ERJ Express. Published on June 18, 2009 as doi: 10.1183/09031936.00074608

CONTROL AND SEVERITY OF ASTHMA DURING PREGNANCY ARE ASSOCIATED WITH THE INCIDENCE OF ASTHMA IN THE OFFSPRING: TWO-STAGE CASE-CONTROL STUDY

Original version: May 15, 2008

ERJ007462008R1
Version following second peer-review: February 7, 2009

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Running Title : Asthma control & severity and childhood asthma

Funding :This research was entirely funded by the Canadian Institutes for Health Research and was independent of the funder.

Keywords : Administrative health databases, Childhood asthma, Control, Maternal asthma, Postal questionnaire, Pregnancy.

Text word count: 4033 words

ABSTRACT

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

A two-stage case-control study, nested in a cohort of 8226 children of asthmatic mothers was conducted using 3 interlinked databases of Quebec and mailed questionnaires. 2681 asthmatic children and 30381 age-matched controls were selected (up to 20 controls/case; stage1), and 3254 selected mothers were mailed questionnaires to obtain additional information (stage2). 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 years. 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 (aOR: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 on which pregnant asthmatic women can intervene, it is of great importance for physicians to optimally treat asthmatic women during pregnancy and to encourage women to be adherent to the prescribed asthma medications.

INTRODUCTION

In the last decade in western countries, asthma has been reported to be present in 4 to 18% of children under age 10.[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 since associations have been reported between the increased severity and/or lack of maternal asthma control during pregnancy and perinatal mortality and low birth weight,[9-13] whereas inconsistent associations have also been reported for prematurity and intrauterine 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 whether or not the lack of maternal asthma control during pregnancy would result in an increased risk of childhood asthma. Since up to 55% of patients suffering from asthma with a severity being moderate-to-severe 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 the impaired lung development which may result from maternal hypoxia occurring among moderate-to-severe asthmatic women experiencing uncontrolled asthma during pregnancy, or to the fact those women may have characteristics which enhance the propensity of a child to develop a type 2 T-Lymphocyte helper (Th2) biased immunity.[10;19-28]

Therefore, the present study was conducted in order to evaluate if 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 years of life. A unique setup consisting of several interlinked health administrative databases and a mailed questionnaire allowed for the consideration of a variety of factors, which 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.

MATERIAL AND METHODS

Data Sources and Study Subjects

This 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 women who had at least one pregnancy between 1990 and 2002 was formed (Figure 1, Online Depository). To be considered as having asthma during a pregnancy, a woman had to have filled at least one prescription for an asthma medication and had to have at least one diagnosis for asthma recorded in the RAMQ or MED-ECHO databases either two years before or during pregnancy.[29]

Subsequently, a sub-cohort of singletons born to women from the cohort was selected. Children were followed from birth until their end of drug insurance coverage, their 10th birthday or December 31, 2002, whichever occurred first. For women who had more than one delivery between 1990 and 2002, only one child per woman was retained in the sub-cohort in order to limit the correlation between children and to avoid asking a mother to fill 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 the closest to 2002 was retained in the sub-cohort of singletons.

Study Design

A case-control design with a two-stage sampling strategy was used for this study. The first-stage of sampling corresponded to a case-control study nested in the sub-cohort of singletons, while

the second-stage of sampling corresponded to the sampling of a proportion of cases and controls for which 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 with the first-stage of sampling from the sub-cohort, a child was considered as a case if he/she had received at least one diagnosis of asthma (ICD-9 code: 493) and a prescription for an asthma medication recorded in the databases within a 2-year 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] Up to twenty controls per case were selected using density sampling and were matched to cases on the 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 filled prescription for asthma occurring within a 2-year period. For controls, the index date corresponded to the day he/she was selected, that is the day his/her 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 5 sections: general information, maternal, paternal and siblings' health, lifestyle habits, environment and child's health. The questionnaire was available both in 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 one month apart, and a 10$CAN compensation was issued to women 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 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 Hôpital du Sacré-Coeur's ethics board and the *Commission d'accès à l'information du Québec* were obtained prior to proceeding with the study.

Exposure Definition

Maternal asthma control and severity during pregnancy were measured with 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 on the exposure definition are available in the Online Depository.

Confounding Variables

A total of 44 risk factors for the development of childhood asthma were obtained via 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 Depository.

Statistical Analysis

From the sub-cohort 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 which the questionnaire was completed. Consequently, for these cases and controls, information on confounding variables from the databases and from the questionnaire was available. To select the right subset of confounders at the second-stage, since the number of potential confounders collected was rather large, a systematic strategy based on backward variable selection was employed (please see the Online Depository). To produce the final main estimates, odds ratios (ORs) found at the 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 low proportion for variables collected in the questionnaire (71% of questionnaire variables had between 0% and 5% of missing values and 29%, between 5% and 13%). Details on how missing values were handled are available in the Online Depository.

