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# Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case–control study

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**ABSTRACT: The extent to which childhood asthma incidence is influenced by asthma control and severity during pregnancy is unknown. We have studied this association during the child's first 10 yrs of life.**

**A two-stage, case–control study, nested in a cohort of 8,226 children of asthmatic mothers, was conducted using three interlinked databases of Quebec, Canada, and mailed questionnaires. A total of 2,681 asthmatic children and 30,318 age-matched controls were selected (⩽20 controls·case$^{-1}$; stage 1), and 3,254 selected mothers were mailed questionnaires to obtain additional information (stage 2). Asthma control and severity was defined using validated indexes and childhood asthma incidence based on at least one asthma-related diagnosis and prescription received within 2 yrs. A total of 44 confounders were considered.**

**Compared with children of mild controlled asthmatic mothers, children whose mothers had moderate-to-severe uncontrolled asthma during pregnancy had an increased risk of asthma (adjusted OR 1.27, 95% CI 1.06–1.52). No increased risk was observed for children of mild uncontrolled and moderate-to-severe controlled mothers.**

**Based on one of the largest studies of children of asthmatic mothers, a significant increase in asthma risk was demonstrated among children whose mothers had poor control and increased severity of asthma during pregnancy, indicating that this element should be added to the expanding list of determinants of childhood asthma. As it constitutes a risk factor where pregnant asthmatic females can intervene, it is of great importance for physicians to optimally treat asthmatic females during pregnancy and to encourage females to be adherent to the prescribed asthma medications.**

**KEYWORDS: Administrative health databases, childhood asthma, control, maternal asthma, postal questionnaire, pregnancy**

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In the last decade in Western countries, asthma has been reported to be present in 4–18% of children <10 yrs of age [1–5]. The maternal history of asthma is one of the most studied risk factors for childhood asthma and many studies have defined it as a diagnosis of asthma established at any time during the mother's life [3, 6–8]. Using this definition of maternal asthma, the mother might or might not have had asthma during pregnancy. The monitoring of the asthma status during pregnancy is important, as associations have been reported between the increased asthma severity and/or lack of maternal asthma control during pregnancy and perinatal mortality and low birthweight [9–13], whereas inconsistent associations have also been reported for prematurity and intra-uterine growth restriction [13–16].

Although many studies have investigated the relationship between maternal asthma status in pregnancy and child-related outcomes manifesting themselves soon after birth, to the best of our knowledge, no study has specifically investigated

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whether or not the lack of maternal asthma control during pregnancy would result in an increased risk of childhood asthma. As up to 55% of patients suffering from asthma with moderate-to-severe severity may have experienced asthma exacerbations at least once during pregnancy [17, 18], this could be proposed as an important feature in the development of childhood asthma. Moreover, potential explanatory hypotheses include impaired lung development, which may result from maternal hypoxia occurring among moderate-to-severe asthmatic females experiencing uncontrolled asthma during pregnancy, or may be due to the fact that those females may have characteristics enhancing the propensity of a child to develop a T-lymphocyte helper (Th) type 2-biased immunity [10, 19–28].

Therefore, the present study was conducted in order to evaluate whether or not maternal asthma control and severity during pregnancy, defined through the use of medications and the need for acute care for asthma, were associated with the incidence of asthma in the offspring in the first 10 yrs of life. A unique set-up consisting of several interlinked health administrative databases and a mailed questionnaire allowed for the consideration of a variety of factors that might intervene in the development of asthma in children, along with a wide range of potential confounders related to the child, its mother and family, along with indoor and outdoor environmental characteristics, as well as dispensed medications.

## MATERIALS AND METHODS

### Data sources and study subjects

The present study was conducted using interlinked data from three administrative health databases of the province of Quebec, Canada, namely the Régie de l'assurance-maladie du Québec (RAMQ), MED-ECHO and the Birth and Death Registry, as well as a mailed questionnaire.

From these databases, a cohort of all asthmatic females who had had at least one pregnancy between 1990 and 2002 was formed (see fig. 1 in the online supplementary material). To be considered as having asthma during a pregnancy, a female had to have filed at least one prescription for an asthma medication and to have at least one diagnosis for asthma recorded in the RAMQ or MED-ECHO databases either during the 2 yrs before or during pregnancy [29].

Subsequently, a subcohort of singletons born to females from the cohort was selected. Children were followed from birth until the end of their drug insurance coverage, their 10th birthday or December 31, 2002, whichever occurred first. For females who had more than one delivery between 1990 and 2002, only one child per female was retained in the subcohort in order to limit the correlation between children and to avoid asking a mother to fill in more than one questionnaire. Moreover, to limit the duration of the period for which the information had to be recalled by the mother when answering the questionnaire, the child born closest to 2002 was retained in the subcohort of singletons.

### Study design

A case–control design with a two-stage sampling strategy was used for our study. The first stage of sampling corresponded to a case–control study nested in the subcohort of singletons, while the second stage of sampling corresponded to the sampling of a proportion of cases and controls for whom a questionnaire was mailed to the mother. The second stage was performed because some potential confounding variables, such as parental lifestyle and living environment during and after pregnancy, were not available in the administrative databases. For the second stage, balanced sampling from each cell of the first-stage exposure-outcome cross-table was performed to allow increasing study power by ensuring an over-representation of small cells [30, 31].

