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Data sources

The following datasets were used in this study:

1. The Better Outcomes Registry & Network (BORN) Ontario Information System (BIS) is the provincial birth registry in Ontario. It captures maternal and perinatal information, including demographics, health behaviours, pregnancy and birth complications, and outcomes from all pregnancies in the province. Mandatory data checks are performed by each entry site to maintain high data quality. A cohort profile\(^1\) and data quality validation\(^2\) have recently been published.

2. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) contains patient-level discharge abstracts for all hospitalizations in acute, rehab, chronic, and day surgery institutions in Ontario. Each record corresponds to one hospitalization and includes up to 25 medical diagnosis fields coded using ICD-10-CA.

3. The CIHI National Ambulatory Care Reporting System (NACRS) contains patient-level information on all hospital- and community-based urgent ambulatory care visits, such as from day surgery, outpatient clinics, and emergency departments. Similar to the DAD, each visit is recorded as a separate entry and includes up to 10 medical diagnosis fields coded using ICD-10-CA codes.

4. The Ontario Health Insurance Plan (OHIP) database contains all services performed by outpatient healthcare providers and reimbursed by the provincial healthcare plan. Each record corresponds to a single service and includes one medical diagnosis field coded using ICD-9.
5. The ICES Ontario Asthma Dataset (ASTHMA) contains all prevalent and incident cases of asthma in Ontario, as identified by a validated\textsuperscript{3-5} algorithm that uses DAD and OHIP claims data. Cases are flagged if the patient has at least one hospital admission with an asthma diagnosis (ICD-10-CA codes J45 or J46 in DAD) or at least two outpatient care visits with an asthma diagnosis (ICD-9 code 493 in OHIP). The date of diagnosis is set to the date of the earliest claim.

6. The Ontario Marginalization Index (ON-MARG) was linked to ascertain neighbourhood-level information. The dataset contains four dimensions of marginalization: residential instability, which refers to the concentration of residents at high risk of family or housing instability in the neighbourhood; material deprivation, which refers to the concentration of residents at high risk of being unable to access basic material needs; dependency, which refers to the area-level prevalence of unemployment; and ethnic diversity, which refers to the concentration of residents who are recent immigrants and/or visible minorities, and who therefore may experience structural racism and discrimination.\textsuperscript{6}

**Data linkage and access**

Records in each dataset at ICES were assigned a unique identification code and subsequently de-identified, allowing for the linkage of datasets through deterministic and probabilistic methods while adhering to strict privacy and confidentiality policies. Both maternal and infant identification codes were used to link the BIS-defined cohort to health administrative datasets to provide additional clinical and sociodemographic information at birth, follow-up, and during
look-back windows. Data were analysed remotely through the secure research analytic environment at ICES.
Algorithms for outcomes in main analyses

**eTable 2.** Validated algorithms used to identify cases of paediatric allergic disease through diagnostic codes from healthcare encounters.