Sensitivity analyses were also conducted in this study: 1) separate analysis of cases and controls who were respectively responders and non-responders to the questionnaire were carried, by including in the regression models variables from the databases only (first-stage of sampling), and 2) analysis with cases and controls who had complete information both for the first-stage and second-stage variables (databases and questionnaire).

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).

RESULTS

A total of 10 512 pregnancies of 8226 asthmatic mothers were selected from the database (Figure 1, Online Depository). A total of 8226 children were part of the sub-cohort forming the base of this study, since only one child per woman was to be retained. In this sub-cohort, the incidence of childhood asthma was of 32.6% (95%CI: 31.6% - 33.6%). At the first-stage of sampling, a total of 2681 childhood asthma cases were identified and 30 318 matched controls were selected (Figure 1, Online Depository). Table 1 displays the characteristics of those cases and controls, along with crude RRs for the association between variables originating from the 3 interlinked databases and childhood asthma. Details of multivariate analyses of the first-stage of the study are available upon request.

A total of 1429 of the 3254 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 non-responders when comparisons were made on all available database variables (data available upon request). Sixty-six questionnaires had to be discarded as the questionnaires had been filled for another child of the family. This subsequently provided a total of 1363 questionnaires to be used 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 the Online Depository (Table 2). 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, daycare attendance, presence of a wood-burning

fireplace during pregnancy and from birth until the index date, 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 newborn's administration of O2 in hospital after birth, diagnosis of a broncho-pulmonary disease, allergies developing prior index date, annual family income on the year of delivery ≤ 18 000$CAN, paternal history of asthma, and history of asthma in siblings.

Adjusted ORs for the final estimates – 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 to 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 gender, previous diagnosis of atopic dermatitis and broncho-pulmonary disease, antibiotic prescription between birth and index date or within the 6 first months of life, newborn's administration of O_2, mother receiving social welfare, child always living with its mother prior index date, antibiotic prescription during pregnancy, paternal and sibling's history of asthma) and reductions (breastfeeding, maternal atopy, daycare attendance, presence of a wood-burning fireplace and presence of pets in the home prior 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 the 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.

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 an 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 which 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 intrauterine 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 relation with a recently proposed hypothesis,[19] a pregnant woman with uncontrolled and severe asthma during pregnancy might be providing her child with an environment and polymorphisms which could increase the risk of developing asthma.

However, despite the numerous variables considered in this 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 to mild controlled asthmatic mothers, and therefore, might consult more readily their physician. The physician could also be more prone 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 odds ratio for the risk of asthma among children whose mothers had moderate-to-severe uncontrolled asthma during pregnancy. This maternal behavior is difficult to measure, but we assessed whether or not the child was living with his/her mother prior to the index date and found it 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 which were statistically significantly associated with childhood asthma were weak confounders and can be described as risk factors of the outcome studied. Male gender 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 24h 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 broncho-pulmonary diseases between birth and the index date were also indicators 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 antibiotics 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 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 behaviors 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] daycare attendance [46;54;58] and pet exposure after birth.[5;44] Those 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 mold, as wood heating could reduce the level of humidity in the household,[60] or again, as an indicator of maternal behaviors which would favor a limited exposure to environmental triggers.

It was interesting to note that a usually recognized risk factor, parental cigarette smoking, was not found to be statistically significantly associated with the risk of childhood asthma in the multivariate analyses. Although this 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 here is relatively homogeneous and do not allow for the distinction of a difference between the high proportions of smokers seen in this study. The high proportion of female smokers seen here is in accordance with the situation found in Quebec, where women between 25 - 44 years old are those who smoke the most in the population and the high prevalence of smoking has been reported in individuals of lower socio-economic status.[61;62]

Some potential limitations of this study will also be discussed. Firstly, no clinical measurements are included in the databases, leaving an unexplored facet of asthma, both in the child and in the mother. However and according to Cockcroft et al., asthma severity is best described by the level of asthma medication required to obtain disease control.[63] This is where a validated definition of asthma severity and control based on medications' use established using prescriptions fillings recorded in the RAMQ database becomes a valuable tool to assess the condition of women. Those types of databases were shown to reflect the actual intake of prescribed medications,[64]

help to prevent recall bias as patients are not required to remember details of the medications they took or their child took, and allows to capture drug history over a long period of time.[65] Furthermore, the definition used in this 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 women who did not use their medications will be classified as exposed if they had filled a prescription, than the opposite. Also, the small number of children born to women 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 women 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 to 15 years 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 those 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.

