315 days) and 20,229 (2.1%) children missing linkage to their fathers (Figure 1).

2.1 Maternal asthma history.

Mothers were considered to have asthma if they received asthma treatment before the index delivery. Asthma treatment was defined as ever (from mother's birth until the birth of the index child) having had a hospital contact for asthma, or the redemption of two or more prescriptions for antiasthma medications, less than 12 months apart. Information on hospital contact for asthma was recorded in the National Patient Register (Andersen et al., 1999), which contains data on inpatient contacts since 1977, and also emergency room and outpatient treatments from 1995 onwards. The International Classification of Diseases (ICD), 8th Revision (ICD-8) codes were used before 1994 and ICD-10 codes from 1994 onwards. Information on asthma was identified based on ICD-8 code 493 and ICD-10 codes J45 or J46. Information on prescriptions of antiasthma medications was obtained from the National Prescription Registry (Kildemoes et al., 2011), which contains information on the Anatomical Therapeutic Chemical (ATC) classification codes and the dispensing date of all prescriptions dispensed in community pharmacies in Denmark since 1995. The ATC codes for antiasthma medications are: inhaled β 2-agonists (R03AC02–04, –12, and –13), inhaled glucocorticoids/corticosteroids (ICS; R03BA01, –02, and –05), fixed-dose combination of inhaled β 2-agonists and glucocorticoids (R03AK06 and –07), leukotriene receptor antagonists (R03DC03), and anti-IgE treatment (R03DX05) (Liu et al., 2017). We defined paternal asthma using the same exposure window. Mothers who did not have documented antenatal asthma were classified as “non-asthmatic”.

2.2 Asthma exacerbations

Mothers were considered to have an exacerbation if they received inpatient treatment, had an emergency room visit for asthma or filled a prescription for an oral corticosteroid. We defined three periods for exacerbations: a) during the index pregnancy, b) the two years period leading up to the index pregnancy or c) the two years period after the index delivery. Pregnancy was defined as the first day of the last menstrual period up until delivery. Paternal exacerbations were defined using the same window.

Mothers with asthma were further categorized hierarchically, according to asthma exacerbations and the timing of these: a) exacerbations during pregnancy, regardless of previous or later exacerbations; b) exacerbations before pregnancy, regardless of exacerbations after delivery; c) exacerbations after delivery only; and d) no exacerbations before, during pregnancy or after delivery. The number of exacerbations before, during pregnancy and after delivery was calculated by adding all the exacerbations and was categorized into 1, 2, 3, or 4 or more exacerbations.

2.3 Identification of ADHD.

ADHD cases were defined as having either a hospital diagnosis of ADHD or redemption of at least one ADHD medication prescription. Information on hospital contact for ADHD was retrieved from the Danish Psychiatric Central Research Register (Mors et al., 2011) and the National Patient Register. The ADHD diagnosis identified from the National Patient Register was included if the diagnosis was made by pediatricians or neurologists. The ICD-codes for ADHD were 308.01 in ICD-8 and F90 and F98.8 in ICD-10. Data on medications used to treat ADHD dispensed from pharmacies were extracted from the National Prescription Register. The ATC codes for ADHD medications were: N06BA01 (amfetamine), N06BA02 (dexamphetamine), N06BA04 (methylphenidate), N06BA09 (atomoxetine), N06BA11 (dexmethylphenidate), and N06BA12 (lisdexamfetamine). The date of the first diagnosis of ADHD was defined as the first day of hospital contact or first date of dispensation for ADHD medication, whichever occurred first.

2.4 Covariates

The following covariates were identified *a priori* based on causal diagrams using directed acyclic graphs and were included in the models: sex, maternal age at delivery (<25, 25–34, or 35 years), parity (1st, 2nd or above), smoking during pregnancy (yes, no), mental disorders before conception (no mental disorders, ADHD, or other mental disorders excluding ADHD), cohabiting status at delivery (yes, no), low social class (yes, no), large family size (yes, no), place of residence at delivery (capital or capital suburb, provincial city or town, or rural areas), paternal asthma before delivery (yes, no), and calendar year of birth (1997–2000, 2001–2005, 2006–2012).

