

Association of Maternal Diabetes and Child Asthma

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Summary. Background: Perinatal programming is an emerging theory for the fetal origins of chronic disease. Maternal asthma and environmental tobacco smoke (ETS) are two of the best-known triggers for the perinatal programming of asthma, while the potential role of maternal diabetes has not been widely studied. Objective: To determine if maternal diabetes is associated with child asthma, and if so, whether it modifies the effects of ETS exposure and maternal asthma. Methods: We studied 3,574 Canadian children, aged 7–8 years, enrolled in a population-based birth cohort. Standardized questionnaires were completed by the children's parents, and data were analyzed by multivariable logistic regression. Results: Asthma was reported in 442 children (12.4%). Compared to those without asthma, asthmatic children were more likely to have mothers ($P = 0.003$), but not fathers ($P = 0.89$), with diabetes. Among children without maternal history of diabetes, the likelihood of child asthma was 1.4-fold higher in those exposed to ETS (adjusted odds ratio, 1.40; 95% confidence interval, 1.13–1.73), and 3.6-fold higher in those with maternal asthma (3.59; 2.71–4.76). Among children born to diabetic mothers, these risks were amplified to 5.7-fold (5.68; 1.18–27.37) and 11.3-fold (11.30; 2.26–56.38), respectively. In the absence of maternal asthma or ETS, maternal diabetes was not associated with child asthma (0.65, 0.16–2.56). Conclusion: Our findings suggest that maternal diabetes may contribute to the perinatal programming of child asthma by amplifying the detrimental effects of ETS exposure and maternal asthma. **Pediatr Pulmonol.**

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INTRODUCTION

The origins of asthma are increasingly thought to be rooted in gene–environment interactions occurring in early development.¹ Perinatal programming, a dominant theory for the origins of chronic disease, proposes that environmental stimuli influence developmental pathways during critical periods of prenatal and postnatal development, inducing adaptive responses that lead to permanent changes in gene expression, metabolism, and disease susceptibility.² Since immune and lung development occur largely in utero and during early childhood, perinatal programming is a plausible pathway for asthma.³ Indeed, there is mounting evidence that early life events have lifelong effects on respiratory health.¹ Understanding the exposures responsible for the perinatal programming of asthma is critical to identifying children at risk for this disease, improving diagnosis and developing effective therapies and intervention strategies.

Environmental tobacco smoke (ETS) and maternal asthma are two of the best-known triggers for the perinatal programming of asthma. Exposure to ETS during fetal development and early childhood is linked to altered lung morphogenesis, reduced pulmonary function,

and increased risk of asthma.⁴ In terms of maternal asthma, research indicates that familial transmission occurs not only through genetic inheritance, but also through perinatal programming. This notion is based on evidence that maternal asthma is a stronger risk factor than paternal asthma for the development of asthma in

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offspring,^{1,5} suggesting that fetuses and infants of asthmatic mothers are exposed to a unique biological environment that increases their susceptibility to asthma. The underlying mechanisms appear to include a complex interaction between maternal antibodies, maternal cytokines, and factors in breast milk, all of which are dysregulated in asthmatic mothers.⁵

Perinatal programming is also a hypothesis for the association of diabetic pregnancy with child health outcomes including obesity, type 2 diabetes and cardiovascular disease.^{6,7} As with maternal asthma during pregnancy and prenatal ETS exposure, the adverse intrauterine environment associated with diabetic pregnancy has been shown to alter fetal metabolism and epigenetic regulation of gene expression.⁸ Furthermore, all three exposures have been linked to dysregulated fetal immune development and intrauterine hypoxia, both of which are risk factors for asthma.^{9–16} Given this evidence for common biological pathways, we hypothesized that maternal diabetes may contribute to the perinatal programming of asthma, possibly by moderating the effects of maternal asthma and ETS exposure. Indeed, two reports have suggested that maternal diabetes may be a risk factor for child asthma,^{17,18} but perinatal programming could not be inferred since neither study evaluated paternal diabetes to control for genetic transmission and shared environmental factors between parents. Research has shown that the effects of early ETS exposure on allergic sensitization can be modified by maternal phenotype,¹⁹ but this has not been studied in the context of asthma development and maternal diabetes.

Thus, the aim of this population-based study was to explore whether maternal diabetes may contribute to the perinatal programming of asthma, and if so, whether the effect is additive or synergistic with respect to ETS exposure and maternal asthma.