The 44% response rate for the questionnaire was not as high as expected, even if a reminder card, a second questionnaire, and a financial compensation were sent to mothers. This has affected the power of the study and thus, raises the potential of a selection bias, as responders could differ from non-responders. However, the database used at the first-stage of the study

confers the advantage of providing profuse information on non-responders. Almost all of the 20 compared variables measured at first-stage were found to be distributed likewise between responders and non-responders, 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.

This study's great strengths include one of the largest sample of children of asthmatic mothers studied (2681 cases and 30 318 controls born to asthmatic mothers and 1363 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 its 10th birthday. This led to a study setting which 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, those 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, O2 administration in the newborn or breastfeeding, it constitutes a risk factor on which pregnant asthmatic women can intervene, as appropriate use of asthma medications can optimise asthma control. Also, it is of great importance for physicians to adequately treat asthmatic women during pregnancy, not only for the favourable outcome of pregnancy on its own but also for the benefit of the child.

Acknowledgements

We thank Mrs Marie-Claude Giguère from the Régie de l'assurance maladie du Québec, Mrs Chantal Girard from the Institut de la statistique du Québec and Mrs Louise Légaré and collaborators from the Ministère de la Santé et des Services sociaux du Québec for assistance with the data. We are grateful to the Commission d'accès à l'information du Québec for authorizing the study. We thank Mrs Karine Chouinard and Mrs Myriam Fortin for data entry and are also grateful to Mrs Chouinard for helping with the logistics of the study. Finally, many thanks to all women who kindly participated in this study by filling out the questionnaire.

Statement of Interest

MJM has received a doctoral research scholarship from the K. M. Hunter Foundation–Canadian Institutes for Health Research. MFB has received grant support from AstraZeneca Canada Inc and GlaxoSmithKline Canada Inc for the conduct of her research projects. She has also received consulting fees from GlaxoSmithKline Canada Inc and speaking fees from GlaxoSmithKline Canada Inc, Boehringer Ingelheim Canada Inc., AstraZeneca Inc, and Pfizer Canada Inc. She co-chairs the Astra-Zeneca Endowment Pharmaceutical Chair in Respiratory Health.. SP is the recipient of a Chercheur Boursier Senior II salary support from the Fonds de la recherche en santé du Québec. LB has done research contracts for AstraZeneca (Canada and US) and Amgen Canada Inc, has received grant support from the Canadian Institutes for Health Research, the Fonds de la recherche en santé du Québec, and the Conseil du medicament du Québec, co-chairs the AstraZeneca Endowment Pharmaceutical Chair in Respiratory Health, and is the recipient of a Chercheur Boursier Junior II salary support from the Fonds de la recherche en santé du Québec.

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Table 1 – Characteristics of asthma cases and matched controls selected in the administrative databases (first-stage of sampling)

	Childhood asthma cases (n= 2 681)	**Controls** (n= 30 318)	**Crude RR** (95%CI)
Control and severity of maternal asthma during pregnancy			
Mild controlled	1 579 (58.9%)	19 081 (62.9%)	reference
Mild uncontrolled	526 (19.6%)	5 889 (19.4%)	1.09 (0.98 ; 1.21)
Moderate-severe controlled	7 (0.3%)	82 (0.3%)	0.99 (0.45 ; 2.21)
Moderate-severe uncontrolled	569 (21.2%)	5 266 (17.4%)	**1.29 (1.16 ; 1.43)**
Child			
Male gender	1 551 (57.9%)	14 299 (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%)	2 079 (6.9%)	**1.44 (1.24 ; 1.67)**
At least 1 antibiotic prescription filled between birth and index date or within the first 6 months of life	1159 (43.2%)	9928 (32.8%)	**1.59 (1.46 ; 1.72)**
Maternal socio-demographics			
≥ 35 years old at conception	176 (6.6%)	2 506 (8.3%)	**0.75 (0.63 ; 0.88)**
Mother receiving social welfare	2 344 (87.4%)	25 712 (84.8%)	**1.29 (1.13 ; 1.46)**
Education			
Missing	182 (6.8%)	2 050 (6.8%)	**1.56 (1.17 ; 2.06)**
< 12 years	1 656 (61.8%)	18 300 (60.4%)	**1.50 (1.18 ; 1.91)**
12-15 years	763 (28.4%)	8 726 (28.8%)	**1.47 (1.15 ; 1.88)**
> 15 years	80 (3.0%)	1 242 (4.1%)	reference
Living in rural area	484 (18.1%)	5 765 (19.0%)	0.94 (0.84 ; 1.04)
Pregnancy			
Number of prenatal visits			
0-5 visits	402 (15.0%)	4 942 (16.3%)	0.91 (0.81 ; 1.03)
6-16 visits	2 141 (79.9%)	23 873 (78.7%)	reference
> 16 visits	138 (5.1%)	1 503 (5.0%)	1.09 (0.88 ; 1.34)
Obstetrician visit during pregnancy (> 1 visit)	2 243 (83.7%)	25 155 (83.0%)	1.03 (0.92 ; 1.16)
Mode of delivery			
Vaginal delivery	2 113 (78.8%)	24 439 (80.6%)	reference
Unplanned caesarean section	289 (10.8%)	3 213 (10.6%)	1.01 (0.88 ; 1.15)
Planned caesarean section	279 (10.4%)	2 666 (8.8%)	**1.20 (1.05 ; 1.38)**
Pregnancy in the preceding year	877 (32.7%)	9 576 (31.6%)	1.05 (0.96 ; 1.15)
Intra-nasal corticosteroids use	209 (7.8%)	2 291 (7.6%)	1.05 (0.90 ; 1.22)
Number of antibiotic prescriptions filled (mean (sd), RR for each additional prescription)	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%)	1 881 (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%)	2 484 (8.2%)	1.00 (0.86 ; 1.17)