| Outcome     | Algorithm                                                                 | Codes                              | Validation                                                                 | Notes                                                                                                                                                                                                 |
|-------------|---------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anaphylaxis | ≥1 inpatient or emergency department encounter (DAD, NACRS)               | ICD-10-CA code T78.2, T80.5, T78.0, T88.6  
ICD-9 code 995.0, 999.4, 995.6 | This represents criterion A of the algorithm, which showed a positive predictive value of 69% and a sensitivity of 75%.  
7  
The ICD codes for anaphylactic shock due to adverse food reaction (T78.0, 995.6) were added to the algorithm due to its importance among young children, with approval from the first author of the original algorithm (personal communication, Kathleen Walsh). Further, we could not implement criterion B of the original algorithm since the OHIP database lacks ICD codes more specific than 3 digits, lacks symptom/intervention/procedure codes, and is an unreliable database for anaphylaxis, since most cases would present in hospital settings and not outpatient visits. |
| Asthma      | ≥1 hospitalization (DAD) and/or ≥2 outpatient care visits (OHIP) for asthma within two years | ICD-10-CA codes J45 or J46  
ICD-9 code 493 | The algorithm was validated twice. Among children aged 1–8, sensitivity and specificity were 91% and 83%, respectively;  
4  
among children aged 1–5, estimates were 81% and 90%, respectively.  
5  
Children identified as asthma cases based on fulfilling the algorithm for asthma diagnosis before the age of 6 months were not classified as asthma cases unless a further hospitalization or outpatient visit for asthma was detected after 12 months of age. |
| Condition  | ≥2 care visits (DAD, NACRS, OHIP) occurring ≥6 months apart | ICD-10-CA code | ICD-9 code | Algorithm Performance |
|------------|----------------------------------------------------------|----------------|-----------|-----------------------|
| Dermatitis | ICD-10-CA code L20                                         | ICD-9 code 691 | The algorithm displayed a positive predictive value of 90%.^8^ |
| Rhinitis   | ICD-10-CA codes J301–J304                                 | ICD-9 code 477 | The algorithm displayed a positive predictive value of 100%.^8^ |
Covariates

Several covariates were included to characterise the study population and/or due to their potential to confound the exposure-outcome relationships. (Refer to the directed acyclic graph in the protocol\textsuperscript{9} [reproduced in eFigure 1] for variables included in the models.) Variables were ascertained from the BIS, unless stated otherwise. Maternal characteristics included age at delivery (< 25 years, 25–29, 30–34, ≥ 35), maternal medication use during pregnancy (including prescribed antibiotics, anti-inflammatory medication, and antihistamines), maternal substance use during pregnancy (including tobacco, alcohol, and illicit drug use), residing with smoker during pregnancy (either at birth or first prenatal visit), parity, and maternal pre-existing conditions (including pre-existing asthma [ascertained from the ASTHMA database], diabetes, hypertension, and other autoimmune and pulmonary disorders). Neighbourhood characteristics based on linked postal codes included rural residence and four marginalization dimensions (residential instability, material deprivation, dependency, and ethnic diversity; ascertained from the ON-MARG database). As recommended by the ON-MARG user guide, since correlations between each dimension and each outcome were not all in the same direction, a summary score was not derived; instead, all four dimensions were adjusted for separately.\textsuperscript{6} Finally, birth and infant characteristics included mode of delivery, complications of pregnancy (encompassing fetal, maternal, and placental complications), season of birth (Spring, March–May; Summer, June–August; Fall, September–November; Winter, December–February), infant sex, gestational age (measured by ultrasonography in BORN, the gold standard in pregnancy dating), birth weight (continuous or categorized as small or large for gestational age, below
10th or above 90th percentiles, respectively), newborn feeding from birth to discharge, and intention to breastfeed during pregnancy or at birth.

The following complications were included in the complications of pregnancy variable:

Fetal complications: fetal anomalies, isoimmunization, alloimmunization, intrauterine growth restriction, large for gestational age, oligohydramnios, polyhydramnios, and other

Maternal complications: 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

Placental complications: placental abruption, placenta accrete, placenta increta, placenta percreta, placenta previa, and other.

As prespecified, we tested whether infant sex, GWG, and pre-pregnancy BMI were effect measure modifiers; estimates of strata were only qualitatively different for infant sex and so we only reported infant sex-specific estimates.
**eFigure 1.** Directed acyclic graph. Reproduced from Srugo *et al*, 2021.

**GEE methods**

We employed generalized estimating equation methods to account for repeated pregnancies to the same mother during the 2012–2014 period. Based on published recommendations, we used the `covs(aggregate)` option in proc phreg, which employs the marginal model approach through a working independence assumption by Wei, Lin, and Weissfeld.