Mothers were considered to have mental disorders if they had hospital contact for mental disorders (ICD-10 F codes) identified from the Danish Psychiatric Central Research Register, or they redeemed at least one prescription for psychotropic medications (ATC codes N05 and N06), retrieved from the Danish National Prescription Registry. Maternal ADHD was defined as hospital treatment or filling a prescription for ADHD medications. Maternal smoking during pregnancy was self-reported at the first midwife visit. Parity refers to the number of births the mother has had, including the index delivery. Large family size was defined as a household with 4 children including the index child. Low social class was defined as both parents being classified as “low” on at least one of the following variables: education, occupation, or income. Within this, lower education was defined as having completed compulsory schooling as a maximum; lower occupation was defined as receiving disability pension; and lower income as income level in the lowest quintile of the general

population by sex and calendar year. A more detailed description of low social class can be found elsewhere (Ostergaard et al., 2016).

2.5 Statistical analysis

Analyses were performed with Stata 15.0 (StataCorp, College Station, TX, USA). Offspring were followed from birth until the date of first ADHD-diagnosis or -prescription, emigration, death, or 31 December 2016, whichever came first. Cox proportional hazards regression was used to test the associations. The proportional hazards assumption was tested using log-log plots. In those instances where hazards are not proportional over time, the Cox proportional hazards model estimates can be interpreted as an average hazard ratio over the entire follow-up period (Xu and O'Quigley, 2000). About 4.2% of the values were missing for any of the potential confounders, and we applied 20 imputations using the Markov Chain Monte Carlo technique for imputing missing values.

To examine whether a possible association between maternal asthma exacerbations and offspring ADHD was affected by the timing of asthma exacerbations, we categorized mothers with asthma exacerbations into two groups: exacerbations in the first trimester or exacerbations in late pregnancy (second or third trimester) only. To test whether in-utero exposure to antiasthma medication excluding oral corticosteroids itself increased offspring ADHD risk, we examined the association between antiasthma medication during pregnancy and offspring ADHD among children of asthmatic mothers with no exacerbations during pregnancy. We considered mothers as receiving antiasthma medication treatment if they redeemed at least one prescription for an antiasthma medication defined above during the index pregnancy.

Sensitivity analyses—First, to examine whether the association between maternal asthma exacerbations and offspring ADHD was confounded by shared environmental or genetic factors (Smith, 2008), we also examined whether paternal asthma exacerbations before, during the index pregnancy, or after the delivery were associated with offspring ADHD. If the association between maternal asthma and offspring ADHD was largely due to genetic predisposition or shared environmental factors, similar associations should be observed with paternal asthma exacerbations. Second, as sex differences have been observed with regards to the effects of maternal asthma during pregnancy (Murphy et al., 2003), we repeated analyses stratifying on the sex of the child. Third, as mothers with ADHD may have poor adherence to medication or may be less likely to redeem prescriptions, we repeated our analyses excluding 1,399 children born to mothers with pre-conception ADHD. Fourth, due to the pattern of inflammatory phenotypes differing between adults and children (Wang et al., 2011), we performed a sensitivity analysis defining maternal asthma as at least one hospital treatment for asthma or two redemptions of antiasthma prescriptions after age 15 years. Fifth, although oral prednisone and dexamethasone are the currently recommended systemic steroids for moderate to severe asthma exacerbations, we cannot be certain that they were always prescribed for this indication, we repeated our analysis defining asthma exacerbations only as receiving inpatient treatment or emergency visit for asthma.

Ethical approval—The study was approved by the Danish Data Protection Agency (Journal no: 2015-57-0002). No ethical approval is required for purely register-based studies on the basis of encrypted data in accordance with laws and regulations in Denmark.

