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Birthweight for gestational age and the risk of asthma in childhood and adolescence: a retrospective cohort study

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ABSTRACT

Objective: To examine the association between birthweight for gestational age and asthma in childhood and adolescence while controlling for potential confounders and considering smoking as an effect modifier.

Methods: A retrospective cohort of all singleton term births in Nova Scotia, Canada between 1989 and 1993 was identified in the provincial perinatal database and followed through 2014 by linking with administrative health data. The outcome, asthma, was defined as having one hospitalization or two physician visits with an ICD code for asthma in a 2-year period. Birthweight was categorized as small (SGA), large (LGA), or appropriate (AGA) for gestational age. Multivariable-adjusted Cox proportional hazards models were used to examine the association between the birthweight for gestational age and asthma and to test for effect modification by maternal smoking in pregnancy.

Results: Of the 40,724 cohort children, 10.5% and 11.7% were born SGA and LGA, respectively, and the risk of developing asthma to age 18 years was 30.2%. The adjusted hazard ratios (HR) for SGA and LGA (relative to AGA) and asthma were 1.07 [95% CI 1.02, 1.14], and 0.96 [95% CI 0.91, 1.02], respectively. Relative to AGA children born to non-smoking mothers, SGA children were not at increased risk of asthma (HR 1.02), whereas both AGA and SGA children born to smoking mothers were at significantly increased risk (HR 1.14 and 1.29, respectively).

Conclusions: Our findings suggest that SGA in term infants is not associated with asthma in childhood in the absence of smoking in pregnancy.

INTRODUCTION

Asthma is one of the most common chronic diseases in children (1) and is associated with considerable burden to the affected children, their families, and the health care system (2). Besides environmental, family, sex, socioeconomic, and lifestyle factors (3), several perinatal factors have been identified as risk factors for asthma (4–6). Low birthweight (LBW, < 2500 g) may be linked to asthma (6) through adaptive processes in utero that lead to impaired lung growth with smaller airways (7). Many studies, however, have not considered the gestational age of the infant; LBW may rather be a proxy for prematurity, which has also been linked to lung disease in childhood (8).

The risk of asthma in childhood is also influenced by other perinatal factors, such as caesarean delivery, maternal pre-pregnancy weight, or smoking in pregnancy (4, 9, 10). Few studies were able to examine the contribution of all of these factors to the risk of asthma in children and youth (11, 12). Moreover, a Swedish study in 2011 found a strong interaction between LBW and maternal smoking during pregnancy (13). It has been speculated that prenatal smoking modifies the association between impaired fetal growth and later asthma such that LBW infants become more susceptible to environmental asthma risk factors in childhood (8). This interaction between has not been assessed in other studies so far. Therefore, the objective of this study was to examine the association between birthweight for gestational age and asthma in childhood and adolescence while considering a range of perinatal confounders and smoking as an effect modifier.

METHODS

Study design and setting

This study was a retrospective cohort study of all children of singleton gestation born in the Canadian province Nova Scotia between January 1, 1989 and December 31, 1993 who were followed until December 31, 2014. The cohort was assembled through linkage of the Nova Scotia Atlee Perinatal Database (NSAPD) and with provincial administrative health data. The linkage was conducted by

Health Data Nova Scotia based on the health card number. Prior to linkage, health card numbers were encrypted to ensure anonymity. For the present analysis, only term infants (≥ 37 weeks) were included.

Perinatal database

The NSAPD captures information on all births to mothers who were resident in Nova Scotia. For each delivery record, the NSAPD includes extensive information on routine demographic variables, medical conditions, reproductive history, delivery events, and neonatal outcomes (14). Trained coders enter this information from standardized clinical forms into the NSAPD. The Reproductive Care Program of Nova Scotia maintains the database; periodic abstraction and validation studies form an ongoing data quality assurance program and have shown that the data are accurate and reliable (15).

Administrative health data

All Canadian provinces have a single-payer universal health care system that pays for essential health services for all residents. The Medical Services Insurance physician billing database contains administrative records for each insured service rendered by a physician and paid for by the provincial health care system since 1989. The database contains diagnostic codes in ICD-9 format (one from 1989-1996, up to three after 1996). Hospital databases comprised the Admissions/Separations/Day Surgery hospital database (1989-1994) and the Canadian Institute for Health Information Discharge Abstract Database (1995 and later). Information in the hospital databases includes patient demographic information, diagnostic and procedure codes, and specialty services received. Diagnostic codes are in ICD-9 format from 1989-2000 and ICD-10CA format from 2001 forward. The Insured Patient Registry keeps an ongoing record of every beneficiary of the provincial health care plan and was used to determine loss to follow-up due to death or relocation.

