Received: 17 April 2021 | Revised: 25 July 2021 | Accepted: 27 July 2021

DOI: 10.1111/ppe.12806

ORIGINAL ARTICLE

Paediatric and Perinatal Epidemiology WILEY

# Examining the role of pre-pregnancy weight and gestational weight gain in allergic disease development among offspring: A population-based cohort study in Ontario, Canada

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**Funding information**
Canadian Institutes of Health Research, Grant/Award Number: FDN-148438

## Abstract

**Background:** Studies suggest maternal weight and weight gain during pregnancy may influence foetal immunological development. However, their role in the aetiology of allergic disease is unclear.

**Objectives:** We sought to examine the impact of maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) on the incidence of four common paediatric allergic diseases.

**Methods:** We conducted a retrospective, population-based cohort study of all singleton live births in Ontario, Canada between 2012 and 2014, using maternal-newborn records from the provincial birth registry linked with health administrative databases. Neonates were followed up to 7 years for anaphylaxis, asthma, dermatitis and rhinitis, identified through validated algorithms based on healthcare encounters. We multiply imputed missing data and employed Cox proportional-hazards models to calculate adjusted hazard ratios (aHR) with 95% confidence intervals (CI). To test the robustness of our findings, we also conducted several sensitivity analyses, including probabilistic bias analyses for exposure and outcome misclassification. All methods were prespecified in a published protocol.

**Results:** Of the 248,017 infants followed, 52% were born to mothers with a pre-pregnancy BMI in the normal range and only 19% were born to mothers with adequate weight gain during pregnancy. Incidence rates (per 100,000 person-days) for anaphylaxis, asthma, dermatitis and rhinitis were 0.22, 6.80, 12.41 and 1.54, respectively. Compared with normal BMI, maternal obesity was associated with increased hazards of asthma in offspring (aHR 1.08, 95% CI 1.05, 1.11), but decreased hazards of anaphylaxis (aHR 0.83, 95% CI 0.69, 0.99) and dermatitis (aHR 0.97, 95% CI 0.94, 0.99). In contrast, maternal underweight was associated with increased hazards of dermatitis (aHR 1.06, 95% CI 1.02, 1.10). We found no associations between pre-pregnancy BMI and rhinitis or GWG and any allergic outcome, and no evidence of effect measures modification by infant sex.

**Conclusions:** These findings provide support for the involvement of maternal pre-pregnancy BMI in paediatric allergic disease development.

KEYWORDS
allergic disease, gestational weight gain, Ontario, pregnancy, pre-pregnancy weight

## 1 | BACKGROUND

Globally, trends in allergic diseases have reached epidemic proportions, becoming the most common and earliest-onset chronic morbidities.[1] In Canada, approximately 30% of the population suffers from at least one allergic disease,[2] with even greater prevalence among children.[3] The greatest burden of allergic disease is among children,[1] with long-term physical, social and financial implications for the child and their family.[4–6] Elucidating the aetiology of these diseases is of high public health importance.

Studies suggest that predisposition to allergic disease may be programmed in early foetal life by inflammatory environments.[7] Insufficient or excess maternal weight and weight gain during pregnancy, now exceedingly common conditions,[8,9] lead to persistent low-grade inflammation, insulin resistance and metabolic dysregulation.[10] In turn, these changes directly affect the intrauterine environment and can alter the immunological development of the foetus,[11,12] potentially conferring increased risk of later-life allergy. Growing evidence supports this hypothesis, linking pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) with the risk of common allergic diseases, such as asthma, rhinitis and dermatitis.[13–28] Nevertheless, previous longitudinal studies have been limited by self-reported measures of exposures or outcomes, sometimes recalled years later, homogenous and non-representative samples, and low response and high attrition rates over follow-up, with a consequent high risk of information and selection bias. Furthermore, while most focused on asthma alone, less is known about the impact of these exposures on other common childhood allergic diseases.

Using population-based health datasets, we aimed to assess the relationship between maternal pre-pregnancy BMI and GWG on the incidence of anaphylaxis, asthma, dermatitis and rhinitis in offspring. We hypothesised that deviations from normal BMI or adequate GWG would increase the hazards of these outcomes.

### Synopsis

#### Study question

Are maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) associated with allergic disease development in offspring?

#### What's already known

Previous studies have linked pre-pregnancy BMI and GWG with offspring asthma risk. However, their methods have been limited by several information and selection biases. Further, less is known about the impact of these exposures on other childhood allergic diseases.

#### What this study adds

Our findings provide support for the involvement of pre-pregnancy BMI in allergic disease development. Compared with normal weight, pre-pregnancy obesity was associated with increased hazards of paediatric asthma, decreased hazards of dermatitis and anaphylaxis and not associated with hazards of rhinitis. In contrast, we found no evidence of a link between maternal GWG and allergic disease development among offspring.

## 2 | METHODS

Detailed methods for this study were prespecified in a published protocol[29] before data access; here, we outline the study methods briefly, following the RECORD reporting checklist (completed in Supplementary File S1).[30] Amendments to the protocol are outlined in Supplementary File S2. The study was conducted externally using datasets housed at ICES (https://www.ices.on.ca/).

### 2.1 | Study design and population

We performed a population-based retrospective cohort study of all singleton live births between 1 April 2012 and 31 March 2014 to residents of Ontario, Canada. Infants were followed up for between 5 and 7 years, until outcome diagnosis, death or healthcare ineligibility, or end of the study period (31 March 2019). Maternal weight data were not adequately collected for births before April 2012. To ensure a sufficient length of follow-up time to ascertain outcome development, we limited to births prior to March 2014. We excluded records with maternal ages <12 or >50 years, infants who died on their date of birth, duplicate records and those that could not be linked to other databases (due to invalid linkages or identifiers), infants born to mothers without continuous provincial healthcare eligibility throughout pregnancy, and infants who did not have documented healthcare eligibility within 90 days following birth.