3. Results

Among 961,202 children, 83,266 (8.7%) children were born to mothers with asthma. Table 1 shows the study population's characteristics. In comparison to non-asthmatic mothers, asthmatic mothers were less likely to be married or cohabiting at the time of childbirth, more likely to have ADHD or other mental disorders, to be of low social class and more likely to smoke during pregnancy. Furthermore, children of asthmatic mothers were more likely to have an asthmatic father.

During 11.4 million person-years of follow-up, 27,780 (2.9%) children were identified as having ADHD. The children were followed up to a maximum of 20.0 years of age, and the median age at ADHD treatment was 9.2 years (interquartile range: 7.3–11.9 years). Parental antenatal asthma was associated with increased risk of ADHD in offspring; the HR for maternal asthma (1.41, 95% CI: 1.36–1.46) was greater than that for paternal asthma (1.13, 95% CI: 1.08–1.18) (P-value <0.001) (Table 2). Altogether, 7,274 children were born to parents who both had asthma; their risk of ADHD was 1.56 (95% CI: 1.39–1.76), in comparison to children with two non-asthmatic parents.

Increased risks of ADHD were seen among those whose mothers experienced asthma exacerbations before pregnancy, during pregnancy, and after delivery, in comparison to children of asthmatic mothers with no exacerbations; HR 1.12 (95% CI: 1.00–1.25), 1.21 (95% CI: 1.00–1.47), and 1.25 (95% CI: 1.08–1.44), respectively. The association between maternal asthma exacerbations during pregnancy and offspring ADHD did not differ by the timing of first exacerbation during pregnancy, with HRs of 1.31 (95% CI: 0.99–1.74) for first-trimester exacerbations and 1.13 (95% CI: 0.87–1.47) for second or third-trimester exacerbations. Associations did not differ with the number of exacerbations. Paternal asthma exacerbations before, during pregnancy, or after delivery were also associated with enhanced offspring ADHD risk (Table 3). Of 69,746 mothers with asthma without exacerbations, 22,206 (31.8%) received antiasthma medications excluding oral corticosteroids. Among mothers with asthma, taking antiasthma medication during pregnancy did not increase ADHD in offspring (HR: 0.94, 95% CI: 0.86–1.02) compared to those who were not treated.

Sex-specific associations between maternal asthma, asthma exacerbations and ADHD in offspring were similar (Table 2, and STable 1 and STable 2 in the supplement). The results remained unchanged after excluding children born to mothers with ADHD before delivery (data not shown). Approximately 77,919 (93.6%) out of 83,266 asthmatic mothers received treatment for asthma after age 15 years. Similar results were obtained when limiting the definition of maternal asthma to those who received asthma treatment after 15 years of age (data not shown). As oral corticosteroids may be prescribed for disorders other than asthma exacerbations, an additional sensitivity analysis was carried out, defining asthma exacerbations based only on inpatient or emergency visit. Associations observed were broadly comparable to analyses in which oral corticosteroid prescriptions were also

included, although the point estimates of the associations decreased and were no longer statistically significant due to smaller sample size (STable 3 in the supplement).

4. Discussion

In this population-based cohort study, we found an increased risk of ADHD among children born to mothers and fathers with asthma, with a higher risk observed for maternal asthma. Additionally, maternal and paternal asthma exacerbations before, during pregnancy or after delivery were associated with a further enhanced risk of offspring ADHD. Maternal use of antiasthma medication during pregnancy did not itself increase the risk of ADHD in children.

