

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

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Background: Severe and uncontrolled asthma during pregnancy has 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: We sought to investigate the extent to which offspring asthma is influenced by maternal asthma severity and control during pregnancy.

Methods: We performed a prospective population-based cohort study. Using 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 4 groups based on dispensed antiasthma 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% 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 with 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.

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. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

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

Asthma is the most common chronic disease complicating pregnancy, affecting 3% to 9% of all pregnancies.¹⁻³ International guidelines recommend that asthma during pregnancy should be managed in the same manner as for nonpregnant women to maintain asthma control.⁴ Nevertheless, a survey revealed that approximately 29% of asthmatic women would discontinue asthma medication during pregnancy, mainly for fear of adverse effects on the fetus,⁵ despite accumulating evidence on the safety of inhaled corticosteroid and β_2 -agonist use during pregnancy.^{4,6} Correspondingly, about one third of the women experienced uncontrolled asthma during pregnancy.⁷

Poorly controlled asthma during pregnancy can deprive the fetus of oxygen and thus affects fetal development negatively.⁸ Studies have linked uncontrolled asthma to preterm birth, low birth weight, and fetal growth restriction,⁹⁻¹¹ which are known risk factors for asthma.¹² Therefore it is likely that uncontrolled asthma during pregnancy can 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.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 can have distinct pathogeneses,¹⁴ and be associated with risk factors differently.^{15,16} For instance, early-onset persistent asthma is more strongly affected by early-life environmental exposure than other phenotypes of asthma.^{15,16}

In the present study we aimed to investigate the association between asthma severity and control during pregnancy and the risk of 3 phenotypes of asthma in the offspring. We hypothesized that children of mothers with uncontrolled asthma had higher asthma risk, in particular early-onset persistent asthma compared with 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

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Abbreviations used

ATC: Anatomical Therapeutic Chemical
 ICD-8: International Classification of Diseases, 8th Revision
 ICD-10: International Classification of Diseases, 10th Edition
 PR: Prevalence ratio

10-digit identifier recorded in the Danish Civil Registration System.¹⁷ 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.¹⁸ We excluded 4,372 children with missing or likely errors in gestational age (<154 or >315 days). Because our outcomes of interest were measured according to asthma treatment at the ages of 0 to 3 and 4 to 6 years, to ensure all children were followed until age 6 years, we excluded a further 11,643 children who emigrated and 3,376 children who died before their 6th birthday (Fig 1). Altogether, 675,379 singletons were included in our analyses.

Maternal asthma history before delivery. We defined maternal asthma as at least 1 inpatient, outpatient, or emergency department visit for asthma before delivery from the Danish National Patient Register.¹⁹ The register contains data on inpatient contacts since 1977 and, from 1995, also emergency department and outpatient treatments. International Classification of Diseases, 8th Revision (ICD-8), codes were used from 1977–1993, and International Classification of Diseases, 10th Edition (ICD-10), codes were used from 1994 and onward. 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 1 antiasthma medication prescription or had 1 or more inpatient, outpatient, or emergency department visit for asthma during the index pregnancy. Pregnancy was counted from the first day of the last menstrual period until delivery. Information on antiasthma medication prescriptions was obtained from the Danish National Prescription Registry,²⁰ 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 antiasthma medication were for inhaled β_2 -agonists (R03AC02-04, R03AC12, and R03AC13), inhaled glucocorticoids (R03BA01, R03BA02, and R03BA05), fixed-dose combination of inhaled β_2 -agonists and glucocorticoids (R03AK06 and R03AK07), 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.^{19,20} We defined asthma severity and control on the basis of the doses of inhaled corticosteroids (in beclomethasone-chlorofluorocarbon equivalents), add-on therapy (theophylline, long-acting β_2 -agonists, and leukotriene receptor antagonists), short-acting β_2 -agonist doses per week, and moderate-to-severe exacerbation (defined as inpatient treatment, emergency department visit for asthma, or a filled prescription of an oral corticosteroid).²¹ The following ATC codes were used: theophylline (R03DA04), long-term acting β_2 -agonists (R03AC12 and R03AC13), short-acting β_2 -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 dose 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 equivalents was calculated according to the equivalency table generated by the Canadian Asthma Consensus Guidelines.²² We created 4 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 (see Table E1 in this article's Online Repository at

www.jacionline.org). The definitions of asthma severity and control have been described in detail elsewhere.²¹

