

Risk of Postpartum Depression Among Women with Asthma



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What is already known about this topic? Several epidemiological studies have suggested that the risk of depression is increased in patients with asthma. The impact of asthma during pregnancy on postpartum depression remains unknown.

What does this article add to our knowledge? In this population-based cohort of 232,577 pregnancies ending in live or still birth, pregnant women with asthma were significantly more likely to develop postpartum depression than women without asthma (adjusted odds ratio, 1.58; 95% CI, 1.50-1.67).

How does this study impact current management guidelines? Asthma is a risk factor of postpartum depression. A close monitoring of signs of depression for pregnant women with asthma is indicated.

BACKGROUND: Several epidemiological studies have suggested that the risk of depression is increased in patients with asthma, but the impact of asthma during pregnancy on postpartum depression remains unknown.

OBJECTIVE: To assess the association between maternal asthma and postpartum depression in a population-based cohort study retrieved from administrative databases.

METHODS: A cohort of 35,520 pregnancies in women with asthma during pregnancy and 197,057 pregnancies in women without asthma who delivered between 1998 and 2009 was extracted from the Quebec Asthma and Pregnancy Database.

They were followed from the day of delivery up to 1 year postpartum. A generalized estimating equation model was used to estimate the adjusted odds ratios of postpartum depression with 95% CIs in women with asthma during pregnancy versus women without asthma.

RESULTS: Postpartum depression within 1 year after delivery occurred in 6.1% of women with asthma versus 2.9% of women without asthma. After adjusting for several potential confounders, including depression/postpartum depression up to 10 years before pregnancy, we found that women with asthma were 58% more likely to experience postpartum depression within 1 year after delivery than women without asthma during pregnancy (adjusted odds ratio, 1.58; 95% CI, 1.50-1.67).

CONCLUSIONS: Our findings suggest that women with asthma are more likely to suffer from postpartum depression. A close monitoring of signs of depression for pregnant women with asthma is indicated, allowing prompt and efficient interventions if needed. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:925-33)

Key words: Asthma; Postpartum depression; Pregnancy; Epidemiology; Quebec Asthma and Pregnancy Database; Maternal asthma

INTRODUCTION

Asthma is one of the most common chronic diseases that can complicate pregnancy.^{1,2} It affects about 3.4% to 12.4% of pregnant women^{3,4} and puts them at increased risk of adverse pregnancy outcomes.^{2,5}

Postpartum depression (PPD) is a nonpsychotic depressive episode that begins after delivery.^{6,7} It is not currently classified as a separate disease; instead, it is included in affective or mood disorders in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and the World Health Organization's *International Classification of Diseases, Tenth Revision (ICD-10)*. Most studies assessed PPD at

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Abbreviations used

ICD- International Classification of Diseases
 ICD-9- International Classification of Diseases, Ninth Revision
 ICD-10- International Classification of Diseases, Tenth Revision
 MED-ECHO- *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière*
 OR- odds ratio
 PPD- *postpartum depression*
 QAPD- *Quebec Asthma and Pregnancy Database*
 RAMQ- *Régie de l'Assurance Maladie du Québec*

1 and 3 months after delivery,⁸⁻¹⁰ but its onset may occur as late as 12 months after delivery.¹¹ It is one of the most common psychological problems in women, with a worldwide prevalence of 6.5% to 12.9%.¹² Also, PPD is associated with impaired cognitive and emotional development of the infant, and the long-term consequences can be substantial.¹³⁻¹⁵

Several epidemiological studies using cross-sectional or retrospective cohort designs have revealed that the risk of depression is increased in patients diagnosed with asthma (women outside of pregnancy and men).¹⁶⁻²³ The largest of these studies was conducted in 57 countries across the 5 continents and included 245,727 women and men 18 years or older.¹⁸ They found that individuals with asthma had higher odds of depression than those without asthma (adjusted odds ratio [OR], 2.37; 95% CI, 2.10-2.66). Despite this well-documented association, we found only 1 previous study that reported data on the association between asthma during pregnancy and PPD. The authors reported an adjusted OR of PPD less than 6 months after delivery of 1.30 (95% CI, 0.98-1.73) comparing women with and without asthma during pregnancy.²⁴ However, that study was primarily designed to explore the impact of the mode and season of delivery on PPD, so maternal asthma was not the main exposure and the confounders considered might not be appropriate to study the association between asthma during pregnancy and PPD.

The purpose of this study was to compare the risk of PPD between women with asthma and those without asthma during pregnancy. We hypothesized that the incidence of women with PPD is higher in women with asthma during pregnancy than in women without asthma.