Studies have demonstrated strong familial risk for ADHD (Chen et al., 2008; Faraone et al., 2000; Thapar and Stergiakouli, 2008). Prevalence of asthma is also higher among those with ADHD than the general population (Grizenko et al., 2015). In our results, associations were seen for both maternal and paternal asthma, with greatest strength seen for children of parents who both had asthma, consistent with findings from previous epidemiological studies (Instanes et al., 2017; Liang et al., 2017), and supporting the attribution of genetic predisposition and/or shared environmental factors to ADHD risk. Additionally, we observed a stronger association between offspring ADHD and maternal asthma than paternal asthma, suggesting intrauterine exposure could also play a role. Alternatively, this may be due to the fact that environmental factors are likely more closely tied to mothers than fathers. Furthermore, the risk was even higher among children of mothers with exacerbations both before, during pregnancy and after delivery compared to children born to asthmatic mothers with no exacerbations. The risk of ADHD did not change with the number of exacerbations. Similarly, we found an association between paternal asthma exacerbations and ADHD in the offspring. These findings do not provide any support for the hypothesis of inflammation during pregnancy being associated with offspring ADHD, and may indicate that asthma with exacerbations is a distinct and more severe asthma phenotype, conveying a greater risk to the offspring (Dougherty and Fahy, 2009).

Liang et al's (Liang et al., 2017) paper observed a positive association with ADHD among children whose mothers had been prescribed a β_2 -agonist not just during pregnancy, but also before pregnancy; leading them to conclude that the association was more likely due to the indication of treatment, rather than asthma medication. Our finding of no increased risk of ADHD among children of mothers who received antiasthma medication (excluding oral corticosteroids) during pregnancy corroborates this. One of the primary goals of asthma management during pregnancy is to prevent acute exacerbations. Although the safety of using asthma medications during pregnancy is reassuring (Murphy et al., 2007; National Heart et al., 2005), it has been estimated that approximately 29% of asthmatic women would discontinue asthma medication during pregnancy (Chambers, 2003), increasing their likelihood of having asthma exacerbations (Murphy et al., 2005). Results of the current study suggest that antenatal exacerbations of asthma in mothers may be associated with a higher risk of offspring ADHD and hence, our findings add to the evidence, that active pharmacological treatment of asthma using antiasthma medication should be continued during pregnancy to prevent exacerbations.

Methodological strengths of this study include its use of the Danish register data, which provide a large and representative sample, with sufficient power to investigate asthma treatment and exacerbations, to try to elucidate the findings. Register data are prospectively collected, so there is no risk of recall bias. The study has some limitations. First, we defined asthma cases as at least one hospital visit or two antiasthma medications. Parents with less severe asthma who have redeemed only one antiasthma medication prescription would not be included as having an asthma diagnosis. Correspondingly, not all patients with asthma exacerbations would receive inpatient treatment, visit an emergency ward or redeem a prescription of oral corticosteroids. We would have misclassified them as having had no exacerbations. These misclassifications will make our exposure and comparison group similar and bias our finding toward the null. Second, methylphenidate is also indicated for narcolepsy; the effect on the specificity of outcome ascertainment is expected to be minimal as narcolepsy is much less common than ADHD, especially during childhood (Ohayon et al., 2002), as the incidence of narcolepsy peaks at higher ages (Wijnans et al., 2013). Third, our findings may not be representative of the full spectrum of ADHD. The Danish health authorities stipulate that only specialists in child and adolescent psychiatry can diagnose ADHD and initiate treatment with ADHD-medications. It is likely that only moderate or severe cases of ADHD were identified. Several studies have examined the validity of register-based ADHD-diagnoses, all showing high positive predictive values (Dalsgaard et al., 2001; Linnet et al., 2009; Mohr-Jensen et al., 2016). However, clinical practice in Denmark regarding the diagnosis of ADHD may be more restrictive than in other countries, such as the United States (Dalsgaard et al., 2014; Dalsgaard et al., 2013), and the hospital register and prescription register may include only the more severe ADHD cases, limiting generalizability. Fourth, it is possible that compliance to antiasthmatic medication may be poorer among mothers with ADHD, meaning they are at higher risk of both asthma exacerbation and having a high genetic load for ADHD. The results were unaltered when we excluded mothers with pre-conception ADHD. Finally, we cannot exclude the possibility of chance findings and confounding by unknown/uncontrolled factors.