Asthma severity. We defined *mild asthma* as treatment with inhaled glucocorticoid doses of 251 to 500 $\mu\text{g}/\text{d}$ with no add-on therapy or inhaled glucocorticoid doses of 0 to 250 $\mu\text{g}/\text{d}$ regardless of add-on therapy. To be categorized as mild asthma, the following situations were not included: (1) moderate-to-severe exacerbations and 4 to 10 doses of short-acting β_2 -agonists per week or (2) more than 10 doses of short-acting β_2 -agonists per week. We defined *moderate-to-severe asthma* as treatment with inhaled glucocorticoids doses of 251 to 500 $\mu\text{g}/\text{d}$ with add-on therapy or inhaled glucocorticoid doses of greater than 500 $\mu\text{g}/\text{d}$.

Asthma control. Asthmatic mothers were considered as having *controlled asthma* if they had no moderate-to-severe exacerbations and were taking 0 to 3 doses of short-acting β_2 -agonists per week for mild asthma and 10 or less doses of short-acting β_2 -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 to 10 doses of short-acting β_2 -agonists per week or (2) greater than 10 doses of short-acting β_2 -agonists per week.

Childhood asthma in offspring: outcomes of interest

Our outcomes of interest were 3 mutually exclusive phenotypes of asthma in the offspring according to asthma treatment (ie, hospital or antiasthma treatment) during 0 to 3 years and 4 to 6 years based on schema from Martinez et al¹⁴:

1. *early-onset transient asthma*: asthma treatment during 0 to 3 years but no treatment during 4 to 6 years;
2. *early-onset persistent asthma*: asthma treatment during both 0 to 3 years and 4–6 years; and
3. *late-onset asthma*: no asthma treatment during 0 to 3 years but with treatment during 4 to 6 years.

Asthma hospital treatment was defined as having an inpatient, outpatient, or emergency department visit for asthma (ICD-10 codes J45 and J46) retrieved from the Danish National Patient Register. Antiasthma treatment was defined as 2 or more dispensed prescriptions of an antiasthma medication mentioned above within 1 year by using the Danish National Prescription Registry. We defined asthma treatment during age 0 to 3 years as at least 2 prescriptions of an antiasthma medication within 1 year or at least 1 hospital treatment for asthma during 0 to 3 years. We similarly defined asthma treatment during age 4 to 6 years.

Statistical analysis

Statistical analyses were done with SAS 9.4 software (SAS Institute, Cary, NC). We calculated the prevalence of each phenotype of asthma: early-onset transient, early-onset persistent, and late-onset asthma. Because asthma is not a rare outcome, we estimated the prevalence ratio (PR) of each phenotype of asthma and their 95% CIs by using a log-binomial model.²³ The log-binomial method was performed with PROC GENMOD by using binomial distribution and the log link. We specified an initial value of -4 for the intercept. A woman can contribute more than 1 pregnancy to the analysis. We used a robust sandwich variance estimator for correction of SEs to account for the dependence between siblings. A P value of less than .05 (2-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 ≥ 35 years), calendar year of birth (1996–1999, 2000–2003, or 2004–2006), parity (first/second 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.²⁴ Death of a close relative (a child, partner/spouse, a parent, or a sibling) is considered one of the most stressful life

