
Risk of perinatal mortality associated with asthma during pregnancy: a 2-stage sampling cohort study

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Background: The association between maternal asthma during pregnancy and perinatal mortality has been investigated in 21 studies, and a significantly increased risk among asthmatic women was found in 4 studies. However, these studies have methodologic limitations, such as lack of adjustment for cigarette smoking, a major risk factor for perinatal mortality.

Objective: To evaluate whether maternal asthma during pregnancy increases the risk of perinatal mortality.

Methods: From the linkage of 3 administrative databases from Québec, Canada, a cohort including 13,100 asthmatic and 28,042 nonasthmatic women who had at least 1 pregnancy between 1990 and 2002 was constructed. We used a 2-stage sampling cohort design to obtain information on cigarette smoking and other potential confounders from the medical records of 1,247 selected mothers.

Results: In the cohort, 353 cases of perinatal mortality were identified, and we were able to retrieve the medical record of the mother for 304 cases. A significantly increased crude risk of perinatal mortality of 34% among asthmatic women compared with nonasthmatic women was found, but the odds ratio did not remain significant after adjustment for placental abruption and cigarette smoking (odds ratio, 1.12; 95% confidence interval, 0.87–1.45).

Conclusion: The risk of perinatal mortality was not found to be significantly associated with maternal asthma after the effect of smoking was removed.

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INTRODUCTION

Asthma is the most prevalent chronic disorder to complicate pregnancy,^{1,2} affecting between 3.4% and 12.4% of pregnant women.^{2–4} Twenty-one studies investigated the effect of asthma on the risk of stillbirth,^{5–14} neonatal mortality,^{5–10,13} and/or perinatal mortality.^{5,9,13,15–25} Four of these 21 studies reported a significantly increased risk of stillbirth, neonatal mortality, and/or perinatal mortality,^{5,13,24,25} and 17 studies found no increased risk for all of these outcomes.^{6–12,14–23} Cigarette smoking is considered an important potential confounder in the association between maternal asthma and the risk of perinatal mortality.²⁶ However, among the 4 positive studies, only 1 reported estimates that were adjusted for cigarette smoking.¹³ Indeed, after adjustment for cigarette smoking, a 52% increased risk of perinatal mortality was reported among asthmatic women who used 3 or more asthma

medications in early pregnancy compared with the general population.¹³ Among the 17 negative studies, only 4 provided measures of association adjusted for cigarette smoking.^{9,10,14,22} However, 3 of these 4 negative studies were underpowered.^{9,10,22}

We recently reported a 30% increased risk of perinatal mortality among 13,100 asthmatic pregnant women compared with 28,142 nonasthmatic pregnant women based on data obtained from the linkage of 3 health administrative databases of Québec, Canada.²⁵ However, these observations were not adjusted or matched for cigarette smoking during pregnancy because this information was not recorded in the administrative databases. Recognizing the role that smoking might play in this association, we performed a new study in which data on cigarette smoking and other potential confounders were retrieved from the mother's medical record and linked to the database cohort to better quantify the effect of maternal asthma on the risk of perinatal mortality.

METHODS

Study Design

The design of this study was a 2-stage sampling cohort (Figure 1).²⁷ The methods for the first stage of sampling have been previously described and are briefly reviewed.²⁵ A cohort of 41,142 singleton pregnancies from asthmatic women (13,100) and nonasthmatic women (28,042) between 13 and 50 years of age at the beginning of pregnancy who had at least 1 delivery (live birth or stillbirth) between 1990 and