RR : rate ratio; sd: standard deviation.

Note: Other asthma-related variables during pregnancy are presented in Table I as additional information. They are features of the definition of maternal asthma control and severity in 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-severe controlled	1.43 (0.54 ; 3.74)
Moderate-severe uncontrolled	1.27 (1.06 ; 1.52)
Child	
Male gender	1.50 (1.18 ; 1.91)
Atopic Dermatitis	2.05 (1.30 ; 3.24)
Antibiotic prescription between birth and index date or within the 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
Newborn's administration of O_2	
> 24h 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 1 diagnosis of a broncho-pulmonary disease prior index date (Wheezing, Bronchiolitis, Bronchitis, Pneumonia)	
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 index date	2.65 (1.14 ; 6.17)
Pregnancy	
Number of antibiotic prescriptions filled (each additional prescription)	1.13 (1.01 ; 1.27)
Maternal health	
Maternal atopy (>1 marker: AR, AD, hay fever or other allergies)	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 index date	0.57 (0.40 ; 0.79)
Daycare attendance prior index date	0.76 (0.60 ; 0.98)
Presence of pets at home (>2months) prior index date	0.63 (0.50 ; 0.81)

Final multivariate analysis, reduced model combining first- and second-stage variables.
Adjusted ORs displayed are adjusted for all other variables presented in the table.
OR: odds ratio, AR: allergic rhinitis, AD: atopic dermatitis

ONLINE DEPOSITORY

Control and severity of asthma during pregnancy are associated with the incidence of asthma in the offspring.

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Databases and Cohort Description

The RAMQ provides information on medical services for all Quebec residents and dispensed medications for Quebec residents covered by governmental insurance (approximately 43 % of Quebec's population, i.e. recipients of social aid and elderly citizens (since 1980) and adherents (since January 1997, those being mainly workers and their families without access to a private drug insurance plan). MED-ECHO provides information on acute care hospitalizations for all Quebec residents.

Details on Exposure Definition

Specifically, maternal asthma control was defined using the weekly doses of inhaled short-acting β_2-agonists consumed, the use of oral corticosteroids and emergency room visits and hospitalizations for asthma during pregnancy. Maternal asthma severity was mainly defined according to the doses of inhaled corticosteroids filled and the use of add-on therapy for asthma (theophylline, long-acting β_2-agonists and leukotriene-receptor antagonists). Details on the definition and related algorithm are available in references 36 and 37.

Confounding Variables

Several risk factors for the development of childhood asthma related to the mother, father, siblings, child, and environment were obtained via the database or the questionnaire, and were used as potential confounders in the analyses.

Maternal Risk Factors

Variables obtained from the database: maternal age at conception (18-34 vs $\geq$ 35 years old), receiving social aid (yes / no), education (< 12, 12-15, > 15 years completed), use of intra-nasal

corticosteroids during pregnancy (yes/no), mean number of antibiotics prescribed per month during pregnancy (continuous), number of prenatal visits (0-5, 6-16, > 16 visits), visit to an obstetrician during pregnancy (yes / no), mode of delivery (vaginal delivery, unplanned caesarean section, planned caesarean section), having a pregnancy in the preceding year (yes / no), chronic hypertension (yes / no), pregnancy-induced hypertension (yes / no), diabetes mellitus (yes / no) and gestational diabetes (yes / no).