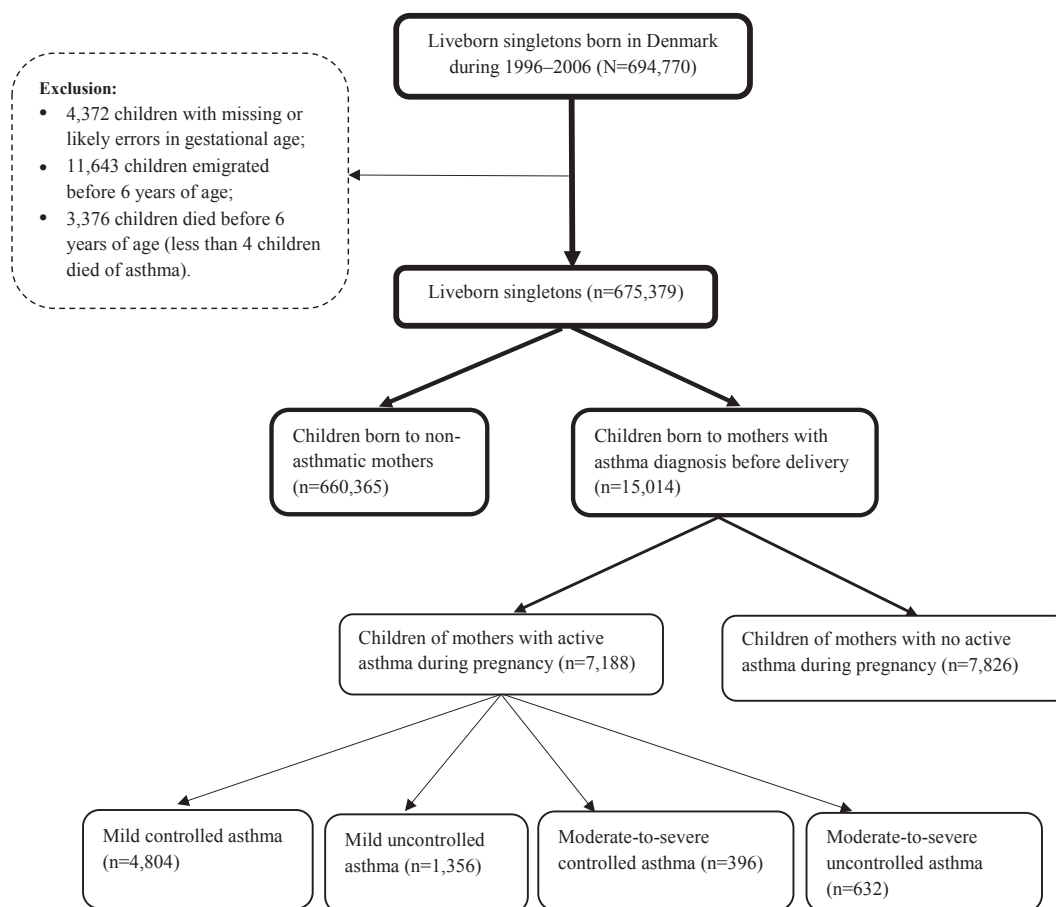


FIG 1. Flow chart illustrating identification of the study population.

events.²⁵ Maternal stress during pregnancy both contributes to maternal active asthma and alters fetal innate and the adaptive immune response, predisposing children to asthma.^{26,27} Therefore we adjusted further for maternal bereavement from 1 year before or during pregnancy (yes/no) retrieved from the Danish Registers of Causes of Death.²⁸

To test whether maternal asthma was associated with an increased prevalence of offspring asthma, we compared the PRs of 3 phenotypes of asthma in children of asthmatic mothers with those in children of non-asthmatic mothers. To examine whether the associations between maternal asthma and offspring asthma was confounded by shared environmental or genetic variables,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 3 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 with those of mothers with mild controlled asthma.

Sensitivity analysis

We implemented 4 sensitivity analyses to test the robustness of our results. First, mothers with no asthma diagnosis but receiving antiasthma treatment might have asthma. Therefore we repeated our analyses by excluding mothers who redeemed any antiasthma prescription before delivery from the non-asthmatic group.

Second, evidence indicates that there might be a sex-specific interplay between the mother, placenta, and fetus.³⁰ To account for 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 reran 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%) were born to asthmatic mothers, among whom 7,188 (1.1%) were born to mothers with active asthma during pregnancy. Asthmatic mothers were younger, more often smoked during pregnancy, and had shorter education than nonasthmatic 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 I).