### 2.2 | Data sources

The provincial birth registry, the Better Outcomes Registry & Network (BORN) Ontario Information System (BIS),[31] was used to define the birth cohort. The dataset includes maternal-newborn records for all births of at least 500g and at least 20 weeks of gestation, as well as clinical and demographic information on the mother and birth. Data from the birth registry were recently validated and found to have good agreement with data from patient charts.[32] The

cohort was subsequently linked to health administrative databases to ascertain outcomes from clinical encounters. We included the Canadian Institute for Health Information's Discharge Abstract Database (DAD) and National Ambulatory Care Reporting System (NACRS), which capture hospital admissions and emergency department visits, respectively, the Ontario Health Insurance Plan (OHIP) database, which captures ambulatory physician visits, and the Ontario Asthma Surveillance Information System (ASTHMA), which captures asthma diagnoses from the above datasets through a validated algorithm.[33–35] We additionally linked the Ontario Marginalization Index (ON-MARG) to ascertain neighbourhood-level marginalisation, a proxy for socioeconomic status. These datasets were linked using unique encoded identifiers and analysed at ICES. Detailed information on each database used is included in Supplementary File S2.

## 2.3 | Exposure assessment

The exposures for this study were pre-pregnancy BMI and GWG. We based our measurement of pre-pregnancy weight on objectively measured weight at the first prenatal visit (approximately 12 weeks of gestation); of those with any available weight data, 56% had this information. A correction was applied to these data by subtracting the average weight gain in the first trimester,[36–38] in order to estimate pre-pregnancy BMI. For the remaining 44% of the study population with weight data, we used data ascertained from another healthcare encounter; the proportion of these data that are self-reported or measured and the date of healthcare encounter from which they originate are not known. Pre-pregnancy BMI was then derived using pre-pregnancy weight and height (kg/m$^2$). Observed GWG was calculated as the difference between weight at delivery and pre-pregnancy weight. To account for gestational length, we ascertained accurate pregnancy dating from prenatal ultrasonography,[39] which is available before 24 weeks' gestation for 90% of Ontario births,[40] and subsequently calculated expected GWG as recommended the first-trimester weight gain + (weekly recommended gain in the second and third trimesters × number of gestational weeks beyond the first trimester).[41] The final exposure variable was calculated as the difference between observed and expected GWG.

We categorised both BMI and GWG into clinically relevant groupings for comparability with other studies and to facilitate interpretation. BMI was categorised based on World Health Organization groupings into underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$) or obese (≥30.0 kg/m$^2$).[42] GWG was categorised based on Institute of Medicine guidelines,[43] accounting for gestational length by calculating the ratio between observed and expected GWG. Ratio ranges determined by Guo and colleagues were used to categorise GWG into inadequate, adequate or excess weight gain.[41] To minimise the influence of extreme outliers, most of which can be assumed to be due to data quality problems, we winsorised data for pre-pregnancy weight, height and weight at delivery below the 0.1th and above the 99.9th percentiles before exposures were derived.

## 2.4 | Outcome assessment

We used validated algorithms to identify cases of anaphylaxis, asthma, dermatitis and rhinitis (Supplementary File S2), which were based on diagnostic codes from healthcare encounters. In Ontario, the DAD and NACRS databases have been coded using the *International Classification of Diseases, 10th Revision, Canada* (ICD-10-CA) since 2002, whereas the OHIP database is still coded using modified ICD-9 codes. Due to questions surrounding the validity of asthma diagnoses in early postnatal life, infants who fulfilled study definitions for asthma before the age of 6 months were not classified as cases unless a further hospitalisation or outpatient visit for asthma was detected after 12 months of age.[44] In a change to our published protocol, we only employed records from DAD and NACRS to ascertain anaphylaxis cases; this was done because OHIP lacks ICD codes more specific than 3 digits and lacks several clinical codes required for the algorithm. Moreover, we expect the majority of children suffering from an episode of anaphylaxis would likely be seen in urgent or inpatient settings (records of which are in NACRS and DAD, respectively) and not in primary care.

## 2.5 | Statistical analysis

We presented characteristics of the study population overall and stratified by exposure group using frequencies with proportions for categorical variables and medians with interquartile ranges for continuous variables. Crude incidence rates, graphically presented using cumulative incidence curves, were calculated per 100,000 person-days of follow-up for each study outcome by exposure group.

We used Cox proportional-hazards regression models to calculate the crude and adjusted associations between maternal pre-pregnancy BMI and GWG and time-to-first paediatric allergic outcome, where the time to each outcome of interest was censored at the time of death, healthcare ineligibility or administratively at the end of the study follow-up period. We accounted for repeated pregnancies using generalised estimating equation methods in all our models,[45,46] details of which are in Supplementary File S2. Results are expressed as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Models were adjusted for the minimal sufficient adjustment set prespecified in our protocol[29] through a directed acyclic graph: maternal age; maternal pre-existing health conditions; maternal smoking alcohol and illicit substance use, and select medication use during pregnancy; neighbourhood rurality; neighbourhood socioeconomic marginalisation; and parity. As prespecified, results are also reported by infant sex in Supplementary File S3. We tested the proportional-hazards assumption of the models by calculating the Wald test for covariate-time interaction and visually inspecting Schoenfeld residual plots and log(-log) survival plots. In secondary analyses, we modelled exposures continuously using Cox models with restricted cubic splines (detailed methods in Supplementary File S2).

All analyses were conducted in SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

## 2.6 | Missing data

Before models were fit, we employed multiple imputations by fully conditional specification to impute missing data in exposures and confounders (M = 10; details in Supplementary File S2).

