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Maternal asthma severity and control during pregnancy and risk of offspring asthma

Xiaoqin Liu, Ph.D.1, Esben Agerbo, Dr.Med.Sci.1, 2, 3, Vivi Schlünssen, M.D., Ph.D. 4, 5, Rosalind J. Wright, M.D., MPH 6, Jiong Li, Ph.D. 7, Trine Munk-Olsen, Ph.D. 1

Affiliations:
1 The National Center for Register-based Research, Aarhus University, Aarhus, Denmark;
2 CIRRAU-Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark;
3 Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark;
4 Section for Environmental and Occupational Medicine, Department of Public Health, Aarhus University, Denmark;
5 National Research Center for the Working Environment, Copenhagen, Denmark;
6 Department of Pediatrics, Kravis Children’s Hospital, Icahn School of Medicine at Mount Sinai, New York, USA;
7 Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Corresponding author: Xiaoqin Liu, the National Center for Register-based Research, Aarhus University, Fuglesangs Allé 26, 8210 Aarhus V, Denmark. Phone: +45 8716 6268. E-mail: lxq@econ.au.dk

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Conflicts of interest: None.
Abstract

**Background:** Severe and uncontrolled asthma during pregnancy have been linked to several unfavorable perinatal outcomes. However, current knowledge on the association between the severity and control of maternal asthma and offspring asthma is sparse.

**Objective:** To investigate the extent to which offspring asthma is influenced by maternal asthma severity and control during pregnancy.

**Methods:** A prospective population-based cohort study. By linkage of Danish national registers, we constructed a cohort of 675,379 singletons, of which 15,014 children were born to asthmatic mothers. Among them, 7,188 children were born to mothers with active asthma during pregnancy. We categorized mothers with active asthma into four groups based on dispensed antiasthmatic prescriptions and on use of medical services: mild controlled, mild uncontrolled, moderate-to-severe controlled, and moderate-to-severe uncontrolled asthma. The outcomes were offspring early-onset transient, early-onset persistent, and late-onset asthma. We estimated prevalence ratios (PRs) of each phenotype of asthma using a log-binomial model with 95% confidence intervals (CIs).

**Results:** Higher prevalence of early-onset persistent asthma was observed among children of asthmatic mothers with mild uncontrolled (PR=1.19, 95% CI:1.05–1.35), moderate-to-severe controlled (PR=1.33, 95% CI:1.09–1.63), and moderate-to-severe uncontrolled asthma (PR=1.37, 95% CI:1.17–1.61), compared to those of mild controlled asthmatic mothers. A borderline increased prevalence of early-onset transient asthma was observed among children of mothers with uncontrolled asthma.
Conclusion: Maternal uncontrolled asthma increases the risk of early-onset persistent and transient asthma. If replicated, this could suggest that maintaining asthma control in pregnancy is an area for possible prevention of specific phenotypes of offspring asthma.

Clinical implications: In-utero exposure to uncontrolled asthma increases early-onset persistent and transient asthma risk. This may suggest that maintaining asthma control during pregnancy is an area for possible prevention of offspring asthma.
Capsule summary:

Children to mothers with uncontrolled and moderate-to-severe asthma during pregnancy have higher prevalence of early-onset persistent asthma and borderline increased risk of early-onset transient asthma, compared to children to mild controlled asthmatic mothers.

Key words: Asthma, cohort study, control, early-onset, late-onset, phenotype, pregnancy, severity

Abbreviations used:

PR: Prevalence ratio
CI: Confidence interval
ICD: International Classification of Diseases
ATC: Anatomical therapeutic chemical
Introduction

Asthma is the most common chronic disease complicating pregnancy, affecting 3–9% of all pregnancies.\textsuperscript{1-3} International guidelines recommend that asthma during pregnancy should be managed in the same manner as for non-pregnant women to maintain asthma control.\textsuperscript{4} Nevertheless, a survey revealed that approximately 29% of asthmatic women would discontinue asthma medication during pregnancy, mainly for fear of adverse impacts on the fetus,\textsuperscript{5} despite accumulating evidence of the safety of inhaled corticosteroid and β2-agonist use during pregnancy.\textsuperscript{4, 6} Correspondingly, about one-third of the women experienced uncontrolled asthma during pregnancy.\textsuperscript{7}

