Title: The effect of gestational diabetes mellitus on the risk of asthma in offspring

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Abstract:

Purpose: To examine the effect of maternal gestational diabetes mellitus on the risk of asthma in the offspring.

Methods: This cohort study used data from 19,933 children in the National Longitudinal Survey of Children and Youth (NLSCY), 1994/1995–2008/2009, Canada. Children were followed until the first-time report of having health professional-diagnosed asthma (hereafter incident asthma), loss to follow-up, or end of the NLSCY follow-up, whichever occurred first. As a surrogate for Cox proportional hazards regression, pooled logistic regression models, crude and adjusted for potential confounders, were fitted to estimate the effect of gestational diabetes mellitus on the risk of asthma in the offspring.

Results: Among the 19,933 children, 1,178 (5.9%) had mothers with gestational diabetes mellitus. The median duration of follow-up was 4 (interquartile range: 4) years. A total of 1,639 children in the cohort had reported incident asthma during the follow-up, and 119 of them had mothers with gestational diabetes mellitus. The adjusted hazard ratio for the association between gestational diabetes mellitus and incident asthma in offspring was 1.25 (95% confidence interval [CI] 1.03, 1.51).

Conclusions: Our findings suggest that gestational diabetes mellitus increases the risk of asthma in the offspring.

Key words: Gestational diabetes mellitus, asthma, cesarean section delivery, pooled logistic regression, marginal structural model

List of abbreviations:

GDM – Gestational diabetes mellitus

NLSCY – National Longitudinal Survey of Children and Youth

PMK – Person most knowledgeable

ECD – Early Childhood Development

SD – Standard deviation

IQR – Interquartile range

HR – Hazard ratio

DAG – Directed acyclic graph

Introduction

Gestational diabetes mellitus (GDM) is diabetes that is “first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes” [1]. The prevalence of GDM varies from <1% to 28% worldwide [2, 3] and has increased significantly over the last few decades [4-8]. It is likely that the rising trend in GDM will continue with the increase in the prevalence of risk factors such as older maternal age and obesity. GDM is associated with different short- and long-term consequences in mother (pre-eclampsia, cesarean section delivery, preterm delivery and future type 2 diabetes), fetus (fetal macrosomia, large for gestational age, fetal hypoxia, immune dysregulation, impaired surfactant production and delayed lung maturation) [9-12] and offspring (perinatal mortality, obesity and metabolic syndrome) [13]. Some of these consequences, notably cesarean section delivery, have also been implicated as risk factors for asthma [14-16]. So, if indeed there is an effect of GDM on asthma in offspring, GDM can be contemplated to have not only an indirect component mediated by cesarean section delivery but also a direct component through other pathways independent of cesarean section delivery. Knowledge on both the total effect of GDM and direct effect beyond cesarean section delivery could help identify opportunities for interventions to reduce the risk of asthma in children. Few studies have investigated the total effect of maternal diabetes in pregnancy, including GDM on childhood wheezing or asthma. However, results from these studies remain inconclusive [17, 18]. Some studies suggested that GDM increases the risk of asthma in the offspring [19-24], while others suggested that GDM reduces the risk of asthma [25]. The direct effect of GDM accounting for the mediating role of cesarean section delivery remains unknown.

In this study, we set to investigate the total effect of GDM on the risk of asthma in offspring and the controlled direct effect of GDM not mediated by cesarean section delivery by assuming a fixed value of cesarean section delivery.