## 2.7 | Sensitivity analysis

We tested the robustness of our results in multiple prespecified sensitivity analyses (detailed methods and results available in Supplementary File S4). To evaluate the impact of missing data and residual confounding, we reran our models using a complete-case analysis, compared response, complete-case and imputed samples by demographics, and additionally adjusted for maternal healthcare utilisation (outpatient visits in OHIP) in a 1-year look-back period before the start of the index pregnancy among mothers who were continuously eligible for healthcare during that time period. To assess the potential for exposure misclassification, we compared complete-case results of mothers whose pre-pregnancy weight was measured objectively during the first prenatal visit with those whose pre-pregnancy weight was likely to be self-reported during healthcare encounters. Finally, we conducted two probabilistic bias analyses[47] to quantify the impact of non-differential outcome and exposure misclassification on our results.

## 2.8 | Ethics approval

Ethics approval for this study was granted by the Research Ethics Board of the Children's Hospital of Eastern Ontario (protocol No. 19/14PE) and the ICES Privacy Office (protocol No. 2020 0901 237 000). Ontario legislation, specifically the Personal Health Information Protection Act of 2004, dictates that secondary analyses of routinely collected data do not require individual patient consent.

# 3 | RESULTS

Of the 275,898 infants born in Ontario between April 2012 and March 2014, 248,017 (89.9%) were included in our study population after sample and administrative exclusions (Figure 1).

Approximately half of the infants were born to overweight or obese mothers and a third to mothers who gained excess weight, though missingness in both exposures was high (Table 1). Nearly all infants were censored due to the end of follow-up or loss of healthcare eligibility, while few were censored due to death (Table 1). The median follow-up time was close to 6 years. Similar distributions of baseline characteristics of the study population were found after stratification by exposures (Tables S4 and S5).

After follow-up, 1184 (0.5%) infants were diagnosed with anaphylaxis, 33,336 (13.4%) with asthma, 54,119 (21.8%) with dermatitis and 8076 (3.3%) with rhinitis (Table 1). Crude incidence rates were highest for dermatitis, followed by asthma, rhinitis and anaphylaxis (Table 2). Additional results, including cumulative incidence plots stratified by exposure group and infant sex (Figures S2, S3 and S4), are available in Supplementary File S3.

In adjusted models, maternal pre-pregnancy obesity was associated with decreased hazards of anaphylaxis in offspring compared with normal weight (aHR 0.83, 95% CI 0.69, 0.99; Figure 2). The hazards of offspring asthma increased with increasing maternal pre-pregnancy BMI category, though the magnitude of the point estimates was small (maternal underweight: aHR 0.97, 95% CI 0.92, 1.02; maternal overweight: aHR 1.03, 95% CI 1.00, 1.06; maternal obesity: aHR 1.08, 95% CI 1.05, 1.11; Figure 2). In contrast, an inverse relationship was observed between pre-pregnancy BMI category and dermatitis; compared with normal pre-pregnancy BMI, maternal underweight was associated with slightly increased hazards of dermatitis (aHR 1.06, 95% CI 1.02, 1.10), while maternal obesity was associated with slightly decreased hazards (aHR 0.97, 95% CI 0.94, 0.99; Figure 2). There was no association between maternal pre-pregnancy BMI and infant rhinitis. Although GWG was not associated with any of the paediatric allergic outcomes assessed, our results suggested a pattern towards decreased hazards with inadequate weight gain and increased hazards with excess weight gain, compared with adequate weight gain (Figure 2).

Stratification by infant sex revealed little evidence of effect measure modification (Figures S8 and S9). Similar results were observed when we assessed the exposures continuously using restricted cubic splines, both overall (Figure 3) and after stratification by infant sex (Figure S10). The Cox models met proportional-hazard assumptions (Table S6 and Figures S5, S6 and S7).

## 3.1 | Sensitivity analysis

Several pre-planned sensitivity analyses were conducted in order to test the robustness of our findings. Due to high missingness in both exposures, we compared maternal and infant characteristics among the response sample, complete-case samples for pre-pregnancy BMI and GWG, and pooled imputed sample (Table S10). Characteristics among all samples were found to be generally comparable. To further evaluate the impact of missingness on our results, we reran our main Cox proportional-hazard models among complete-case samples (Table S11); the point estimates were slightly inflated compared with imputed results, but our conclusions were unchanged.

To ensure that infant diagnoses in healthcare encounters were not influenced by maternal propensity to access health care, we further adjusted our main models for the total number of maternal outpatient visits during a one-year look-back period before the start of the index pregnancy (Table S12); no changes in point estimates were identified.

To assess the impact of self-reported weight on our results, we stratified the complete-case results by the method of weight ascertainment (i.e., objectively measured at first prenatal visit vs likely self-report during another healthcare encounter); our interpretations