Taken together, these findings support theories on both shared genetic and common environmental risk factors having etiological roles in the development of ADHD. Moreover, our study's finding of increased risk with exacerbations, but no obvious increased risk with maternal antiasthma medication treatment, supports the continued use of antiasthma medication during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable condition. The etiology of ADHD has not been fully elucidated but is considered multifactorial; both genetic risk factors and prenatal exposures may play a role in its development. In this population-based cohort study comprising 961,202 live singletons, we found that both maternal and paternal asthma and asthma exacerbations during the pre- and perinatal period were associated with an increased risk of offspring ADHD, suggesting shared genetic and environmental risk factors having a role in the development of ADHD.

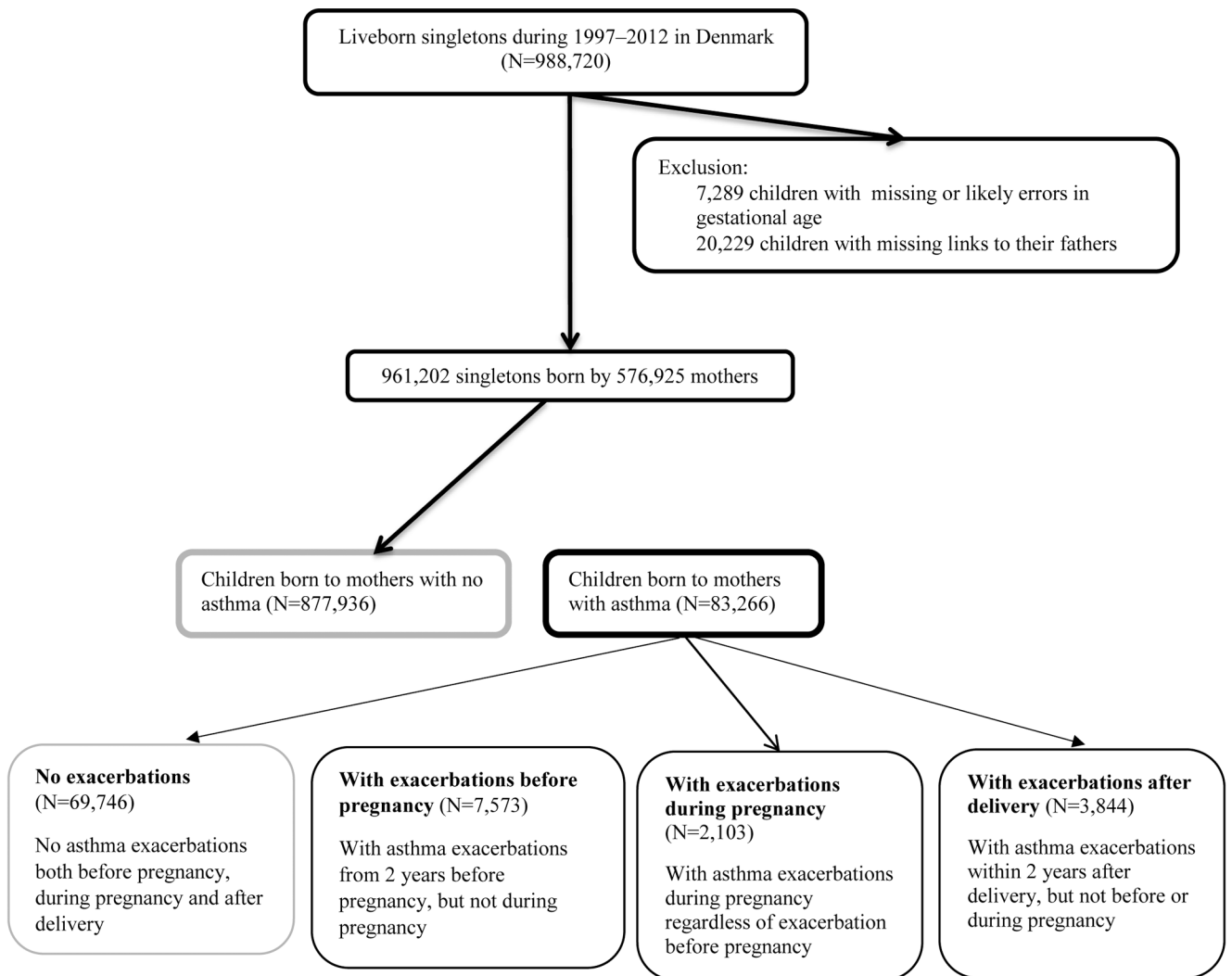


Figure 1.
Flow chart illustrating the identification of the study population

Table 1.

Characteristics of study population

Characteristics	Non-asthmatic mothers (N=877,936)	Asthmatic mothers				
		All asthmatic mothers (N=83,266)	No exacerbations (N=69,746)	With exacerbations before pregnancy only (N=7,573)	With exacerbations during pregnancy (N=2,103)	With exacerbations after delivery (N=3,844)
Maternal age at delivery (years)						
25	111,758 (12.7)	13,050 (15.7)	11,076 (15.9)	1,136 (15.0)	305 (14.5)	533 (13.9)
25–34	614,502 (70.0)	56,050 (67.3)	47,012 (67.4)	5,094 (67.3)	1,302 (61.9)	2,642 (68.7)