Methods

Data source

Data from the National Longitudinal Survey of Children and Youth (NLSCY) were used for this study. Details of the NLSCY are available elsewhere [26]. Briefly, the NLSCY was a longitudinal population-based study that collected information every two years from infancy to early adulthood. The first survey cycle of the NLSCY was conducted in 1994/1995 among 22,831 children aged 0–11 years living in 10 provinces of Canada using a multi-stage cluster sampling. In the longitudinal part of this study, 15,405 children included in cycle 1 (1994/1995 original cohort) were followed every two years until the last cycle (cycle 8) in 2008/2009. A maximum of two children were included from each household. One person most knowledgeable (PMK) about the child was interviewed using questionnaire to collect information on socio-demographics, pregnancy with child and birth-related conditions for young children, and health professional-diagnosed chronic conditions in parents and children, children's physical development, learning, behavior, and social environment. Maternal pregnancy-related information at enrollment was available for children aged 0–6 years. New cohorts of children aged 0–6 years, known as Early Childhood Development (ECD) cohorts, were added in each subsequent cycle to monitor early childhood development. The ECD cohort enrolled in cycle 2 of the 1994/1995 original NLSCY included younger siblings of the members of the original cohort. The ECD cohorts included one child per household except for twins. Same questionnaire was used for all ECD cohorts as in the original cohort.

Study population

We pooled data from cohorts of children enrolled in NLSCY cycles 1–7 for this study. Children having a biological parent as the PMK, full information on the model variables and information on asthma in at least two survey cycles were included in this study. We excluded children with reported asthma defined as a positive response to the question “Has this child ever had asthma that was diagnosed by a health professional?” by the PMK at enrollment into the corresponding cohort (n=1053). Children with reported asthma diagnosed during 0–2 years of age were also excluded (n=693) as it is difficult to diagnose asthma in young children [27], and the majority of the children with wheezing before two years of age do not develop asthma later in childhood [28]. Some children with reported asthma had inconsistent asthma response on “ever diagnosed with asthma” during the follow-up (‘no’ response in a survey after ‘yes’ response in a previous survey) and were excluded (n=394). In households where more than one child was enrolled in the same or different cohorts, only one randomly selected child was retained, and others were excluded (n=404). This led to an analytic sample of 19,933 children.

Study outcome and exposure

The study outcome was incident asthma, defined as the first-time report of having health professional-diagnosed asthma. Children were followed until incident asthma, loss to follow-up, or end of the NLSCY follow-up, whichever happened first. Loss to follow-up was defined as missing outcome data in two consecutive survey cycles.

The study exposure was maternal gestational diabetes mellitus, as ascertained by a positive response to the question “During pregnancy with this child did you suffer from any of the following: Pregnancy diabetes?”

Covariates

The covariates relevant for our analyses were measured at NLSCY enrollment and included the sex of the child, the birthweight of the child, maternal age at birth of the child, maternal asthma, maternal smoking during pregnancy, maternal high blood pressure in pregnancy, multiple gestation (e.g. twin, triplet or more), cesarean section delivery, preterm delivery, maternal race, maternal educational attainment, annual household income, urban residence. Mothers were considered to have asthma if they were reported to have had health professional-diagnosed asthma. Maternal high blood pressure in pregnancy and maternal smoking in pregnancy were ascertained from an affirmative response to the questions "During the pregnancy with this child did you suffer from high blood pressure?" and "Did you smoke during your pregnancy with this child?" Cesarean section delivery was ascertained from response to the question "Was the delivery vaginal or cesarean?" Preterm delivery was ascertained from response to the following two questions: "Was this child born before, after or on his due date?" and "How many days or weeks before/after the due date was this child born?". Multiple gestation was ascertained from response to the question "Was this a single birth or twins, or triplets?"

Statistical analysis

Descriptive statistics for the child and maternal characteristics according to GDM status were computed and summarized by means (standard deviation, SD) or medians (interquartile range, IQR), depending on the distribution of the continuous variables, and by percentages for categorical variables.

Total effect of GDM on asthma in offspring

To estimate the total effect of GDM on the risk of asthma in offspring, we fitted a pooled logistic regression model to emulate a Cox proportional hazards model [29-31]. First, we estimated the crude hazard ratio (HR) conditional on time since enrollment (hereafter time) and $time^2$. Then we estimated the HR additionally adjusting for the following potential confounders selected based on biological plausibility and review of literature on studies assessing the GDM-asthma association [20, 23, 25]: sex of the child, maternal age at birth of the child, maternal smoking during pregnancy, maternal high blood pressure in pregnancy, multiple gestation, maternal educational attainment, annual household income and urban residence. We also adjusted for the NLSCY cohort membership indicating the NLSCY survey cycle of enrollment.