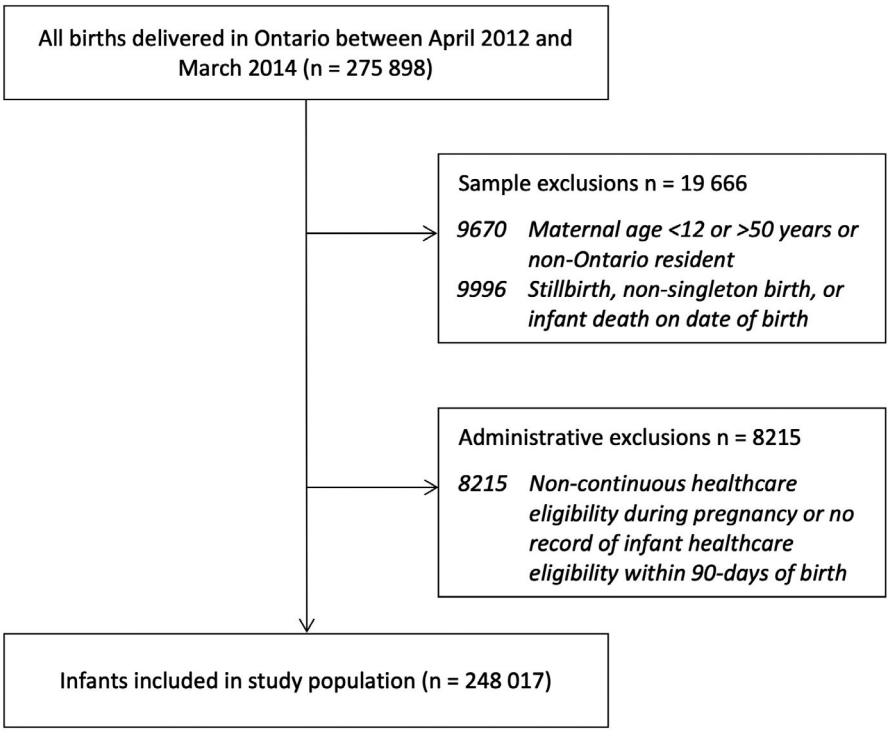


**FIGURE 1** Flow diagram of study. Some prespecified exclusion criteria did not omit any infants and are thus not listed

and conclusions remained largely the same, though some important changes in results were noted. The greatest change observed was in the point estimate for the association between maternal obesity and dermatitis, which was qualitatively different among those with measured weight (aHR 0.93, 95% CI 0.90, 0.97) and those with self-reported weight (aHR 1.05, 95% CI 1.00, 1.10; Figure S11). A similar change was observed for the association between maternal excess weight gain and hazards of asthma (measured weight: aHR 0.98, 95% CI 0.94, 1.02; self-reported weight: aHR 1.07, 95% CI 1.02, 1.13; Figure S11), though the 95% confidence interval was slightly overlapping. In our last sensitivity analyses, we evaluated the potential for non-differential exposure and outcome misclassification through two probabilistic bias analyses. We found that both types of misclassification most likely biased our results by ≤10%, with the greatest potential impacts to anaphylaxis, the rarest outcome examined (Tables S14 and S16).

## 4 | COMMENT

### 4.1 | Principal findings

In this population-based study of 248,017 infants, exposure to maternal pre-pregnancy weight above normal BMI and GWG above recommended guidelines was highly prevalent. After a maximum of 7 years of follow-up, we found a slight positive relationship between maternal pre-pregnancy BMI and hazards of asthma in children and weak inverse associations with hazards of dermatitis. We additionally observed that maternal pre-pregnancy obesity was associated with reduced hazards of anaphylaxis. No associations were found between pre-pregnancy BMI and rhinitis or between GWG and any allergic outcome. The data were limited by potential exposure and outcome misclassification, selection bias and residual confounding due to a lack of non-clinical information in health administrative datasets; nevertheless, the results were robust in prespecified sensitivity analyses designed to assess impacts of these biases.

### 4.2 | Strengths of the study

The main strength of our study was the use of population-based datasets in a large study population. By linking the provincial birth registry with health administrative databases, we followed a representative cohort of infants from a diverse population and objectively ascertained exposure and outcome data for a majority of the group, and thus, selection bias and non-response were minimised. We also employed rigorous and open methods,[29] including prespecifying all analyses, multiply imputing missing data, modelling continuous exposures with restricted cubic splines and evaluating the impact of biases in several sensitivity analyses.

### 4.3 | Limitations of the data

Nevertheless, our study also suffers from several limitations, mainly as health administrative datasets were not intended or designed for research purposes.[48] Although we employed previously validated algorithms to identify cases of paediatric allergic disease, some non-differential outcome misclassification is expected due to physician misdiagnoses and imperfect algorithm accuracy. We evaluated the impact of outcome misclassification in a probabilistic bias analysis,

**TABLE 1** Maternal and infant characteristics of all singleton live births in Ontario, Canada, between fiscal years 2012 and 2014 ($n$ = 248,017)