**Imputation methods**

The prevalence of missing data ranged from 0% to 29.7% across the variables used in the main analyses. Comparisons between those with and without missing data are presented in a
sensitivity analysis (Supplementary File 4). Based on a qualitative assessment, the missing data displayed an arbitrary missingness pattern, which was taken into account when choosing the imputation method. As such, we used the fully conditional specification (FCS) approach to multiple imputation using PROC MI to generate 10 imputed datasets, saving the datasets at every 20th iteration (i.e., 20 burn-in iterations, the SAS default). The FCS approach employs a different conditional distribution based on the type of variable being imputed and allows for unique imputation models for each variable; this allows for the imputation of variables which can only take on plausible values (such as height or quantiles of neighbourhood deprivation). It is important to note that while multiple imputation can increase the accuracy and statistical power of analyses compared to other missing data procedures,\textsuperscript{12} it only produces unbiased results when the MAR assumption is held.\textsuperscript{13} As the MAR assumption is only held if a sufficient number of variables predictive of missing data are used, a lenient inclusion strategy for auxiliary variables in imputation models is recommended.\textsuperscript{13} Auxiliary variables were included if they were thought to be predictive of missing values as determined by our theoretical framework.

Based on the above recommendations, we included all variables from the main analysis models and six auxiliary variables (placental, fetal, and maternal complications, mother residing with smoker during pregnancy, small for gestational age at 10th percentile, and infant sex) in the imputation models. Instead of including final exposure variables (pre-pregnancy body mass index and gestational weight gain), we included the original variables used to derive these, including maternal height, pre-pregnancy weight, and weight at delivery, and derived the continuous and categorical versions of the exposures afterwards. Based on the SAS User Guide,
the discriminant function method was employed for binary variables, the logistic regression method for ordinal variables, and the predictive mean matching method for continuous variables. Main analyses were then fit on each imputed dataset and parameter estimates and standard errors were combined using PROC MIANALYZE to output the final results.

Due to computational restrictions, we generated only 10 multiply imputed datasets. In papers by Bodner\textsuperscript{15} and von Hippel,\textsuperscript{16} the authors create two formulas to determine the number of imputations necessary to reduce the variability of standard errors (SEs) for betas between MI datasets. They both suggest that the coefficient of variation (CV) for SEs between all imputation datasets be <0.05 and that the standard deviation (SD) of SEs be <0.001. We tested the CV of the SEs for each beta of BMI category in our adjusted asthma model; CVs ranged from 0.0008 to 0.004 and SDs of SEs ranged from 0.00001 to 0.0001 — well below the thresholds the authors set. Based on this, we believe that our 10 multiply imputed datasets are highly reliable and generating additional datasets would have been unlikely to meaningfully change our results.

**Proportional hazards assumption**

The proportional hazards assumption of each Cox model was first tested by checking the statistical significance of Wald tests for interaction between exposure and time; a p-value below 0.05 was identified as a potential violation and reassessed graphically using Schoenfeld residual plots to identify potential correlations with time. We used a conservative strategy as directed by Kleinbaum and Klein, assuming no violation unless there was strong evidence to the contrary.\textsuperscript{17}
Restricted cubic splines

We followed guidelines by Harrell on restricted cubic splines. Specifically, Harrell recommends five spline knots for sample sizes of 100 records or more, with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. This approach was implemented in SAS using proc phreg with the effect statement and spline option.

Protocol amendments

In some instances, we deviated from our published protocol. The following table (eTable 3) details these amendments and our rationale.

eTable 3. Amendments and rationale for deviations from the original protocol.

| Amendment                                                                 | Rationale                                                                                   |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Some women had multiple entries for weight at first prenatal visit. In this case, the earliest entry was used. | First prenatal visit weight data were needed to estimate pre-pregnancy weight; therefore, earliest weight at first trimester visit would be closest to the average first trimester weight gain used to estimate pre-pregnancy weight. |
| Gestational age had a small number of non-equal duplicate values for the same pregnancy (n~1000). Most of these duplicates (~80%) did not differ by more than a week. These differences were due to different methods to determine estimated date of birth, since gestational age is derived from estimated date of birth minus actual date of birth. If more than one gestational | The order of methods was chosen based on our knowledge of which methods would be most accurate. |
age estimate was recorded, we chose the one based on the following this order:

1. Assisted reproductive technology
2. First trimester dating ultrasound
3. Second trimester dating ultrasound
4. Obstetrical clinical estimate
5. Last menstrual period
6. Unknown

In the case that two entries were recorded and both used the same methods, the most recent value was taken.