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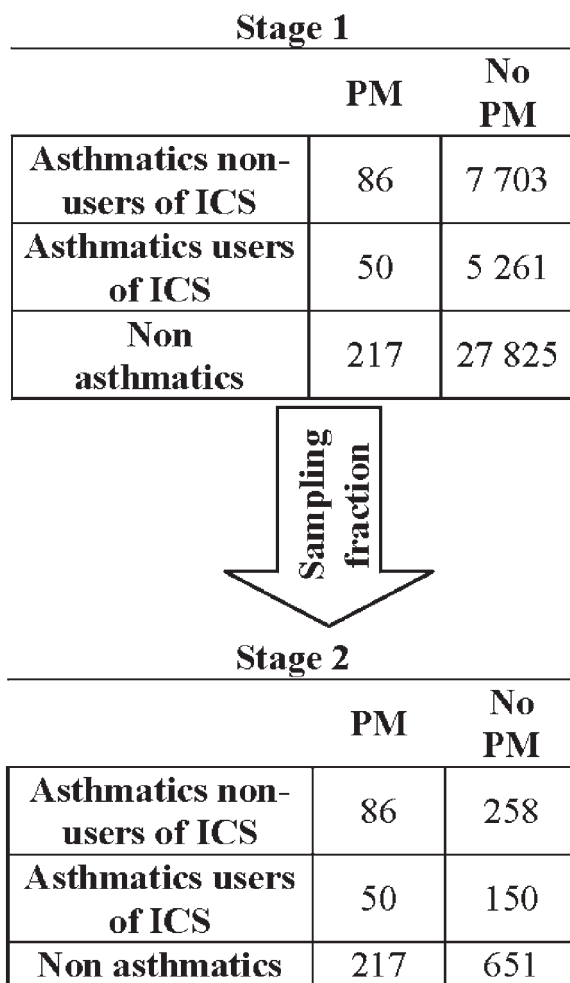


Figure 1. The 2-stage sampling design. ICS indicates inhaled corticosteroid; PM, perinatal mortality.

2002 and were covered by the Quebec's Public Prescription Drug Insurance Plan for at least 1 year before and during pregnancy has been formed through the linkage of 3 administrative databases from Québec, Canada.²⁵ Specifically, the database of the Régie de l'assurance-maladie du Québec (RAMQ) providing medical services and pharmacy claims data, the MED-ECHO hospital database, and the birth and death registries administered by the Institut de la statistique du Québec (ISQ) were linked.

For the second stage of sampling, we used the medical records of a sample of women included in the cohort to collect information on important potential confounding variables not recorded in the administrative databases, such as cigarette smoking, use of illicit drugs, and history of stillbirth. These variables are routinely recorded in the medical record during prenatal visits or at delivery. With the cohort constructed from the linkage of the databases, we identified the main exposure (asthma) and the outcome (perinatal deaths)

and displayed the frequencies in a 3×2 table that contained all the 41,142 pregnancies (Figure 1). The 3 rows represented nonasthmatic women, asthmatic women who did not use inhaled corticosteroids (ICSs) during pregnancy, and asthmatic women who used ICSs during pregnancy. At the second stage of sampling, we sampled from this 3×2 table the mothers from whom we collected confounding variables in the medical record. Sampling fractions were based on cell frequencies, and a computer program was used to generate sampling within each cell. Three of the cells (cases of perinatal mortality) were selected at 100%, whereas only samples of the other cells were selected (3 noncases per case matched for the administrative region of residence of the mother, the average daily dose of ICSs taken during pregnancy [0, <500, or ≥ 500 $\mu\text{g}/\text{d}$], and year of birth of the infant) (Figure 1).

A power calculation was performed before the beginning of the study to estimate the sample size needed. With a ratio of 3 noncases for each case and an α error of .05, we had a statistical power of 81% to detect a relative risk of perinatal mortality of 1.5 comparing asthmatic women with nonasthmatic women.

For the selected pregnancies, the RAMQ provided us the name of the hospital in which the mother gave birth and provided the medical records department of the hospital with the insurance number of the mother and the date of birth of the infant. The data collection in the medical record of the mother was performed by medical archivists, a research nurse, or 1 of the authors (M.-C.B.), and data were recorded on a paper data collection form. A double entry of the information collected in the medical record was performed in 2 Microsoft Access databases. The 2 databases were compared to identify and correct data entry errors.

No consent was needed from the study participant because we did not have access to any information that could identify a participant. An authorization was obtained from the Commission d'Accès à l'information du Québec before retrieving information from medical records and for linking the information from the RAMQ, MED-ÉCHO, ISQ, and medical records. Moreover, this research project was initially approved by the ethics committee and the Direction of Professional Services of the Hôpital du Sacré-Coeur de Montréal and then by all other hospital centers involved.

Main Exposure

The main exposure was maternal asthma. A woman was considered as being asthmatic if she filled at least 1 prescription for an asthma medication and had at least 1 diagnosis of asthma (*International Classification of Diseases, Ninth Revision [ICD-9]* codes 493.0, 493.1, and 493.9) either 2 years before or during pregnancy. Once a woman was identified as having asthma, her status was kept unchanged for all subsequent pregnancies. The medical diagnoses for asthma recorded in the RAMQ medical services database have been formally evaluated and found to be valid.²⁸ A woman was considered as nonasthmatic if she filled no prescription for an

asthma medication and had no asthma diagnosis between 1988 and 2002.