| Characteristics | No. | (%) |
|---|---|---|
| Maternal characteristics | | |
| Pre-pregnancy BMI (exposure)[a] | | |
| Underweight | 11,324 | (4.6) |
| Normal weight | 108,213 | (43.6) |
| Overweight | 49,802 | (20.1) |
| Obesity | 37,721 | (15.2) |
| Missing | 40,957 | (16.5) |
| Median (IQR) BMI, kg/m$^2$ | 24.0 | (21.2–28.1) |
| GWG (exposure)[b] | | |
| Inadequate | 32,438 | (13.1) |
| Adequate | 50,101 | (20.2) |
| Excess | 91,800 | (37.0) |
| Missing | 73,678 | (29.7) |
| Median (IQR) difference between observed and expected GWG, kg | 3.0 | (-0.7–7.3) |
| Maternal age at birth, years | | |
| <25 | 44,888 | (18.1) |
| 25–29 | 58,871 | (23.7) |
| 30–34 | 88,733 | (35.8) |
| ≥35 | 55,525 | (22.4) |
| Parity | | |
| 0 (nulliparous) | 104,711 | (42.2) |
| 1 (uniparous) | 87,619 | (35.3) |
| ≥2 (multiparous) | 51,553 | (20.8) |
| Missing | 4134 | (1.7) |
| Pre-existing health condition[c] | | |
| No | 202,914 | (81.8) |
| Yes | 45,103 | (18.2) |
| Asthma | 40,133 | (16.2) |
| Any autoimmune condition | 1160 | (0.5) |
| Diabetes | 2304 | (0.9) |
| Pre-existing hypertension | 2389 | (1.0) |
| Any pulmonary condition, excluding asthma | 739 | (0.3) |
| Alcohol use during pregnancy | | |
| No | 222,907 | (89.9) |
| Yes | 4001 | (1.6) |
| Missing | 21,109 | (8.5) |
| Smoking during pregnancy | | |
| No | 217,032 | (87.5) |
| Yes | 26,217 | (10.6) |
| Missing | 4768 | (1.9) |
| Resides with smoker during pregnancy | | |
| No | 162,939 | (65.7) |
| Yes | 37,925 | (15.3) |
| Missing | 47,153 | (19.0) |
| Substance use during pregnancy | | |
| No | 224,420 | (90.5) |
| Yes | 4792 | (1.9) |
| Missing | 18,805 | (7.6) |
| Select medication use during pregnancy[d] | | |
| No | 185,987 | (75.0) |
| Yes | 55,137 | (22.2) |
| Missing | 6893 | (2.8) |
| Any complication of pregnancy[c] | | |
| No | 164,247 | (66.2) |
| Yes | 83,770 | (33.8) |
| Foetal complication[e] | 11,122 | (4.5) |
| Maternal complication[f] | 74,053 | (29.9) |
| Placental complication[g] | 3995 | (1.6) |
| Quintile of neighbourhood material deprivation | | |
| 1 (lowest) | 37,256 | (15.0) |
| 2 | 45,095 | (18.2) |
| 3 | 48,205 | (19.4) |
| 4 | 50,954 | (20.5) |
| 5 (highest) | 64,144 | (25.9) |
| Missing | 2363 | (1.0) |
| Quintile of residential instability | | |
| 1 (lowest) | 55,019 | (22.2) |
| 2 | 46,304 | (18.7) |
| 3 | 44,133 | (17.8) |
| 4 | 46,572 | (18.8) |
| 5 (highest) | 53,626 | (21.6) |
| Missing | 2363 | (1.0) |
| Quintile of neighbourhood dependency | | |
| 1 (lowest) | 84,705 | (34.2) |
| 2 | 50,239 | (20.3) |
| 3 | 42,638 | (17.2) |
| 4 | 36,635 | (14.8) |
| 5 (highest) | 31,437 | (12.7) |
| Missing | 2363 | (1.0) |
| Quintile of neighbourhood ethnic diversity | | |
| 1 (lowest) | 34,175 | (13.8) |
| 2 | 36,137 | (14.6) |
| 3 | 40,723 | (16.4) |
| 4 | 50,048 | (20.2) |

(Continues)

(Continues)

TABLE 1 (Continued)

| Characteristics | No. | (%) |
|---|---|---|
| 5 (highest) | 84,571 | (34.1) |
| Missing | 2363 | (1.0) |
| Rural residence | | |
| No | 222,178 | (89.6) |
| Yes | 25,833 | (10.4) |
| Missing | 6 | (0.0) |
| Infant characteristics | | |
| Allergic disease development during follow-up (outcome)[c] | | |
| Anaphylaxis | 1184 | (0.5) |
| Asthma | 33,336 | (13.4) |
| Dermatitis | 54,119 | (21.8) |
| Rhinitis | 8076 | (3.3) |
| Sex | | |
| Female | 120,766 | (48.7) |
| Male | 127,251 | (51.3) |
| Median (IQR) birthweight, grams | 3396.0 | (3070.0–3724.0) |
| Small for gestational age at 10th percentile | 22,421 | (9.0) |
| Large for gestational age at 90th percentile | 25,971 | (10.5) |
| Median (IQR) gestational age, weeks | 39.0 | (38.0–40.0) |
| Vaginal birth | | |
| No | 66,799 | (26.9) |
| Yes | 181,218 | (73.1) |
| Season of birth | | |
| Spring (March–May) | 61,531 | (24.8) |
| Summer (June–August) | 65,171 | (26.3) |
| Fall (September–November) | 62,996 | (25.4) |
| Winter (December–February) | 58,319 | (23.5) |
| Infant feeding from birth to discharge | | |
| Breastfed only | 126,011 | (50.8) |
| Combination | 53,362 | (21.5) |
| Substitute | 21,966 | (8.9) |
| Missing | 46,678 | (18.8) |
| Intention to breastfeed | | |
| No | 16,833 | (6.8) |
| Yes | 212,987 | (85.9) |
| Missing | 18,197 | (7.3) |
| Reason for censor | | |
| Death | 614 | (0.2) |
| End of follow-up *or* loss of healthcare eligibility[h] | 247,403 | (99.8) |
| Median (IQR) follow-up, days | 2183.0 | (2001.0–2374.0) |

(Continues)

TABLE 1 (Continued)

*Notes:* Data are presented as numbers (percentages), unless otherwise stated.

Abbreviations: BMI, body mass index; GWG, gestational weight gain; IQR, interquartile range.

[a]Pre-pregnancy BMI was classified according to World Health Organization categories: underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), or obese (≥30.0 kg/m$^2$).

[b]GWG was classified according to Institute of Medicine categories and accounted for gestational length.

[c]Categories are not mutually exclusive.

[d]Includes prescribed antibiotics, anti-inflammatory medication, and antihistamines.

[e]Includes foetal anomalies, isoimmunisation, alloimmunisation, intrauterine growth restriction, large for gestational age, oligohydramnios, polyhydramnios and other.

[f]Includes anaemia unresponsive to therapy, antepartum bleeding, gestational diabetes, complications of diabetes, preterm labour prior to admission, preterm premature rupture of the membranes, premature rupture of the membranes, infection and other.

[g]Includes placental abruption, placenta accrete, placenta increta, placenta percreta, placenta previa and other.

[h]Due to privacy and confidentiality policies governing data access, these two categories were combined to prevent calculation of infant birthdates.

which suggested little impact on our results. As well, since 44% of mothers were not measured for weight, our study may be limited by non-differential exposure misclassification. After identifying differences in results by the method of weight ascertainment, we ran an additional probabilistic bias analysis and found that exposure misclassification was unlikely to be a large contributor of bias.