### Methods

Operationally and in relation to the first stage of sampling from the subcohort, a child was considered as a case if the subject had received at least one diagnosis of asthma (International Classification of Diseases, version 9: code 493) and a prescription for an asthma medication recorded in the databases within a 2-yr period. Asthma diagnostic codes recorded in the RAMQ Medical Services database and data on medications recorded in the RAMQ Prescriptions database have been previously found to be valid and precise [32, 33]. Per case, $\leqslant$20 controls were selected using density sampling and were matched to cases by their age at diagnosis [34]. For cases, the index date (*i.e.* date of occurrence of asthma) was defined as the later date between the first occurrence of a diagnostic code and a filed prescription for asthma occurring within a 2-yr period. For controls, the index date corresponded to the day the subject was selected, *i.e.* the day that the subject's matched case was identified.

The questionnaire sent as part of the second stage of sampling contained 15 pages, which included a total of 40 questions and was divided into five sections: general information, maternal, paternal and siblings' health, lifestyle habits, environment and child's health. The questionnaire was available in both French and English. In order to increase the questionnaire's response rate, a postal reminder card and a second copy of the questionnaire were sent to the mothers 1 month apart and a 10$CAN compensation was issued to mothers who sent back a completed questionnaire. To ensure the quality of the data, the questionnaire was pre-tested and double-entry of questionnaire information was made by two research assistants in two independent Access databases. Additional details may be found in the article by MARTEL *et al.* [35].

For ethical purposes, mothers of a deceased child, families of deceased mothers, along with mothers whose child did not have the same mailing address, were not eligible for the second stage of the study and, for practical purposes, nor were mothers whose mailing addresses were outside Canada. Approvals from the ethics board of the Hôpital du Sacré-Coeur, Montréal, QC, Canada, and the Commission d'accès à l'information du Québec, Quebec, QC, Canada were obtained prior to proceeding with the study.

#### *Exposure definition*

Maternal asthma control and severity during pregnancy were measured using validated indexes based on the use of medications and acute care for asthma [36], as stated in the definitions of control and severity of the Canadian Asthma Consensus Guidelines [37]. Four categories of exposure were defined using the various combinations of maternal asthma control and severity: mild controlled, mild uncontrolled,

moderate-to-severe controlled and moderate-to-severe uncontrolled. Details of the exposure definitions are available in the online supplementary material.

*Confounding variables*

A total of 44 risk factors for the development of childhood asthma were obtained *via* either the database or the questionnaire and were used as potential confounders in the analyses. They were related to the child's health, maternal socio-demographics, pregnancy, maternal medical conditions, paternal and siblings' health, parental lifestyle and environment. Details on confounding variables can be found in the online supplementary material.

### Statistical analysis

From the subcohort of children, the overall rate of childhood asthma was first estimated. For the first stage of sampling, crude and adjusted rate ratios (RRs) of the association between maternal asthma control and severity during pregnancy and the incidence of childhood asthma were obtained using conditional logistic regression models. All potential confounding variables available from the databases were included in this model and backward selection of variables was used to obtain the final first-stage model [34].

For the second stage of sampling, a logistic regression model was fitted using the subset of cases and controls for whom the questionnaire was completed. Consequently, for these cases and controls, information on confounding variables from the databases and from the questionnaire was available. In order to select the right subset of confounders at the second stage, as the number of potential confounders collected was rather large, a systematic strategy based on backward variable selection was employed (see online supplementary material). To produce the final main estimates, odds ratios (ORs) found at second-stage sampling were then corrected using the sampling fractions and estimates found at the first stage of sampling, according to the technique proposed by COLLET *et al.* [31].

Missing values were present in a low proportion for variables collected in the questionnaire (71% of questionnaire variables had 0–5% of missing values and 29% had 5–13% missing). Details of how missing values were handled are available in the online supplementary material.

Sensitivity analyses were also conducted in our study as follows: 1) Separate analysis of cases and controls who were responders and nonresponders, respectively, to the questionnaire were carried out by including in the regression model variables from the databases only (first stage of sampling), and 2) analysis with cases and controls who had complete information for both the first- and second-stage variables (databases and questionnaire) was also performed.

Confidence intervals at 95% were calculated for RRs and ORs, and all analyses were performed using the SAS 9.1 software package (SAS Institute, Cary, NC, USA).

## RESULTS

A total of 10,512 pregnancies of 8,226 asthmatic mothers were selected from the database (fig. 1 in online supplementary material). A total of 8,226 children were part of the subcohort forming the base of this study, since only one child per mother was to be retained. In this subcohort, the incidence of childhood asthma was 32.6% (95% CI 31.6–33.6%). At the first stage of sampling, a total of 2,681 childhood asthma cases were identified and 30,318 matched controls were selected (fig. 1 in online supplementary material). Table 1 displays the characteristics of those cases and controls, along with crude RRs for the association between variables originating from the three interlinked databases and childhood asthma. Details of multivariate analyses of the first stage of the study are available upon request.