>35	151,676 (17.3)	14,166 (17.0)	11,658 (16.7)	1,343 (17.7)	496 (23.6)	669 (17.4)
Parity						
1	380,386 (43.3)	36,530 (43.9)	30,831 (44.2)	3,392 (44.8)	819 (38.9)	1,488 (38.7)
2	493,723 (56.2)	46,296 (55.6)	38,555 (55.3)	4,136 (54.6)	1,270 (60.4)	2,335 (60.7)
Unknown	3,827 (0.4)	440 (0.5)	360 (0.5)	45 (0.6)	14 (0.7)	21 (0.6)
Maternal smoking during pregnancy						
Yes	146,268 (16.7)	17,540 (21.1)	14,573 (20.9)	1,607 (21.2)	506 (24.1)	854 (22.2)
No	705,865 (80.4)	63,497 (76.3)	53,359 (76.5)	5,755 (76.0)	1,522 (72.4)	2,861 (74.4)
Unknown	25,803 (2.9)	2,229 (2.7)	1,814 (2.6)	211 (2.8)	75 (3.6)	129 (3.4)
Maternal mental disorder before pregnancy						
No mental disorder	731,199 (83.3)	59,216 (71.1)	50,287 (72.1)	4,975 (65.7)	1,339 (63.7)	2,615 (68.0)
ADHD	1,108 (0.1)	367 (0.4)	309 (0.4)	28 (0.4)	10 (0.5)	20 (0.5)
Other mental disorders	145,629 (16.6)	23,683 (28.4)	19,150 (27.5)	2,570 (33.9)	754 (35.9)	1,209 (31.5)
Maternal cohabiting status						
Married or cohabiting	773,997 (88.2)	71,590 (86.0)	60,045 (86.1)	6,465 (85.4)	1,744 (82.9)	3,336 (86.8)
Single, divorced, or widow	95,348 (10.9)	11,446 (13.7)	9,498 (13.6)	1,097 (14.5)	351 (16.7)	500 (13.0)
Unknown	8,591 (1.0)	230 (0.3)	203 (0.3)	11 (0.2)	8 (0.4)	8 (0.2)
Place of residence at delivery						
Capital or capital suburb	258,780 (29.5)	22,844 (27.4)	19,386 (27.8)	1,864 (24.6)	664 (31.6)	930 (24.2)
Provincial city or town	345,904 (39.4)	33,107 (39.8)	27,575 (39.5)	3,129 (41.3)	791 (37.6)	1,612 (41.9)
Rural areas	273,252 (31.1)	27,315 (32.8)	22,785 (32.7)	2,580 (34.1)	648 (30.8)	1,302 (33.9)