MATERIALS AND METHODS

Study Design

This was a secondary analysis of data collected for the Study of Asthma, Genes and Environment (SAGE), an ongoing population-based birth cohort study described elsewhere in detail.²⁰ Briefly, the cohort was created from the Manitoba provincial healthcare registry, comprising the 13,980 children born in Manitoba, Canada in 1995 and still residing there in 2002 (at age 7). In 2002, a one-page survey was mailed to the households of the cohort children to inquire about their health, family history, and home environment exposures. A total of 3,684 surveys were returned; the urban–rural distribution of asthma prevalence from survey responders was very similar to provincial statistics.²¹ All survey responders were considered for the current

study, including 449 children with parent-reported asthma. (Previous SAGE cohort publications have been limited to those families participating in follow-up analyses.) Due to the increased prevalence of diabetes in Canadian First Nations (FN) populations,²² we intended to perform both separate and combined analyses for FN and non-FN families; however, due to the small number of FN families in our cohort, we could not adjust for maternal asthma and ETS exposure in this population. Therefore, FN families (N = 106) were excluded from our study. An additional four families were excluded due to missing home exposure data, resulting in a final study population of 3,574 families. The study was approved by the University of Manitoba Health Research Ethics Board and the Health Information Privacy Committee. Parents also provided written consent.

Medical Histories

Our 2002 survey queried the following chronic medical conditions, asking whether they were experienced in the previous 12 months: asthma, food allergy, hay fever, and diabetes (requiring insulin or controlled by diet). Earlier medical histories (i.e., pre-2001) were not specifically requested. Parents answered “yes” or “no” for each condition, on behalf of their 7-year-old child and each birth parent. Individuals were considered atopic if they reported food allergy and/or hay fever. Missing values for parent health data were considered as negative responses; the proportion of missing values was lower than 5% for each question. Validated against a pediatric allergist diagnosis of asthma in a nested case–control cohort,²⁰ parent report of child asthma achieved 79.8% sensitivity and 80.8% specificity.

ETS Exposure and Other Covariates

On the mailed survey, parents also answered questions regarding their home environment, including the cohort child’s current and birth-year exposure to pets, mold, and ETS. Children were considered “exposed” to a given variable if current or birth-year exposure was reported. Exposure to ETS was determined based on parents’ response to the questions: “Does anyone living in your home smoke (cigarettes or tobacco)?” and “In 1995 (child’s birth year), did anyone living in your home smoke (cigarettes or tobacco)?” The location of the current family home was classified according to mailing address as either “urban” (municipality population >40,000) or “rural” (all other families).

Statistical Analysis

Univariate analyses (chi-squared tests) were performed to determine associations between child asthma

or maternal diabetes and parent health conditions or home exposures. Multiple logistic regression was conducted to mutually adjust for the association of multiple parent histories, environmental exposures, and residence location with child asthma. Associations are presented as crude or adjusted odds ratios (OR) with 95% confidence intervals (95% CI). Planned contrasts were implemented to address our a priori question regarding the interaction between maternal diabetes, and maternal asthma or ETS. To increase statistical power for detecting effect modification by maternal diabetes, interaction terms were tested using the recommended relaxed type 1 error rate of 20%.²³ Data were analyzed using SAS statistical software package version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Prevalence of Child Asthma and Parent Health Conditions

The prevalence of reported child and parent asthma, atopy, and diabetes is shown in Table 1. Overall, asthma was reported in 442 children (12.4%). Among parents, asthma was reported in 327 mothers (9.1%) and 246 fathers (6.9%), such that 540 children (15.1%) had at least one parent with asthma. Atopy was relatively common among parents (17.4% of mothers, 13.7% of fathers, 26.8% parent history) while diabetes was comparatively rare (1.4% of mothers, 1.3% of fathers, 2.6% parent history). The prevalence of asthma and atopy varied according to residence location, as shown in Table 1. While diabetes was equally prevalent in urban and rural populations, asthma and atopy were more common in parents and children living in urban centers compared to rural areas, consistent with previous reports.²⁴ In our cohort, asthma was reported in 13.7% of urban children compared to 10.6% of rural children ($P = 0.007$). Similarly, maternal history of asthma was

reported for 10.3% of urban children, compared to 7.6% of rural children ($P = 0.005$). Due to these observed differences, all subsequent analyses were adjusted for residence location.