Controlled direct effect of GDM on asthma in offspring

According to the directed acyclic graph (DAG), preterm delivery and birth weight were exposure GDM-induced confounders of cesarean section delivery-asthma in offspring association [32] (Figure 1). Thus, we fitted a pooled marginal structural logistic regression model with inverse probability weighting to estimate the controlled direct effect of GDM on the risk of asthma in offspring, not mediated by cesareans section delivery [33, 34].

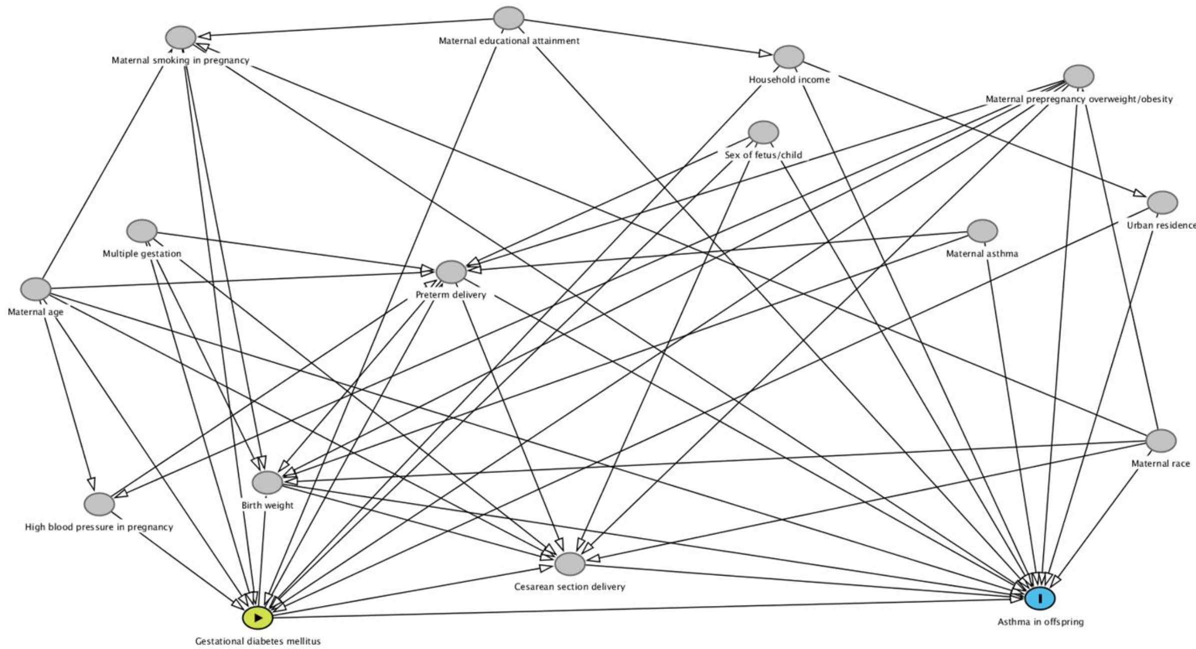

Figure 1: Directed acyclic graph showing paths between gestational diabetes mellitus and asthma in offspring

For the inverse probability weighting, we calculated a weight for the mediator, cesarean section delivery. We fitted pooled logistic regression models to estimate the numerator and denominator inputs for the mediator weight. The numerator input was the probability of having the value of cesarean section that a child's mother had, conditional on having the exposure GDM, and the denominator input was the probabilities of having the value of cesarean section delivery that a child's mother had, conditional on GDM (exposure), potential confounders of the GDM-asthma, GDM-cesarean section delivery and cesarean section delivery-asthma associations (i.e., sex of the child, maternal age at pregnancy, maternal asthma, maternal smoking in pregnancy, high blood pressure in pregnancy, multiple gestation, maternal race, maternal educational attainment, annual household income and urban residency), exposure-induced confounders of the mediator-outcome association (i.e., preterm delivery and birthweight), and