A total of 1,429 of the 3,254 postal questionnaires, mailed as part of the second stage of the study, were received from asthmatic mothers during the 23 weeks allocated to this process. This yielded a response rate of 44% (671 cases and 758 controls). No major disparities were found between responders and nonresponders when comparisons were made on all available database variables (data available upon request). 66 questionnaires had to be discarded as the questionnaires had been filled in for another child of the family. This subsequently provided a total of 1,363 questionnaires suitable for use in the second-stage analysis (639 cases and 724 controls). The characteristics obtained *via* the questionnaire of those cases and controls along with crude ORs for the association between individual potential confounding variables and childhood asthma are displayed in table 2 of the online supplementary material. Crude statistically significant reductions in the risk of childhood asthma were found for breastfeeding, maternal atopy, living in the countryside (farm without farm animals) from birth until the index date, presence of pets at home in pregnancy and from birth until the index date, day-care attendance, presence of a wood-burning fireplace during pregnancy and from birth until the index date, and main type of heating system involving wood in home from birth until the index date. Crude statistically significant increases in the risk of childhood asthma were found for administration of oxygen to the newborn in hospital after birth, diagnosis of a bronchopulmonary disease, allergies developing prior to index date, annual family income on the year of delivery $\leqslant$18,000$CAN, paternal history of asthma, and history of asthma in siblings.

Adjusted ORs for the final estimates, *i.e.* second-stage estimates adjusted for variables obtained from the databases and questionnaire and corrected for sampling fractions, are presented in table 2. The increased risk of childhood asthma found in the first-stage analysis for children of mothers with moderate-to-severe uncontrolled asthma during pregnancy compared with mothers with mild controlled asthma remained statistically significant in the final analysis (adjusted OR 1.27, 95% CI 1.06–1.52). There were also no statistically significant increases in the risk of asthma for children of mothers who had mild uncontrolled asthma and moderate-to-severe controlled asthma during pregnancy. Table 2 also presents variables statistically significantly associated with increases (male sex, previous diagnosis of atopic dermatitis and bronchopulmonary disease, antibiotic prescription between birth and index date or within the first 6 months of life, administration of oxygen to the newborn, mother receiving social welfare, child always living with its mother prior to the index date, antibiotic prescription during pregnancy, paternal and siblings' history of asthma) and reductions (breastfeeding, maternal atopy,

**TABLE 1** Characteristics of asthma cases and matched controls selected in the administrative databases (first stage of sampling)

| | Childhood asthma cases | Controls | Crude RR (95% CI) |
|---|---|---|---|
| **Subjects n** | 2681 | 30318 | |
| **Control and severity of maternal asthma during pregnancy** | | | |
| Mild controlled | 1579 (58.9) | 19081 (62.9) | Reference[#] |
| Mild uncontrolled | 526 (19.6) | 5889 (19.4) | 1.09 (0.98–1.21) |
| Moderate-to-severe controlled | 7 (0.3) | 82 (0.3) | 0.99 (0.45–2.21) |
| Moderate-to-severe uncontrolled | 569 (21.2) | 5266 (17.4) | **1.29 (1.16–1.43)** |
| **Child** | | | |
| Male sex | 1551 (57.9) | 14299 (47.2) | **1.55 (1.42–1.68)** |
| Small for gestational age | 426 (15.9) | 4567 (15.1) | 1.11 (0.97–1.28) |
| Allergic rhinitis | 73 (2.7) | 499 (1.7) | **1.63 (1.25–2.14)** |
| Atopic dermatitis | 246 (9.2) | 2079 (6.9) | **1.44 (1.24–1.67)** |
| ⩾1 antibiotic prescription between birth and index date or within first 6 months of life | 1159 (43.2) | 9928 (32.8) | **1.59 (1.46–1.72)** |
| **Maternal socio-demographics** | | | |
| ⩾35 yrs of age at conception | 176 (6.6) | 2506 (8.3) | **0.75 (0.63–0.88)** |
| Mother receiving social welfare | 2344 (87.4) | 25712 (84.8) | **1.29 (1.13–1.46)** |
| Education | | | |
| Missing | 182 (6.8) | 2050 (6.8) | **1.56 (1.17–2.06)** |
| <12 yrs | 1656 (61.8) | 18300 (60.4) | **1.50 (1.18–1.91)** |
| 12–15 yrs | 763 (28.4) | 8726 (28.8) | **1.47 (1.15–1.88)** |
| >15 yrs | 80 (3.0) | 1242 (4.1) | Reference |
| Living in rural area | 484 (18.1) | 5765 (19.0) | 0.94 (0.84–1.04) |
| **Pregnancy** | | | |
| Pre-natal visits n | | | |
| 0–5 | 402 (15.0) | 4942 (16.3) | 0.91 (0.81–1.03) |
| 6–16 | 2141 (79.9) | 23873 (78.7) | Reference |
| >16 | 138 (5.1) | 1503 (5.0) | 1.09 (0.88–1.34) |
| >1 obstetrician visit during pregnancy | 2243 (83.7) | 25155 (83.0) | 1.03 (0.92–1.16) |
| Mode of delivery | | | |
| Vaginal delivery | 2113 (78.8) | 24439 (80.6) | Reference |
| Unplanned Caesarean section | 289 (10.8) | 3213 (10.6) | 1.01 (0.88–1.15) |
| Planned Caesarean section | 279 (10.4) | 2666 (8.8) | **1.20 (1.05–1.38)** |
| Pregnancy in preceding year | 877 (32.7) | 9576 (31.6) | 1.05 (0.96–1.15) |
| Intra-nasal corticosteroid use | 209 (7.8) | 2291 (7.6) | 1.05 (0.90–1.22) |
| Antibiotic prescriptions filed n | 0.97±1.13 | 0.82±1.05 | **1.13 (1.09–1.17)**[¶] |
| **Maternal medical conditions** | | | |
| Chronic hypertension | 76 (2.8) | 726 (2.4) | 1.10 (0.86–1.42) |
| Pregnancy-induced hypertension | 161 (6.0) | 1881 (6.2) | 0.96 (0.81–1.14) |
| Diabetes mellitus | 72 (2.7) | 733 (2.4) | 1.12 (0.86–1.45) |
| Gestational diabetes | 220 (8.2) | 2484 (8.2) | 1.00 (0.86–1.17) |