Association of Parent Health Conditions and Home Exposures With Child Asthma and Maternal Diabetes

The distribution of parent health conditions and home exposures according to child asthma status (our outcome measure) and maternal diabetes (our exposure of interest) is shown in Table 2. Compared to healthy children, those with asthma were more likely to have parents with asthma or atopy ($P < 0.001$). They were also more likely to have mothers, but not fathers, with diabetes ($P = 0.003$, $P = 0.89$, respectively). Exposure to mold or cigarette smoke in the home was significantly associated with child asthma (both $P < 0.001$). Finally, diabetes was more frequently reported among asthmatic versus non-asthmatic mothers ($P < 0.001$). Because of these associations, subsequent analyses were mutually adjusted for maternal and paternal health conditions, and corrected for home exposures.

As expected, maternal and paternal asthma were the strongest predictors of child asthma in unadjusted analyses, with crude ORs (95% CI) of 4.68 (3.63–6.04) and 2.74 (2.02–3.72), respectively (Table 3). Interestingly, the next-strongest predictor was maternal diabetes (crude OR: 2.53, 1.34–4.81), yet paternal diabetes was not associated with child asthma (crude OR: 1.06, 0.45–2.52). After mutual adjustment for all reported parent health conditions and correction for residence location and home exposures, maternal and paternal asthma remained the strongest independent predictors of child asthma, with adjusted ORs of 3.85 (2.89–5.13) and 2.19 (1.57–3.05), respectively (Table 3). In the adjusted model, maternal diabetes remained positively

TABLE 1—Prevalence of Child and Parent Health Conditions by Residence Location, N (%)

	Overall (N = 3,574)	Rural (N = 1,516)	Urban (N = 2,058)	P-value
Mothers				
Asthma	327 (9.1)	115 (7.6)	212 (10.3)	0.005
Atopy	621 (17.4)	216 (14.2)	405 (19.7)	<0.001
Diabetes	50 (1.4)	24 (1.6)	26 (1.3)	0.42
Fathers				
Asthma	246 (6.9)	92 (6.1)	154 (7.5)	0.10
Atopy	489 (13.7)	168 (11.1)	321 (15.6)	<0.001
Diabetes	46 (1.3)	16 (1.1)	30 (1.5)	0.29
Children				
Asthma	442 (12.4)	161 (10.6)	281 (13.7)	0.007
Atopy	375 (10.5)	113 (7.5)	262 (12.7)	<0.001
Diabetes [†]	9 (0.3)	3 (0.2)	6 (0.3)	0.74

Urban versus rural comparisons by chi-square test, [†]or by Fisher's exact test due to small N.

TABLE 2—Distribution of Parent Histories and Home Exposures by Child Asthma Status and Maternal Diabetes, N (%)

	Overall (N = 3,574)	Child asthma		<i>P</i> -value	Maternal diabetes		<i>P</i> -value
		No (N = 3,132)	Yes (N = 442)		No (N = 3,524)	Yes (N = 50)	
FH asthma							
Maternal	327 (9.1)	214 (6.8)	113 (25.6)	<0.001	314 (8.9)	13 (26.0)	<0.001
Paternal	246 (6.9)	182 (5.8)	64 (14.5)	<0.001	239 (6.8)	7 (14.0)	0.05
FH atopy							
Maternal	621 (17.4)	494 (15.8)	127 (28.7)	<0.001	608 (17.3)	13 (26.0)	0.11
Paternal	489 (13.7)	387 (12.4)	102 (23.1)	<0.001	481 (13.6)	8 (16.0)	0.63
FH diabetes							
Maternal	50 (1.4)	37 (1.2)	13 (2.9)	0.003			
Paternal	46 (1.3)	40 (1.3)	6 (1.4)	0.89	43 (1.2)	3 (6.0)	†0.03
Residence location							
Rural	1,516 (42.4)	1,355 (43.3)	161 (36.4)	0.007	1,492 (42.3)	24 (48.0)	0.42
Urban	2,058 (57.6)	1,777 (56.7)	281 (63.6)	0.007	2,032 (57.7)	26 (52.0)	0.42
Home exposures							
Mold	1,225 (34.3)	1,031 (32.9)	194 (43.9)	<0.001	1,206 (34.2)	19 (38.0)	0.58
ETS	1,262 (35.3)	1,070 (34.2)	192 (43.4)	<0.001	1,243 (35.3)	19 (38.0)	0.69
Cat	1,188 (33.2)	1,041 (33.2)	147 (33.3)	0.99	1,169 (33.2)	19 (38.0)	0.47
Dog	1,390 (38.9)	1,229 (39.2)	161 (36.4)	0.26	1,365 (38.7)	25 (50.0)	0.10

ETS, environmental tobacco smoke; FH, family history.