Variables obtained from the questionnaire: history of allergy and atopy (including allergic rhinitis, atopic dermatitis, hay fever, and other allergies – (at least 1 marker: yes / no)), maternal weight gain during pregnancy (> 9 kg), smoking during pregnancy (yes / no), breastfeeding duration (< 6 months, ≥ 6 months, unknown duration, no breastfeeding).

Paternal Risk Factors

Variables obtained from the questionnaire: history of asthma (yes / no), history of allergy and atopy (atopic dermatitis, allergic rhinitis, hay fever, other allergies – (at least 1 marker: yes / no)), paternal smoking during pregnancy (yes / no) and from birth until index date (yes / no).

Childhood Risk Factors

Variables obtained from the database: gender (male vs female), being small-for-gestational-age (yes / no), diagnosis of allergic rhinitis (yes / no) or atopic dermatitis (yes / no) prior to the index date, having at least one antibiotic prescription filled prior to the index date or in the first 6 months of life (yes / no).

Variables obtained from the questionnaire: atopy indicators developing prior to the index date (allergies to acetylsalicylic acid, animals, dust mites, hay fever, pollen, other aeroallergens, cutaneous allergies, mold, metal – (yes / no)), diagnosis of a broncho-pulmonary disease (wheezing, bronchiolitis or bronchitis, pneumonia – (at least 1 diagnosis prior to the index date, diagnosis at unknown age, no diagnosis)), newborn's administration of O_2 in hospital after birth (administration for more than 24h, administration of unknown duration, no administration), child's siblings' history of asthma (yes / no / no siblings), child's siblings' history of allergy and atopy (including atopic dermatitis, allergic rhinitis, hay fever, other allergies – (at least 1 marker: yes / no / no siblings)).

Socio-Economic and Environmental Risk Factors

Variables obtained from the questionnaire: annual family income on the year of delivery (≤18 000$CAN, 18 001$CAN-30 000$CAN, ≥ 30 001$CAN), child always living with mother prior index date (yes / no), daycare attendance from birth until index date (yes / no), presence of pets at home at least 2 months during pregnancy (yes / no) and at least 2 months prior to the index date (yes/no), presence of wood-burning fireplace in the house during pregnancy (yes / no) and prior to the index date (yes/no), area of residence during pregnancy (farm with farm animals, farm without farm animals, village or town, no answer) and prior to the index date (farm with farm animals, farm without farm animals, village or town, no answer), main type of heating system used in home during pregnancy (electric, wood, electric and wood, other) and from birth until the index date (electric, wood, electric and wood, other), presence of mold in mother's bedroom during pregnancy (yes / no), and presence of mold in child's bedroom from birth until the index date (yes / no) .

Second-stage analysis variable selection

To select the right subset of confounders at the second-stage, since the number of potential confounders collected was rather large, a systematic strategy was employed: 1) potential confounders associated with childhood asthma in a univariate manner with a p-value of at most 0.20 were retained; 2) two independent models, including variables measured during pregnancy (model 1) and after the birth of the child (model 2), were built and backward selection was used to select two preliminary sets of confounders; and 3) the two reduced models were combined in one final model which was subsequently reduced using backward selection to obtain the reduced second-stage model. As an additional test for confounding, variables eliminated in steps 1 and 2 were individually re-entered in the final model to verify if they could influence the main estimates. Additional details may be found in Reference 35 (Martel et al. Determinants of the incidence of childhood asthma: Two-stage case-control study. Am J Epidemiol 2009;169:195–205).

Missing values

Missing values were handled as follow: 1) for continuous variables, the mean of the values available was calculated for cases and controls separately and was assigned to cases and controls respectively; 2) missing values for categorical variables not involving the estimation of a duration were set to 0; and 3) missing values for categorical variables involving the estimation of a duration were grouped in a separate category labeled “unknown duration”.

Figure 1

Figure Title: Two-stage nested case-control study course

Figure Legend: Description of the two-stage nested case-control study course: 1) a cohort of children of asthmatic mothers was isolated; 2) stage 1: cases and matched controls were selected from the cohort; 3) stage 2: balanced sampling was subsequently performed to obtain a sub-sample of cases and controls to which questionnaires were mailed. Information on the questionnaire response is also provided.

Figure 1 Footnote: In the first-stage of sampling, cases of asthma were identified within the cohort and up to 20 controls were selected among the "riskset" of children at risk of asthma at the occurrence of the case. In stage 2, balanced sampling of cells of the first-stage exposure-outcome cross-table was performed, allowing an over-representation of small cells and an increase in study power. Therefore, in this stage of sampling, the asthma status of the mother and the occurrence of childhood asthma were considered. Random sampling without replacement was used, cases could only contribute as cases to the sampling pool, controls were selected among non-cases at the end of follow-up, and a child could be selected only once as a control. Estimates obtained for maternal asthma in the statistical analyses were corrected using sampling fractions and maternal asthma estimates of the first-stage of the study.