Poorly controlled asthma during pregnancy may deprive the fetus of oxygen, and thus affects fetal development negatively.\textsuperscript{8} Studies have linked uncontrolled asthma to preterm birth, low birth weight, and fetal growth restriction,\textsuperscript{9-11} which are known risk factors for asthma.\textsuperscript{12} It is, thereby, likely that uncontrolled asthma during pregnancy may carry additional risks for offspring asthma along with conferring a genetic risk. At present, only one study has focused on the severity and control of asthma during pregnancy and offspring asthma risk, showing a higher risk of asthma among children of mothers with moderate-to-severe uncontrolled asthma than those of mothers with mild controlled asthma.\textsuperscript{13} However, this study was underpowered to provide precise estimates for the influence of maternal moderate-to-severe controlled asthma. Moreover, it is becoming increasingly evident that asthma is not a single disorder but a syndrome encompassing several phenotypes, which may have distinct pathogeneses,\textsuperscript{14} and be associated with risk factors differently.\textsuperscript{15, 16} For instance, early-onset persistent asthma is more strongly affected by early-life environmental exposure than other phenotypes of asthma.\textsuperscript{15, 16}
In the present study, we aimed to investigate the association between asthma severity and control during pregnancy and the risk of three phenotypes of asthma in the offspring. We hypothesized that children of mothers with uncontrolled asthma had higher risks of asthma, in particular, early-onset persistent asthma, compared to those of mothers with mild controlled asthma.

Methods

Study population

The study was a population-based cohort study built on Danish national registers. All liveborn and new residents in Denmark are assigned a unique 10-digit identifier recorded in the Danish Civil Registration System. The identifier enables us to link individual-level data between and within all national registers. We first identified 694,770 liveborn singletons during 1996–2006 from the Danish Medical Birth Registry. We excluded 4,372 children with missing or likely errors in gestational age (<154 or >315 days). As our outcomes of interest were measured according to asthma treatment at age 0–3 years and 4–6 years, to ensure all children were followed until age 6 years, we further excluded 11,643 children who emigrated, and 3,376 children who died before their 6th birthday (Figure 1). Altogether 675,379 singletons were included in our analyses.

Maternal asthma history before delivery. We defined maternal asthma as at least one inpatient, outpatient or emergency room visit for asthma before delivery from the Danish National Patient Register. The register contains data on inpatient contacts since 1977, and from 1995 also emergency room and outpatient treatments. The International Classification of Diseases (ICD), 8th Revision (ICD-8) codes was used during 1977–1993 and ICD-10 codes from 1994 and onwards. Information on
maternal asthma was identified based on ICD-8 code 493 and ICD-10 codes J45 or J46. We similarly
defined paternal asthma history.

**Active asthma during pregnancy.** Asthmatic mothers were categorized as having active asthma if they
redeemed at least one antiasthmatic prescription or had one or more inpatient, outpatient or emergency
room visit for asthma during the index pregnancy. Pregnancy was counted from the first day of the last
menstrual period until delivery. Information on antiasthmatic prescription was obtained from the
Danish National Prescription Registry, which covers all prescriptions dispensed in Denmark since
1995. It contains the anatomical therapeutic chemical (ATC) classification codes, the number of
defined daily dose per package, the number of packages dispensed, and the dispensation date. The
ATC codes for antiasthmatics were for inhaled β2-agonists (R03AC02–04, -12, and -13), inhaled
glucocorticoids (R03BA01, -02, and -05), fixed-dose combination of inhaled β2-agonists and
glucocorticoids (R03AK06 and -07), leukotriene receptor antagonists (R03DC03), and anti-IgE
treatment (R03DX05).

**Asthma severity and control during pregnancy.** Information on the severity and control of active
asthma during pregnancy was obtained from the Danish National Prescription Registry and the Danish
National Patient Register. We defined asthma severity and control on the basis of the doses of
inhaled corticosteroids (in beclomethasone-chlorofluorocarbon equivalent), add-on therapy
(theophylline, long-acting β2-agonists and leukotriene-receptor antagonists), short-acting β2-agonists
doses per week, and moderate-to-severe exacerbation (defined as inpatient treatment, emergency room
visit for asthma or a filled prescription of an oral corticosteroid). The following ATC codes were
used: theophylline (R03DA04), long-term acting β2-agonists (R03AC12 and R03AC13), short-acting
β₂-agonists (R03AC02–04), and oral corticosteroid (H02AB). The number of days exposed per
prescription of a specific drug was calculated by multiplying the number of defined daily doses per
package by the number of packages dispensed. The number of days exposed to a specific drug was
calculated by adding all prescriptions’ durations. The equivalence of the average daily dosage of
inhaled corticosteroids into beclomethasone-chlorofluorocarbon was calculated according to the
equivalency Table generated by the Canadian Asthma Consensus Guidelines. We created four
mutually exclusive groups according to the various combinations of maternal asthma severity and
control as described below: 1) mild controlled, 2) mild uncontrolled, 3) moderate-to-severe controlled,
and 4) moderate-to-severe uncontrolled asthma (Table E1 in the supplement). The definition of asthma
severity and control have been described in detail elsewhere.

