

ORIGINAL RESEARCH ARTICLE

Prepregnancy asthma and the subsequent risk of central nervous system defects in offspring

Nathalie Auger^{1,2}  | Laura Arbour³ | Adeline Kabageni^{2,4} | Jessica Healy-Profitt^{1,2} |
Aimina Ayoub^{1,2} | William D. Fraser⁵

¹Health Innovation Hub, University of Montreal Hospital Research Centre, Quebec, Canada

²Bureau d'information et d'études en santé des populations, Institut national de santé publique du Québec, Quebec, Canada

³Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada

⁴Department of Human Biology, Claude Bernard University Lyon 1, Lyon, France

⁵Department of Obstetrics & Gynecology, Sherbrooke University Hospital Research Centre, Sherbrooke, Canada

Correspondence

Dr. Nathalie Auger, 190 Cremazie Blvd E., Montreal, Quebec H2P 1E2, Canada.
Email: nathalie.auger@inspq.qc.ca

Funding information

Fonds de Recherche du Québec - Santé, Grant/Award Number: 34695; Public Health Agency of Canada, Grant/Award Number: 6D02363004; Spina Bifida and Hydrocephalus Association of Canada

Background: The relationship between childhood asthma and central nervous system defects in offspring is poorly understood. We assessed if childhood asthma was associated with the risk of having an infant with neural tube or other nervous system defects compared with asthma during pregnancy.

Methods: We analyzed a longitudinal cohort of 128,060 women who were 5 years or less at study entry and later delivered an infant in Quebec, Canada (1989–2014). We identified women hospitalized for asthma before pregnancy, including childhood and adolescence, and determined if asthma was present during pregnancy based on obstetric records. Main outcomes were neural tube and non-neural tube defects in pregnancy. We used log-binomial regression models to determine risk ratios (RR) and 95% confidence intervals (CI) for the association between asthma and risk of nervous system defects, adjusting for patient characteristics.

Results: Asthma was associated with a greater risk of neural tube defects in offspring (RR 2.39, 95% CI 1.03–5.53) compared with no asthma, but not non-neural tube defects (RR 1.10, 95% CI 0.71–1.71). Women whose asthma resolved before pregnancy had a greater risk of neural tube defects (RR 3.43, 95% CI 1.35–8.69), while women with asthma during pregnancy were at greater risk of non-neural tube defects, especially microcephaly (RR 2.80, 95% CI 1.23–6.40).

Conclusions: Asthma that resolved before pregnancy was associated with an increased risk of neural tube defects in offspring but not non-neural tube defects. Further investigation is needed to determine the pathophysiology connecting childhood asthma with nervous system defects in offspring.

KEYWORDS

asthma, central nervous system, cohort studies, neural tube defects, pregnancy

1 | INTRODUCTION

A growing number of studies suggest that asthma is linked with birth defects in offspring (Blais, Kettani, Elftouh, & Forget, 2010; Lin et al., 2012). Asthma affects up to 12% of pregnant women (Murphy & Schatz, 2014; Namazy et al., 2013), but the association with central nervous system defects in offspring receives relatively little attention compared with other congenital anomalies. There is conflicting evidence that asthma during pregnancy is associated with nervous system defects (Blais et al., 2010; Garne et al., 2015; Garne et al.,

2016; Lin et al., 2012). One study suggests that asthma increases the risk up to 1.8 times (Blais et al., 2010). Associations with asthma merit attention as central nervous system defects are among the most common congenital anomalies, with neural tube defects affecting between 1 and 10 per 1,000 births (Imbard, Benoist, & Blom, 2013). Central nervous system defects are a major cause of morbidity and mortality (Irvine, Luo, & León, 2015), as well as a significant burden on families and health systems (Higashi et al., 2015).

Although asthma is a chronic condition often appearing in childhood (Martinez & Vercelli, 2013), symptoms may

resolve or improve during adulthood (Sears et al., 2003). However, the majority of research on central nervous system defects focuses on asthma in pregnancy only (Blais et al., 2010; Garne et al., 2015; Garne et al., 2016; Lin et al., 2012). Much less is known on how asthma early in life is related to risk of nervous system defects in offspring. Asthma that presents during childhood but improves later in life may have a unique phenotype that continues to affect risk of central nervous system defects (Martinez & Vercelli, 2013). In addition, a growing number of studies suggest that there may be shared pathways between immune disorders such as asthma, and folate-sensitive neural tube defects (Denny et al., 2013). Studies that focus on asthma during pregnancy only (Blais et al., 2010; Garne et al., 2015; Garne et al., 2016; Lin et al., 2012), however, do not address risks in women whose asthma resolved before pregnancy. Our objective was to determine the risk of neural and non-neural tube defects in offspring of women with asthma, and if the risk differs between childhood asthma that resolved before pregnancy and active asthma during pregnancy.