In the healthcare datasets, we included scheduled emergency department (ED) visits, ED visits transferred from another ED, ED visits that lead to inpatient hospitalization, and diagnosis codes from any encounter (not just the final encounter), and removed duplicate ED visits. These methods were used since we wanted to ascertain study outcomes from any healthcare encounter.

Maternal age was categorized (<25 years, 25–29, 30–34, ≥35) and Ontario portion of the federal Immigration, Refugees and Citizenship Canada Permanent Resident Database, which would have been used to ascertain maternal country of birth, was not given in data access.

We added an age restriction to the asthma outcome algorithm. Children identified as asthma cases based on fulfilling the algorithm for asthma diagnosis before the age of 6 months were not classified as asthma cases unless a further hospitalization or outpatient visit for asthma was detected after 12 months of age. This was restriction added due to questions surrounding the validity of asthma diagnoses in very young children. These methods were based on previously published research from the team who created the initial algorithm.1

To ascertain anaphylaxis cases using the algorithm, we excluded records from OHIP and only employed records from DAD and NACRS. The OHIP database lacks ICD codes more specific than 3 digits, lacks symptom/intervention/procedure codes, and is an unreliable database for anaphylaxis, since most cases would present in hospital settings and not outpatient visits.
Analyses were conducted in SAS Enterprise Guide version 7.1, instead of SAS version 9.4. SAS EG was used because it was the only software available when remotely accessing the data, whereas SAS 9.4 would have been available on site.

Outliers for height, pre-pregnancy weight, weight at delivery, and parity were winsorized below the 0.1th and above the 99.9th percentiles before exposures were derived.

These methods were used to minimize the influence of extreme outliers, most of which can be assumed to be due to data quality problems. This was also done to reduce multiple imputation computing time and increase likelihood of convergence.

We first tested the proportional hazards assumption based on the Wald test for interaction and, if significant, examined the Schoenfeld residual plots, using a conservative approach.

These methods were added to clarify the order and importance of the tests, especially in the case where one test shows a violation while the other does not, and were based previous recommendations.\(^\text{17}\)

Individuals with missing data for maternal pre-existing conditions were coded as having none.

Maternal pre-existing conditions are more likely to be missing in healthcare administrative datasets if the mother has none.

Added more information on multiple imputation methods, including on imputation models, burn-in iterations, and the functional conditional specification approach (details in sections above).

These were added to clarify our approach and allow for reproducibility and scrutiny.

Removed a pre-specified sensitivity analysis, which aimed to use the Ontario Drug Benefit database to employ new, validated algorithms for rhinitis and dermatitis using hospital diagnoses and dispensed prescription medications. This sensitivity analysis was proposed to evaluate potential outcome misclassification, as we would be able to compare the results among the ODB-eligible infants using the main algorithms and the new algorithms.

Infants were only eligible for ODB under the OHIP+ program that ran from January 2018 to April 2019, leaving little to no time for follow-up. Before then, only the few infants on social assistance or disability programs were eligible; however, information on start and stop dates of eligibility were not recorded in the database for that cohort. Therefore, we would not be able to capture infants who were eligible but were not prescribed medications. Further, if an infant ceased being prescribed a medication in the database, it would not be known whether they no longer needed the medication or
whether they gained access to private payer coverage or were paying out of pocket.