METHODS

Data sources

The Quebec Asthma and Pregnancy Database (QAPD) has been used to examine the impact of asthma, asthma exacerbations, and asthma medications on congenital malformations.^{25,26} Briefly, it was developed by linking 2 administrative health databases in the province of Quebec (Canada): the Régie de l'Assurance Maladie du Québec (RAMQ) and the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) database. The RAMQ database includes data on medical services provided to all residents of Quebec and data on prescription medications dispensed in community pharmacies for residents covered by RAMQ's Public Drug Insurance Plan, which covers about 42% of all residents in Quebec. This includes welfare recipients, employees

without access to a drug plan from their employer or their partner's employer, and about 90% of individuals 65 years or older. The MED-ECHO database contains data on acute care hospitalizations and covers all Quebec residents.

The QAPD includes all women who delivered in a hospital between January 1, 1990, and March 31, 2010, and who had at least 1 asthma diagnosis recorded in the RAMQ or MED-ECHO database up to 2 years before 1 or more of their deliveries, plus a 4-fold larger random sample of other women who delivered during the same period.²⁵ Data recorded in the provincial databases between January 1988 and March 2010 were obtained for these pregnant women and their newborns. Drug claims data were available for women and newborns covered by RAMQ's Public Drug Insurance Plan only. By using gestational age at birth and the date of birth of the newborns, we retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy using validated algorithms.²⁷

Study design

The design of the study is a population-based cohort study. The cohort was selected from the QAPD on the basis of the following inclusion criteria: (1) deliveries (ie, pregnancies of 20 weeks of gestation or more ending with a live or a stillbirth) in a Quebec hospital between January 1998 and March 2009 (regardless of the woman's drug insurance plan), to ensure they had (a) 1 or more year of follow-up data after delivery and (b) 10 years of data before pregnancy for all women; (2) gestational age between 20 and 45 weeks at delivery; (3) maternal age between 15 and 45 years at the beginning of pregnancy; (4) fulfilling the operational definition of asthma or no asthma between 1988 and delivery; (5) no diagnosis of chronic bronchitis, emphysema, chronic airway obstruction, tuberculosis, bronchiectasis, lung cancer, or cystic fibrosis recorded in the RAMQ or MED-ECHO database up to 2 years before delivery; (6) mother alive on the day after delivery; and (7) information available about the newborn(s) in the RAMQ and MED-ECHO database.

Pregnant women were followed from the day of delivery until the date on which PPD was first diagnosed, death from any cause, the end of the follow-up period (365 days postpartum), the end of the study period (March 31, 2010), or the start of a new pregnancy, whichever came first. It is worth mentioning that pregnancy losses before week 20 were not included in the cohort.

Identification of women with and without asthma

Women with asthma were identified using the following validated operational definition: at least 1 hospitalization with a primary, admission, or secondary diagnosis of asthma (*International Classification of Disease [ICD]* diagnostic codes for asthma: *International Classification of Diseases, Ninth Revision [ICD-9]* code 493, except 493.2; or *ICD-10* code J45) recorded in the MED-ECHO database or at least 2 medical claims for asthma recorded in the RAMQ database within 2 consecutive years between 1988 and delivery. This operational definition had a sensitivity of 80.6% and a specificity of 81.4% for detecting asthma in the Ontario Health Insurance Plan database when compared with diagnoses recorded in the patients' medical chart.²⁸ To confirm that asthma was present during pregnancy, women needed to have at least 1 diagnosis of asthma recorded in the RAMQ or MED-ECHO database within 2 years before delivery. Women without a diagnosis of asthma between 1988 and delivery were included in the group of women without asthma.

Postpartum depression

Because there are no specific diagnoses for PPD, the definition proposed by Statistics Canada was used to identify women with PPD.²⁹ This definition included at least 1 diagnosis of depression based on *ICD* diagnostic codes (*ICD-9* codes 296.2, 296.3, 300.4, and 311; and *ICD-10* codes F32-F33, F34.1, and F38.1) recorded in the RAMQ or MED-ECHO database. The specific definitions of each *ICD-9* and *ICD-10* code are listed in [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org. In addition, the list of diagnoses was verified by a psychologist from the Hôpital du Sacré-Coeur de Montréal. We used 3 different time periods to assess PPD: 1 year postpartum as the primary outcome, and 1 month and 3 months postpartum as secondary outcomes.