Characteristics	Non-asthmatic mothers (N=877,936)	Asthmatic mothers				
		All asthmatic mothers (N=83,266)	No exacerbations (N=69,746)	With exacerbations before pregnancy only (N=7,573)	With exacerbations during pregnancy (N=2,103)	With exacerbations after delivery (N=3,844)
Low social class at delivery						
Yes	85,382 (9.7)	10,602 (12.7)	8,687 (12.5)	1,042 (13.8)	353 (16.8)	520 (13.5)
No	764,450 (87.1)	71,626 (86.0)	60,243 (86.4)	6,434 (85.0)	1,695 (80.6)	3,254 (84.7)
Missing	28,104 (3.2)	1,038 (1.3)	816 (1.2)	97 (1.3)	55 (2.6)	70 (1.8)
Large family size at delivery						
Yes	40,573 (4.6)	4,384 (5.3)	3,493 (5.0)	475 (6.3)	175 (8.3)	241 (6.3)
No	837,363 (95.4)	78,882 (94.7)	66,253 (95.0)	7,098 (93.7)	1,928 (91.7)	3,603 (93.7)
Calendar year of birth						
1997–2000	238,719 (27.2)	14,008 (16.8)	11,381 (16.3)	1,432 (18.9)	437 (20.8)	758 (19.7)
2001–2005	276,070 (31.4)	23,709 (28.5)	19,584 (28.1)	2,279 (30.1)	634 (30.2)	1,212 (31.5)
2006–2012	363,147 (41.4)	45,549 (54.7)	38,781 (55.6)	3,862 (51.0)	1,032 (49.1)	1,874 (48.8)
Paternal asthma before delivery						
Yes	59,890 (6.8)	7,274 (8.7)	6,102 (8.8)	647 (8.5)	202 (9.6)	323 (8.4)
Sex of the child						
Boys	427,372 (48.7)	40,560 (48.7)	33,972 (48.7)	3,733 (49.3)	1,021 (48.5)	1,834 (47.7)
Girls	450,564 (51.3)	42,706 (51.3)	35,774 (51.3)	3,840 (50.7)	1,082 (51.5)	2,010 (52.3)
Preterm birth (gestational age <37 weeks)						
Yes	41,472 (4.7)	4,725 (5.7)	3,827 (5.5)	481 (6.4)	173 (8.2)	244 (6.3)
No	836,464 (95.3)	78,541 (94.3)	65,919 (94.5)	7,092 (93.6)	1,930 (91.8)	3,600 (93.7)
Low birth weight (<2500 g)						
Yes	30,790 (3.5)	3,462 (4.2)	2,808 (4.0)	355 (4.7)	120 (5.7)	179 (4.7)
No	847,146 (96.5)	79,804 (95.8)	66,938 (96.0)	7,218 (95.3)	1,983 (94.3)	3,665 (95.3)

Figures are numbers (%).

Table 2.

Hazard ratios of attention-deficit/hyperactivity disorder according to maternal and paternal asthma