Figure 1

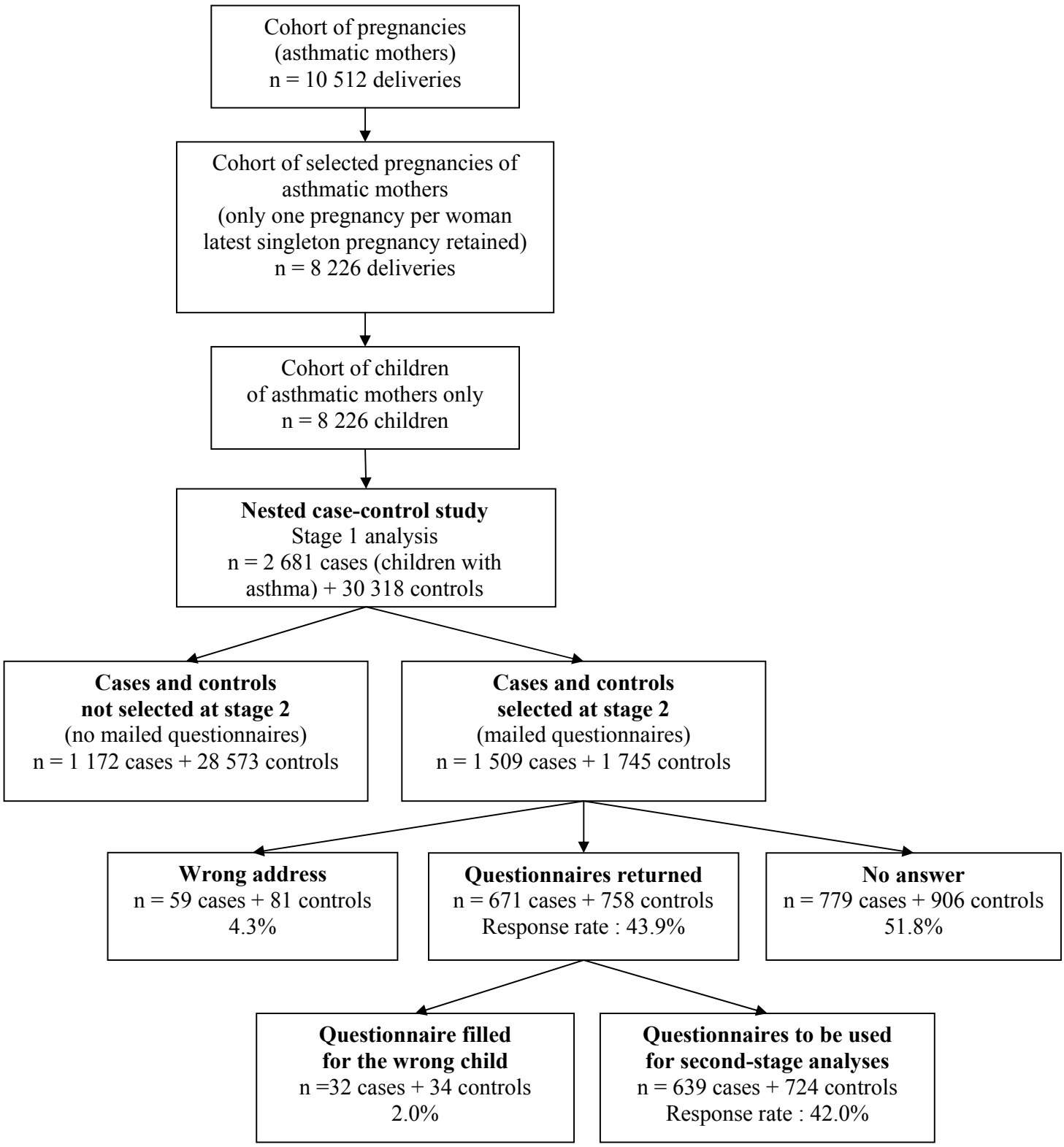
Cohort of pregnancies
(asthmatic mothers)
n = 10 512 deliveries
Cohort of selected pregnancies of asthmatic mothers
(only one pregnancy per woman
latest singleton pregnancy retained)
n = 8 226 deliveries
Cohort of children
of asthmatic mothers only
n = 8 226 children
Nested case-control study
Stage 1 analysis
n = 2 681 cases (children with asthma) + 30 318 controls
Cases and controls not selected at stage 2
(no mailed questionnaires)
n = 1 172 cases + 28 573 controls
Cases and controls selected at stage 2
(mailed questionnaires)
n = 1 509 cases + 1 745 controls
Wrong address
n = 59 cases + 81 controls
4.3%
Questionnaires returned
n = 671 cases + 758 controls
Response rate : 43.9%
No answer
n = 779 cases + 906 controls
51.8%
Questionnaire filled for the wrong child
n =32 cases + 34 controls
2.0%
Questionnaires to be used for second-stage analyses
n = 639 cases + 724 controls
Response rate : 42.0%