Comparisons by chi-square test, †or by Fisher's exact test due to small N.

associated with child asthma, approaching statistical significance (adjusted OR: 1.95, 0.98–3.86), while paternal diabetes remained unassociated with child asthma (0.82, 0.33–2.05).

Effect Modification by Maternal Diabetes: Amplification of ETS and Maternal Asthma Effects

To address our a priori question regarding the possibility of shared mechanisms between maternal diabetes, ETS exposure, and maternal asthma in the perinatal programming of child asthma, planned contrasts were

applied to our adjusted model. This enabled us to test the associations of maternal asthma and ETS exposure with child asthma in the presence or absence of maternal diabetes (Table 4). We found that maternal diabetes amplified the effects of maternal asthma and ETS exposure on child asthma development. In children without maternal history of diabetes, ETS exposure increased the likelihood of asthma by 1.4-fold (adjusted OR: 1.40, 1.13–1.73), while the corresponding increase was 5.7-fold in children born to diabetic mothers (5.68, 1.18–27.36; *P* for interaction, 0.08). Similarly, maternal asthma was associated with a 3.6-fold increased risk of

TABLE 3—Likelihood of Childhood Asthma by Parent Medical History, Residence Location and Home Exposures

	Unadjusted			Adjusted ^a		
	OR	95% CI	<i>P</i> -value	OR	95% CI	<i>P</i> -value
FH asthma						
Maternal	4.68	(3.63–6.04)	<0.001	3.85	(2.89–5.13)	<0.001
Paternal	2.74	(2.02–3.72)	<0.001	2.19	(1.57–3.05)	<0.001
FH atopy						
Maternal	2.15	(1.72–2.70)	<0.001	1.25	(0.96–1.63)	0.10
Paternal	2.13	(1.66–2.72)	<0.001	1.70	(1.30–2.22)	<0.001
FH diabetes						
Maternal	2.53	(1.34–4.81)	0.003	1.95	(0.98–3.86)	0.06
Paternal	1.06	(0.45–2.52)	0.89	0.82	(0.33–2.05)	0.67
Home exposures						
Mold	1.59	(1.30–1.95)	<0.001	1.39	(1.13–1.72)	0.002
ETS	1.48	(1.21–1.81)	<0.001	1.48	(1.19–1.83)	<0.001
Cat	1.00	(0.81–1.24)	0.99	0.96	(0.77–1.21)	0.74
Dog	0.89	(0.72–1.09)	0.26	0.78	(0.62–0.97)	0.02

CI, confidence interval; ETS, environmental tobacco smoke; FH, family history; OR, odds ratio.

^aMutual adjustment for all variables shown, plus residence location. Total N = 3,574.

TABLE 4—Effect Modification by Maternal Diabetes: Adjusted Likelihood of Child Asthma by ETS Exposure and Maternal Asthma

	No maternal diabetes			Maternal diabetes		
	OR	95% CI	P-value	OR	95% CI	P-value
ETS exposure	1.40	(1.13–1.73)	0.002	5.68	(1.18–27.36)	0.03
Maternal asthma	3.59	(2.71–4.76)	<0.001	11.30	(2.26–56.38)	0.003

CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio for child asthma.

ORs are adjusted for maternal and paternal asthma and diabetes, parent atopy, residence location, and exposure to ETS, dogs and mold. Impact of maternal diabetes tested with contrasts.

child asthma in the absence of maternal diabetes (3.59, 2.71–4.76), while the corresponding increase was 11.3-fold when combined with maternal diabetes (11.30, 2.26–56.38; *P* for interaction, 0.17). Furthermore, we found that in the absence of maternal asthma or ETS, maternal diabetes was not associated with child asthma (0.65, 0.16–2.56). Post hoc analyses indicated that maternal diabetes did not substantially alter the effects of parent atopy, residence location, mold, or pet exposures on child asthma (data not shown).