Parental asthma	Offspring ADHD (n)	N	Person-years at risk	Crude HR	Adjusted HR (95% CI)
All children					
Non-asthmatic mothers	24,619	877,936	10,456,945	1 (ref)	1 (ref)
Asthmatic mothers	3,161	83,266	880,402	1.67 (1.61 – 1.73)	1.41 (1.36 – 1.46)
Non-asthmatic fathers	25,879	894,038	10,625,998	(ref)	1 (ref)
Asthmatic fathers	1,901	67,164	711,349	1.19 (1.14 – 1.25)	1.13 (1.08 – 1.18)
Boys					
Non-asthmatic mothers	17,607	450,564	5,334,356	1 (ref)	1 (ref)
Asthmatic mothers	2,242	42,706	448,652	1.63 (1.56 – 1.70)	1.39 (1.33 – 1.45)
Non-asthmatic fathers	18,465	458,980	5,422,165	1 (ref)	1 (ref)
Asthmatic fathers	1,384	34,290	360,843	1.20 (1.14 – 1.27)	1.14 (1.08 – 1.21)
Girls					
Non-asthmatic mothers	7,012	427,372	5,122,589	1 (ref)	1 (ref)
Asthmatic mother	919	40,560	431,750	1.79 (1.67 – 1.91)	1.46 (1.36 – 1.57)
Non-asthmatic fathers	7,414	435,058	5,203,833	1 (ref)	1 (ref)
Asthmatic fathers	517	32,874	350,506	1.18 (1.08 – 1.29)	1.09 (0.99 – 1.19)

Abbreviations: HR, hazard ratio; CI, confidence interval.

Adjusted for maternal age at delivery, parity, maternal smoking during pregnancy, maternal mental disorders before pregnancy, maternal cohabiting status, place of residence at delivery, low social class at delivery, large family size, sex of the child, and calendar year of birth. Maternal asthma and paternal asthma were mutually adjusted in the models.

Table 3.

Hazard ratios of attention-deficit/hyperactivity disorder according to maternal and paternal asthma exacerbations

Parental asthma exacerbations	Offspring ADHD (n)	N	Person-years at risk	Crude HR	Adjusted HR (95% CI)
Asthmatic mothers					
No exacerbations	2,520	69,746	731,491	1 (ref)	1 (ref)
Timing at exacerbations					
Exacerbations before pregnancy	341	7,573	82,719	1.16 (1.04 – 1.30)	1.12 (1.00 – 1.25)
Exacerbations during pregnancy	106	2,103	23,158	1.28 (1.05 – 1.55)	1.21 (1.00 – 1.47)
During early pregnancy	49	891	9,758	1.41 (1.06 – 1.87)	1.31 (0.99 – 1.74)
During late pregnancy	57	1,212	13,400	1.18 (0.91 – 1.54)	1.13 (0.87 – 1.47)
Exacerbations after delivery	194	3,844	43,034	1.25 (1.08 – 1.45)	1.25 (1.08 – 1.44)
Number of exacerbations before, during pregnancy and after delivery					
One	331	7,176	78,830	1.18 (1.05–1.32)	1.18 (1.05 – 1.32)
Two	123	2,796	30,631	1.13 (0.94–1.35)	1.12 (0.94 – 1.35)
Three	71	1,407	15,169	1.33 (1.05–1.69)	1.35 (1.07 – 1.71)
four	116	2,141	24,281	1.31 (1.09–1.58)	1.28 (1.07 – 1.55)
Asthmatic fathers					
No exacerbations	1,418	53,043	554,163	1 (ref)	1 (ref)
Exacerbations before pregnancy	182	5,765	63,433	1.08 (0.92 – 1.26)	1.07 (0.92 – 1.25)
Exacerbations during pregnancy	172	4,864	53,904	1.19 (1.02 – 1.40)	1.17 (1.00 – 1.37)
Exacerbations after delivery	129	3,492	39,849	1.18 (0.99 – 1.42)	1.18 (0.98 – 1.41)

Abbreviations: HR, hazard ratio; CI, confidence interval.

Adjusted for maternal age at delivery, parity, maternal smoking during pregnancy, maternal mental disorders before pregnancy, maternal cohabiting status, place of residence at delivery, low social class at delivery, large family size, sex of the child, and calendar year of birth. Maternal asthma exacerbations and paternal asthma exacerbations were mutually adjusted in the models.