Given these limitations, it was not possible to construct a subgroup of eligible infants, identify cases of rhinitis or dermatitis, and compare these results to the main findings. As such, this sensitivity analysis was not employed, given that it would not be able to evaluate potential outcome misclassification.

Ran an additional probabilistic bias analysis to measure the extent to which non-differential exposure misclassification had an impact on our results.

After finding evidence of a potential impact of exposure misclassification on our results in a prespecified sensitivity analysis, we aimed to further examine this possible bias in a probabilistic bias analysis, similar to the one prespecified for outcome misclassification.
References

1  Murphy MSQ, Fell DB, Sprague AE, Corsi DJ, Dougan S, Dunn SI, et al. Data Resource Profile: Better Outcomes Registry & Network (BORN) Ontario. *International Journal of Epidemiology* 2021:dyab033.

2  Dunn S, Lanes A, Sprague AE, Fell DB, Weiss D, Reszel J, et al. Data accuracy in the Ontario birth Registry: a chart re-abstraction study. *BMC Health Services Research* 2019;19:1001.

3  Radhakrishnan DK, Dell SD, Guttmann A, Shariff SZ, Liu K, To T. Trends in the age of diagnosis of childhood asthma. *The Journal of Allergy and Clinical Immunology* 2014;134:1057-1062.e5.

4  To T, Dell S, Dick PT, Cicutto L, Harris JK, MacLusky IB, et al. Case verification of children with asthma in Ontario. *Pediatric Allergy and Immunology* 2006;17:69–76.

5  Omand JA, Maguire JL, O’Connor DL, Parkin PC, Birken CS, Thorpe KE, et al. Agreement between a health claims algorithm and parent-reported asthma in young children. *Pediatric Pulmonology* 2019;54:1547–1556.

6  Matheson F, van Ingen T. *2016 Ontario marginalization index: user guide*. Toronto, ON: St. Michael’s Hospital; 2018.

7  Walsh KE, Cutrona SL, Foy S, Baker MA, Forrow S, Shoaiib A, et al. Validation of anaphylaxis in the Food and Drug Administration’s Mini-Sentinel. *Pharmacoepidemiology and Drug Safety* 2013;22:1205–1213.

8  Hill DA, Grundmeier RW, Ram G, Spergel JM. The epidemiologic characteristics of healthcare provider-diagnosed eczema, asthma, allergic rhinitis, and food allergy in children: a retrospective cohort study. *BMJ Pediatrics* 2016;16:133.

9  Srugo SA, Gaudet L, Corsi D, Fakhraei R, Guo Y, Fell DB. Examining the effects of pre-pregnancy weight and gestational weight gain on allergic disease development in offspring: a protocol for a population-based study using health administrative databases in Ontario, Canada. *BMJ Paediatrics Open* 2021;5:e000893.

10 Gharibvand L, Liu L. Analysis of Survival Data with Clustered Events. In: *Proceedings from the SAS Global Forum 2009 Conference* Cary, NC: SAS Institute Inc., 2009.

11 Wei LJ, Lin DY, Weissfeld L. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. *Journal of the American Statistical Association* 1989;84:1065–1073.

12 Enders CK. *Applied Missing Data Analysis*. New York, NY: Guilford Press; 2010.
13 Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.

14 SAS Institute Inc. The MI Procedure: FCS Statement. (last accessed December 2020).

15 Bodner TE. What Improves with Increased Missing Data Imputations? *Structural Equation Modeling* 2008;15:651–675.

16 von Hippel PT. How Many Imputations Do You Need? A Two-stage Calculation Using a Quadratic Rule. *Sociological Methods & Research* 2020;49:699–718.

17 Kleinbaum DG, Klein M. Evaluating the Proportional Hazards Assumption. In: *Survival Analysis: A Self-Learning Text* New York, NY: Springer, 2012; pp. 161–200.

18 Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Cham, Switzerland: Springer; 2015.