2 | MATERIALS AND METHODS

2.1 | Study design and population

We conducted a longitudinal cohort study of all women who were 5 years or less at study entry and later gave birth to a live infant in Quebec (Canada) before March 31, 2014 ($N = 128,060$). Women were eligible for entry to the cohort if they were aged 5 years or less in 1989 or thereafter, and delivered their infant in any hospital in Quebec. We followed the cohort through childhood and prepregnancy reproductive years to identify hospitalizations in which asthma was documented, and during pregnancy to determine if asthma was present in prenatal follow-up. We obtained the data from hospital discharge abstracts in the Maintenance and Use of Data for the Study of Hospital Clientele registry, an administrative database containing discharge summaries for all hospitalizations in Quebec (Ministère de la Santé et des Services Sociaux, 2016). In Quebec, women are followed prenatally using standardized obstetrics charts that are added to the hospital chart at delivery (Collège des Médecins du Québec, 2005), providing the physician with the entire obstetric history including asthma. The physician, therefore, completes the discharge abstract using the entire pregnancy history, not only hospitalization records.

In the data, maternal hospital charts are linked with the neonate, allowing us to determine if central nervous system defects were present at delivery. Follow-up for central nervous system defects during pregnancy ended on March 31, 2014 for all women. Almost all deliveries in Quebec occur in hospital (99%) (Auger, Fraser, Healy-Profitós, & Arbour, 2015), thus, the cohort is representative of the

majority of women in the province from 1989 onward who subsequently gave birth. However, we did not include women who had only stillbirths, as information on birth defects was not available for fetal deaths.

2.2 | Asthma

We defined asthma using the 9th and 10th revisions of the International Classification of Diseases (ICD-9 493; ICD-10 J45). The main exposure measure was a diagnosis of asthma any time during follow-up (yes, no). We further categorized asthma according to timing (childhood asthma that resolved before pregnancy, asthma in pregnancy, no asthma). Although there was no age cut off for prepregnancy asthma hospitalizations, 84% occurred before age 18, and 71% before age 15. We identified childhood asthma using primary or secondary diagnosis codes during any hospital admission before pregnancy. Thus, we mainly captured hospitalizations for severe or poorly controlled asthma (Hasegawa, Tsugawa, Brown, & Camargo, 2013), but not mild or well controlled asthma that never resulted in hospitalization. During pregnancy, however, we captured both mild and severe asthma because diagnosis codes reflected the prenatal obstetric chart and did not rely on hospitalizations during gestation. Asthma that is not documented on the obstetric chart represents potentially resolved or inactive disease (Sears et al., 2003). We could not determine the sensitivity and specificity of diagnostic codes for asthma, but previous studies report high validity for other codes in the data (Landry, Croitoru, & Menzies, 2012; Tairou, De Wals, & Bastide, 2006).

2.3 | Central nervous system defects

The main outcome measure was presence of a central nervous system defect in any pregnancy. We grouped central nervous system defects into two major categories: neural tube versus non-neural tube. We did so because the pathogenesis of neural tube defects is primarily related to folic acid deficiency (Wallingford, Niswander, Shaw, & Finnell, 2013), whereas the pathways leading to non-neural tube defects differ (McAllister, 2012; Woods & Parker, 2013). As secondary outcomes, we assessed the three most prevalent defects, including (1) spina bifida, (2) microcephaly, and (3) hydrocephaly. We used International Classification of Disease codes to identify nervous system defects, as well as procedure codes for spina bifida and hydrocephaly from the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures and the Canadian Classification of Health Interventions (Table S1).

2.4 | Covariates

We accounted for several covariates, including maternal age at delivery (<25, 25–34, ≥35 years), parity (0, 1, ≥2 previous deliveries), socioeconomic deprivation (quintiles ranging

from least to most disadvantaged neighborhoods for income, education and employment) (Auger et al., 2015), rural residence (rural, urban, unknown), time period at delivery (1989–1996, 1997–2004, 2005–2014), and comorbidities diagnosed before or during the pregnancy hospitalization (epilepsy, obesity, substance abuse, type I or type II diabetes). These comorbidities are associated with potentially greater risk of birth defects (Blais et al., 2010; Lin et al., 2012). We used ICD codes to identify epilepsy, obesity, substance abuse (including alcohol or illicit drugs), and diabetes (Supporting Information Table S1).