Perinatal Mortality

Perinatal mortality included stillbirth and neonatal mortality.²⁹ Stillbirth was defined as fetal loss beyond 20 weeks of gestation or when birth weight was 500 g or more.³⁰ Stillbirths were identified from the death registry or with ICD-9 codes 656.4, V27.1, V27.3, V27.4, V27.6, V27.7, V32, V35, or V36 recorded in the RAMQ and/or MED-ECHO databases. Neonatal mortality was defined as the death of a liveborn neonate within the first 29 days of life. Deaths occurring within the first 29 days of life were identified from the death registry or the RAMQ database.

Potential Confounding Variables

Retrieved from the administrative databases (first stage of sampling). The variables considered as potential confounders were risk factors of perinatal mortality identified in the literature. Two categories of variables retrieved from the administrative databases were considered as potential confounders. Maternal characteristics included age at the beginning of pregnancy, receipt of social assistance during pregnancy, and level of education attained during the pregnancy. The pregnancy-related variables included parity, pregnancy-induced hypertension, diabetes mellitus, gestational diabetes, placental abruption, infection of the amniotic cavity, and cord around the neck.

Retrieved from the mother's medical record (second stage of sampling). We collected information on cigarette smoking (including women who stopped smoking), use of illicit drugs during pregnancy, and the history of stillbirth in preceding pregnancies.

Statistical Analysis

To evaluate the association between asthma during pregnancy and the risk of perinatal mortality, generalized estimation equations (GEE) models with logistic linkage were used at the first stage of sampling (to adjust for first-stage sampling confounding variables retrieved from administrative databases) because 23% of the women contributed more than 1 pregnancy in the analysis. GEE models were used to take into account the correlation between pregnancies from the same woman and to provide valid variance estimates. Two models were used: (1) a model that included only maternal asthma as the independent variable, providing a crude first-stage odds ratio (OR) for the asthma–perinatal mortality association, and (2) a reduced model that included maternal asthma and first-stage variables that were found to act as confounders, providing a first-stage adjusted OR for the asthma–perinatal mortality association. Confounding variables were identified using a backward selection procedure, starting with a model that included all first-stage potential confounders listed herein.³¹ The reduced model was obtained when no variable can be removed from the model without modifying the OR of maternal asthma by 10% or more.

We then tried to fit a GEE model with the subsample of pregnancies selected at the second stage of sampling, but the GEE model did not converge because the proportion of women with 2 pregnancies or more was too small. The second stage of sampling analysis was thus performed with only 1 pregnancy per woman (more recent pregnancy) using logistic regression models: (1) a model that included only maternal asthma as the independent variable, providing a crude second-stage sampling OR, and (2) a reduced model that included maternal asthma and confounding variables (including those retrieved from the administrative databases and those retrieved from the medical record of the mother) was built, providing an adjusted second-stage OR for the asthma–perinatal mortality association. The backward selection procedure was also used to select the reduced model.

To produce the final crude and adjusted OR estimates for maternal asthma, we corrected the second-stage crude OR and adjusted OR estimates using the second-stage sampling fractions and the crude and adjusted first-stage OR estimates following the method described by Collet et al.²⁷ Analyses were performed with SAS statistical software, version 9 (SAS Institute Inc, Cary, North Carolina).

RESULTS

At the first stage of sampling, the cohort was formed of 13,100 and 28,042 singleton pregnancies from 9,978 asthmatic and 22,622 nonasthmatic women, respectively. The rate of perinatal mortality was 1.04% ($n = 136$) among asthmatic women and 0.77% ($n = 217$) among nonasthmatic women.²⁵

Figure 2 describes the selection process for the second stage of sampling in which we initially selected all cases of perinatal mortality ($n = 353$) and 1,039 matched noncases (for 20 cases only 2 noncases were available) from the cohort. We were not able to retrieve the information on potential confounders from the mothers' medical record for 41 cases of perinatal mortality and 89 noncases (missing data for all variables [$n = 73$] or missing record [$n = 57$]). Because the second-stage models were fitted with only 1 pregnancy per woman, we had to remove from the second-stage analysis an additional 8 cases of perinatal mortality and 7 noncases. The information on potential confounders retrieved from the medical record was thus available for 90% of the pregnancies initially selected for the second stage of sampling.