Asthma severity. We defined mild asthma as treatment with inhaled glucocorticoids doses of 251–
500µg/day with no add-on therapy or inhaled glucocorticoids doses of 0–250µg/day regardless add-on
therapy. To be categorized as mild asthma, the following situations were not included: 1) moderate-to-
severe exacerbations and 4–10 doses of short-acting β₂-agonists per week; 2) >10 doses of short-acting
β₂-agonists per week. We defined moderate-to-severe asthma as treatment with inhaled

glucocorticoids doses of 251–500µg/day with add-on therapy or inhaled glucocorticoids doses
of >500µg/day.

Asthma control. Asthmatic mothers were considered as having controlled asthma if they had no
moderate-to-severe exacerbations and were taking 0–3 doses of short-acting β₂-agonists per week for
mild asthma and ≤10 doses of short-acting β₂-agonists per week for moderate-to-severe asthma.
Moreover, a woman was considered to have moderate-to-severe uncontrolled asthma if she had one of
the following situations: 1) moderate-to-severe exacerbations and 4–10 doses of short-acting β₂-agonists per week; or 2) >10 doses of short-acting β₂-agonists per week.

Childhood asthma in the offspring—outcomes of interest

Our outcomes of interest were three mutually exclusive phenotypes of asthma in the offspring according to asthma treatment (i.e. hospital or antiasthmatic treatment) during 0–3 years of age and during 4–6 years based on the schema from Martinez et al.¹⁴.  
1) Early-onset transient asthma: asthma treatment during 0–3 years but no treatment during 4–6 years;  
2) Early-onset persistent asthma: asthma treatment both during 0–3 years and during 4–6 years;  
3) Late-onset asthma: no asthma treatment during 0–3 years but with treatment during 4–6 years.

Asthma hospital treatment was defined as having an inpatient, outpatient or emergency room visit for asthma (ICD-10 codes J45 and J46), retrieved from the Danish National Patient Register. Antiasthmatic treatment was defined as two or more dispensed prescriptions of an antiasthmatic mentioned above within one year by using the Danish National Prescription Registry. We defined asthma treatment during age 0–3 years as at least two prescriptions of an antiasthmatic within one year or at least one hospital treatment for asthma during 0–3 years. We similarly defined asthma treatment during age 4–6 years.

Statistical analysis

Statistical analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC). We calculated the prevalence of each phenotype of asthma—early-onset transient, early-onset persistent, and late-onset asthma, respectively. Since asthma is not a rare outcome, we estimated the prevalence ratio (PR) of
each phenotype of asthma and their 95% confidence intervals (CIs) using a log-binomial model.\textsuperscript{23} The log-binomial method was performed with PROC GENMOD using the binomial distribution and the log link. We specified an initial value of -4 for the intercept. A woman may contribute more than one pregnancy to the analysis. To account for the dependence between siblings, we used robust sandwich variance estimator for correction of standard errors. A \textit{P}-value of <0.05 (two-sided test) was considered statistically significant. We included missing values as separate groups in the models. We adjusted for the following covariates: maternal age (<25, 25–34, or $\geq$35 years), calendar year of birth (1996–1999, 2000–2003, or 2004–2006), parity (1st/2nd or higher), maternal smoking during pregnancy (yes/no), place of residence (capital or capital suburb, provincial city or town, or rural areas), income status (lowest quartile/above lowest quartile), education (elementary school/above elementary school), and paternal asthma (yes/no) at the time of childbirth. Data on these covariates were extracted from the registers mentioned above as well as from Statistics Denmark’s registers on socioeconomic status.\textsuperscript{24} 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.\textsuperscript{25} Maternal stress during pregnancy contributes to both maternal active asthma and alter fetal innate and adaptive immune response, predisposing to asthma.\textsuperscript{26, 27} We, therefore, further adjusted for maternal bereavement from one year before or during pregnancy (yes/no), retrieved from the Danish Registers of Causes of Death.\textsuperscript{28}

To test whether maternal asthma was associated with an increased prevalence of offspring asthma, we compared the PRs of three phenotypes of asthma in children of asthmatic mothers to children of non-asthmatic mothers. To examine whether the associations between maternal asthma and offspring asthma was confounded by shared environmental or genetic variables,\textsuperscript{29} we included comparisons with
associations between paternal asthma and offspring asthma. Maternal and paternal asthma were mutually adjusted for in the models.