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

TABLE I. Characteristics of the study population

Characteristics	Nonasthmatic mothers (n = 660,365)	All asthmatic mothers (n = 15,014)	Asthmatic mothers	
			With no active asthma during pregnancy (n = 7,826)	With active asthma during pregnancy (n = 7,188)
Maternal age at delivery (y)				
<25	93,630 (14.2)	3,007 (20.0)	1,868 (23.9)	1,139 (15.8)
25-34	431,573 (65.3)	9,390 (62.6)	4,857 (62.1)	4,533 (63.1)
≥35	135,162 (20.5)	2,617 (17.4)	1,101 (14.1)	1,516 (21.1)
Parity				
1	284,257 (43.0)	6,977 (46.5)	3,806 (48.6)	3,171 (44.1)
≥2	376,108 (57.0)	8,037 (53.5)	4,020 (51.4)	4,017 (55.9)
Maternal smoking during pregnancy	118,988 (18.0)	3,460 (23.0)	1,921 (24.6)	1,539 (21.4)
Maternal bereavement before or during pregnancy				
Yes	18,630 (2.8)	408 (2.7)	206 (2.6)	202 (2.8)
No	641,735 (97.2)	14,606 (97.3)	7,620 (97.4)	6,986 (97.2)
Place of residence at delivery				
Capital or capital suburb	185,935 (28.2)	4,211 (28.1)	2,163 (27.6)	2,048 (28.5)
Provincial city or town	262,150 (39.7)	6,057 (40.3)	3,167 (40.5)	2,890 (40.2)
Rural areas	212,280 (32.1)	4,746 (31.6)	2,496 (31.9)	2,250 (31.3)
Maternal income status				
Lowest quartile	118,748 (18.0)	2,507 (16.7)	1,179 (15.1)	1,328 (18.5)
Greater than lowest quartile	541,617 (82.0)	12,507 (83.3)	6,647 (84.9)	5,860 (81.5)
Maternal education status				
Elementary school	140,148 (21.2)	4,363 (29.1)	2,418 (30.9)	1,945 (27.1)
Greater than elementary school	505,032 (76.5)	10,447 (69.6)	5,314 (67.9)	5,133 (71.4)
Unknown	15,185 (2.3)	204 (1.4)	94 (1.2)	110 (1.5)
Calendar year of birth				
1996-1999	247,246 (37.4)	3,616 (24.1)	1,605 (20.5)	2,011 (28.0)
2000-2003	238,119 (36.1)	5,592 (37.2)	2,948 (37.7)	2,644 (36.8)
2004-2006	175,000 (26.5)	5,806 (38.7)	3,273 (41.8)	2,533 (35.2)
Paternal asthma before delivery	10,072 (1.5)	373 (2.5)	199 (2.5)	174 (2.4)
Sex of the child				
Boys	338,802 (51.3)	7,677 (51.1)	3,996 (51.1)	3,681 (51.2)
Girls	321,563 (48.7)	7,337 (48.9)	3,830 (48.9)	3,507 (48.8)

Values are presented as numbers (percentages).

persistent asthma, and 21,858 (3.2%) as having late-onset asthma. Both maternal and paternal asthma were associated with increased prevalence of 3 phenotypes of asthma, whereas more pronounced associations were observed between maternal asthma and offspring asthma (*P* values for PR differences were less than .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 with nonasthmatic mothers (*P* values for comparing the PR differences between early-onset persistent, early-onset transient, and late-onset asthma were less than .01). Children of asthmatic mothers with no active asthma during pregnancy also had an increased prevalence of 3 phenotypes of asthma, although a more increased prevalence was observed among children of mothers with active asthma during pregnancy (*P* values for PR differences were less than .05, [Table II](#)).

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 with 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 were not associated with offspring late-onset asthma ([Fig 2](#)).

Sensitivity analyses

We excluded 76,542 pregnancies by mothers who redeemed an antiasthma medication prescription but with no asthma diagnosis to ensure not to misclassify asthmatic mothers with no hospital treatment as nonasthmatic mothers. After exclusion, children of 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 with children of nonasthmatic mothers. Associations between the severity and control of maternal asthma and offspring 3 phenotypes of asthma were not modified by the sex of the child (*P* values for interaction were greater than .15, see [Table E2](#) in this article's Online Repository at www.jacionline.org). 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

TABLE II. PRs 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)