As in all epidemiological studies, selection bias may be impacting our results, though we used multiple imputation methods to handle high exposure missingness and found little evidence of selection bias in a sensitivity analysis.

Due to the lack of non-clinical data collected in health administrative datasets, our models may be biased by residual confounding. In another sensitivity analysis, we further adjusted for maternal propensity to access care and found no changes to our results. Still, our models may be insufficiently adjusted for maternal race and ethnicity, perinatal health behaviours, such as diet and exercise, and personal, rather than neighbourhood-level socioeconomic status (SES), which could not be captured in our study. As marginalisation, poor diet and exercise, and low SES may be associated with an increased risk of high BMI, excess GWG, and an increase in the study outcomes, the potential direction of this residual confounding bias may be away from the null.

Finally, even though we conducted sensitivity analyses to evaluate the impact of these limitations on our findings, no sensitivity analysis is likely to fully quantify the impact of bias.

## 4.4 | Interpretation

Several longitudinal studies have examined the relationship between maternal pre-pregnancy BMI and asthma development in

**TABLE 2** Crude incidence rate (per 100,000 person-days) for all paediatric allergic disease outcomes, overall and stratified by exposure group[a]

| Outcome | Exposure | Category | Person-days at risk | No. of events | Incidence rate (95% CI) |
|---|---|---|---|---|---|
| Anaphylaxis | Overall | | 5338.94 | 1184 | 0.22 (0.22, 0.22) |
| | Pre-pregnancy BMI | Underweight | 304.46 | 70 | 0.23 (0.21, 0.25) |
| | | Normal weight | 2776.57 | 657 | 0.24 (0.23, 0.24) |
| | | Overweight | 1293.02 | 292 | 0.23 (0.21, 0.24) |
| | | Obese | 964.88 | 165 | 0.17 (0.16, 0.18) |
| | GWG | Inadequate | 1028.73 | 222 | 0.22 (0.19, 0.24) |
| | | Adequate | 1502.07 | 316 | 0.21 (0.20, 0.22) |
| | | Excess | 2808.14 | 647 | 0.23 (0.22, 0.24) |
| Asthma | Overall | | 4904.72 | 33,336 | 6.80 (6.73, 6.86) |
| | Pre-pregnancy BMI | Underweight | 280.76 | 1878 | 6.69 (6.37, 7.01) |
| | | Normal weight | 2556.20 | 17,098 | 6.69 (6.59, 6.78) |
| | | Overweight | 1186.16 | 8149 | 6.87 (6.72, 7.01) |
| | | Obese | 881.59 | 6212 | 7.04 (6.88, 7.21) |
| | GWG | Inadequate | 943.93 | 6421 | 6.80 (6.63, 6.97) |
| | | Adequate | 1381.86 | 9288 | 6.72 (6.57, 6.87) |
| | | Excess | 2578.93 | 17,627 | 6.83 (6.72, 6.94) |
| Dermatitis | Overall | | 4360.55 | 54,119 | 12.41 (12.28, 12.54) |
| | Pre-pregnancy BMI | Underweight | 240.93 | 3480 | 14.44 (13.80, 15.08) |
| | | Normal weight | 2250.10 | 29,041 | 12.90 (12.71, 13.09) |
| | | Overweight | 1063.62 | 12,726 | 11.96 (11.69, 12.23) |
| | | Obese | 805.91 | 8872 | 11.01 (10.71, 11.30) |
| | GWG | Inadequate | 845.58 | 10,122 | 11.97 (11.62, 12.32) |
| | | Adequate | 1223.26 | 15,344 | 12.54 (12.26, 12.81) |
| | | Excess | 2291.72 | 28,653 | 12.50 (12.29, 12.71) |
| Rhinitis | Overall | | 5238.23 | 8076 | 1.54 (1.52, 1.56) |
| | Pre-pregnancy BMI | Underweight | 298.25 | 502 | 1.68 (1.57, 1.80) |
| | | Normal weight | 2722.93 | 4312 | 1.58 (1.55, 1.61) |
| | | Overweight | 1269.70 | 1893 | 1.49 (1.44, 1.54) |
| | | Obese | 947.35 | 1369 | 1.44 (1.40, 1.49) |
| | GWG | Inadequate | 1009.99 | 1494 | 1.48 (1.41, 1.55) |
| | | Adequate | 1473.35 | 2296 | 1.56 (1.51, 1.60) |
| | | Excess | 2754.89 | 4286 | 1.56 (1.52, 1.59) |

Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain.
[a]Exposure data are pooled estimates from 10 multiply imputed datasets.

offspring.[13–22] Consistent with our findings, most reported a positive association.[14–17,19–22] Less is known about the relationship with other common allergic diseases.

Of the five prospective studies that explored the association with dermatitis, three observed inverse associations similar to ours, where lower BMI category was generally associated to higher risk of dermatitis,[21,23,24] whereas two found no association, though neither studied underweight mothers.[22,26] Likewise, in a recent meta-analysis of ten observational studies, Chen and colleagues found an inverse association between maternal pre-pregnancy BMI category and atopic dermatitis development among offspring.[28] Three cohort studies investigated rhinitis as an outcome,[21,22,24] all finding no relationship with pre-pregnancy BMI, consistent with our study. Finally, to our knowledge, no previous study has examined the association between maternal pre-pregnancy BMI and anaphylaxis; here, we showed 17% lower hazards of anaphylaxis for infants born to obese compared with normal weight mothers.