2.5 | Data analysis

We calculated the prevalence of central nervous system defects in offspring for every 10,000 deliveries in women with and without asthma. We used log-binomial regression models to calculate risk ratios (RR) and risk differences (RD) for the association of maternal asthma with central nervous system defects in offspring, using generalized estimating equations for deliveries nested in women. Because the outcome was rare, we accounted for potential confounders through propensity scores (Austin, 2011; Stürmer, Wyss, Glynn, & Brookhart, 2014). We computed the propensity score for asthma using age, parity, socioeconomic deprivation, rural residence, time period and comorbidity as predictors (Martinez & Vercelli, 2013). We subsequently computed the inverse probability of the propensity score and produced stabilized weights normalized to the original sample size (Lanehart et al., 2012; Leslie & Thiebaud, 2007). We verified that the weights were balanced, and used the inverse probability of the propensity score to weight the log-binomial regression models (Austin, 2011; Stürmer et al., 2014). Use of inverse probability weights creates a fictitious population that is distributed equally on study characteristics, ruling out bias due to the confounders (Austin, 2011). Inverse probability weights are ideal for rare outcomes that prohibit standard adjustment in regression models due to small cell sizes (Stürmer et al., 2014).

We carried out sensitivity analyses in which we removed 14 infants with central nervous system defects that also had chromosomal anomalies and 7,267 women aged less than 18 years at pregnancy to ensure that the results were robust. Where sample sizes were sufficient, we estimated standard regression models adjusted for confounders to ensure that results were similar to the propensity score models. We also examined models in which we used women as the unit of analysis as opposed to pregnancies.

We used SAS v9.3 (SAS Institute Inc., Cary, NC) for data analysis. The data contained no identifying information and the University of Montreal Hospital Centre institutional review board waived ethical review.

3 | RESULTS

There were 128,060 women in the cohort, including 6,559 hospitalized for asthma during follow-up (Table 1). Among the 6,559 women with asthma, 3,611 had childhood asthma that resolved before pregnancy. An additional 2,948 had asthma during pregnancy, including 2,203 (74.7%) who were never hospitalized for asthma during childhood. Compared with no asthma, women with any asthma had a higher prevalence of central nervous system defects in their offspring. Women with asthma had younger age at first delivery, higher total parity, greater material deprivation, and more comorbidity. Among 3,611 women with asthma that resolved before pregnancy, 2,049 (56.7%) were less than 10 years old when first hospitalized, and an additional 996 (27.6%) were between 10 and 18 years.

Women with any asthma had a greater but nonsignificant risk of later delivering an infant with a nervous system defect compared with women with no asthma (RR 1.23, 95% CI 0.83–1.82) after accounting for potential

TABLE 1 Characteristics of women with and without asthma

	Number of women (%)	
	Asthma ^a (N = 6,559)	No asthma (N = 121,501)
Central nervous system defect		
Yes	29 (0.4)	402 (0.3)
No	6,530 (99.6)	121,099 (99.7)
Age at delivery, years ^b		
<25	5,075 (77.4)	80,733 (66.4)
25–34	1,484 (22.6)	40,768 (33.6)
≥35	–	–
Total parity		
1	3,683 (56.2)	73,496 (60.5)
2	2,101 (32.0)	37,335 (30.7)
≥3	775 (11.8)	10,670 (8.8)
Socioeconomic deprivation ^b		
Low	1,845 (28.1)	31,520 (25.9)
Low-moderate	1,493 (22.8)	27,193 (22.4)
Moderate	1,264 (19.3)	23,992 (19.8)
Moderate-high	998 (15.2)	20,036 (16.5)
High	617 (9.4)	13,300 (11.0)
Rural residence ^b		
Yes	1,404 (21.4)	27,510 (22.6)
No	5,014 (76.4)	91,608 (75.4)
Time period ^b		
1989–1996	0 (0.0)	5 (0.0)
1997–2004	817 (12.5)	11,786 (9.7)
2005–2013	5,742 (87.5)	109,710 (90.3)
Comorbidity ^{b,c}		
Yes	900 (13.7)	5,849 (4.8)
No	5,659 (86.3)	115,652 (95.2)

^a Asthma before (N = 3,611) or during pregnancy (N = 2,948).

^b Measured at first delivery.

^c Epilepsy, obesity, substance abuse, Type I or II diabetes.

TABLE 2 Association of asthma with central nervous system defects in offspring

	No. deliveries	No. defects in offspring	Prevalence per 10,000 (95% confidence interval)	Risk ratio (95% confidence interval) ^a	Risk difference per 10,000 (95% confidence interval) ^a
Neural tube defect					
Asthma ^b	10,594	7	6.6 (1.7, 11.5)	2.39 (1.03, 5.53)	2.83 (−1.25, 6.90)
No asthma	184,711	43	2.3 (1.6, 3.0)	Referent	Referent
Non-neural tube defect					
Asthma ^b	10,594	23	21.7 (12.8, 30.6)	1.10 (0.71, 1.71)	1.21 (−7.88, 10.30)
No asthma	184,711	360	19.5 (17.5, 21.5)	Referent	Referent
Any nervous system defect					
Asthma ^b	10,594	30	28.3 (18.2, 38.4)	1.23 (0.83, 1.82)	4.03 (−5.97, 14.04)
No asthma	184,711	403	21.8 (19.7, 23.9)	Referent	Referent