Confounding variables

We identified possible risk factors for PPD on the basis of previous reports, and we classified them as either potential mediators (gestational diabetes, preeclampsia, preterm birth, poor fetal growth, low birth weight, etc. Please see [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org for the complete list of mediators) or potential confounders. Only confounders were included in the model to avoid adjusting for mediators, because they are likely to be intermediate variables in the causal pathway between maternal asthma and postpartum depression and therefore likely to bias association estimates toward the null.³⁰ We considered maternal age (15-7, 18-25, 26-35, and 36-45 years),^{24,31-33} area of residence (rural/urban),³⁴ and drug insurance plan (public with social welfare, public without social welfare, and private at the beginning of pregnancy).³⁵ We also considered the following factors occurring up to 10 years before the index pregnancy: previous miscarriage (yes/no),³⁶ history of depression or PPD (yes/no),^{9,37-39} and the occurrence of at least 1 delivery as a proxy of parity (≥ 1 previous pregnancy/no previous pregnancy). Other factors included history of anxiety (yes/no),⁴⁰ other psychiatric disorders (schizophrenia, bipolar, psychotic, and personality disorders; yes/no),^{36,41} diabetes mellitus (yes/no), heart disease (yes/no), epilepsy (yes/no) up to 1 year before the index pregnancy, and the season of delivery (winter, autumn, spring, and summer).²⁴

Statistical analysis

The characteristics of women with and without asthma during pregnancy were compared using proportions. We also compared the proportions of women with PPD between women with and without asthma during pregnancy for each period of time postpartum (ie, 1 month, 3 months, and 1 year postpartum). For the primary prespecified analysis between women with asthma during pregnancy and women without asthma, we used generalized estimating equation models with a logistic link and an exchangeable correlation matrix to estimate the crude and adjusted ORs for PPD, with 95% CI.⁴² Generalized estimating equation models were used to account for the correlation between consecutive pregnancies in individual women⁴³ because women could contribute more than 1 pregnancy. The ORs were adjusted with all the potential confounders listed before. The model was run for each of the 3 periods of time postpartum. Moreover, we conducted 2 sensitivity analyses. First, we estimated the associations between asthma during pregnancy and PPD separately for women with and without a history of depression or PPD up to 10 years before the current pregnancy. For simplicity, these histories will be referred to as history of depression. To test whether history of depression modified the association under study, an interaction term between history of depression and asthma during

pregnancy was added to the model. Second, we estimated the association between asthma during pregnancy and PPD among the subgroup of women free of depression during pregnancy and 10 years before pregnancy. All analyses performed are reported in this article and the 95% CI are 2-sided. All analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC).

Ethics approval

This research project was approved by the Ethics Committee of the Hôpital du Sacré-Coeur de Montréal. Authorization was obtained from the Commission d'Accès à l'Information du Québec before accessing and linking information from the RAMQ and MED-ECHO database.

RESULTS

Of 583,071 pregnancies included in the QAPD, we first selected pregnancies delivered between 1998 and 2009 (52.6%). The eligible study cohort included 232,577 pregnancies, of which 35,520 were in women with asthma and 197,057 were in women without asthma, all of them having reached week 20 of gestation or later ([Figure 1](#)). A total of 63.2% of the 160,838 women contributed 2 pregnancies or more in the cohort. [Table E3](#) in this article's Online Repository at www.jaci-inpractice.org presents the detailed distribution of the number of pregnancies per woman. Ninety-two percent of the women in the cohort had 365 days of follow-up or more.

[Table I](#) presents the characteristics of pregnancies in women with and without asthma during pregnancy. The proportion of women younger than 25 years, residing in an urban area, and having public drug insurance was larger in women with than in women without asthma. The proportions of women with chronic diseases or pregnancy-related disorders were also greater in women with asthma. In addition, we found that the proportions of preterm birth, cesarean delivery, low birth weight, poor fetal growth, or a congenital malformation at delivery were greater in women with asthma.

The crude analyses presented in [Table II](#) indicate that the proportion of women who experienced PPD was 2 times higher in women with asthma than in women without asthma at 1 month (0.8% vs 0.4%), 3 months (2.0% vs 1.0%), and 1 year (6.1% vs 2.9%) postpartum.

When adjusted for all potential confounders, maternal asthma during pregnancy was significantly associated with an increased risk of PPD at 1 year (adjusted OR, 1.58; 95% CI, 1.50-1.67) ([Table III](#)). Furthermore, as shown in [Table IV](#), we found a statistically significant association between maternal asthma and PPD at 1 month (adjusted OR, 1.32; 95% CI, 1.15-1.52) and 3 months (adjusted OR, 1.46; 95% CI, 1.33-1.60) following delivery.