DISCUSSION

Our population-based study of over 3,000 Canadian children provides evidence that maternal diabetes may enhance the perinatal programming of child asthma. To our knowledge, only two previous studies have reported associations between maternal diabetes and child asthma.^{17,18} From a population-based survey, Rusconi et al.¹⁸ found that Italian children born to mothers with diabetes were 72% more likely to have persistent wheezing at age 7 (OR: 1.72, 0.99–3.00). In a Swedish record linkage study, Asperg et al.¹⁷ reported that maternal diabetes was associated with a 19% increased likelihood of having a child who would be prescribed anti-asthmatic medication (OR: 1.19, 1.12–1.28). Our initial results confirm this association in a North American population (OR: 1.95, 0.98–3.86) with the extended finding that paternal diabetes is not associated with child asthma, suggesting direct intrauterine effects. Our subsequent analyses provide new mechanistic insight, showing that maternal diabetes increases the likelihood of child asthma by augmenting the impact of two established perinatal risk factors. On their own, ETS exposure and maternal asthma independently increased the risk of child asthma by 1.4- and 3.6-fold, respectively, whereas in combination with maternal diabetes, these effects were synergistically amplified to 5.7- and 11.3-fold. Finally, our findings suggest that maternal diabetes *alone* (without maternal asthma or ETS exposure) is not associated with child asthma, with an effect estimate of 0.16–2.56 (no evidence of association).

Ours is the first study to separately assess the impact of both maternal and paternal diabetes on the development of child asthma, providing the appropriate means to test for perinatal programming. Whereas a strictly genetic risk factor will be inherited equally through maternal and paternal lineages, the maternal influence will be stronger when mechanisms of perinatal programming are involved. Indeed, there is evidence that mothers exert a disproportionate influence on the development of many health conditions,^{25,26} and that the intrauterine environment plays a crucial role in shaping the fetal–infant immune system.²⁷ Our study provides evidence to implicate maternal diabetes in the perinatal programming of asthma, as we found that children of diabetic mothers, but not diabetic fathers, were at increased risk of developing asthma. Perinatal programming is a plausible mechanism for this association because human studies have shown that fetal lung maturation is delayed in diabetic pregnancies, leading to increased risk for infant respiratory distress syndrome,^{1,28} which is a risk factor for preschool asthma.²⁹ There is growing appreciation for the role of diabetic pregnancy in developmental programming, with studies demonstrating long-term metabolic and epigenetic effects.⁸

We have specifically identified two pathways by which maternal diabetes may contribute to the programming of childhood asthma, showing that maternal asthma and ETS exposure exert stronger asthma-promoting effects in children of diabetic mothers. Our results illustrate the synergistic (rather than additive) effect of maternal diabetes with respect to these co-exposures, providing evidence for effect modification (rather than a clustering of independent risk factors). These findings may explain why we and others¹⁸ observed only a borderline “maternal diabetes effect” in the overall cohort, since maternal diabetes was ultimately found to enhance the risk imposed by maternal asthma and ETS exposure, without a significant independent effect on child asthma.

Further investigation is required to determine how maternal diabetes interacts with maternal asthma and ETS exposure to promote the development of asthma in

offspring; however, speculation is possible based on previous research. For example, dysregulated cytokine profiles have been detected in the cord blood of neonates born to mothers with asthma,⁹ mothers with diabetes,¹³ and mothers who smoke,¹⁴ suggesting that disruption of fetal immune development may be a common pathway for these risk factors. Another shared complication of asthmatic and diabetic pregnancy is intrauterine hypoxia,^{10,15} which is also commonly observed in pregnant women exposed to ETS.¹⁶ Both intrauterine hypoxia (leading to fetal growth restriction) and immune system dysregulation have been associated with asthma.^{11,12} Thus, in combination with previous research, our findings suggest that fetal hypoxia and/or disruption of immune development may be synergistically amplified when pregnancy is complicated by diabetes in combination with maternal asthma or ETS exposure, leading to an especially elevated risk of asthma development.