^aWeighted by the inverse probability of the propensity score.^bAsthma before ($N = 5,335$) or during pregnancy ($N = 5,259$).

confounders (Table 2). The association was somewhat stronger for neural tube defects (RR 2.39, 95% CI 1.03–5.53) than non-neural tube defects (RR 1.10, 95% CI 0.71–1.71). Women with asthma had 2.83 excess infants with neural tube defects per 10,000 births (95% CI −1.25–6.90), and 4.03 excess infants with any nervous system defect (95% CI −5.97–14.04), compared with no asthma. Among specific defects, women with any asthma had a greater risk of spina bifida (RR 2.61, 95% CI 1.08–6.34) in offspring, but not microcephaly (RR 1.86, 95% CI 0.90–3.85) or hydrocephaly (RR 0.86, 95% CI 0.50–1.48) (Table 3).

Childhood asthma was related to the type of nervous system defect (Table 4). Compared with no asthma, women with asthma that resolved before pregnancy had a significantly greater risk of neural tube defects (RR 3.43, 95% CI 1.35–8.69) in offspring, but not non-neural tube defects (RR 0.60, 95% CI 0.26–1.39). In contrast, women with active asthma in pregnancy had a borderline elevated risk of non-neural tube defects (RR 1.59, 95% CI 0.95–2.67) but not neural tube defects (RR 1.24, 95% CI 0.27–5.62).

A similar pattern emerged for specific nervous defects (Table 5). Compared with no asthma, women with asthma before pregnancy had significantly greater risk of spina

bifida (RR 4.35, 95% CI 1.69–11.16) in offspring, but not microcephaly (RR 0.77, 95% CI 0.19–3.12) or hydrocephaly (RR 0.55, 95% CI 0.19–1.55). In contrast, there was no association between active asthma during pregnancy and spina bifida, but an association was present with microcephaly and hydrocephaly, although the risk of hydrocephaly was modest and not statistically significant.

In sensitivity analyses, exclusion of infants with chromosomal defects or women aged less than 18 years at pregnancy did not influence the results. Similar associations were obtained with standard regression models adjusted for individual covariates, and when using women as the unit of analysis.

4 | DISCUSSION

In this population-based study, we found that asthma was associated with an increased risk of delivering an infant with a neural tube defect, even if asthma resolved before pregnancy. The association with non-neural tube defects was weaker and statistically nonsignificant. Non-neural tube defects were however more strongly associated with

TABLE 3 Association of asthma with spina bifida, microcephaly, and hydrocephaly in offspring

	No. deliveries	No. defects in offspring	Prevalence per 10,000 (95% confidence interval)	Risk ratio (95% confidence interval) ^a	Risk difference per 10,000 (95% confidence interval) ^a
Spina bifida					
Asthma ^b	10,594	6	5.7 (1.1, 10.2)	2.61 (1.08, 6.34)	2.98 (−1.03, 6.98)
No asthma	184,711	34	1.8 (1.2, 2.5)	Referent	Referent
Microcephaly					
Asthma ^b	10,594	9	8.5 (2.9, 14.0)	1.86 (0.90, 3.85)	3.69 (−1.93, 9.31)
No asthma	184,711	79	4.3 (3.3, 5.2)	Referent	Referent
Hydrocephaly ^c					
Asthma ^b	10,594	15	14.2 (7.0, 21.3)	0.86 (0.50, 1.48)	−2.18 (−9.37, 5.00)
No asthma	184,711	282	15.3 (13.5, 17.0)	Referent	Referent

^aWeighted by the inverse probability of the propensity score.^bAsthma before ($N = 5,335$) or during pregnancy ($N = 5,259$).^cHydrocephaly, reduction deformities (lissencephaly) and other specified anomalies (macrogyria, amyelia, Arnold-Chiari syndrome).

TABLE 4 Timing of asthma and risk of central nervous system defects in offspring of girls followed over time

	No. deliveries	No. defects in offspring	Prevalence per 10,000 (95% confidence interval)	Risk ratio (95% confidence interval) ^a	Risk difference per 10,000 (95% confidence interval) ^a
Neural tube defect					
Asthma before pregnancy	5,335	5	9.4 (1.2, 17.6)	3.43 (1.35, 8.69)	5.68 (−1.43, 12.78)
Asthma in pregnancy ^b	5,259	<5	3.8 (0.0, 9.1)	1.24 (0.27, 5.62)	0.56 (−3.79, 4.92)
No asthma	184,711	43	2.3 (1.6, 3.0)	Referent	Referent
Non-neural tube defect					
Asthma before pregnancy	5,335	7	13.1 (3.4, 22.8)	0.60 (0.26, 1.39)	−7.86 (−17.83, 2.11)
Asthma in pregnancy ^b	5,259	16	30.4 (15.5, 45.3)	1.59 (0.95, 2.67)	11.50 (−4.41, 27.42)
No asthma	184,711	360	19.5 (17.5, 21.5)	Referent	Referent
Any nervous system defect					
Asthma before pregnancy	5,335	12	22.5 (9.8, 35.2)	0.90 (0.48, 1.69)	−2.19 (−14.66, 10.29)
Asthma in pregnancy ^b	5,259	18	34.2 (18.4, 50.0)	1.55 (0.95, 2.54)	12.08 (−4.42, 28.58)
No asthma	184,711	403	21.8 (19.7, 23.9)	Referent	Referent