The first set of sensitivity analyses were stratified by the presence or the absence of a history of depression or PPD before the index pregnancy. They revealed that the risk of PPD was significantly higher among women with asthma in both strata, regardless of the period of time in which PPD was measured ([Table IV](#)). However, we observed that the association between asthma and PPD was significantly lower in women with a history of depression than in women without such history for the outcome measured at 3 months and 1 year (*P* value for the interaction term at 1 year <.0001; 3 months .0172; and 1 month .4998). [Table IV](#) also shows that the results were unchanged when we restricted the analysis to women free of

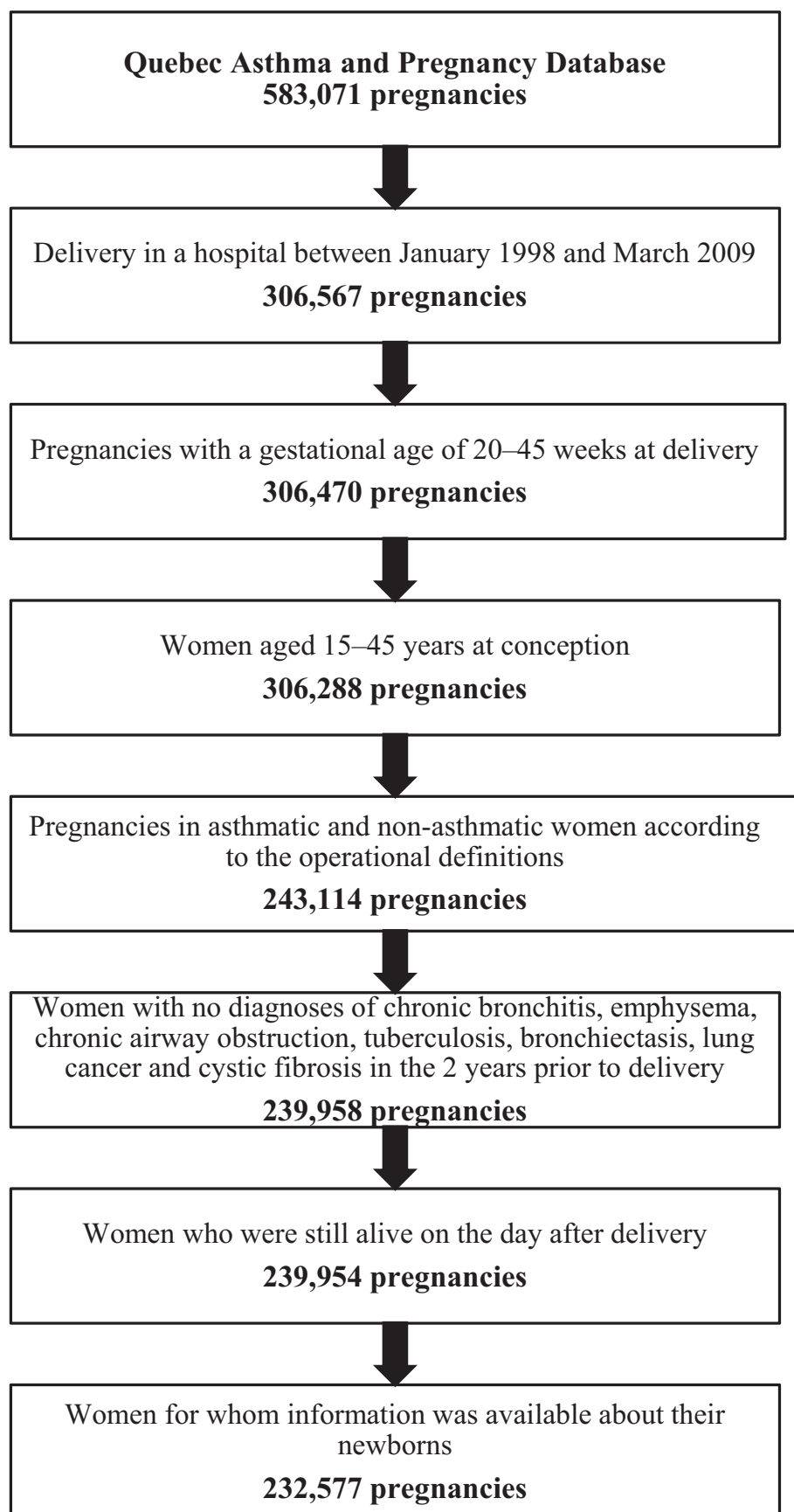
**FIGURE 1.** Flow diagram and selection of eligible pregnancies.