In Table 1, we present the characteristics of all asthmatic and nonasthmatic pregnant women included in the cohort (first stage of sampling). More asthmatic women were 18 years or younger, received social assistance, and had 11 years or less of education compared with nonasthmatic women. Moreover, we observed that asthmatic women were more likely to have pregnancy-induced hypertension, diabetes mellitus, gestational diabetes, and placental abruption.

Table 2 presents the characteristics retrieved from the medical record of the mother for the women selected at the second stage of sampling. Asthmatic women were more likely to smoke cigarette and use illicit drugs during preg-

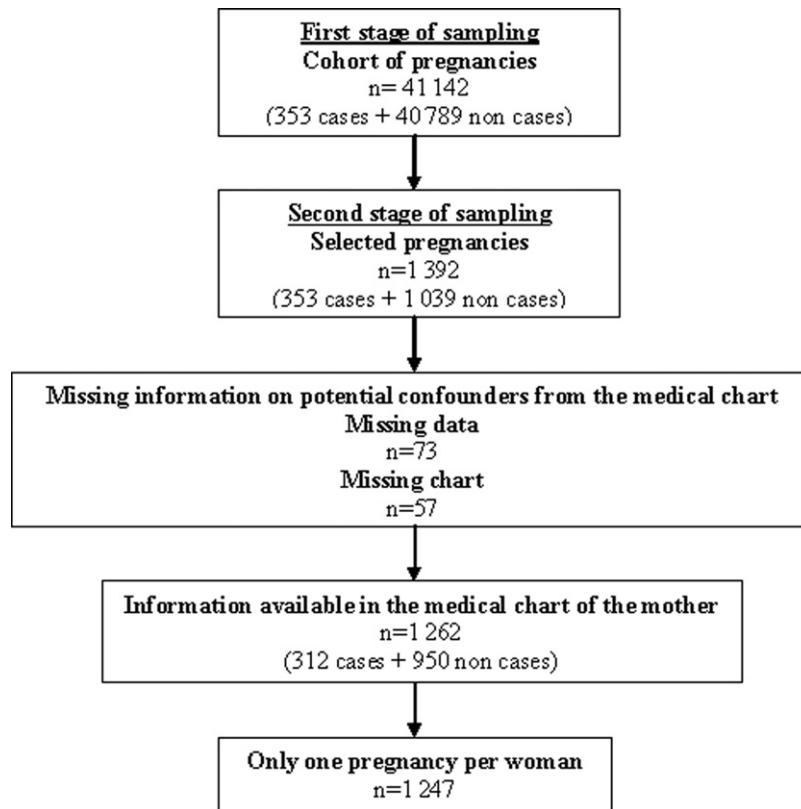


Figure 2. Selection process for the second stage of sampling.

nancy and to have a previous pregnancy with a stillbirth than nonasthmatic women.

In Table 3, we present the first-stage and final estimates of the ORs of perinatal mortality comparing pregnancies from asthmatic and nonasthmatic women. The final crude OR was similar to the one found at the first stage of sampling (OR, 1.34; 95% confidence interval [CI], 1.08–1.66). We observed a statistically significant adjusted increased risk of perinatal mortality among asthmatic women compared with nonasthmatic women (adjusted OR, 1.30; 95% CI, 1.05–1.57) at the first stage of sampling.²⁵ However, the final adjusted OR decreased to 1.12 (95% CI, 0.87–1.45) after adjustment for placental abruption and cigarette smoking (all other covariables did not act as confounders).

DISCUSSION

Final estimates reported in this study showed a significantly increased crude risk of perinatal mortality of 34% among asthmatic women compared with nonasthmatic women, but the OR did not remain significant after adjustment for placental abruption and cigarette smoking (OR, 1.12; 95% CI, 0.87–1.45).