Data are presented as n (%) or mean±SD, unless otherwise indicated. RR: rate ratio. [#]: reference category for variables composed of >2 categories; [¶]: RR for each additional prescription. Values in bold are statistically significant. Note: Other asthma-related variables during pregnancy are presented in table 1 of the online supplementary material as additional information. They are features of the definition of maternal asthma control and severity in pregnancy.

day-care attendance, presence of a wood-burning fireplace and presence of pets in the home prior to the index date) in the risk of childhood asthma.

Sensitivity analyses conducted did not sizably modify the results (data available upon request).

## DISCUSSION

The present study showed a statistically significant relationship between the lack of control and increased severity of maternal asthma during pregnancy and the incidence of asthma in offspring. To the best of our knowledge, this is the first study to investigate this association, and the results suggest that, among children who possess a more analogous genetic background in terms of maternal asthma, the incidence of childhood asthma is influenced by the presence or absence of certain familial characteristics or environmental exposures during pregnancy and childhood, as well as the control and severity of their mother's asthma during pregnancy.

**TABLE 2** Risk of incident asthma in children in association with the level of control and severity of maternal asthma during pregnancy

| | Adjusted OR (95% CI) |
|---|---|
| **Control and severity of maternal asthma during pregnancy** | |
| Mild controlled | Reference[#] |
| Mild uncontrolled | 1.04 (0.87–1.25) |
| Moderate-to-severe controlled | 1.43 (0.54–3.74) |
| Moderate-to-severe uncontrolled | 1.27 (1.06–1.52) |
| **Child** | |
| Male sex | 1.50 (1.18–1.91) |
| Atopic dermatitis | 2.05 (1.30–3.24) |
| Antibiotic prescription between birth and index date or within first 6 months of life | 1.71 (1.33–2.20) |
| Breastfeeding | |
| <6 months | 0.60 (0.44–0.80) |
| ⩾6 months | 0.75 (0.54–1.04) |
| Unknown duration | 0.67 (0.33–1.38) |
| No breastfeeding | Reference |
| Administration of $O_2$ to newborn | |
| >24 h in hospital after birth | 1.95 (1.26–3.03) |
| Unknown duration | 1.33 (0.83–2.11) |
| No $O_2$ administration | Reference |
| At least one diagnosis of a bronchopulmonary disease[¶] prior to index date | |
| No | Reference |
| Yes | 2.96 (2.28–3.83) |
| Yes, but at unknown age | 3.25 (2.11–5.01) |
| **Maternal socio-demographics** | |
| Mother receiving social welfare | 1.88 (1.39–2.53) |
| Child always living with mother prior to index date | 2.65 (1.14–6.17) |
| **Pregnancy** | |
| Number of antibiotic prescriptions filed[+] | 1.13 (1.01–1.27) |
| **Maternal health** | |
| Maternal atopy[§] | 0.71 (0.51–0.98) |
| **Siblings' health** | |
| Paternal history of asthma | 1.46 (1.00–2.13) |
| History of asthma in siblings | 1.45 (1.09–1.94) |
| No history of asthma in siblings | Reference |
| No siblings | 0.93 (0.69–1.26) |
| **Environment** | |
| Presence of wood-burning fireplace in home prior to index date | 0.57 (0.40–0.79) |
| Day-care attendance prior to index date | 0.76 (0.60–0.98) |
| Presence of pets at home (>2 months) prior to index date | 0.63 (0.50–0.81) |

Final multivariate analysis: reduced model combining first- and second-stage variables. Adjusted odds ratios (ORs) displayed are adjusted for all other variables presented in the table. [#]: reference category for variables composed of >2 categories; [¶]: wheezing, bronchiolitis, bronchitis or pneumonia; [+]: each additional prescription; [§]: >1 marker for maternal atopy: allergic rhinitis, atopic dermatitis, hay fever or other allergies.