TABLE I. Characteristics of women with and without asthma

Characteristic	Women with asthma (no. of pregnancies = 35,520), n (%)	Women without asthma (no. of pregnancies = 197,057), n (%)	P value
At conception			
Maternal age (y)			<.001
<18	957 (2.7)	2,701 (1.4)	
18-25	12,974 (36.5)	56,883 (28.8)	
26-35	19,095 (53.8)	120,327 (61.1)	
36-45	2,494 (7.0)	17,146 (8.7)	
Urban residential area	29,792 (83.9)	161,219 (81.8)	<.0001
Drug insurance type			<.0001
Public with social welfare	5,562 (15.7)	15,888 (8.1)	
Public without social welfare	8,142 (22.9)	43,786 (22.2)	
Private	21,816 (61.4)	137,383 (69.7)	
Up to 1 y before the index pregnancy			
Heart disease	532 (1.5)	1,505 (0.8)	<.0001
Epilepsy	177 (0.5)	484 (0.3)	<.0001
Diabetes mellitus	580 (1.6)	2,079 (1.1)	<.0001
Anxiety	3,248 (9.1)	10,086 (5.1)	<.0001
Other psychiatric disorders*	697 (2.0)	1,156 (0.6)	<.0001
Up to 10 y before the index pregnancy			
Miscarriage	8,528 (24.0)	38,816 (19.7)	<.0001
Depression or PPD	5,449 (15.3)	14,472 (7.3)	<.0001
At least 1 delivery	8,428 (23.7)	65,442 (33.2)	<.0001
Maternal disorders during pregnancy			
Depression	950 (2.7)	2,401 (1.2)	<.0001
Anxiety	1,796 (5.1)	5,630 (2.9)	<.0001
Anemia	959 (2.7)	4,012 (2.0)	<.0001
Gestational diabetes	2,678 (7.5)	10,618 (5.4)	<.0001
Preeclampsia	1,165 (3.3)	4,489 (2.3)	<.0001
Hyperemesis gravidarum	465 (1.3)	1,377 (0.7)	<.0001
Delivery characteristics			
Preterm birth (before week 37 of gestation)	3,269 (9.2)	13,711 (7.0)	<.0001
Mode of delivery during current pregnancy			<.0001
Cesarean delivery	5,977 (16.8)	28,154 (14.3)	
Vaginal delivery	20,837 (58.7)	121,396 (61.6)	
Unknown	8,706 (24.5)	47,507 (24.1)	
Season of delivery			.0182
Winter	8,960 (25.2)	49,400 (25.1)	
Spring	8,967 (25.2)	50,815 (25.8)	
Summer	9,009 (25.4)	50,510 (25.6)	
Autumn	8,584 (24.2)	46,332 (23.5)	
Fetal/infant characteristics			
Low birth weight (≤ 2500 g)	2,415 (6.8)	9,248 (4.7)	<.0001
Poor fetal growth during pregnancy†	1,028 (2.9)	4,183 (2.1)	<.0001
Stillbirth (fetal loss at week 20 or later)	150 (0.4)	773 (0.4)	.4074
Any congenital malformation at delivery	3,716 (10.5)	18,722 (9.5)	<.0001

*Psychiatric disorders include schizophrenia and bipolar, psychotic, and personality disorders.

†Poor fetal growth during pregnancy was defined using the ICD diagnostic codes (ICD-9 code 656.5 and ICD-10 code O36.5).

depression during pregnancy and in the 10 years before pregnancy (second sensitivity analysis).

DISCUSSION

Women with asthma during pregnancy were found to be more at risk of developing PPD at 1 month (OR, 1.32), 3

months (OR, 1.46), and 1 year (OR, 1.58) postpartum, after adjusting for several potential confounders including history of depression or PPD up to 10 years before the index pregnancy. Our results indicate that this association was also present in women without depression before and during pregnancy, confirming that the diagnosis of PPD was not the continuation of a depression present before delivery. We also observed a