To determine whether the prevalence of three phenotypes of asthma was influenced by maternal asthma severity and control, we restricted our analysis to children of mothers with active asthma during pregnancy. We compared the PRs of phenotypes of asthma in children of mothers who had mild uncontrolled asthma, moderate-to-severe controlled, or moderate-to-severe uncontrolled asthma to those of mild controlled asthmatic mothers.

Sensitivity analysis

We implemented four sensitivity analyses to test the robustness of our results. First, mothers with no asthma diagnosis but on antiasthmatic treatment may potentially have asthma. We, therefore, repeated our analyses by excluding mothers who redeemed any antiasthmatic prescription before delivery from the non-asthmatic group. Second, evidence indicates that there may be a sex-specific interplay between the mother, placenta, and the fetus.30 To account for the fetal sex-specific differences, we recalculated the PRs by stratifying on the sex of the child. Third, 5.2% of the values were missing for any of the potential confounders. We imputed missing values with the most common values and re-ran all analyses. Fourth, to study whether the associations were modified by the definition of asthma control, we redefined asthma control by considering moderate-to-severe exacerbation only.

Ethics

The study was approved by the Danish Data Protection Agency (Journal no: 2015-57-0002). According to Danish law, no informed consent is required for a register-based study based on anonymized data.
Results

Of 675,379 children, 15,014 (2.2%) children were born to asthmatic mothers, among whom 7,188 (1.1%) to mothers with active asthma during pregnancy. Asthmatic mothers were younger, more often smoked during pregnancy and had shorter education than non-asthmatic mothers. Mothers with active asthma during pregnancy were more likely to be older and multiparous, smoke less often, and have longer education than asthmatic mothers with no active asthma (Table 1).

Parental asthma and offspring asthma. A total of 56,438 (8.4%) children were classified as having early-onset transient asthma, 45,900 (6.8%) as having early-onset persistent asthma, and 21,858 (3.2%) as having late-onset asthma. Both maternal and paternal asthma were associated with increased prevalence of three phenotypes of asthma, whereas more pronounced associations were observed between maternal asthma and offspring asthma (P-values for PR differences were < 0.05). Maternal asthma was more strongly associated with offspring early-onset persistent asthma (PR=2.11, 95% CI: 2.03–2.20), as opposed to early-onset transient (PR=1.42, 95% CI: 1.36–1.48) and late-onset asthma (PR=1.89, 95% CI: 1.77–2.02), compared to non-asthmatic mothers (P-values for comparing the PR differences between early-onset persistent, early-onset transient and late-onset asthma were < 0.01). Children of asthmatic mothers with no active asthma during pregnancy also had an increased prevalence of three phenotypes of asthma, although a more elevated prevalence was observed among children of mothers with active asthma during pregnancy (P-values for PR differences were <0.05) (Table 2).

Severity and control of maternal asthma and offspring asthma. Higher prevalence of early-onset persistent asthma was observed among children of mothers with mild uncontrolled asthma (PR=1.19,
95% CI: 1.05–1.35), moderate-to-severe controlled asthma (PR=1.33, 95% CI:1.09–1.63), and moderate-to-severe uncontrolled asthma (PR=1.37, 95% CI:1.17–1.61), compared to those of mothers with mild controlled asthma. A borderline increased prevalence of early-onset transient asthma was observed among children of mothers with uncontrolled asthma. Maternal asthma severity and control was not associated with offspring late-onset asthma (Figure 2).