NLSCY cohort membership, time, and time^2. The mean of the mediator weight was 1.00 (range= 2.46). The controlled direct effect of GDM was then estimated by regressing the logit of incident asthma probability on GDM, cesarean section delivery (fixed to '0', i.e., delivery not by cesarean section for all children), an interaction between GDM and cesarean section delivery and confounders of the GDM-asthma association (i.e., sex of the child, maternal age at pregnancy, maternal smoking during pregnancy, maternal high blood pressure during pregnancy, multiple gestation, maternal educational attainment, annual household income, urban residency), NLSCY cohort membership, time and time^2 using the mediator weight.

Sensitivity analyses for unmeasured confounding for the total effect

To assess the effect of a possible unmeasured confounding factor maternal prepregnancy overweight/obesity on the estimates of the total effect of GDM on the risk of asthma in offspring, we performed a sensitivity analysis under a range of potential bias conditions [33]. The estimated prevalence of overweight and/or obesity in pregnant women in general varies between 10% and 60% globally [35, 36] and in women with GDM varies between 35% and 71% [37-39]. In the sensitivity analyses, we allowed the prevalence of maternal prepregnancy overweight/obesity to vary between 10% and 60% among mothers without GDM and between 35% and 75% among mothers with GDM, and the association between maternal prepregnancy overweight/obesity and asthma in offspring to vary between HR of 2.0 and 10.0. We also calculated the E-value to estimate the minimum strength of association that an unmeasured confounder would need to have with both GDM and asthma in the offspring to nullify the observed estimated total effect of GDM on asthma in the offspring [40, 41].

SAS software v 9.4 (SAS Institute Inc., Cary, North Carolina) was used in all analyses.

Results

Among the 19,933 children, a total of 1,178 children (5.9%) had mothers with GDM. A higher proportion of mothers with GDM smoked during pregnancy and had high blood pressure during pregnancy compared with mothers without GDM (Table 1). A higher proportion of children whose mothers had GDM had high birth weight were delivered by cesarean section and were born preterm compared with children whose mothers did not have GDM. Maternal race was black in 227 (1%) children and the majority of them did not have maternal GDM. The frequencies of maternal race according to the GDM status are not reportable because of small sample size (n<15) among mothers with GDM. The median follow-up was 4 years (interquartile range [IQR]: 4). A total of 1,639 children in the cohort reported incident asthma during the follow-up, and 119 of them had mothers with GDM.

Table 1: Characteristics of children and mothers, National Longitudinal Survey of Children and Youth, 1994/1995–2008/2009

Characteristic	**Mothers did not have GDM, frequency (%) N=18,755**	**Mothers had GDM, frequency (%) N=1,178**
Sex of the child, male	9,415(50)	591 (50)
Birth weight		
Normal (2500 to 3900 g)	15,193 (81)	899 (76)
Low birth weight (<2500 g)	922 (5)	76 (6)
High birth weight ((≥4000 g)	2,640 (14)	203 (17)
Maternal age at birth in years, mean (SD)	29 (5.2)	30 (5.4)

Maternal asthma	1,160 (6)	84 (7)
Maternal smoking during pregnancy	3,390 (18)	260 (22)
Maternal high blood pressure in pregnancy	2,004 (11)	241 (20)
Multiple gestation	345 (2)	26 (2)
Cesarean section delivery	4,004 (21)	362 (31)
Preterm delivery (gestational age ≤258 days)	1,750 (9)	183 (16)
Maternal educational attainment		
Less than secondary school graduation	2,040 (11)	148 (13)
Secondary school graduation	3,081 (16)	222 (19)
Some post-secondary	4,042 (22)	277 (24)
College or university degree	9,592 (51)	531 (45)
Annual household income		
<$10,000	328 (2)	20 (2)
$10,000–$14,999	895 (5)	73 (6)
$15,000–$19,999	827 (4)	74 (6)
$20,000–$29,999	1,862 (10)	141 (12)
$30,000–$39,999	2,437 (13)	157 (13)
≥$40,000	12,406 (66)	713 (61)
Urban residence	14,887 (79)	925 (79)
NLSCY cohort membership		
Cycle 1	1,047 (6)	56 (5)
Cycle 2	2,707 (14)	200 (17)
Cycle 3	5,212 (28)	351 (30)
Cycle 4	1,761 (9)	109 (9)