^aWeighted by the inverse probability of the propensity score.^bAsthma in pregnancy with or without asthma in childhood.

active asthma in pregnant women. To our knowledge, this is the first study to find that women with childhood asthma that resolved before pregnancy continue to have an elevated risk of neural tube defects in offspring. This study provides novel evidence that the pathways linking asthma with nervous system defects in offspring may differ depending on asthma onset time. A better understanding of the pathways by which childhood asthma affects the risk of nervous system defects in offspring has potential to improve prevention of central nervous system anomalies.

There is evidence that maternal asthma increases the risk of congenital anomalies, with studies finding links with cleft palate, gastroschisis, renal dysplasia, and anal atresia (Garne et al., 2015; Lin et al., 2012). Evidence for the association between asthma and central nervous system defects is more conflicting. Studies investigating a wide-range of congenital defects report no association between maternal asthma and spina bifida or other neural tube defects (Garne et al., 2016; Lin et al., 2012), while others have found increased risks of encephalocele (Garne et al., 2015) and non-neural tube defects (Blais et al., 2010). Much of this literature addresses asthma that is active only during pregnancy (Blais et al., 2010; Garne et al., 2015; Garne et al., 2016; Lin et al., 2012; Namazy et al., 2013), with most studies looking at asthma medication or symptoms up to 1 year before pregnancy (Blais et al., 2010; Charlton et al., 2016). Some of the suspected pathways include the possibility that maternal hypoxia and inflammation are somehow involved in the genesis of birth defects (Blais et al., 2010; Lin et al., 2012). Another possible pathway is exposure to asthma medications, although current research suggests that associations with inhaled corticosteroids and beta-agonists are unlikely (Eltonsy, Forget, Beauchesne, & Blais, 2015). While our results support an association between active asthma and

microcephaly, we could not investigate drug-related pathways as we did not have data on prescription medications.

Studies have not investigated the possibility that childhood asthma that resolves before pregnancy can continue to affect the risk of central nervous system defects in offspring, despite evidence of phenotypic and genetic differences between childhood and adult onset asthma (Martinez & Vercelli, 2013). In our study, asthma that had resolved before pregnancy was associated with neural tube, but not non-neural tube defects. Evidence suggests that folate deficiency and impaired folate metabolism is involved in the development of asthma and atopic diseases (Thuesen et al., 2010). While the origins of nervous system defects are not fully established, it is generally accepted that folic acid pathways are important in the development of neural tube defects (Wallingford et al., 2013), while non-neural tube defects appear to have a wider range of genetic and environmental causes (McAllister, 2012; Woods & Parker, 2013). The association we found between resolved asthma and neural tube defects supports folate dependent pathways, including the hypothesis of an immunologic component in neural tube defects that are resistant to folic acid supplementation (Denny et al., 2013). There is also evidence that DNA methylation is implicated in childhood onset asthma (Perera et al., 2009; Rastogi, Suzuki, & Grealley, 2013), as well as folic acid metabolism and neural tube defects (Blom, 2009; Imbard et al., 2013). Thus, epigenetic mechanisms may be involved. Use of asthma medications for extended periods in childhood may be an additional contributor (Chauhan, Chartrand, Ni Chroinin, Milan, & Ducharme, 2015; Zhang, Prietsch, & Ducharme, 2014).

This study had several limitations. We used information from administrative hospital data and misclassification of variables is possible, although differential misclassification is unlikely. We adjusted for a wide range of potential confounders, but cannot rule out residual confounding from

TABLE 5 Timing of asthma and risk of spina bifida, hydrocephaly, and microcephaly in offspring of girls followed over time