Among the 21 studies on the risk of stillbirth, neonatal mortality, and/or perinatal mortality among asthmatic women,^{5–24} only 1 study reported a significantly increased risk of peri-

natal mortality while adjusting for cigarette smoking^{13,25} and no study adjusted for placental abruption. Indeed, Kallen and Otterblad¹³ reported a 52% significantly increased risk of perinatal mortality in 1,785 asthmatic women who used 3 or more asthma medications in early pregnancy compared with 846,635 pregnant women from the general population.¹³ However, a part of this increased risk could be explained by the use of asthma medication because a significantly increasing trend of perinatal mortality was found with an increased number of antiasthmatic drugs used during pregnancy ($P = .04$) and/or by the severity of asthma (asthmatic women who used 3 or more antiasthmatic drugs had probably more severe asthma). No significant increased risk was found among infants whose mothers used 1 or 2 antiasthmatic medications (OR, 0.90 and 1.10, respectively), and these ORs were comparable to the final OR estimate observed in our study. Our study had not enough statistical power to stratify the analysis by asthma severity or lack of control, but we cannot exclude the possibility that offspring of women with severe or uncontrolled asthma might have been found to be at increased risk of perinatal mortality. Our estimate of the effect of asthma on perinatal mortality is largely based on women with mild asthma because they represent 83% of our cohort. Mild asthma corresponds to ICS doses of less than 500 $\mu\text{g}/\text{d}$ for patients who do not have an additional controller therapy and

Table 1. Characteristics of All Asthmatic and Nonasthmatic Pregnant Women Included in the Cohort (First Stage of Sampling, n = 41,142)

Characteristics	Asthmatic women (n = 13,100), No. (%)	Nonasthmatic women (n = 28,042), No. (%)
Maternal characteristics		
Age, y		
<18	881 (6.7)	994 (3.6)
18–34	11,411 (87.1)	24,353 (86.8)
≥35	808 (6.2)	2,695 (9.6)
Social assistance	10,420 (79.5)	16,091 (57.4)
Years of education		
≤11	7,795 (59.5)	11,816 (42.2)
≥12	4,336 (33.1)	13,925 (49.6)
Missing	969 (7.4)	2,301 (8.2)
Pregnancy-related variables		
First pregnancy	4,190 (32.2)	9,620 (34.6)
Pregnancy-induced hypertension	845 (6.4)	1,440 (5.1)
Diabetes mellitus	309 (2.4)	368 (1.3)
Gestational diabetes	1,008 (7.7)	1,899 (6.8)
Placental abruption	486 (3.7)	844 (3.0)
Infection of amniotic cavity	608 (4.6)	1,407 (5.0)
Cord around neck	2,202 (16.8)	4,990 (17.8)

ICS doses of less than 250 µg/d for patients who have an additional controller therapy.

On the other hand, 4 of the 21 studies reported nonsignificant ORs adjusted for cigarette smoking,^{5,10,14,24} but these results should be interpreted with caution because 3 of these 4 studies were underpowered.^{5,10,24} Tata et al,¹⁴ the only powered study, observed a nonsignificant OR of 1.04 (95% CI, 0.86–1.24) for stillbirth, comparing 37,585 pregnancies of asthmatic women with 243,434 pregnancies of nonasthmatic women.

In our first study on this topic that was based only on the data retrieved from the administrative databases (first stage of sampling) and that resulted in an analysis in which it was not possible to adjust for cigarette smoking, we observed a significantly increased risk of perinatal mortality of 30% among asthmatic women compared with nonasthmatic women.²⁵ However, in the present study, after adjusting for cigarette smoking, the risk of perinatal mortality decreased to 12% and did not remain statistically significant.

A large proportion of smokers was observed among asthmatic women, which could be explained by the fact that asthmatic women tend to be more likely to smoke than nonasthmatic women^{9,25} and that a large proportion of asthmatic women in our cohort had a low socioeconomic status, a characteristic that is associated with high prevalence of smoking.³² We found that smoking during pregnancy was associated with a significantly increased risk of perinatal mortality of 37%. Several studies found that smoking during pregnancy increased the risk of stillbirth, neonatal mortality,

and/or perinatal mortality of 20% to 70%.^{33–38} Surprisingly, the risk of perinatal mortality found among women who had missing information for smoking cigarettes was higher than the risk found among women who reported smoking 1 cigarette or more per day. Missing data on cigarette smoking could be encountered when women with complications during delivery were transferred to another hospital center. In such cases, only parts of the obstetrical medical record of the mother are transferred to the host hospital, and the information regarding cigarette smoking might not have been transferred. We can also hypothesize that the risk of perinatal mortality is higher among transferred women, which would explain the higher OR found among women with missing information on cigarette smoking.