Main exposure of interest

The main exposure of interest was birthweight for gestational age and sex relative to a Canadian reference population (16). Infants were categorized as SGA (< 10^{th} percentile), LGA (> 90^{th} percentile), or appropriate for gestational age (AGA, 10^{th} to 90^{th} percentile). Birthweight z-scores were calculated using sex- and gestational age-specific means and standard deviations from the same reference population.

Outcome

The outcome was asthma, defined as having at least one hospitalization or two physician visits with a diagnosis code for asthma (ICD-9: 493; ICD-10: J45) in a two-year period. The date of the earliest of visit that meets this definition will be considered as the date of asthma diagnosis.This definition has been validated using chart abstraction studies and has a sensitivity of 89% and a specificity of 72% to detect asthma cases in children 0-17 years of age (17).

Confounders

A directed acyclic graph was used to determine confounding variables (Figure 1). These included maternal age, area of residence (urban vs. rural, based on the Canadian postal code), area-level household income quintile at birth (from Census of Canada information (18)), parity (1, 2, 3, or ≥ 4, including the current pregnancy), pre-pregnancy weight status (normal weight, overweight, or obese), asthma during pregnancy, mode of delivery (vaginal delivery vs. caesarean section), and smoking in pregnancy (yes/no). Information on all confounding variables was obtained from the NSAPD.

Mothers' pre-pregnancy weight was recorded on standard provincial prenatal forms and would be either self-reported or measured weight at the first prenatal visit. Self-report of pre-pregnancy weight has been shown to agree closely with measured weight (19). Maternal height has been routinely

collected for the NSAPD since 2003 and has been retroactively entered where available for women with pregnancies before that year. Where maternal height was not available, we predicted maternal body mass index (BMI) category from maternal weight based on data from 77,297 mothers for whom height and weight were recorded in the NSAPD from 2003-2015 (normal weight: < 68.0 kg; overweight: 68.0-76.6 kg; obese: ≥ 76.7 kg). The sensitivity of these weight-based categories was between 89 and 96%, and specificity was between 90 and 95%. When regressing common perinatal outcomes (gestational diabetes, mode of delivery, 5-min Apgar score <7, birthweight for gestational age, pre-eclampsia) based on imputed and recorded weight status, the effect estimates from the corresponding models did not differ by more than 10%, and the imputation-based estimates were conservative (i.e. closer to the null than the complete case estimates). Smoking during pregnancy was assessed by care providers based on maternal self-report at two timepoints (at a mother's first prenatal visit and on admission to the labour ward); any smoking at either of these times was considered smoking during pregnancy.

Statistical analysis

Descriptive statistics were estimated by birthweight for gestational age category. Unadjusted and adjusted Cox proportional hazards regression with robust standard errors was used to estimate the association between birthweight for gestational age category and diagnosis of asthma. Observations were censored when a child's health care coverage ended due to relocation outside the province or death. The Efron approximation was used to handle ties. Hot deck multiple imputation with five iterations was used to impute missing values of the confounding variables.

We also examined potential interactions between birthweight for gestational age category and smoking in pregnancy. Multiplicative interaction was investigated by assessing the statistical significance of the cross product terms of the two variables. Additive interaction was estimated by the

relative excess risk due to interaction (RERI) and the attributable proportion (AP) due to interaction (20).

Lastly, to describe the shape of the relationship between birthweight for gestational age and asthma, we developed a generalized additive model regressing asthma on birthweight for gestational age z-score, stratified by maternal smoking status during pregnancy.

Ethics

Approval for this study was given by the IWK Health Centre Research Ethics Board (File # 1015756), the Joint Data Access Committee of the Reproductive Care Program, and the Health Data Nova Scotia Data Access Committee.

RESULTS

A total of 48,790 births were recorded in the NSAPD between January 1, 1989 and December 31, 1993. Plausible birthweight and gestational age information was available for 47,450 children, and 42,999 of these could be linked with administrative health data. After exclusion of children born before 37 weeks of gestation, the final sample consisted of 40,724 children (83.5%). The administrative data algorithm (17) identified 10,155 (23.6%) and 12,997 (30.2%) of children as having had asthma at some point during the first 6 and 18 years of life, respectively. The sociodemographic and clinical characteristics of the women and children are summarized in Table 1 by birthweight for gestational age category. Compared to mothers of AGA infants, mothers of SGA infants were more likely to be younger, single, primiparous, and of normal weight, live in areas with a lower average household income, and smoke during pregnancy, whereas mothers of LGA infants tended to be older and obese, have a partner, live in higher income neighbourhoods, deliver by caesarean section, and not smoke in pregnancy.