Parental asthma	No.	Early-onset transient asthma			Early-onset persistent asthma			Late-onset asthma		
		Cases (%)	Crude PR	Adjusted PR (95% CI)	Cases (%)	Crude PR	Adjusted PR (95% CI)	Cases (%)	Crude PR	Adjusted PR (95% CI)
Nonasthmatic mothers	660,365	54,467 (8.2)	1	1 (reference)	43,610 (6.6)	1	1 (reference)	20,944 (3.2)	1	1 (reference)
Asthmatic mothers	15,014	1,971 (13.1)	1.59	1.42 (1.36-1.48)	2,290 (15.3)	2.31	2.11 (2.03-2.20)	914 (6.1)	1.92	1.89 (1.77-2.02)
With no active asthma	7,826	1,021 (13.0)	1.58	1.36 (1.29-1.45)	1,016 (13.0)	1.97	1.76 (1.66-1.87)	435 (5.6)	1.75	1.72 (1.57-1.88)
With active asthma	7,188	950 (13.2)	1.60	1.49 (1.41-1.58)	1,274 (17.7)	2.68	2.52 (2.39-2.65)	479 (6.7)	2.10	2.08 (1.90-2.27)
Nonasthmatic fathers	664,934	55,254 (8.3)	1	1 (reference)	44,474 (6.7)	1	1 (reference)	21,285 (3.2)	1	1 (reference)
Asthmatic fathers	10,445	1,184 (11.3)	1.36	1.21 (1.15-1.28)	1,426 (13.7)	2.04	1.83 (1.74-1.93)	573 (5.5)	1.71	1.69 (1.55-1.83)

Early-onset transient asthma is defined as asthma treatment during 0 to 3 years but no treatment during 4 to 6 years of age. *Early-onset persistent asthma* is defined as asthma treatment during both 0 to 3 years and 4 to 6 years of age. *Late-onset asthma* is defined as no asthma treatment during 0 to 3 years but with treatment during 4 to 6 years of age. Results are adjusted for maternal age at delivery, parity, smoking during pregnancy, maternal bereavement before 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.