Sensitivity analyses. We excluded 76,542 pregnancies by mothers who redeemed antiasthmatic prescription but with no asthma diagnosis to ensure not to misclassify asthmatic mothers with no hospital treatment as non-asthmatic mothers. After exclusion, children to asthmatic mothers had increased prevalence of early-onset transient asthma (PR=1.50, 95% CI: 1.44–1.56), early-onset persistent asthma (PR=2.34, 95% CI: 2.24–2.43), and late-onset asthma (PR=2.00, 95% CI: 1.88–2.13), compared to children of non-asthmatic mothers. The associations between the severity and control of maternal asthma and offspring three phenotypes of asthma were not modified by the sex of the child (P-values for interaction were greater than 0.15) (Table E2 in the Supplement). Similar results were obtained when we imputed the missing values with the most common values (Results not shown). The results remained identical by redefining asthma control according to moderate-to-severe exacerbations, although the association between mild uncontrolled asthma and offspring early-onset persistent asthma was no longer significant (Figure E1 in the supplement).

Discussion

In this population-based cohort study, we found that children of asthmatic mothers had a higher prevalence of all three phenotypes of asthma, compared to those of non-asthmatic mothers. A stronger association was observed with early-onset persistent asthma as opposed to early-onset transient or late-
onset asthma. Maternal moderate-to-severe or uncontrolled asthma during pregnancy was associated
with an increased prevalence of offspring early-onset persistent asthma and a borderline increased
prevalence of early-onset transient asthma, compared to children of mothers with mild controlled
asthma.

We found increased prevalence of three phenotypes of asthma among children of asthmatic mothers.
This increased prevalence was observed among children of asthmatic mothers with no active asthma
during pregnancy, providing evidence for a genetic predisposition of asthma. Such a genetic
susceptibility has frequently been noted. In addition to genetic predisposition, two lines of
evidence suggest that maternal asthma may also affect offspring asthma via environmental exposures.
First, we found that maternal asthma conferred a greater risk than paternal asthma, which is consistent
with most of the previous observations. Second, adding to this assumption, we observed a higher
prevalence of three phenotypes of asthma among children of mothers with active asthma during
pregnancy than those of asthmatic mothers with no active symptoms.

We found a stronger association between maternal asthma and early-onset persistent asthma as opposed
to early-onset transient and late-onset asthma, which is in line with existing studies. Our finding
supports the hypothesis that asthma is not a single disorder, but consists of several phenotypes which
have different associations with risk factors.

A higher prevalence of early-onset persistent asthma and a borderline increased prevalence of early-
onset transient asthma were seen in children of asthmatic mothers with uncontrolled asthma. Our
finding is in agreement with one previous study. The underlying mechanisms linking uncontrolled
asthma and offspring early-onset transient or persistent asthma have not been defined. A child’s susceptibility to the development of asthma is determined by both a genetic risk/heritability and environmental exposures. Maternal uncontrolled asthma may be a distinct phenotype from controlled asthma and confer different susceptibility to offspring asthma. Furthermore, it is known that parental or grandparental asthma may induce epigenetic changes that can be inherited to the next generation as observed in experimental studies. Epigenetic characteristics and airway inflammation are interrelated. Thus, maternal uncontrolled asthma might influence the risk of offspring asthma independent of genetic heritability. In addition to genetic susceptibility and epigenetic regulations, maternal uncontrolled asthma may also influence offspring asthma through environmental exposures, both in-utero or during upbringing. Martinez et al. reported that children with early-onset transient and early-onset persistent asthma had reduced lung function. It is possible that uncontrolled asthma may amplify the effect of maternal asthma on fetal hypoxia, with consequences for reduced fetal growth and impaired lung development of the fetus through alterations in placental function. Another possible explanation for the observed association is a shared physical or social environment between the mothers and children. These above-mentioned possible underlying mechanisms may not be mutually exclusive but might coexist. We found that maternal moderate-to-severe asthma, regardless of whether or not it was controlled, was predictive of offspring early-onset asthma. In addition to the mechanisms proposed above, another possible interpretation is that moderate-to-severe asthma is a different asthma phenotype and conveys a greater risk of asthma to the offspring. Little knowledge is currently available about the potential mechanisms linking maternal asthma severity and control and asthma phenotypes in the offspring. Future studies, in particular studies on mechanistic investigations, are warranted to confirm our findings.
Poor asthma control constitutes a risk factor that potentially can be targeted in clinical practice and intervened upon, with nonadherence and inhaler misuse being two most common reasons that hinder better asthma control.\textsuperscript{40} It is reported that 24\% of women do not take prescribed antiasthmatics during pregnancy,\textsuperscript{41} and the frequency of poor inhaler technique ranges from 41\% to 54\%.\textsuperscript{42} Noncompliance and inhaler misuse can be difficult to detect as they are not routinely evaluated.\textsuperscript{40} It is, therefore, essential for health professionals to be alert to the possibility of noncompliance and improper inhaler technique when women experienced poor asthma control.