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

	Childhood asthma cases (n= 2 681)	**Controls** (n= 30 318)	**Crude RR** (95%CI)
Other asthma-related variables during pregnancy*			
Inhaled corticostroids (dose per day)			
0 µg/day	1 478 (55.1%)	18 208 (60.1%)	reference
1-500 µg/day	1 080 (40.3%)	11 041 (36.4%)	1.21 (1.11 ; 1.32)
501-1000 µg/day	88 (3.3%)	766 (2.5%)	1.39 (1.09 ; 1.76)
> 1000 µg/day	35 (1.3%)	303 (1.0%)	1.21 (0.84 ; 1.76)
Oral corticosteroids (yes/no)	299 (11.2%)	2313 (7.6%)	1.53 (1.34 ; 1.75)
Inhaled short-acting $beta_2$-agonists (>3 doses/wk)	892 (33.3%)	9125 (30.1%)	1.16 (1.07 ; 1.27)
Additional controller therapy (leukotriene-receptor antagonists, long-acting beta2 agonists and theophylline - yes/no).	50 (1.9%)	339 (1.1%)	1.43 (1.04 ; 1.96)
Emergency room visit or hospitalization for asthma (yes/no)	424 (15.8%)	3871 (12.8%)	1.27 (1.13 ; 1.43)
Respiratory specialist visit in pregnancy (>1 visit)	203 (7.6%)	1 885 (6.2%)	1.18 (1.00 ; 1.38)

RR : rate ratio.

* For reference only, as those are features of the definition of maternal asthma control and severity during pregnancy.

Table 2 – Characteristics of asthma cases and matched controls who answered the postal questionnaire (second-stage of sampling).

	Childhood asthma cases (n=639)	**Controls** (n=724)	**Crude OR** (95%CI)
Control and severity of maternal asthma during pregnancy			
Mild controlled	218 (29.3%)	221 (25.3%)	reference
Mild uncontrolled	188 (25.2%)	198 (23.8%)	1.08 (0.97 ; 1.20)
Moderate-severe controlled	2 (0.3%)	12 (1.4%)	1.03 (0.48 ; 2.24)
Moderate-severe uncontrolled	231 (31.0%)	303 (36.4%)	1.31 (1.18 ; 1.44)
Child			
Breastfeeding			
< 6 months	137 (21.4%)	204 (28.2%)	0.59 (0.46 ; 0.77)
≥ 6 months	105 (16.4%)	155 (21.4%)	0.60 (0.49 ; 0.80)
Unknown duration	16 (2.5%)	29 (4.0%)	0.49 (0.26 ; 0.91)
No breastfeeding	381 (59.7%)	336 (46.4%)	reference
Newborn's administration of O2 in hospital			
> 24h after birth	91 (14.2%)	38 (5.3%)	3.15 (2.12 ; 4.68)
Unknown duration	59 (9.2%)	43 (5.9%)	1.80 (1.20 ; 2.72)
No O2 administration after birth	489 (76.6%)	643 (88.8%)	reference
At least 1diagnosis of a broncho-pulmonary disease (Wheezing, Bronchiolitis, Bronchitis, Pneumonia)			
Prior index date	333 (52.1%)	220 (30.4%)	3.10 (2.46 ; 3.92)
At unknown age	81 (12.7%)	43 (5.9%)	3.86 (2.58 ; 5.77)
No diagnosis	225 (35.2%)	461 (63.7%)	reference
Allergies developing prior index date (ASA, animals, dust mites, hay fever, pollen, other aeroallergens, cutaneous allergies, mold, metal)	35 (5.5%)	22 (3.0%)	1.85 (1.07 ; 3.19)
Maternal socio-demographics			
Child always living with mother prior index date	628 (98.3%)	702 (97.0%)	1.79 (0.86 ; 3.72)
Annual family income (year of delivery, in $CAN)			
≤ 18 000$	459 (71.8%)	414 (57.2%)	2.13 (1.52 ; 2.98)
18 001$-30 000$	119 (18.6%)	193 (26.7%)	1.18 (0.81 ; 1.74)
> 30 000$	61 (9.6%)	117 (16.2%)	reference
Maternal health			
Maternal weight gain > 9kg in pregnancy	522 (81.7%)	616 (85.1%)	0.78 (0.59 ; 1.04)
Maternal atopy (>1 marker: AR, AD, hay fever or other allergies)	513 (80.3%)	622 (85.9%)	0.67 (0.50 ; 0.89)
Paternal and siblings' health			
Paternal history of asthma	91 (14.2%)	70 (9.7%)	1.55 (1.11 ; 2.16)
History of asthma in siblings	260 (40.7%)	212 (29.3%)	1.43 (1.11 ; 1.84)
No history of asthma in siblings	220 (34.4%)	256 (35.4%)	reference
No siblings	159 (24.9%)	256 (35.4%)	0.72 (0.55 ; 0.95)
History of atopy in siblings (> 1 marker : AR, AD, hay fever or other allergies)			
Yes	248 (38.8%)	231 (31.9%)	1.13 (0.88 ; 1.45)
No	234 (36.6%)	246 (34.0%)	reference
No siblings	157 (24.6%)	247 (34.1%)	0.67 (0.51 ; 0.87)