	No. deliveries	No. defects in offspring	Prevalence per 10,000 (95% confidence interval)	Risk ratio (95% confidence interval) ^a	Risk difference per 10,000 (95% confidence interval) ^a
Spina bifida					
Asthma before pregnancy	5,335	5	9.4 (1.2, 17.6)	4.35 (1.69, 11.16)	6.17 (−0.92, 13.27)
Asthma in pregnancy ^b	5,259	<5	1.9 (0.0, 5.6)	1.08 (0.15, 7.90)	0.15 (−3.81, 4.11)
No asthma	184,711	34	1.8 (1.2, 2.5)	Referent	Referent
Microcephaly					
Asthma before pregnancy	5,335	<5	3.7 (0.0, 8.9)	0.77 (0.19, 3.12)	−1.00 (−5.66, 3.65)
Asthma in pregnancy ^b	5,259	7	13.3 (3.5, 23.2)	2.80 (1.23, 6.40)	7.74 (−1.87, 17.35)
No asthma	184,711	79	4.3 (3.3, 5.2)	Referent	Referent
Hydrocephaly^c					
Asthma before pregnancy	5,335	5	9.4 (1.2, 17.6)	0.55 (0.19, 1.55)	−6.90 (−15.72, 1.93)
Asthma in pregnancy ^b	5,259	10	19.0 (7.2, 30.8)	1.30 (0.68, 2.49)	4.62 (−8.20, 17.45)
No asthma	184,711	282	15.3 (13.5, 17.0)	Referent	Referent

^aWeighted by the inverse probability of the propensity score.^bAsthma in pregnancy with or without asthma in childhood.^cHydrocephaly, reduction deformities (lissencephaly) and other specified anomalies (macrogyria, amyelia, Arnold-Chiari syndrome).

unmeasured covariates such as teratogenic medication use, unreported substance use, or supplementary folic acid. However, Quebec has universal folic acid food fortification since the late 1990s. Although, we used an analytic method that allowed adjustment for total parity, alternate approaches could be used. We could not identify women with childhood asthma who were lost to follow-up or were never pregnant in Quebec; however, selection bias due to having asthma during pregnancy was not possible because all pregnant women were included in the cohort regardless of prior disease. We could not review charts to obtain details on asthma severity, or confirm the absence of asthma in women with childhood asthma that was no longer documented at delivery. It is possible that asthma was not correctly documented on obstetric records due to coding errors or unreported use of asthma medication. We did not have access to asthma prescriptions or types of medications taken. We analyzed women whose prepregnancy asthma required hospitalization, but could not identify milder forms. It is likely that we identified cases of more severe or poorly controlled asthma. Thus, the nonasthmatic category contains a fraction of women with mild asthma, which may have attenuated the differences and resulted in conservative associations. Likewise, asthma recorded on obstetric charts reflects a mixture of mild and severe cases, an issue that should be considered when comparing the results with the predominantly severe cases captured during childhood admissions.

As central nervous system defects are rare, we had low statistical power and cannot exclude the possibility of Type I or II error. However, a body of evidence suggests that asthma during pregnancy is associated with central nervous system defects (Blais et al., 2010; Garne et al., 2015), thus a relationship with childhood asthma is not implausible. Some women may not have completed reproduction by the end of the study, and the outcome may be misclassified for women

who were pregnant after the study ended. We did not have information on women who had abortions, including the presence of nervous system defects in aborted fetuses. Although, it is unlikely that abortion rates differ between women with and without asthma, central nervous system defects are a common reason for pregnancy terminations (Rossi & Prefumo, 2016). Thus, pregnancy terminations may have reduced the study power, and statistical significance of associations between asthma and nervous system defects. This problem may also explain why previous studies have found conflicting evidence for the association between asthma and nervous system defects, particularly studies with small sample sizes (Blais et al., 2010). Nonetheless, the results are likely generalizable to the majority of women with severe asthma, including those who undergo abortion.

This study suggests that asthma during childhood is associated with the later risk of some types of nervous system defects in offspring, even if asthma resolves before pregnancy. Childhood asthma may be more strongly associated with neural tube than non-neural tube defects. The findings merit follow-up in future mechanistic studies as asthma is common (Murphy & Schatz, 2014; Sears et al., 2003), and central nervous system defects place significant pressure on health care and families. Further investigation of these patterns may provide insight into the pathology of both asthma and central nervous system defects, perhaps leading to therapeutic or preventive approaches.

ACKNOWLEDGMENTS

This work was supported by the Spina Bifida and Hydrocephalus Association of Canada and the Public Health Agency of Canada (6D02363004). NA received a career award from the Fonds de recherche du Québec-Santé (grant 34695).

CONFLICT OF INTEREST

None.