**Strengths and limitations**

Important strengths of the present study included being representative, large sample size, and sufficient power to investigate the impact of several levels of maternal asthma severity and control on phenotypes of offspring asthma. We used validated indexes for categorizing asthma severity and control. Data on asthma severity and control have been collected prospectively and independently of the outcome, thus avoid recall bias. We investigated three phenotypes of asthma respectively, which may be more informative for mechanism exploration.

Several methodological features should be accounted for. First, we determined maternal asthma severity and control based on dispensed prescriptions and the patient register, with no clinical measurements. We did not have information on the allergic status of asthma. Therefore we cannot discriminate between the influence of maternal allergic and non-allergic asthma on offspring asthma. Although the definition used in our study has been validated against pulmonary function tests in a previous study,\textsuperscript{21} we may still have misclassified the level of asthma severity and control. It is probable that women with mild uncontrolled asthma may comprise a heterogeneous group, and some of them are
moderate-to-severe cases. Inversely, due to over-treatment, women with moderate-to-severe controlled
asthma may be mild asthma cases. Such misclassifications would bias the effect estimate of mild
uncontrolled and moderate-to-severe asthma toward each other and overestimate the influence of mild
uncontrolled asthma. Second, asthma in the offspring was identified using patient and prescription
registers. It is possible that children with mild asthma who did not seek health services were not
included. Conversely, not all the children who redeemed asthma medications had been diagnosed with
asthma. It seems, however, the outcome misclassification would be nondifferential and would have
biased the findings toward the null. Moreover, we determined asthma phenotypes according to
asthma treatment during 0–3 years and 4–6 years. Some asthmatic children may seek medical treatment
at a later stage. We would thus have misclassified the timing of treatment, leading to the
misclassification of asthma phenotypes. This misclassification would be nondifferential and bias the
prevalence ratios of three phenotypes toward one another. Third, despite the numerous confounders
adjusted for in our models, some residual confounding from unmeasured confounders such as father’s
smoking may still prevail. Lastly, although our study indicates an association between maternal
uncontrolled asthma and offspring early-onset asthma, our study is limited by its observational nature.
We were not able to assess the extent to which better optimization of asthma control during pregnancy
reduces risk of early-onset asthma in the offspring.

Conclusion: Maternal uncontrolled and moderate-to-severe asthma during pregnancy increases the risk
of both offspring early-onset persistent and transient asthma. If replicated, this could suggest that
maintaining asthma control in pregnancy is an area for possible prevention of specific phenotypes of
offspring asthma. Moreover, further studies are needed that more directly examine potential
mechanisms underlying the association between uncontrolled asthma in pregnancy and offspring asthma risk.
References


Table 1. Characteristics of study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-asthmatic mothers (N=660,365)</th>
<th>All asthmatic mothers (N=15,014)</th>
<th>Asthmatic mothers With no active asthma during pregnancy (N=7,826)</th>
<th>Asthmatic mothers With active asthma during pregnancy (N=7,188)</th>
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<td>&lt;25</td>
<td>93,630 (14.2)</td>
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<td>≥35</td>
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<td>2,617 (17.4)</td>
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<td>284,257 (43.0)</td>
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<td>3,460 (23.0)</td>
<td>1,921 (24.6)</td>
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<td>Maternal bereavement prior to or during pregnancy</td>
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<td>Yes</td>
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<td>408 (2.7)</td>
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<td>5,860 (81.5)</td>
</tr>
<tr>
<td>Maternal education status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>140,148 (21.2)</td>
<td>4,363 (29.1)</td>
<td>2,418 (30.9)</td>
<td>1,945 (27.1)</td>
</tr>
<tr>
<td>Above elementary school</td>
<td>505,032 (76.5)</td>
<td>10,447 (69.6)</td>
<td>5,314 (67.9)</td>
<td>5,133 (71.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15,185 (2.3)</td>
<td>204 (1.4)</td>
<td>94 (1.2)</td>
<td>110 (1.5)</td>
</tr>
<tr>
<td>Calendar year of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996–1999</td>
<td>247,246 (37.4)</td>
<td>3,616 (24.1)</td>
<td>1,605 (20.5)</td>
<td>2,011 (28.0)</td>
</tr>
<tr>
<td>2000–2003</td>
<td>238,119 (36.1)</td>
<td>5,592 (37.2)</td>
<td>2,948 (37.7)</td>
<td>2,644 (36.8)</td>
</tr>
<tr>
<td>2004–2006</td>
<td>175,000 (26.5)</td>
<td>5,806 (38.7)</td>
<td>3,273 (41.8)</td>
<td>2,533 (35.2)</td>
</tr>
<tr>
<td>Paternal asthma before delivery</td>
<td>10,072 (1.5)</td>
<td>373 (2.5)</td>
<td>199 (2.5)</td>
<td>174 (2.4)</td>
</tr>
<tr>
<td>Sex of the child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>338,802 (51.3)</td>
<td>7,677 (51.1)</td>
<td>3,996 (51.1)</td>
<td>3,681 (51.2)</td>
</tr>
<tr>
<td>Girls</td>
<td>321,563 (48.7)</td>
<td>7,337 (48.9)</td>
<td>3,830 (48.9)</td>
<td>3,507 (48.8)</td>
</tr>
</tbody>
</table>