Fetal hypoxia has been put forward as a potential mechanism to explain the link between the lack of maternal asthma control during pregnancy and a child's adverse outcomes. It has been suggested that child development could be altered by fetal hypoxia induced by impairment in maternal oxygenation as a consequence of maternal smoking or maternal asthma exacerbations [10, 20–22]. As expressed by Dombrowski, in pregnancy, ''poor control of asthma leading to chronic or episodic fetal hypoxia is thought to be important'' [20]. As childhood asthma has been associated with an impaired development of the lungs [21, 38, 39], uncontrolled maternal asthma during pregnancy, especially in the course of asthma exacerbations, could trigger a transient but important hypoxic state in the fetus that, by affecting lung development, could subsequently increase the likelihood of the baby to develop asthma during childhood [23].

Conversely, the neonatal T-cell switching between Th1 and Th2 lymphocyte type has been proposed as a mechanism affecting the propensity of children to develop asthma [27, 40]. Environmental triggers, such as maternal allergen exposure or maternal infections during pregnancy, along with maternal

antibodies and intra-uterine cytokine profile, have been suspected to promote the skewing towards the expression of a Th2-type immunity in the fetus [1, 24–28]. In addition, the influence of genetic factors on asthma susceptibility is known to be important [23]. Consequently, and in agreement with a recently proposed hypothesis [19], a pregnant female with uncontrolled and severe asthma during pregnancy might be providing her child with an environment and polymorphisms that could increase the risk of developing asthma.

However, despite the numerous variables considered in our study, some residual confounding may also remain, as it is possible that moderate-to-severe asthmatic mothers may be more knowledgeable of the symptoms of asthma in their children, compared with mild controlled asthmatic mothers and, therefore, might consult their physician more readily. The physician could also be more likely to investigate and diagnose asthma in the child based on the information provided by the mother. If this phenomenon is present, it could tend to increase the OR for the risk of asthma among children whose mothers had moderate-to-severe uncontrolled asthma during pregnancy. This maternal behaviour is difficult to measure, but we assessed whether or not the child was living with their mother prior to the index date and found that if so, this was associated with an increased risk of childhood asthma. However, it did not act as a confounder, but as a predictor of childhood asthma. Furthermore, having siblings with a history of asthma was shown to be a marker of an increased risk of childhood asthma in this study, in accordance with some of the evidence from the literature [8, 41, 42].

All other determinants that were statistically significantly associated with childhood asthma were weak confounders and can be described as risk factors of the outcome studied. Male sex and having previously been diagnosed with atopic dermatitis have long been known as risk factors for childhood asthma [1, 5, 43–47]. Being born in a family with a low socioeconomic status has also been associated with an increased risk of childhood asthma in some studies [23, 48, 49]. The administration of oxygen for at least 24 h after birth can be viewed as a marker of respiratory morbidity after birth and was associated with an increased risk of childhood asthma [7, 50].

Antibiotics prescribed between birth and index date or within the first 6 months of life were proxies for infections occurring shortly after birth [51, 52], and reporting of at least one diagnosis of a bronchopulmonary diseases between birth and the index date was also an indicator of infections occurring over a longer period [7, 8, 42, 44, 45, 53, 54]. However, it is unclear whether the observed associations could be due to the influence of childhood infections on the Th1/Th2 lymphocyte type balance, or to reversed causality, as antibiotics could have been prescribed because of asthma symptoms in a child not yet diagnosed as asthmatic [55]. As in some other studies, the number of maternal antibiotic prescriptions during pregnancy as a proxy for maternal infections was also a strong predictor for childhood asthma [1, 23]. This factor has also been suggested to influence the priming of the child's Th1/Th2 immune profile prior to birth [24]. Interestingly, maternal reports of a physician's diagnosis of at least one atopic condition prior to or during pregnancy were associated with reductions in the risk of childhood asthma. This finding has an opposite direction to what would be expected and a potential explanation might be that this determinant could act as an indicator of maternal behaviour among asthmatic mothers, which would tend to limit exposure to some environmental triggers of atopic manifestations.

In accordance with other previously published studies, other protective determinants of childhood asthma were breastfeeding [48, 54, 56, 57], day-care attendance [46, 54, 58] and pet exposure after birth [5, 44]. These would tend to support the hygiene hypothesis and the role of those factors in the shift toward the expression of a Th1 phenotype. Finally, the presence of a wood-burning fireplace in the child's house prior to the index date was associated with a strong reduction in the risk of childhood asthma. This determinant could act as an indicator of adequate ventilation generated by the presence of a chimney [59], or of reduced exposure to allergens, such as mould, as wood heating could reduce the level of humidity in the household [60], or again, as an indicator of maternal behaviours that would favour a limited exposure to environmental triggers.