Cycle 5	1,887 (10)	122 (10)
Cycle 6	3,029 (16)	160 (14)
Cycle 7	3,115 (17)	180 (15)

SD standard deviation

In the unadjusted time-conditional model, the HR for the total effect of GDM was 1.27 (95% CI: 1.05, 1.54). After adjusting for the potential confounders, the association attenuated slightly (HR: 1.25, 95% CI: 1.03, 1.51). When estimating the controlled direct effect of GDM on incident asthma in offspring by adjusting for the cesarean section delivery (i.e. removing the mediated effect of cesarean section delivery), the HR was 1.17 (95% CI: 0.91, 1.49).

The bias-corrected HR estimates from the sensitivity analyses across the range of potential bias conditions suggest that the HR for incident asthma would be overestimated in scenarios where the prevalence of prepregnancy overweight/obesity was higher in mothers with GDM than mothers without GDM. However, the HR for the association between GDM and incident asthma would be underestimated in scenarios where the prevalence of prepregnancy overweight/obesity among mothers without GDM is higher than the prevalence among mothers with GDM (Table 2). The E-value for the estimated total effect of GDM suggests that the observed HR of 1.25 could be explained away by an unmeasured confounder that was associated with both GDM and asthma in offspring by an HR of 1.81-fold each, above and beyond the measured confounders (and other potential sources of error). The E-value for the lower 95% limit of the total effect was 1.21.

Table 2: Bias-corrected hazard ratios for quantifying the total effect of GDM on asthma, considering unmeasured confounder maternal prepregnancy overweight/obesity with a range of determinants of bias

Prevalence of unmeasured confounder maternal prepregnancy overweight/obesity		**Bias-Corrected Hazard Ratio**				
		The effect size of the unmeasured maternal prepregnancy overweight/obesity in Hazard Ratio				
No GDM (%)	**GDM (%)**	**2.0**	**4.0**	**6.0**	**8.0**	**10.0**
10	35	1.02	0.79	0.68	0.62	0.57
10	40	0.98	0.74	0.63	0.56	0.52
10	45	0.95	0.69	0.58	0.51	0.47
10	50	0.92	0.65	0.54	0.47	0.43
10	55	0.89	0.61	0.50	0.44	0.40
10	60	0.86	0.58	0.47	0.41	0.37
10	65	0.83	0.55	0.44	0.38	0.35
10	70	0.81	0.52	0.42	0.36	0.33
10	75	0.79	0.50	0.39	0.34	0.31
20	35	1.11	0.98	0.91	0.87	0.84
20	40	1.07	0.91	0.83	0.79	0.76
20	45	1.03	0.85	0.77	0.72	0.69
20	50	1.00	0.80	0.71	0.67	0.64
20	55	0.97	0.75	0.67	0.62	0.59