OR: odds ratio, AR: allergic rhinitis, AD: atopic dermatitis, ASA: acetylsalicylic acid

Table 2 – Characteristics of asthma cases and matched controls who answered the postal questionnaire (second-stage of sampling) (continued)

	Childhood asthma cases (n=639)	**Controls** (n=724)	**Crude OR** (95%CI)
Parental lifestyle			
Maternal smoking during pregnancy	388 (60.7%)	409 (56.5%)	1.19 (0.96 ; 1.48)
Maternal smoking from birth until the index date	400 (62.6%)	427 (59.0%)	1.16 (0.94 ; 1.45)
Paternal smoking during pregnancy	241 (37.7%)	249 (34.4%)	1.16 (0.93 ; 1.44)
Environment			
Area of residence during pregnancy			
Countryside			
Farm with farm animals	7 (1.1%)	14 (1.9%)	0.54 (0.22 ; 1.35)
Farm without farm animals	122 (19.1%)	153 (21.1%)	0.86 (0.66 ; 1.12)
Village or town	484 (75.7%)	522 (72.1%)	reference
Missing	26 (4.1%)	35 (4.8%)	0.80 (0.48 ; 1.35)
Area of residence from birth until the index date			
Countryside			
Farm with farm animals	11 (1.7%)	22 (3.0%)	0.53 (0.25 ; 1.10)
Farm without farm animals	142 (22.2%)	198 (27.4%)	0.76 (0.59 ; 0.97)
Village or town	460 (72.0%)	484 (66.9%)	reference
Missing	26 (4.1%)	20 (2.8%)	1.37 (0.75 ; 2.48)
Presence of pets at home (>2months) in pregnancy	319 (49.9%)	410 (56.6%)	0.76 (0.62 ; 0.95)
Presence of pets at home (>2months) from birth until the index date	336 (52.6%)	478 (66.0%)	0.57 (0.46 ; 0.71)
Daycare attendance from birth until the index date	268 (41.9%)	385 (53.2%)	0.63 (0.51 ; 0.79)
Presence of wood-burning fireplace in home during pregnancy	88 (13.8%)	154 (21.3%)	0.59 (0.44 ; 0.79)
Presence of wood-burning fireplace in home from birth until the index date	108 (16.9%)	207 (28.6%)	0.51 (0.39 ; 0.66)
Main type of heating system used in home during pregnancy			
Electric	492 (77.0%)	522 (72.1%)	1.09 (0.79 ; 1.49)
Wood	32 (5.0%)	52 (7.2%)	0.71 (0.42 ; 1.20)
Electric and Wood	30 (4.7%)	52 (7.2%)	0.67 (0.39 ; 1.14)
Other	85 (13.3%)	98 (13.5%)	reference
Main type of heating system used in home from birth until the index date			
Electric	491 (76.8%)	497 (68.7%)	1.00 (0.71 ; 1.42)
Wood	23 (3.6%)	49 (6.8%)	0.48 (0.26 ; 0.86)
Electric and Wood	53 (8.3%)	105 (13.5%)	0.51 (0.32 ; 0.81)
Other	72 (11.3%)	73 (10.1%)	reference
Presence of mold in mother's bedroom during pregnancy	63 (9.9%)	77 (10.6%)	0.92 (0.65 ; 1.31)
Presence of mold in child's bedroom from birth until the index date	69 (10.8%)	78 (10.8%)	1.00 (0.71 ; 1.41)

OR: odds ratio, AR: allergic rhinitis, AD: atopic dermatitis