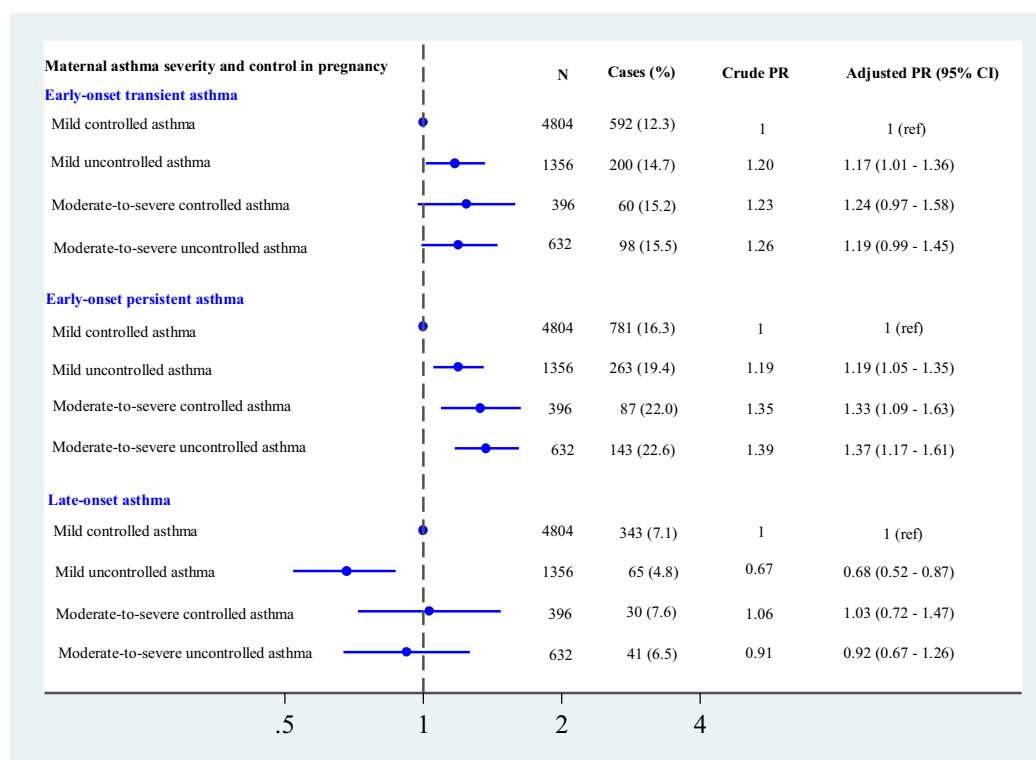


FIG 2. PRs of early-onset transient, early-onset persistent, and late-onset asthma according to maternal asthma severity and control among children of asthmatic mothers with active asthma during pregnancy (n = 7,188). *Early-onset transient asthma* is defined as asthma treatment during 0 to 3 years but no treatment during 4 to 6 years of age. *Early-onset persistent asthma* is defined as asthma treatment during both 0 to 3 years and during 4 to 6 years of age. *Late-onset asthma* is defined as no asthma treatment during 0 to 3 years but with treatment during 4 to 6 years of age. Children of mothers with mild controlled asthma in pregnancy were used as the reference group for estimating the PRs of asthma among children of mothers with mild uncontrolled, moderate-to-severe controlled, and moderate-to-severe uncontrolled asthma in pregnancy. Results are adjusted for maternal age at delivery, parity, smoking during pregnancy, maternal bereavement before or during pregnancy, place of residence at delivery, income status, education status, calendar year of birth, and paternal asthma before delivery.

moderate-to-severe exacerbations, although the association between mild uncontrolled asthma and offspring early-onset persistent asthma was no longer significant (see Fig E1 in this article's Online Repository at www.jacionline.org).

DISCUSSION

In this population-based cohort study we found that children of asthmatic mothers had a higher prevalence of all 3 phenotypes of asthma compared with those of nonasthmatic 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 with children of mothers with mild controlled asthma.

We found increased prevalence of 3 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 been noted frequently.^{15,31-34} In addition to genetic predisposition, 2 lines of evidence suggest that maternal asthma can also affect offspring asthma through environmental exposures. First, we found that maternal asthma conferred a greater risk than paternal asthma, which is consistent with most of the previous observations.^{33,34} Second, adding to this assumption, we observed a higher prevalence of 3 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.^{15,16} Our finding supports the hypothesis that asthma is not a single disorder but consists of several phenotypes that have different associations with risk factors.¹⁴⁻¹⁶

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 1 previous study.¹³ 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 might be a distinct phenotype from controlled asthma and confer different susceptibility to offspring asthma.³⁵ Furthermore, it is known that parental or grandparental asthma might induce epigenetic changes that can be inherited by the next generation, as observed in experimental studies.^{36,37} Epigenetic characteristics and airway inflammation are interrelated.³⁸ 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 might also influence offspring asthma through environmental exposures both *in utero* and during upbringing.

Martinez et al¹⁴ reported that children with early-onset transient and early-onset persistent asthma had reduced lung function. It is possible that uncontrolled asthma might 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.³⁹ 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 might not be mutually exclusive but might coexist. We found that maternal moderate-to-severe asthma, regardless of whether 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 can be subject to intervention, with nonadherence and inhaler misuse being the 2 most common reasons that hinder better asthma control.⁴⁰ It is reported that 24% of women do not take prescribed antiasthma medications during pregnancy,⁴¹ and the frequency of poor inhaler technique ranges from 41% to 54%.⁴² Noncompliance and inhaler misuse can be difficult to detect because they are not routinely evaluated.⁴⁰ Therefore it is 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 effect 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 and thus avoid recall bias. We investigated 3 phenotypes of asthma, which might be more informative for mechanism exploration.

We should account for several methodological features. 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 nonallergic asthma on offspring asthma. Although the definition used in our study has been validated against pulmonary function tests in a previous study,²¹ we might still have misclassified the level of asthma severity and control. It is probable that women with mild uncontrolled asthma comprise a heterogeneous group, and some of them are moderate-to-severe cases. Inversely, because of overtreatment, women classified as having moderate-to-severe controlled asthma might be seen as having mild asthma. 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 offspring was identified by 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 medication prescriptions had been given a diagnosis of asthma. However, it seems the outcome misclassification would be nondifferential and would have biased the findings toward the null.⁴³ Moreover, we determined asthma phenotypes according to asthma treatment during 0 to 3 and 4 to 6 years of age. Some asthmatic children might seek medical treatment at a later stage. Thus we would have misclassified the timing of treatment, leading to misclassification of asthma phenotypes. This misclassification would be nondifferential and bias the PRs of 3 phenotypes toward one another.⁴³

Third, despite the numerous confounders adjusted for in our models, some residual confounding from unmeasured confounders, such as father's smoking, might 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 the 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.