One of the major strengths of our study is the use of a 2-stage sampling design that allowed us to obtain exposure and outcome data for a large cohort of asthmatic and nonasthmatic women and data on a large number of potential confounders through the combination of data recorded in the administrative databases and the medical record of the mother. Another strength is that 99% of the cases of perinatal mortality identified in the cohort based on information recorded in the administrative databases were confirmed by the information recorded in the mother's medical record. Moreover, several variables related to pregnancy recorded in administrative databases in Quebec were considered extremely valid compared with information recorded in the medical record of mothers.³⁹ In addition, asthma medications and medical diagnoses recorded in the administrative databases and used to classify pregnant woman as asthmatic or not were prospectively collected, independently of the outcome. Moreover, the physician-based diagnoses of asthma recorded in the RAMQ databases have been shown to be valid.²⁸ Finally, by collecting the data from the medical record to measure confounders, we avoided recall bias because these data were collected before the outcome of pregnancy was known.

Table 2. Characteristics of Asthmatic and Nonasthmatic Pregnant Women Selected at the Second Stage of Sampling (n = 1,247)

Characteristics	Asthmatic women (n = 491), No. (%)	Nonasthmatic women (n = 756), No. (%)
Cigarette smoking during pregnancy		
Yes	277 (56.4)	249 (32.9)
No	182 (37.1)	457 (60.5)
Missing	32 (6.5)	50 (6.6)
Use of illicit drug during pregnancy		
Yes	31 (6.3)	38 (5.0)
No	405 (82.5)	650 (86.0)
Missing	55 (11.2)	68 (9.0)
Preceding pregnancy with stillbirth		
Yes	23 (4.7)	21 (2.8)
No	434 (88.3)	681 (90.1)
Missing	34 (7.0)	54 (7.1)

Table 3. Adjusted Odds Ratio of Perinatal Mortality Comparing Asthmatic and Nonasthmatic Women

	First stage of sampling		Final estimates	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Asthma (yes/no)	1.35 (1.08–1.67)	1.30 (1.05–1.57)	1.34 (1.08–1.66)	1.12 (0.87–1.45)
Placental abruption (yes/no)	7.33 (5.59–9.62)	7.24 (5.52–9.50)	5.81 (3.74–9.03)	6.05 (3.87–9.45)
Cigarette smoking during pregnancy ^a				
Yes	NA	NA	1.31 (1.00–1.73)	1.37 (1.03–1.83)
No	NA	NA	1 [Reference]	1 [Reference]
Missing	NA	NA	2.39 (1.47–3.87)	2.49 (1.51–4.10)

Abbreviations: CI, confidence interval; OR, odds ratio; NA, not available in the administrative databases for the first stage of sampling.

^a For 304 cases of perinatal mortality and 943 matched noncases, data on cigarette smoking were retrieved from the mothers' medical record.

This study has a few limitations that should be taken into account in the interpretation of the results. Collecting data from medical records led to missing data, but none of the retrieved variables had more than 11% of missing data. Moreover, the information obtained on maternal smoking was self-reported, and we can expect an underreporting because of the known adverse perinatal outcomes associated with smoking during pregnancy (social desirability bias). If present, this bias will tend to underestimate the impact of cigarette smoking on perinatal mortality. In addition, we were not able to adjust for the mother's body mass index because the information to calculate this index was not recorded in the medical record for several women. Because obesity has been shown to be more prevalent among asthmatic women⁴⁰ and obesity has been reported to increase the risk of stillbirth,⁴¹ we could have overestimated the impact of asthma on perinatal mortality. Finally, the cohort was selected from the RAMQ databases, which provide medication information only for welfare recipients and Quebec residents who are covered by the Public Prescription Drug Insurance Plan (residents who have private drug insurance were not included). Our study population is therefore not fully representative of the general population of Québec, and the generalization of our results may be limited to women with lower socioeconomic status.

In summary, the risk of perinatal mortality was not found to be significantly associated with maternal asthma after the effect of cigarette smoking was removed, explaining the results of some previous studies that reported increased risk of perinatal mortality based on estimates unadjusted for cigarette smoking. However, more research is needed to know whether offspring of women with severe or uncontrolled asthma are at increased risk of perinatal mortality.

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1. c
2. a
3. b
4. b
5. c