It was interesting to note that a usually recognised risk factor, parental cigarette smoking, was not found to be statistically significantly associated with the risk of childhood asthma in the multivariate analyses. Although our study was well powered, crude ORs for maternal and paternal smoking during pregnancy and after the birth of the child were borderline statistically significant. It may be that the population studied by us is relatively homogeneous and does not allow for the distinction of a difference between the high proportion of smokers seen in our study. The high proportion of female smokers seen herein is in accordance with the situation found in Quebec, where females aged 25–44 yrs are those who smoke the most in the population and a high prevalence of smoking has been reported in individuals of lower socioeconomic status [61, 62].

Some potential limitations of our study will also now be discussed. First, no clinical measurements are included in the databases, leaving an unexplored facet of asthma, both in the child and in the mother. However, according to COCKCROFT and SWYSTUN [63], asthma severity is best described by the level of asthma medication required to obtain disease control. This is where a validated definition of asthma severity and control based on medication use established using prescription filings recorded in the RAMQ database becomes a valuable tool to assess the condition of females. These types of databases were shown to reflect the actual intake of prescribed medications [64], to help to prevent recall bias as patients are not required to remember details of the medications they or their child took, and to allow capture of drug history over a long period of time [65]. Furthermore, the definition used in our study has been validated against pulmonary function measures [36]. Nevertheless, misclassification of the exposure to asthma medications may occur, but would presumably underestimate the association of interest, as it is more likely that females who did not use their medications will be classified as exposed if they had filed a prescription, rather than the opposite. Also, the small number of children born to females with moderate-to-severe controlled asthma during pregnancy did not allow for the estimation of a risk estimate as precise as that obtained for children born to

females with mild uncontrolled or moderate-to-severe uncontrolled asthma during pregnancy.

The questionnaire strategy is probably subject to recall bias, but a recent study has demonstrated that even 10–15 yrs after giving birth, mothers could accurately and reliably report perinatal events in which they directly participated [66]. Since the vast majority of children were living with their mother for the period investigated, it is likely that they were closely involved as caregivers. Nevertheless, an imprecise measure of the potential confounders *via* the questionnaire might limit the ability to adjust the main estimates for these confounders. Since most of the effect sizes obtained for the retained questionnaire variables are consistent with the current literature, the magnitude of this phenomenon is likely to be minimal.

Even when a reminder card, a second questionnaire and a financial compensation were sent to mothers, the 44% response rate for the questionnaire was not as high as expected. This has affected the power of the study and, thus, raises the potential of selection bias, as responders could differ from nonresponders. However, the database used at the first stage of our study confers the advantage of providing profuse information on nonresponders. Almost all of the 20 compared variables measured at first stage were found to be distributed similarly between responders and nonresponders, except for social welfare, level of education, area of residence, mode of delivery and pregnancy in the preceding year, for which small differences were observed. Furthermore, sensitivity analyses provided results that were very similar to those from the main analysis. Consequently, selection bias, if present, would have a limited impact on the results obtained.

Our study's great strengths include one of the largest samples of children of asthmatic mothers studied (2,681 cases and 30,318 controls born to asthmatic mothers and 1,363 questionnaire responders) and its particular study design, which allowed the combination of administrative health databases with questionnaire information involving determinants related to the mother, the child and the family, perinatal events, and indoor and outdoor environmental characteristics for the mother during pregnancy and for the child from birth up to their 10th birthday. This led to a study setting that is more representative of ''real life'', as it aimed at considering, within a single statistical analysis, a wide variety of variables believed to intervene in the development of childhood asthma.

Thus, these results obtained from one of the largest studies conducted among children of asthmatic mothers provide evidence of the influence of a lack of control and increased severity of maternal asthma during pregnancy on the incidence of asthma in the offspring and allowed for the isolation of the independent effects of numerous determinants of childhood asthma. Consequently, for children of asthmatic mothers, the control and severity of asthma during pregnancy should be added to the expanding list of potential determinants of childhood asthma. Although the control and severity of maternal asthma did not have the same influence in terms of magnitude as, for example, a previous diagnosis of atopic dermatitis in the child, family history of asthma, oxygen administration in the newborn or breastfeeding, it constitutes a risk factor in which pregnant asthmatic females can intervene, as appropriate use of asthma medications can optimise asthma control. Also, it is of great importance for physicians to adequately treat asthmatic females during pregnancy, not only for the favourable outcome of pregnancy but also for the benefit of the child.