20	60	0.94	0.71	0.63	0.58	0.55
20	65	0.91	0.68	0.59	0.54	0.51
20	70	0.88	0.65	0.56	0.51	0.48
20	75	0.86	0.62	0.53	0.48	0.45
30	35	1.20	1.16	1.14	1.12	1.11
30	40	1.16	1.08	1.04	1.02	1.01
30	45	1.12	1.01	0.96	0.93	0.92
30	50	1.08	0.95	0.89	0.86	0.84
30	55	1.05	0.90	0.83	0.80	0.78
30	60	1.02	0.85	0.78	0.75	0.72
30	65	0.98	0.81	0.74	0.70	0.68
30	70	0.96	0.77	0.69	0.66	0.63
30	75	0.93	0.73	0.66	0.62	0.60
40	35	1.30	1.34	1.36	1.38	1.39
40	40	1.25	1.25	1.25	1.25	1.25
40	45	1.21	1.17	1.15	1.14	1.14
40	50	1.17	1.10	1.07	1.06	1.05
40	55	1.13	1.04	1.00	0.98	0.97
40	60	1.09	0.98	0.94	0.91	0.90
40	65	1.06	0.93	0.88	0.86	0.84
40	70	1.03	0.89	0.83	0.81	0.79
40	75	1.00	0.85	0.79	0.76	0.74
50	35	1.39	1.52	1.59	1.63	1.66
50	40	1.34	1.42	1.46	1.48	1.49

50	45	1.29	1.33	1.35	1.36	1.36
50	50	1.25	1.25	1.25	1.25	1.25
50	55	1.21	1.18	1.17	1.16	1.16
50	60	1.17	1.12	1.09	1.08	1.07
50	65	1.14	1.06	1.03	1.01	1.00
50	70	1.10	1.01	0.97	0.95	0.94
50	75	1.07	0.96	0.92	0.90	0.89
60	35	1.48	1.71	1.82	1.88	1.93
60	40	1.43	1.59	1.67	1.71	1.74
60	45	1.38	1.49	1.54	1.57	1.58
60	50	1.33	1.40	1.43	1.44	1.45
60	55	1.29	1.32	1.33	1.34	1.34
60	60	1.25	1.25	1.25	1.25	1.25
60	65	1.21	1.19	1.18	1.17	1.17
60	70	1.18	1.13	1.11	1.10	1.10
60	75	1.14	1.08	1.05	1.04	1.03

Discussion

In this study, we estimated the total effect of maternal GDM on the risk of asthma in the offspring using data from a large Canadian population-based longitudinal study. We also examined the controlled direct effect of GDM not mediated by cesarean section delivery. GDM was positively associated with incident asthma and independent of cesarean section delivery.

Our finding of the positive association between GDM and asthma in offspring is similar to the findings from most of the previous studies. Maternal diabetes was associated with around 20% higher odds of asthma in children followed from 2 years of age in two studies using proxy measures for asthma (i.e. hospitalization for asthma and asthma medication) [21, 22]. In another study, maternal diabetes was associated with a 95% higher odds of asthma (95% CI: 0.98, 3.86) in children at 7-8 years of age [23]. That study, however, did not adjust for important confounders such as sex, gestational age, and birth weight of the child as well as maternal age and socioeconomic status, which may have resulted in the stronger association compared with our study. In yet another study, the HR for the association between maternal GDM and asthma was 1.09 among children followed from 5 years of age [20]. One study reported a decreased rate of asthma-associated hospitalization in children having mothers with diet-treated GDM (HR 0.93, 95% CI: 0.82, 1.06) and pharmacologically-treated GDM (HR 0.94, 95% CI: 0.61, 1.42) compared to children having mothers without GDM [25]. Nonetheless, the effect ranging from a 39% reduction to a 42% increase, a substantial positive association for pharmacologically-treated GDM was also compatible with their data reflected by the 95% confidence interval.

If indeed GDM is a risk factor for asthma, approaches to prevent GDM might help in prevention of asthma in the offspring. Different lifestyle modification strategies, dietary supplementation, and pharmacological and non-pharmacological approaches have been evaluated as potential GDM prevention strategies. Among these interventions, healthy eating alone, healthy eating with physical activity, myoinositol (a vitamin B complex) supplementation and probiotic treatment have shown some promising results in high-risk women in reducing GDM but require replication [42, 43]. Identification of effective measures to prevent GDM, particularly in women at risk of developing GDM, would be the first step in this regard followed by evaluating effectiveness in preventing outcomes in offspring, including asthma.