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

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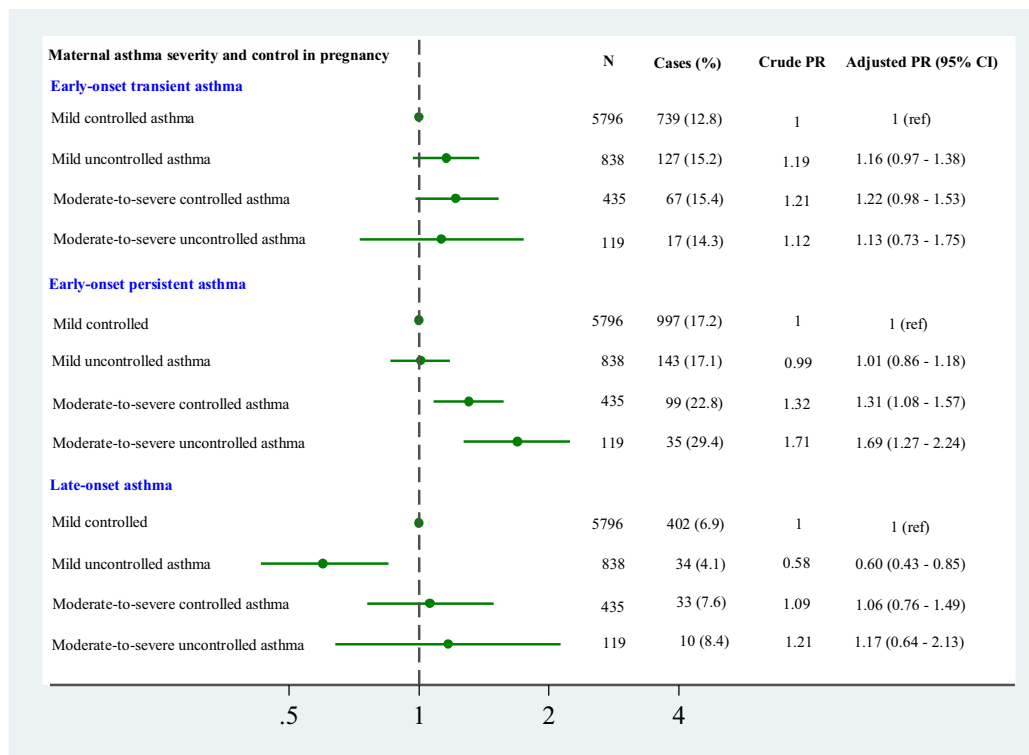


FIG E1. PRs of early-onset transient, early-onset persistent, and late-onset asthma among children of mothers with active asthma during pregnancy according to maternal asthma severity and control by assessing control according to exacerbations solely ($n = 7,188$). *Early-onset transient asthma* is defined as asthma treatment during 0 to 3 years but no treatment during 4 to 6 years of age. *Early-onset persistent asthma* is defined as asthma treatment during both 0 to 3 years and 4 to 6 years of age. *Late-onset asthma* is defined as no asthma treatment during 0 to 3 years but with treatment during 4 to 6 years of age. Children of mothers with mild controlled asthma in pregnancy were used as the reference group for estimating the PRs of asthma among children of mothers with mild uncontrolled, moderate-to-severe controlled, and moderate-to-severe uncontrolled asthma in pregnancy. Results are adjusted for maternal age at delivery, parity, smoking during pregnancy, maternal bereavement before or during pregnancy, place of residence at delivery, income status, education status, calendar year of birth, and paternal asthma before delivery.