TABLE II. Proportions of women with PPD at different time points

Time point	Women with asthma during pregnancy (n = 35,520), n (%)	Women without asthma during pregnancy (n = 197,057), n (%)	P value
1 mo postpartum	297 (0.8)	839 (0.4)	<.0001
3 mo postpartum	721 (2.0)	1,917 (1.0)	<.0001
1 year postpartum	2,150 (6.1)	5,738 (2.9)	<.0001

stronger association among women without a history of depression compared with women with a history of depression. To our knowledge, this is the first study to assess the association between maternal asthma and PPD as the primary objective. A previous case-control study based on Taiwanese administrative databases also reported data on this association, but as mentioned before, maternal asthma was included only as a potential confounder.²⁴ The study included 2107 women with PPD and 8428 women without PPD included in the databases between 2003 and 2006. The authors reported that asthma during pregnancy was associated with an increased risk of PPD within 6 months after delivery, although this association did not reach statistical significance (OR, 1.30; 95% CI, 0.98-1.73).²⁴ However, because maternal asthma was not the exposure of interest, the association was adjusted for variables that might be in the causal pathway (ie, mediators) between maternal asthma and PPD, including antepartum depression, early onset of delivery, and poor fetal growth. Adjustment for these potential mediators could have biased the estimate for the association between asthma during pregnancy and PPD toward the null.

Although the underlying biological mechanisms explaining the link between asthma and depression are unclear, several hypotheses have been made. The first hypothesis suggests a link with an early exposure to stress leading to glucocorticoid resistance, which causes disturbances to the immune system through several pathways. These deregulations induce inflammation, which has been associated with both asthma and depression.^{44,45}

The second hypothesis involves proinflammatory circulating cytokines. Levels of several cytokines, including IL-6, IL-1, and TNF- α , are increased in the plasma and cerebrospinal fluid of patients with depression and asthma. These cytokines disturb the hypothalamic-pituitary-adrenal systems, affecting the immune system. They also regulate inflammatory responses through pathways that may be involved in asthma and depression.^{45,46}

A third hypothesis relates to the learned helplessness model of depression.⁴⁷ It is possible that new mothers with asthma may have experienced increased feelings of anxiety and helplessness due to the potential negative consequences of having a chronic, life-threatening disease. It is also possible that mothers with asthma may have experienced greater stress during the postpartum period due to the added strain of managing a chronic disease as well as looking after the infant. Finally, others have described the link between depression and autoimmune diseases, with inflammation being associated with behavioral changes such as depression-like symptoms.⁴⁸ Future studies are warranted to explore these hypotheses.

Another result that merits attention is that the effect of asthma on PPD was larger among women without than among women with a history of depression. This result might be explained by

the fact that women with asthma with a history of depression might be as likely as women without asthma to have their PPD diagnosed, whereas women with asthma but without a history of depression might be more likely to be diagnosed with PPD than women without asthma and without past depression. Women with chronic conditions might be more often in contact with health care professionals and therefore more likely to have a PPD diagnosed than women without a chronic condition. Consequently, this might lead to differential misclassification of the outcome and would bias the association away from the null.

This study has some important methodological strengths. Data on asthma diagnosis were collected prospectively and independently of the outcome, avoiding recall bias. The cohort of pregnant women was very large and highly representative of the general population. In addition, the asthma diagnoses recorded in the RAMQ database,^{49,50} the operational definition of asthma,²⁸ and the pregnancy variables recorded in the RAMQ and MED-ECHO database²⁷ were previously shown to be highly valid. Finally, the outcome was assessed in 3 different time periods (1 month, 3 months, and 1 year postpartum) because there is no consensus in the published literature regarding the most appropriate period of time to assess PPD.

However, our study has some limitations that should be taken into account when interpreting the results. PPD was identified using an operational definition based on diagnostic codes recorded in the RAMQ and MED-ECHO database that was not previously validated and this might bias the association between asthma and PPD toward the null. Moreover, we were not able to assess the severity of depression and therefore not able to evaluate whether there is an association between maternal asthma and the severity of depression. However, although the outcome in the main analysis captures new-onset depression and continuing depression, the subcohort analyses were able to isolate new-onset depression. In addition, we included many known risk factors for PPD in our models, but we were unable to adjust for some well-known risk factors, such as smoking,⁵¹ unplanned pregnancy,^{36,52,53} women's and partners' education level,^{32,36} unemployment,⁵⁴ financial problems,^{52,55} domestic violence,^{41,53} childhood physical abuse,⁹ lack of social support by the partner or family,⁵² poor marital relationship,⁵² and alcohol use during pregnancy.⁵⁶ Not adjusting for these variables might cause residual confounding, but we cannot confirm the direction of this bias because the distribution of these variables in pregnant women with asthma is unknown. In addition, we did not control for the use of medications to treat asthma or depression in our analysis because drug claims data were available for only 40% of women with public drug insurance, who are likely to have lower socioeconomic status (welfare recipients and employees without access to a drug plan provided by their employer or their partner's employer). Therefore, we decided to include all pregnancies ending in a live or still birth from a random sample regardless of their drug insurance plan, to ensure the study cohort was representative of the population. It is possible that some women did not take their asthma medications as prescribed because they were pregnant, and therefore had uncontrolled asthma, which might increase their anxiety and depression. Moreover, lack of information regarding the effect of asthma severity or control on the increased risk of PPD is a limitation and it would be valuable to address this issue in future studies. Having 63.2% of women contributing 2 pregnancies or more to the analysis can increase the power of the study and make the cohort more representative