When considering the controlled direct effect of GDM on the risk of asthma not mediated by cesarean section delivery, GDM appeared to increase the risk of asthma in the offspring. The point estimate suggests that in this hypothetical scenario where cesarean section delivery was not practiced (i.e., none of the children delivered by cesarean section), GDM would still have retained much of its effect on asthma in the offspring on the population level. However, the effect estimate was imprecise considering the width of the 95% confidence intervals. This could further suggest that there are other intermediaries in the pathway between GDM and asthma in the offspring or the effect of GDM on asthma in the offspring varies according to the duration, severity and control of hyperglycemia or both. Future studies should examine the direct effect of GDM according to GDM severity or treatment status and aim to identify other intervenable mediators to effectively reduce the risk of developing asthma in children whose mothers had GDM, considering the absence of confirmed effective GDM prevention strategies.

Strengths and limitations

The use of data from a national population-based large longitudinal study enabled us to follow children up to 16 years of age. We were able to adjust for relevant potential confounders except for maternal prepregnancy overweight or obesity. We had longitudinal data and we used longitudinal data analysis, particularly pooled logistic regression to emulate a Cox proportional hazards model to estimate the effect of GDM on the risk of asthma in the offspring.

Information on asthma was based on reported physician-diagnosed asthma and therefore, subject to misclassification of asthma status. Parent-reported physician-diagnosed asthma had an estimated 59% to 89% sensitivity and 81% to 96% specificity when validated against medical records, health claims diagnosis or pediatric allergist diagnosis of asthma in previous studies [23, 44-46]. Because NLSCY was not an asthma-focused study, misclassifications of the outcome, asthma are expected to be non-differential with regard to the exposure, maternal GDM status. As a result, the non-differential misclassification of asthma will bias associations toward the null. We were unable to differentiate between pregestational and gestational diabetes mellitus of mothers reporting diabetes during pregnancy with the child, as mothers were not asked if they had diabetes before pregnancy. However, most of the diabetes mellitus during pregnancy are likely to be GDM [47]. There may have been inaccuracies in reporting of pregnancy and birth-related information, including the exposure, GDM. Nevertheless, studies have suggested high reproducibility and accuracy of maternal recall of pregnancy- and birth-related events occurring from 3–9 years ago to even ≥30 years ago [48-50]. As a result, we believe that misclassification of exposure, and pregnancy and delivery-related confounders was relatively minor and consequently was not a source of major bias. There may have been errors in reporting of the socio-demographic confounders resulting in residual confounding. Moreover, we did not have information on a potential confounder maternal prepregnancy overweight/obesity, which has not been considered in previous studies. We conducted sensitivity analysis across a range of scenarios of unmeasured confounding by maternal prepregnancy overweight/obesity to estimate bias corrected total effect, which suggested that in plausible scenarios, the association is likely overestimated. We also estimated the E-value for an unmeasured confounder. While the sensitivity analyses for unmeasured confounder maternal prepregnancy overweight/obesity or any confounder suggest overestimation of the effect measure or the potential for explaining away the observed effect, non-differential misclassification of the outcome could bias the estimate towards the null. As such, the net effect of unmeasured confounders and nondifferential misclassification of exposure remains unknown. Future studies should collect data on maternal prepregnancy weight and consider it as a potential confounder when examining the association between GDM and asthma in offspring. This, together with accurate diagnosis of asthma in children, would help estimate relative unbiased effect of GDM on asthma in the offspring.

Conclusions

The findings from our study suggest, albeit weakly, that GDM increases the risk of asthma in the offspring overall and directly beyond the mediating role of cesarean section delivery. Interventions on preventing GDM or identification of intervenable intermediaries (other than cesarean section delivery) in the pathway between GDM and asthma in the offspring could provide opportunities for prevention of asthma.

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Conflicts of interest:

The authors declare that they have no conflict of interest.

Ethics approval

Ethical approval was not needed as the study relied on anonymous and secondary data from the Statistics Canada. However, the proposal for this study was approved by the Social Science and Humanities Research Council (SSHRC), Canada to gain access to the data in Statistic Canada's Research Data Centre (RDC) at Western University.

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