TABLE E1. Definition of asthma severity and control during pregnancy based on dispensed antiasthma prescriptions and on use of medical services*

ICS daily doses and add-on therapy during pregnancy	Asthma moderate-to-severe exacerbations and doses of SABA per week during pregnancy					
	No moderate-to-severe exacerbations			With moderate-to-severe exacerbations		
	Zero to 3 doses of SABA per week	Four to 10 doses of SABA per week	More than 10 doses of SABA per week	Zero to 3 doses of SABA per week	Four to 10 doses of SABA per week	More than 10 doses of SABA per week
ICS doses of 0-250 µg/d regardless of add-on therapy	Mild controlled	Mild uncontrolled	Moderate-to-severe uncontrolled	Mild uncontrolled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled
ICS doses of 251-500 µg/d						
With no add-on therapy	Mild controlled	Mild uncontrolled	Moderate-to-severe uncontrolled	Mild uncontrolled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled
With add-on therapy	Moderate-to-severe controlled	Moderate-to-severe controlled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled
ICS doses of >500 µg/d regardless of add-on therapy	Moderate-to-severe controlled	Moderate-to-severe controlled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled	Moderate-to-severe uncontrolled

Add-on therapy was defined as at least 6 prescriptions for theophylline, long-acting β_2 -agonists, or leukotriene receptor antagonists. An asthma moderate-to-severe exacerbation was defined as inpatient treatment, an emergency department visit for asthma, or a filled prescription of an oral corticosteroid.

ICS, Inhaled corticosteroid; SABA, short-acting β_2 -agonist.

*Adapted from Firoozi F, Lemiere C, Beauchesne MF, Forget A, Blais L. Development and validation of database indexes of asthma severity and control. *Thorax* 2007;62:581-7.

TABLE E2. PRs of early-onset transient, early-onset persistent, and late-onset asthma according to maternal asthma severity and control among children of asthmatic mothers with symptoms during pregnancy stratified on sex of the child (n = 7,188)

Control among children of asthmatic mothers with symptoms during pregnancy stratified on sex of the child (N = 7,755)										
Maternal asthma severity and control	No.	Early-onset transient asthma			Early-onset persistent asthma			Late-onset asthma		
		Cases (%)	Crude PR	Adjusted PR (95% CI)	Cases (%)	Crude PR	Adjusted PR (95% CI)	Cases (%)	Crude PR	Adjusted PR (95% CI)
Boys										
Mild controlled	2,468	323 (13.1)	1	1 (Reference)	466 (18.9)	1	1 (Reference)	187 (7.6)	1	1 (Reference)
Mild uncontrolled	682	115 (16.9)	1.29	1.29 (1.06-1.57)	162 (23.8)	1.26	1.26 (1.07-1.48)	34 (5.0)	0.66	0.65 (0.46-0.94)
Moderate-to-severe controlled	205	35 (17.1)	1.30	1.27 (0.93-1.75)	46 (22.4)	1.19	1.18 (0.90-1.54)	20 (9.8)	1.29	1.26 (0.81-1.96)
Moderate-to-severe uncontrolled	326	56 (17.2)	1.31	1.21 (0.93-1.58)	92 (28.2)	1.49	1.47 (1.21-1.79)	21 (6.4)	0.85	0.87 (0.56-1.36)
Girls										
Mild controlled	2,336	269 (11.5)	1	1 (Reference)	315 (13.5)	1	1 (Reference)	156 (6.7)	1	1 (Reference)
Mild uncontrolled	674	85 (12.6)	1.10	1.04 (0.83-1.31)	101 (15.0)	1.11	1.11 (0.90-1.36)	31 (4.6)	0.69	0.73 (0.50-1.06)
Moderate-to-severe controlled	191	25 (13.1)	1.14	1.17 (0.80-1.71)	41 (21.5)	1.59	1.58 (1.18-2.10)	10 (5.2)	0.78	0.75 (0.40-1.40)
Moderate-to-severe uncontrolled	306	42 (13.7)	1.19	1.17 (0.86-1.59)	51 (16.7)	1.24	1.22 (0.93-1.61)	20 (6.5)	0.98	1.00 (0.63-1.58)

Early-onset transient asthma is defined as asthma treatment during 0 to 3 years but no treatment during 4 to 6 years of age. *Early-onset persistent asthma* is defined as asthma treatment during both 0 to 3 years and 4 to 6 years of age. *Late-onset asthma* is defined as no asthma treatment during 0 to 3 years but with treatment during 4 to 6 years of age. Children of mothers with mild controlled asthma in pregnancy were used as the reference group for estimating the PRs 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 before or during pregnancy, place of residence at delivery, income status, education status, calendar year of birth, and paternal asthma before delivery.