## SUPPORT STATEMENT

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## STATEMENT OF INTEREST

Statements of interest for M-F. Beauchesne and L. Blais can be found at www.erj.ersjournals.com/misc/statements.dtl

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## REFERENCES

1 Xu B, Pekkanen J, Jarvelin MR, *et al.* Maternal infections in pregnancy and the development of asthma among offspring. *Int J Epidemiol* 1999; 28: 723–727.
2 Beasley R, Keil U, Von Mutius E, *et al.* Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; 351: 1225–1232.
3 Litonjua AA, Carey VJ, Burge HA, *et al.* Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998; 158: 176–181.
4 Groupe de travail national sur la lutte contre l'asthme. Prevention et prise en charge de l'asthme au Canada [The National Asthma Control Task Force. The Prevention and management of asthma in Canada: a major challenge now and in the future]. Catalogue no. H49-138/2000E: Ottawa, Public Health Agency of Canada, 2000.
5 Ronmark E, Lundback B, Jonsson E, *et al.* Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in northern Sweden: prevalence rates and risk factor pattern. *Respir Med* 1998; 92: 316–324.
6 Rona RJ, DuranTauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. *J Allergy Clin Immunol* 1997; 99: 454–460.
7 Oliveti JF, Kercsmar CM, Redline S. Pre- and perinatal risk factors for asthma in inner city African-American children. *Am J Epidemiol* 1996; 143: 570–577.
8 Infante-Rivard C, Gautrin D, Malo JL, *et al.* Maternal smoking and childhood asthma. *Am J Epidemiol* 1999; 150: 528–531.

9 Lipkowitz MA, Schatz M, Cook TJ, *et al.* When allergies and asthma complicate pregnancy. *Ann Allergy Asthma Immunol* 1998; 81: 30–34.
10 Schatz M, Dombrowski MP, Wise R, *et al.* The relationship of asthma medication use to perinatal outcomes. *J Allergy Clin Immunol* 2004; 113: 1040–1045.
11 Tan KS, Thomson NC. Asthma in pregnancy. *Am J Med* 2000; 109: 727–733.
12 Passalacqua G, Albano M, Canonica GW, *et al.* Inhaled and nasal corticosteroids: safety aspects. *Allergy* 2000; 55: 16–33.
13 Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006; 61: 169–176.
14 Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. *Chest* 1990; 98: 389–392.
15 Dombrowski M, Schatz M, Wise R, *et al.* Asthma during pregnancy. *Obstet Gynecol* 2004; 103: 5–12.
16 Bakhireva LN, Jones KL, Schatz M, *et al.* Asthma medication use in pregnancy and fetal growth. *J Allergy Clin Immunol* 2005; 116: 503–509.
17 Murphy VE, Gibson P, Talbot PL, *et al.* Severe asthma exacerbations during pregnancy. *Obstet Gynecol* 2005; 106: 1046–1054.
18 Schatz M, Dombrowski MP, Wise R, *et al.* Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003; 112: 283–288.
19 Warner JA. Primary sensitization in infants. *Ann Allergy Asthma Immunol* 1999; 83: 426–430.
20 Dombrowski MP. Chapter 20. The obstetrical management of pregnant asthmatics. *In:* Schatz M, Zeiger RS, Claman HN, eds. Asthma and Immunological Diseases in Pregnancy and Early Infancy. Lung Biology in Health and Disease. New York, Marcel Dekker, 1998; pp. 487-495.
21 Maritz GS, Morley CJ, Harding R. Early developmental origins of impaired lung structure and function. *Early Hum Dev* 2005; 81: 763–771.
22 Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. *Am J Public Health* 2004; 94: 136–140.
23 Bracken MB, Belanger K, Cookson WO, *et al.* Genetic and perinatal risk factors for asthma onset and severity: a review and theoretical analysis. *Epidemiol Rev* 2002; 24: 176–189.
24 Rusconi F, Galassi C, Forastiere F, *et al.* Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. *Am J Respir Crit Care Med* 2007; 175: 16–21.
25 Donovan CE, Finn PW. Immune mechanisms of childhood asthma. *Thorax* 1999; 54: 938–946.
26 Warner JO. The early life origins of asthma and related allergic disorders. *Arch Dis Child* 2004; 89: 97–102.
27 Sears MR. Epidemiology of childhood asthma. *Lancet* 1997; 350: 1015–1020.
28 Bousquet J, Jacot W, Yssel H, *et al.* Epigenetic inheritance of fetal genes in allergic asthma. *Allergy* 2004; 59: 138–147.
29 Martel MJ, Rey É, Beauchesne M-F, *et al.* Use of inhaled corticosteroids during pregnancy and risk of pregnancy-induced hypertension: nested case–control study. *BMJ* 2005; 330: 230–233.
30 Schaubel D, Hanley J, Collet JP, *et al.* Two-stage sampling for etiologic studies. Sample size and power. *Am J Epidemiol* 1997; 146: 450–458.
31 Collet JP, Schaubel D, Hanley J, *et al.* Controlling confounding when studying large pharmacoepidemiologic databases: a case study of the two-stage sampling design. *Epidemiology* 1998; 9: 309–315.
32 Tamblyn R, Lavoie G, Petrella L, *et al.* The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol* 1995; 48: 999–1009.
33 Blais L, Lemière C, Menzies D, *et al.* Validity of asthma diagnoses recorded in the Medical Services database of Quebec. *Pharmacoepidemiol Drug Saf* 2006; 15: 245–252.
34 Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989; 79: 340–349.
35 Martel MJ, Rey E, Malo JL, *et al.* Determinants of the incidence of childhood asthma: two-stage case–control study. *Am J Epidemiol* 2009; 169: 195–205.
36 Firoozi F, Lemière C, Beauchesne M-F, *et al.* Development and validation of database indexes of asthma severity and control. *Thorax*, 2007; 62: 581–587.
37 Boulet LP, Becker A, Berube D, *et al.* Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group. *CMAJ* 1999; 161: Suppl. 11, S1–S61.
38 Stick S. The contribution of airway development to paediatric and adult lung disease. *Thorax* 2000; 55: 587–594.
39 Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung-function in childhood. *BMJ* 1993; 306: 817–820.
40 Holt PG, Sly PD. Allergic respiratory disease: strategic targets for primary prevention during childhood. *Thorax* 1997; 52: 1–4.
41 Ehrlich RI, Du TD, Jordaan E, *et al.* Risk factors for childhood asthma and wheezing. Importance of maternal and household smoking. *Am J Respir Crit Care Med* 1996; 154: 681–688.
42 Infante-Rivard C. Childhood asthma and indoor environmental risk factors. *Am J Epidemiol* 1993; 137: 834–844.
43 Nafstad P, Magnus P, Jaakkola JJ. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *J Allergy Clin Immunol* 2000; 106: 867–873.
44 Hessel PA, Klaver J, Michaelchuk D, *et al.* The epidemiology of childhood asthma in Red Deer and Medicine Hat, Alberta. *Can Respir J* 2001; 8: 139–146.
45 Dik N, Tate RB, Manfreda J, *et al.* Risk of physician-diagnosed asthma in the first 6 years of life. *Chest* 2004; 126: 1147–1153.
46 Oddy WH, Holt PG, Sly PD, *et al.* Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999; 319: 815–819.
47 Xu B, Pekkanen J, Jarvelin MR. Obstetric complications and asthma in childhood. *J Asthma* 2000; 37: 589–594.
48 Lewis S, Richards D, Bynner J, *et al.* Prospective study of risk factors for early and persistent wheezing in childhood. *Eur Respir J* 1995; 8: 349–356.
49 Sin DD, Svenson LW, Cowie RL, *et al.* Can universal access to health care eliminate health inequities between children of poor and nonpoor families? A case study of childhood asthma in Alberta. *Chest* 2003; 124: 51–56.
50 Grischkan J, Storfer-Isser A, Rosen CL, *et al.* Variation in childhood asthma among former preterm infants. *J Pediatr* 2004; 144: 321–326.
51 Von Mutius E, Illi S, Hirsch T, *et al.* Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 1999; 14: 4–11.
52 McKeever TM, Lewis SA, Smith C, *et al.* Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database. *J Allergy Clin Immunol* 2002; 109: 43–50.
53 Raby BA, Celedon JC, Litonjua AA, *et al.* Low-normal gestational age as a predictor of asthma at 6 years of age. *Pediatrics* 2004; 114: e327–e332.
54 Rusconi F, Galassi C, Corbo GM, *et al.* Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. *Am J Respir Crit Care Med* 1999; 160: 1617–1622.
55 Schaub B, Lauener R, Von Mutius E. The many faces of the hygiene hypothesis. *J Allergy Clin Immunol* 2006; 117: 969–977.
56 Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001; 139: 261–266.