ORCID

Nathalie Auger  <https://orcid.org/0000-0002-2412-0459>

REFERENCES

- Auger, N., Fraser, W., Healy-Profitts, J., & Arbour, L. (2015). Association between preeclampsia and congenital heart defects. *JAMA*, 314, 1588–1598.
- Austin, P. C. (2011). An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behavioral Research*, 46, 399–424.
- Blais, L., Kettani, F.-Z., Elftouh, N., & Forget, A. (2010). Effect of maternal asthma on the risk of specific congenital malformations: A population-based cohort study. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 88, 216–222.
- Blom, H. J. (2009). Folic acid, methylation and neural tube closure in humans. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, 85(4), 295–302. <https://doi.org/10.1002/bdr2.20581>
- Charlton, R. A., Pierini, A., Klungsøyr, K., Neville, A. J., Jordan, S., de Jong-Van Den Berg, L. T., ... Garne, E. (2016). Asthma medication prescribing before, during and after pregnancy: A study in seven European regions. *BMJ Open*, 6, e009237. <https://doi.org/10.1136/bmjopen-2015-009237>
- Chauhan, B. F., Chartrand, C., Ni Chroinin, M., Milan, S. J., & Ducharme, F. M. (2015). Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database of Systematic Reviews*, 11, CD007949. <https://doi.org/10.1002/14651858.CD007949.pub2>
- Denny, K. J., Jeanes, A., Fathe, K., Finnell, R. H., Taylor, S. M., & Woodruff, T. M. (2013). Neural tube defects, folate, and immune modulation. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, 97(9), 602–609. <https://doi.org/10.1002/bdr2.23177>
- Collège des Médecins du Québec. (2005). La tenue des dossiers par le médecin en centre hospitalier de soins généraux et spécialisés. Montreal, Quebec, pp. 1–38. Retrieved from <http://www.cmq.org/publications-pdf/p-1-2005-12-01-fr-tenue-des-dossiers-par-medecin-en-centre-hospitalier-de-soins-generaux-et-specialises.pdf>
- Eltonsy, S., Forget, A., Beauchesne, M.-F., & Blais, L. (2015). Risk of congenital malformations for asthmatic pregnant women using a long-acting β_2 -agonist and inhaled corticosteroid combination versus higher-dose inhaled corticosteroid monotherapy. *The Journal of Allergy and Clinical Immunology*, 135(1), 123–130. <https://doi.org/10.1016/j.jaci.2014.07.051>
- Game, E., Hansen, A. V., Morris, J., Zaupper, L., Addor, M.-C., Barisic, I., ... Dolk, H. (2015). Use of asthma medication during pregnancy and risk of specific congenital anomalies: A European case-malformed control study. *The Journal of Allergy and Clinical Immunology*, 136, 1496–1502.e1–7, 1502.e7.
- Game, E., Vinkel Hansen, A., Morris, J., Jordan, S., Klungsøyr, K., Engeland, A., ... Dolk, H. (2016). Risk of congenital anomalies after exposure to asthma medication in the first trimester of pregnancy - a cohort linkage study. *BJOG*, 123, 1609–1618.
- Hasegawa, K., Tsugawa, Y., Brown, D. F. M., & Camargo, C. A. (2013). Childhood asthma hospitalizations in the United States, 2000–2009. *The Journal of Pediatrics*, 163, 1127–1133.e3.
- Higashi, H., Barendregt, J. J., Kassebaum, N. J., Weiser, T. G., Bickler, S. W., & Vos, T. (2015). The burden of selected congenital anomalies amenable to surgery in low and middle-income regions: Cleft lip and palate, congenital heart anomalies and neural tube defects. *Archives of Disease in Childhood*, 100(3), 233–238.
- Imbard, A., Benoist, J.-F., & Blom, H. J. (2013). Neural tube defects, folic acid and methylation. *International Journal of Environmental Research and Public Health*, 10(9), 4352–4389. <https://doi.org/10.3390/ijerph10094352>
- Irvine, B., Luo, W., & León, J. A. (2015). Congenital anomalies in Canada 2013: A perinatal health surveillance report by the Public Health Agency of Canada's Canadian perinatal surveillance system. *Health Promotion and Chronic Disease Prevention in Canada*, 35(1), 21–22.
- Landry, J. S., Croitoru, D., & Menzies, D. (2012). Validation of ICD-9 diagnostic codes for bronchopulmonary dysplasia in Quebec's provincial health care databases. *Chronic Diseases and Injuries in Canada*, 33(1), 47–52.
- Lanehart, R. E., de Gil, P. R., Kim, E. S., Bellara, A. P., Kromrey, J. D., & Lee, R. S. (2012). Propensity score analysis and assessment of propensity score approaches using SAS procedures. In *SAS Global Forum: Statistics and Data Analysis*. Retrieved from <http://support.sas.com/resources/papers/proceedings12/314-2012.pdf>
- Leslie, S., & Thiebaud, P. (2007). Using propensity scores to adjust for treatment Selection bias. In *SAS Global Forum: Statistics and Data Analysis*. Retrieved from <http://www2.sas.com/proceedings/forum2007/184-2007.pdf>
- Lin, S., Munsie, J. P. W., Herdt-Losavio, M. L., Druschel, C. M., Campbell, K., Browne, M. L., ... Bell, E. M. (2012). Maternal asthma medication use and the risk of selected birth defects. *Pediatrics*, 129, e317–e324.
- Martinez, F. D., & Vercelli, D. (2013). Asthma. *Lancet*, 382, 1360–1372.
- McAllister, J. P. (2012). Pathophysiology of congenital and neonatal hydrocephalus. *Seminars in Fetal and Neonatal Medicine*, 17, 285–294.
- Ministère de la Santé et des Services Sociaux. (2016). *Cadre normatif du système Med-Écho. (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière)* (pp. 1–259). Gouvernement du Québec, Québec.
- Murphy, V. E., & Schatz, M. (2014). Asthma in pregnancy: A hit for two. *European Respiratory Review*, 23, 64–68.
- Namazy, J. A., Murphy, V. E., Powell, H., Gibson, P. G., Chambers, C., & Schatz, M. (2013). Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *European Respiratory Journal*, 41, 1082–1090.
- Perera, F., Tang, W., Herbstman, J., Tang, D., Levin, L., Miller, R., & Ho, S. (2009). Relation of DNA methylation of 5'-CpG Island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. *PLoS One*, 4(2), e4488. <https://doi.org/10.1371/journal.pone.0004488>
- Rastogi, D., Suzuki, M., & Grealley, J. M. (2013). Differential epigenome-wide DNA methylation patterns in childhood obesity-associated asthma. *Scientific Reports*, 3, 2164. <https://doi.org/10.1038/srep02164>
- Rossi, A. C., & Prefumo, F. (2016). Correlation between fetal autopsy and prenatal diagnosis by ultrasound: A systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 210, 201–206.
- Sears, M. R., Greene, J. M., Willan, A. R., Wiecek, E. M., Taylor, D. R., Flannery, E. M., ... Poulton, R. (2003). A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *New England Journal of Medicine*, 349(15), 1414–1422.
- Stürmer, T., Wyss, R., Glynn, R. J., & Brookhart, M. A. (2014). Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *Journal of Internal Medicine*, 275, 570–580.
- Tairou, F., De Wals, P., & Bastide, A. (2006). Validity of death and stillbirth certificates and hospital discharge summaries for the identification of neural tube defects in Quebec City. *Chronic Diseases in Canada*, 27, 120–124.
- Thuesen, B. H., Husemoen, L. L., Ovesen, L., Jørgensen, T., Fengler, M., Gilderson, G., & Linneberg, A. (2010). Atopy, asthma, and lung function in relation to folate and vitamin B(12) in adults. *Allergy*, 65(11), 1446–1454.
- Wallingford, J. B., Niswander, L. A., Shaw, G. M., & Finnell, R. H. (2013). The continuing challenge of understanding and preventing neural tube defects. *Science*, 339, 1222002.
- Woods, C. G., & Parker, A. (2013). Investigating microcephaly. *Archives of Disease in Childhood*, 98, 707–713.
- Zhang, L., Prietsch, S. O., & Ducharme, F. M. (2014). Inhaled corticosteroids in children with persistent asthma: Effects on growth. *Cochrane Database of Systematic Reviews*, 17, CD009471. <https://doi.org/10.1002/14651858.CD009471.pub2>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Auger N, Arbour L, Kabageni A, Healy-Profitts J, Ayoub A, Fraser WD. Prepregnancy asthma and the subsequent risk of central nervous system defects in offspring. *Birth Defects Research*. 2019;1–7. <https://doi.org/10.1002/bdr2.1452>