TABLE III. Crude ORs between asthma, covariates, and PPD and the adjusted OR between asthma and PPD 1 y after delivery

Asthma and covariates	No. of pregnancies	n (%) of women with PPD in the year after delivery	Crude OR (95% CI)	Adjusted OR (95% CI)*
Asthma during pregnancy				
Yes	35,520	2,150 (6.1)	2.12 (2.01-2.24)	1.58 (1.50-1.67)
No	197,057	5,738 (2.9)	(Reference)	(Reference)
At conception				
Maternal age (y)				
<18	3,658	163 (4.5)	1.41 (1.20-1.65)	
18-25	69,857	2,598 (3.7)	1.18 (1.12-1.24)	
26-35	139,422	4,379 (3.1)	(Reference)	
36-45	19,640	748 (3.8)	1.21 (1.11-1.30)	
Residential area				
Urban	191,011	6,519 (3.4)	1.03 (0.97-1.09)	
Rural	41,566	1,369 (3.3)	(Reference)	
Drug insurance type				
Public with social welfare	21,450	1,288 (6.0)	2.03 (1.90-2.17)	
Public without social welfare	51,928	1,844 (3.6)	1.19 (1.13-1.26)	
Private	159,199	4,756 (3.0)	(Reference)	
Up to 1 y before the index pregnancy				
Heart disease				
Yes	2,037	134 (6.6)	2.00 (1.68-2.38)	
No	230,540	7,754 (3.4)	(Reference)	
Epilepsy				
Yes	661	48 (7.3)	2.17 (1.60-2.95)	
No	231,916	7,840 (3.4)	(Reference)	
Diabetes mellitus				
Yes	2,659	110 (4.1)	1.21 (1.00-1.47)	
No	229,918	7,778 (3.4)	(Reference)	
Anxiety				
Yes	13,334	1,385 (10.4)	3.55 (3.33-3.78)	
No	219,243	6,503 (3.0)	(Reference)	
Other psychiatric disorders				
Yes	1,853	421 (22.7)	7.86 (6.98-8.85)	
No	230,724	7,467 (3.2)	(Reference)	
Up to 10 y before the index pregnancy				
Previous miscarriage				
Yes	47,344	1,858 (3.9)	1.20 (1.14-1.27)	
No	185,233	6,030 (3.3)	(Reference)	
History of depression or PPD				
Yes	19,921	2,699 (13.5)	6.04 (5.74-6.36)	
No	212,656	5,189 (2.4)	(Reference)	
At least 1 previous delivery				
Yes	73,870	2,333 (3.2)	0.94 (0.89-0.98)	
No	158,707	5,555 (3.5)	(Reference)	
Delivery characteristics				
Season of delivery				
Winter	58,360	1,940 (3.3)	0.98 (0.92-1.04)	
Autumn	54,916	1,915 (3.5)	1.02 (0.96-1.09)	
Spring	59,782	2,008 (3.4)	0.99 (0.93-1.05)	
Summer	59,519	2,025 (3.4)	(Reference)	

*ORs were adjusted for the following variables: maternal age; area of residence; drug insurance type; anxiety, diabetes mellitus, epilepsy, and heart disease up to 1 y before the current pregnancy; previous miscarriage, depression, PPD, and at least 1 delivery up to 10 y before the current pregnancy; and season of delivery. Adjusted ORs for covariates are not presented to avoid causal misinterpretation.

of the population of pregnant women. However, if the correlation matrix of the generalized estimating equation models has not been perfectly specified, we might not have fully taken into

account the correlation between pregnancies of a woman, and therefore might have overestimated the precision of the OR estimates. Finally, the cohort did not include pregnancies losses

TABLE IV. Association between asthma during pregnancy and PPD in women with and without a history of depression