Figures are numbers (%).
Table 2. Prevalence ratios of early-onset transient, early-onset persistent, and late-onset asthma according to maternal and paternal asthma in the whole study population (N=675,379)

<table>
<thead>
<tr>
<th>Parental asthma</th>
<th>N</th>
<th>Early-onset transient asthma</th>
<th>Early-onset persistent asthma</th>
<th>Late-onset asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (%)</td>
<td>Crude PR (95% CI)</td>
<td>Cases (%)</td>
<td>Crude PR (95% CI)</td>
</tr>
<tr>
<td>Non-asthmatic mothers</td>
<td>660,365</td>
<td>54,467 (8.2)</td>
<td>1</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Asthmatic mothers</td>
<td>15,014</td>
<td>1,971 (13.1)</td>
<td>1.59</td>
<td>1.42 (1.36–1.48)</td>
</tr>
<tr>
<td>With no active asthma</td>
<td>7,826</td>
<td>1,021 (13.0)</td>
<td>1.58</td>
<td>1.36 (1.29–1.45)</td>
</tr>
<tr>
<td>With active asthma</td>
<td>7,188</td>
<td>950 (13.2)</td>
<td>1.60</td>
<td>1.49 (1.41–1.58)</td>
</tr>
<tr>
<td>Non-asthmatic fathers</td>
<td>664,934</td>
<td>55,254 (8.3)</td>
<td>1</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Asthmatic fathers</td>
<td>10,445</td>
<td>1,184 (11.3)</td>
<td>1.36</td>
<td>1.21 (1.15–1.28)</td>
</tr>
</tbody>
</table>

Abbrevations: PR, prevalence ratio; CI, confidence interval.

Early-onset transient asthma—asthma treatment during 0–3 years but no treatment during 4–6 years of age; Early-onset persistent asthma—asthma treatment both during 0–3 years and during 4–6 years of age; Late-onset asthma—no asthma treatment during 0–3 years but with treatment during 4–6 years of age.

Adjusted for maternal age at delivery, parity, smoking during pregnancy, maternal bereavement prior to or during pregnancy, place of residence at delivery, income status, education status, and calendar year of birth. Maternal asthma and father’s asthma were mutually adjusted in the models.
Figure 1. Flow chart illustrating the identification of the study population
Figure 2. Prevalence ratios of early-onset transient, early-onset persistent, and late-onset asthma according to maternal asthma severity and control among children of asthmatic mothers with active asthma during pregnancy (N=7,188)

Abbreviations: PR, prevalence ratio; CI, confidence interval.

**Early-onset transient asthma**—asthma treatment during 0–3 years but no treatment during 4–6 years of age; **Early-onset persistent asthma**—asthma treatment both during 0–3 years and during 4–6 years of age; **Late-onset asthma**—no asthma treatment during 0–3 years but with treatment during 4–6 years of age.

Children of mothers with mild controlled asthma in pregnancy were used as the reference group for estimating the prevalence ratios of asthma among children of mothers with mild uncontrolled, moderate-to-severe controlled and moderate-to-severe uncontrolled asthma in pregnancy. Adjusted for maternal age at delivery, parity, smoking during pregnancy, maternal bereavement prior to or during pregnancy, place of residence at delivery, income status, education status, calendar year of birth, and paternal asthma before delivery.