Our results are consistent with a “threshold” scenario where, in isolation, maternal diabetes provokes sub-critical levels of harmful physiology (hypoxia or immune dysregulation), which are surpassed when the condition co-occurs with ETS or maternal asthma. This type of scenario is common in multifactorial disorders; for example, vitamin D insufficiency *alone* does not cause multiple sclerosis, but it is thought to be a risk modifier in genetically susceptible individuals.³⁰ Similarly, we find that maternal diabetes *alone* does not cause child asthma, but it appears to be a risk modifier in fetuses concurrently exposed to ETS or maternal asthma. It is also possible that maternal diabetes disrupts fetal lung or immune development such that, after birth, the infant is more susceptible to ETS exposure. Building on our preliminary findings, these hypothesized pathways can now be addressed more directly in exposure-based prospective studies of diabetic pregnancy.

Alternatively, or in addition to its modification of ETS and maternal asthma effects in utero, maternal diabetes could influence the development of child asthma by other means. Studies have shown that diabetic mothers are more likely to deliver pre-term or by cesarean section,^{31,32} and both pre-term birth and cesarean delivery are established risk factors for childhood asthma.^{33,34} In addition, type II diabetes is strongly linked to obesity, and maternal obesity reportedly increases the risk of asthma in offspring.³⁵ Occurring irrespective of the child's own BMI, this association has been attributed to obesity-induced systemic inflammation, which may adversely affect fetal pulmonary and immunological development in utero.³⁶ Because we could not control for birth mode or maternal obesity in our study, it was not possible to determine whether these factors contributed to the association between maternal diabetes and child asthma in our cohort; however, Rusconi et al.¹⁸

showed that neither cesarean section nor maternal weight gain during pregnancy explained the association of maternal diabetes with persistent wheeze. In light of these findings, and on the basis of our results, we therefore speculate that perinatal programming is an important mechanism underlying the association between maternal diabetes and childhood asthma. Possible mediation by maternal pre-pregnancy weight status should be addressed in future prospective studies.

The strengths of our study include the ability to mutually adjust for maternal and paternal health conditions (in order to test for perinatal programming), the validation of our main outcome variable (child asthma) against physician diagnosis, and the large population-based sample. The 26% response rate to our mail-out survey was similar to other population-wide surveys derived from health registries.³⁷ Although we cannot entirely exclude the possibility of non-response bias, we found that the urban–rural distribution of asthma prevalence from survey responders was very similar to provincial statistics.²¹ Also, the prevalence of child asthma and maternal diabetes reported in our cohort (12.4% and 1.4%, respectively) were comparable to other recent studies,^{10,11,35} and the proportion of children exposed to ETS at home (35.3% overall) was similar to the reported national average for the same time period.³⁸

As a secondary analysis, the study was limited by the unavailability of certain information, such as gender, birth weight, gestational age, socioeconomic status, maternal BMI, and maternal age. Confounding has been considered in our analyses, but due to the absence of these data, we acknowledge that residual confounding remains possible. Another limitation is that parent health conditions were self-reported, and our survey did not discriminate between type 1, type 2, or gestational diabetes. Information on the timing of disease onset or ETS exposure relative to pregnancy also was not available. We therefore cannot distinguish between prenatal and postnatal ETS exposure, which are known to have independent effects on respiratory health.³⁹ We also cannot eliminate the possibility that mothers developed reported health conditions during the 7 years following pregnancy. However, asthma is usually diagnosed before reaching child bearing age,⁴⁰ and it is likely that a high proportion of mothers reporting diabetes in 2002 were diabetic during their 1995 pregnancy, either because of child-onset diabetes or gestational diabetes, which is a risk factor for adult-onset diabetes.⁴¹ Our survey would not capture mothers with gestational diabetes resolving after pregnancy; however, this limitation would favor underestimation (rather than false identification) of maternal diabetes effects.

Appropriate designed prospective studies will be required to confirm the results of this hypothesis-

generating secondary analysis. Indeed, we intend to pursue such analyses in the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study, where detailed gene–environment exposure data are collected prospectively from pregnancy and linked to child health outcomes including asthma.

In conclusion, our results suggest that while maternal diabetes *alone* may not stimulate the perinatal programming of childhood asthma, it may be an enhancer of this process when combined with maternal asthma or ETS exposure. These findings identify a previously unrecognized combination of risk factors that may predict an especially high risk of asthma. Given the rapidly rising prevalence of both asthma and diabetes in Western populations,^{42,43} and the tendency for these disorders to co-occur in pregnant women,⁴⁴ our findings could have important clinical and public health implications. Finally, this hypothesis-generating cross-sectional study provides new inspiration for future prospective investigations to confirm our findings and explore possible biological mechanisms for the perinatal programming of asthma.

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