Time periods to assess PPD	Asthma during pregnancy		No asthma during pregnancy		Adjusted OR (95% CI)*
	No. of pregnancies	No. of cases of PPD (%)	No. of pregnancies	No. of cases of PPD (%)	
Entire cohort (n = 232,577)					
1 mo postpartum	35,520	297 (0.8)	197,057	839 (0.4)	1.32 (1.15-1.52)
3 mo postpartum	35,520	721 (2.0)	197,057	1,917 (1.0)	1.46 (1.33-1.60)
1 y postpartum	35,520	2,150 (6.1)	197,057	5,738 (2.9)	1.58 (1.50-1.67)
History of depression or PPD in the 10 y before the index pregnancy					
Women with depression or PPD (n = 19,921)					
1 mo postpartum	5,449	162 (3.0)	14,472	312 (2.2)	1.30 (1.06-1.59)
3 mo postpartum	5,449	364 (6.7)	14,472	702 (4.9)	1.30 (1.13-1.49)
1 y postpartum	5,449	908 (16.7)	14,472	1,791 (12.4)	1.29 (1.18-1.42)
Women without depression or PPD (n = 212,656)					
1 mo postpartum	30,071	135 (0.4)	182,585	527 (0.3)	1.35 (1.12-1.64)
3 mo postpartum	30,071	357 (1.2)	182,585	1,215 (0.7)	1.60 (1.41-1.80)
1 y postpartum	30,071	1,242 (4.1)	182,585	3,947 (2.2)	1.75 (1.64-1.87)
Subcohort of women free of depression during pregnancy and free of depression or PPD 10 y before the index pregnancy (n = 211,196)					
1 mo postpartum	29,716	106 (0.4)	181,480	435 (0.2)	1.30 (1.05-1.61)
3 mo postpartum	29,716	308 (1.0)	181,480	1,076 (0.6)	1.57 (1.38-1.79)
1 y postpartum	29,716	1,158 (3.9)	181,480	3,712 (2.0)	1.75 (1.63-1.87)

*ORs compared women with and without asthma and were adjusted for the following variables: maternal age; area of residence; drug insurance type; anxiety, diabetes mellitus, epilepsy, and heart disease up to 1 y before the current pregnancy; previous miscarriage, depression, PPD, and at least 1 delivery up to 10 y before the current pregnancy; and season of delivery.

before week 20, and the results might not be generalizable to those pregnancies.

In conclusion, we observed a significantly increased risk of PPD among pregnant women with asthma. This result commends close monitoring of women with asthma with the routine use of a depression screening tool such as the Edinburgh Postnatal Depression Scale⁵⁷ after delivery to detect early signs of PPD, allowing prompt and efficient intervention, if necessary.

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TABLE E1. Definitions of PPD based on *ICD-9* and *ICD-10* codes

<i>ICD-9</i> code	<i>ICD-10</i> code	Description
296.20	F32.9	Major depressive disorder, single episode unspecified
296.21	F32.0	Major depressive disorder, single episode mild
296.22	F32.1	Major depressive disorder, single episode moderate
296.23	F32.2	Major depressive disorder, single episode severe, without mention of psychotic behavior
296.24	F32.3	Major depressive disorder, single episode severe, specified as with psychotic behavior
296.25	F32.4	Depressive disorder, single episode, in partial remission
296.26	F32.5	Depressive disorder, single episode, in full remission
296.30	F33.9	Major depressive disorder, recurrent episode unspecified
296.31	F33.0	Major depressive disorder, recurrent episode mild
296.32	F33.1	Major depressive disorder, recurrent episode moderate
296.33	F33.2	Major depressive disorder, recurrent episode severe, without mention of psychotic behavior
296.34	F33.3	Major depressive disorder, recurrent episode severe, specified as with psychotic behavior
296.35	F33.41	Major depressive disorder, recurrent episode in partial or unspecified remission
296.36	F33.42	Major depressive disorder, recurrent episode in full remission
	F33.8	Recurrent depressive disorder, other
300.4	F34.1	Dysthymic disorder
	F38.1	Other recurrent mood disorders
311	F32.9	Depressive episode, unspecified

TABLE E2. Potential mediators of the association between asthma during pregnancy and PPD

Potential mediator	Source
Depression during pregnancy	E1-E7
Anxiety during pregnancy	E1,E2
Anemia during pregnancy	E8,E9
Gestational diabetes	E10
Preeclampsia	E11
Hyperemesis gravidarum	E12
Preterm birth (before week 37 of gestation)	E13
Mode of delivery	E13
Poor fetal growth	E9
Stillbirth (fetal loss at week 20 of gestation or later)	E14
Low birth weight (≤ 2500 g)	E15
Congenital malformations identified at delivery	E13

TABLE E3. Distribution of the number of pregnancies per woman in the cohort

No. of pregnancies per woman	No. of women	%
1	101,728	63.2
2	48,512	30.2
3	8,926	5.5
4	1,386	0.9
5 or more	286	0.2

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