Table S1 Diagnostic and procedural codes

	International Classification of Diseases 9th revision/Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (before 2006)	International Classification of Diseases 10th revision/Canadian Classification of Health Interventions (beginning in 2006)
Central nervous system defect	740-742/15.31-15.43, 16.42, 16.59	Q00-Q07/1.AC.52-1.AC.54, 1.AW.72, 1.AX.73
Neural tube defect		
Spina bifida	741/16.42, 16.59	Q05, Q07.0/1.AW.72, 1.AX.73
Other	740, 742.0	Q00, Q01
Any	740, 741/16.42, 16.59	Q00-Q01, Q05, Q07.0/1.AW.72, 1.AX.73
Nonneural tube defect		
Microcephaly	742.1	Q02
Hydrocephaly	742.3/15.31-15.43	Q03/1.AC.52-1.AC.54
Other	742.2, 742.4-742.9	Q04, Q06, Q07.8, Q07.9
Any	742.1-742.9/15.31-15.43	Q02-Q04, Q06, Q07.8, Q07.9/1.AC.52-1.AC.54
Asthma	493	J45
Comorbidity		
Epilepsy	345, 649.4	G40
Obesity	278.0	E66
Substance abuse	291, 292, 303-305, 357.5, 357.6, 425.5, 535.3, 571.0-571.3, 577.0, 577.9, 655.4, 655.5, 790.3, 965.0, 967.0, 967.4, 969.1-969.9, 970.8, 980.0, V11.3, V65.42, V79.1	F10-F16, F18, F19, K29.2, K70, K85.2, K86.0, K86.9, O35.4, O35.5, R78.1-R78.5, T51.0, X42, X45, X62, X65, Y12, Y15, Z50.2, Z71.4, Z71.5, Z72.1, Z72.2, Z86.4
Diabetes	648.0	O24.5-O24.7