**57** Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. *J Allergy Clin Immunol* 2002; 110: 65–67.

**58** Infante-Rivard C, Amre D, Gautrin D, *et al.* Family size, day-care attendance, and breastfeeding in relation to the incidence of childhood asthma. *Am J Epidemiol* 2001; 153: 653–658.

**59** Volkmer RE, Ruffin RE, Wigg NR, *et al.* The prevalence of respiratory symptoms in South-Australian preschool children. 2. Factors associated with indoor air-quality. *J Paediatr Child Health* 1995; 31: 116–120.

**60** Levesque B, Lajoie P, Rhainds M, *et al.* Enquete sociale et de sante de 1998 au Quebec: divers determinants des maladies chroniques respiratoires [1998 Social and Health Survey in Quebec: potential determinants of chronic respiratory diseases]. *Can J Public Health* 2001; 92: 228–232.

**61** Levesque B, Rhainds M, Ernst P, *et al.* Asthma and allergic rhinitis in Quebec children. *Can Respir J* 2004; 11: 343–348.

**62** Institut de la statistique du Québec. Enquête sociale et de santé 1998 [1998 Health and Social Survey]. Québec, Gouvernement du Québec, 2000.

**63** Cockcroft DW, Swystun VA. Asthma control *versus* asthma severity. *J Allergy Clin Immunol* 1996; 98: 1016–1018.

**64** De Jong van den Berg LT, Feenstra N, Sorensen HT, *et al.* Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: pharmacist and mother as sources for drug exposure data during pregnancy. EuroMAP Group. European Medicine and Pregnancy Group. *Teratology* 1999; 60: 33–36.

**65** West SL, Savitz DA, Koch G, *et al.* Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol* 1995; 142: 1103–1112.

**66** Yawn BP, Suman VJ, Jacobsen SJ. Maternal recall of distant pregnancy events. *J Clin Epidemiol* 1998; 51: 399–405.