Varying associations between pre-pregnancy BMI and allergic disease have been shown before,[21,22,24] though the mechanism remains to be elucidated. Previous studies have hypothesised potential explanation by distinct allergic and non-allergic aetiologies of each outcome. For example, pre-pregnancy BMI may be acting through a non-allergic biological pathway since it has been shown to reduce levels of maternal IgE in cord blood[26]; as a result, pre-pregnancy BMI

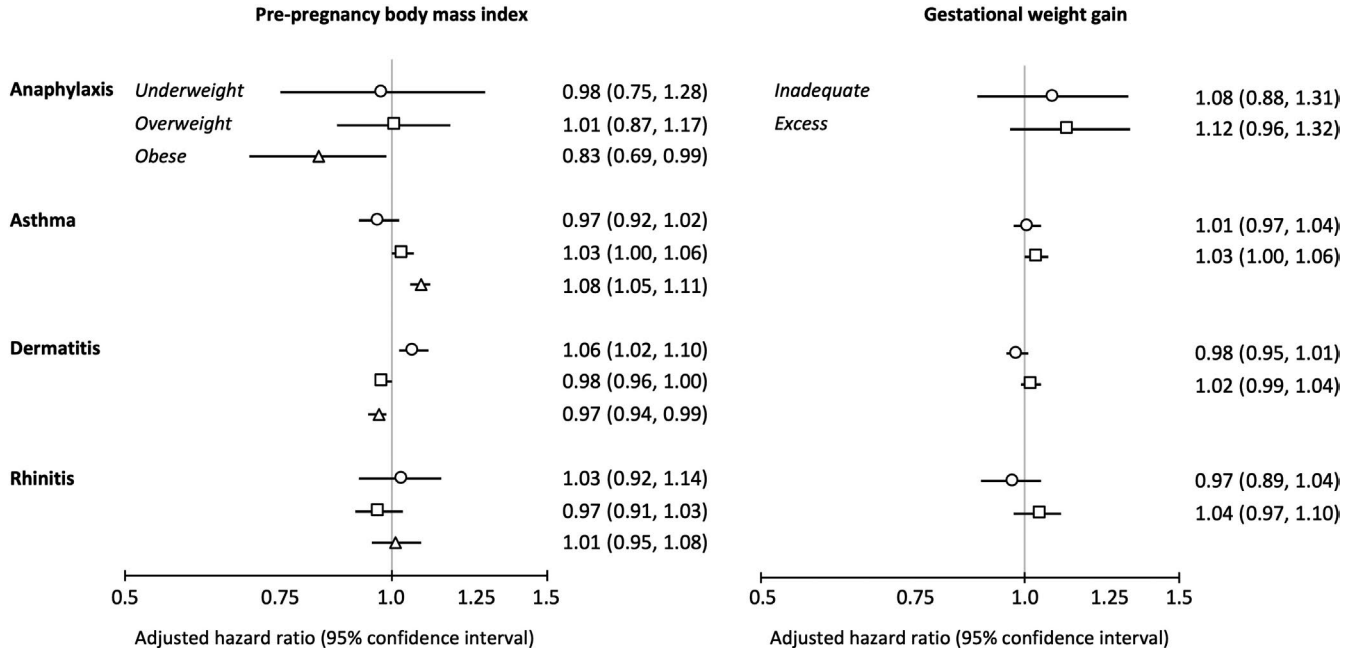


**FIGURE 2** Adjusted hazard ratios (95% confidence intervals) between categorical exposures and paediatric allergic disease development during follow-up. Referent groups for pre-pregnancy body mass index and gestational weight gain were normal weight and adequate weight gain, respectively. Horizontal lines represent 95% confidence intervals. Circles represent pre-pregnancy underweight or inadequate weight gain; squares, overweight or excess; and triangles, obesity. Data are pooled estimates from 10 multiply imputed datasets. Tabular data are available in Supplementary File S3

would affect the development of non-allergic asthma, while slightly reducing or having no impact on allergic rhinitis and atopic dermatitis, both which are mediated by IgE.[21,22,24,26] Unfortunately, no validated algorithm exists to differentiate between allergic and non-allergic asthma using health administrative databases.

Fewer studies have investigated the association between GWG and paediatric allergic disease development,[13,15,16,21,23,25] and findings have been inconsistent, with some reporting an association between GWG and increased[13,21] or reduced asthma risk,[15,25] or no association.[15,16] Studies examining the association between GWG and dermatitis have observed both increased risk[23] and no association.[21,23] Lastly, no association was found between GWG and rhinitis in a large longitudinal study from Denmark.[21]

In this study, we found no association between GWG and any paediatric allergic disease, including anaphylaxis, which had not been previously assessed. This finding held true both when GWG was categorised by IOM guidelines accounting for gestational length and when a continuous measure was modelled using restricted cubic splines. The conflicting findings published by previous studies may be explained by the various methods used to categorise GWG; for instance, previous studies have employed tertiles,[13] dichotomisation[25] and categorisation into five[16,23] or six unvalidated groups.[15,21] Still, null results have been reported by studies using IOM guidelines or continuous GWG,[15,23] supporting our findings.

Our results may also be supported biologically. A growing number of longitudinal studies have found that pre-pregnancy BMI is associated with greater changes in inflammatory and metabolic markers compared with GWG.[49–54] For example, pre-pregnancy BMI has been shown to influence circulating levels of inflammatory regulators (leptin, TLR4 and C-protein)[49–54] and pro-inflammatory cytokines (IL-6 and IL-8)[52,54] more so than GWG, exposing the infant to inflammation both prenatally in the placenta[54] and postnatally in breastmilk.[51] Given that inflammation and metabolic dysfunction are theorised to predispose offspring to allergic disease, these findings may explain our associations between paediatric allergic disease and pre-pregnancy BMI, but null results with GWG.

## 4.5 | Conclusions

Overall, our results suggest maternal weight, but not GWG, may have consequences on allergic disease development in offspring. Similar to previous studies, our data were subject to potential information and selection biases; however, we assessed the potential impact of these biases in prespecified sensitivity analyses and detected little impact on our results. Moreover, although statistically significant, many of the associations were of low magnitude. Nevertheless, given the high prevalence of maternal pre-pregnancy overweight and obesity, even small increases in risk may be impactful at a population level. Interventions to promote normal pre-pregnancy BMI may, therefore, be an important and cost-effective upstream target to ease the epidemic trends of allergic diseases in childhood. Future work should aim to assess the impact of maternal and paternal health behaviours before, during and after pregnancy on this relationship.

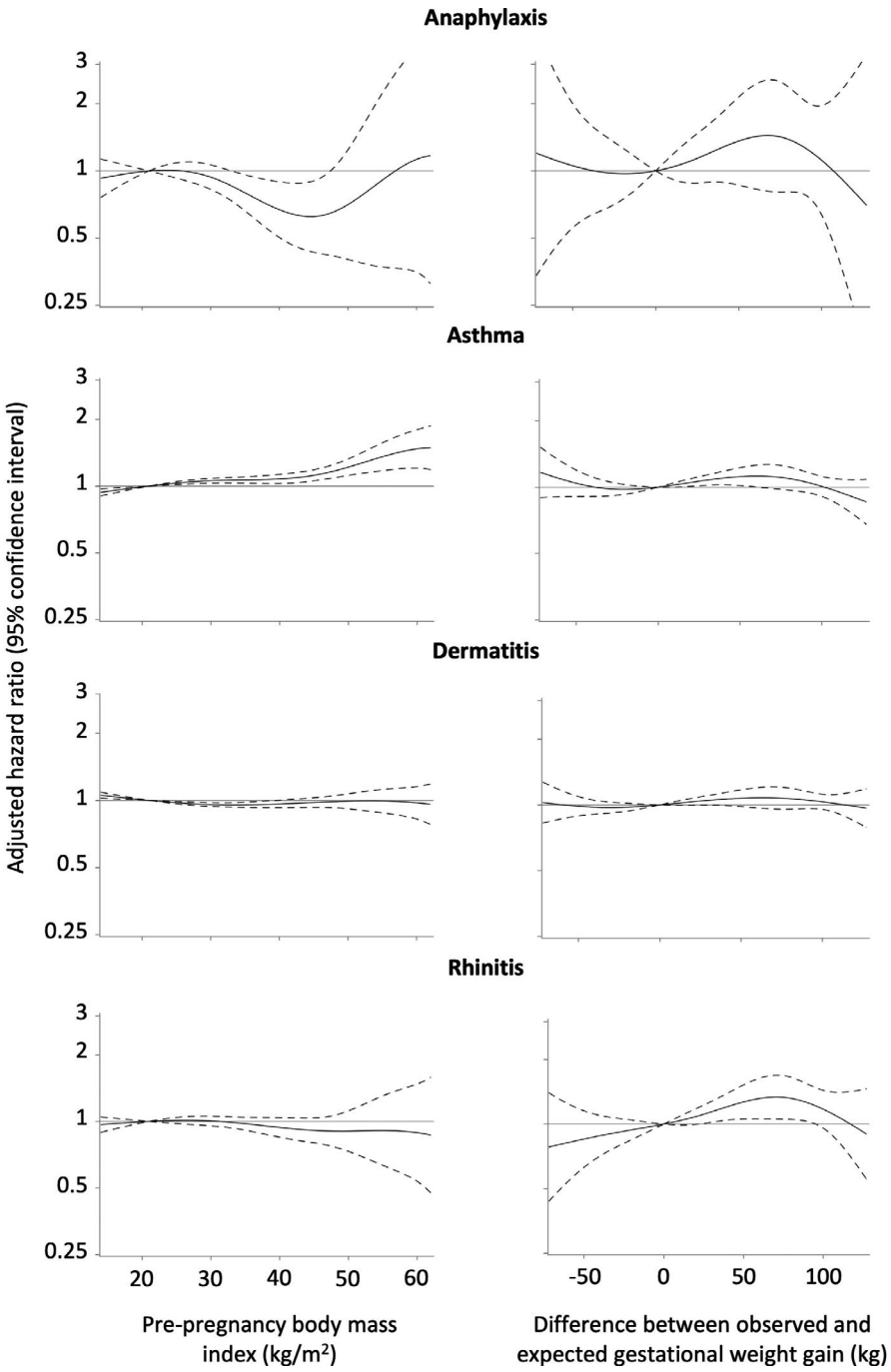


**FIGURE 3** Adjusted hazard ratios (95% confidence intervals) between continuous exposures and paediatric allergic disease development during follow-up using restricted cubic splines. Referent groups for pre-pregnancy body mass index and difference between observed and expected gestational weight gain were 21 kg/m$^2$ and 0 kg, respectively. Data are pooled estimates from 10 multiply imputed datasets

## ACKNOWLEDGEMENTS

Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI. This study is based in part on data provided by Better Outcomes Registry and Network ('BORN'), part of the Children's Hospital of Eastern Ontario. The interpretation and conclusions contained herein do not necessarily represent those of BORN Ontario. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This work also received funding from a Canadian Institutes of Health Research (CIHR) Foundation Grant (grant number FDN-148438) to LMG, and a CIHR Frederick Banting and Charles Best Canada Graduate Scholarship–Master's Award and an Ontario Graduate Scholarship to SAS. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

## CONFLICT OF INTEREST

None declared.

## DATA AVAILABILITY STATEMENT

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (eg healthcare organisations and government) prohibit ICES

from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are, therefore, either inaccessible or may require modification.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Srugo SA, Fell DB, Corsi DJ, Fakhraei R, Guo Y, Gaudet LM. Examining the role of pre-pregnancy weight and gestational weight gain in allergic disease development among offspring: A population-based cohort study in Ontario, Canada. *Paediatr Perinat Epidemiol*. 2022;36:144–155. https://doi.org/10.1111/ppe.12806