Hazard ratios for the association between birthweight for gestational age and the development of asthma are shown in Table 2. In both the unadjusted and adjusted models, SGA was associated with an elevated risk for asthma compared to AGA. LGA was not associated with the risk of developing asthma. Further adjustment for the hypothesized mediator, mode of delivery, did not change the estimates (data not shown). Analysis of the Schoenfeld residuals showed that the proportionality assumption was met. There was no multiplicative but an additive interaction between SGA and smoking (RERI 0.13, 95% CI 0.01, 0.26) as shown in Table 3. Relative to AGA infants of non-smoking mothers, the asthma risk for SGA infants of non-smoking mothers was not different (HR 1.02), whereas the HR were elevated for AGA/smoking (HR 1.14) and SGA/smoking (HR 1.29), respectively. The AP due to interaction was 0.10, indicating that approximately 10% of asthma risk in the SGA/smoking group is due to the interaction.

The generalized additive model (Figure 2) showed that among children whose mothers smoked in their pregnancy, the lowest risk of asthma was in children with birthweight for gestational age z-scores > 1; risk increased steadily as birthweight for gestational age decreased below 0.5 units. By contrast, virtually no change in asthma risk was observed across the birthweight z-score spectrum among children whose mothers did not smoke during pregnancy.

DISCUSSION

We demonstrated in a large population-based sample that SGA in term infants was not associated with asthma risk in the absence of smoking. We found no association between LGA and asthma.

An association between SGA or LBW and asthma has been described in several studies; two meta-analyses have reported pooled odds ratios of 1.16 and 1.34, respectively, for later asthma in LBW compared to normal birthweight (2500-4000 g) infants (6, 21). Some studies did not consider smoking as a confounder or effect modifier and, therefore, may have overestimated the effect of LBW. One

study from Sweden recently reported a strong multiplicative interaction between LBW and smoking. The authors found no association of LBW with asthma and a moderate association of smoking with asthma but a strong combined association of both factors with asthma (13). Similarly, an analysis from the PIAMA study found only a weak association of LBW with asthma in the absence of maternal smoking in pregnancy but a strong association in the presence of smoking during pregnancy (22). In keeping with these two studies, our study found no association between SGA and asthma in the children of non-smoking mothers, and a strong combined effect in SGA infants whose mothers smoked during pregnancy. A possible explanation is that among children born to mothers who smoked in pregnancy, being born SGA may indicate heavier smoking compared to children born LGA or AGA, and, hence, the association appears more pronounced in the SGA group. However, limited information on the number of cigarettes smoked in the present study does not support this hypothesis; the proportion of smokers who reported smoking more than half a pack per day during pregnancy did not differ between the SGA and AGA group (67% and 62%, respectively). Since we did not have information on postnatal smoking for our cohort, we are unable to attribute the observed association to adverse intrauterine influences of smoking as opposed to highly correlated postnatal smoke exposure. Two previous studies that compared the prenatal and postnatal influences of smoking found that prenatal smoking had a stronger association with asthma or wheezing than early life exposure to smoking (23, 24). A review of studies on parental smoking and childhood asthma has also suggested that (postnatal) environmental smoke exposure triggers wheezing attacks rather than being the cause of an asthmatic predisposition (25).

The literature on the association between LGA (or high birthweight) and asthma is conflicting; some studies did not find an association (26, 27), while others reported a positive association (5, 28, 29). Two of the studies that reported a positive association were Canadian and also used administrative health data. To et al. using Ontario data found a slightly lower risk of asthma in infants with high birthweight but a trend toward a higher risk among infants with extremely large birthweight (> 6.5 kg)

(29). The authors suggested that confounding by parity or ethnicity may explain the findings. Sin et al. using Alberta data found that high birthweight infants (> 4.5 kg) had 16% more emergency visits for asthma than infants with a normal birthweight (5). The results from our survival analysis and the generalized additive model do not suggest an increase in asthma risk with increasing birthweight. The finding is somewhat surprising considering that LGA infants are at a higher risk for later obesity (30), which in turn is a risk factor for asthma (31).

Our study has several notable strengths, including the use of a large population-based dataset with a long follow-up. By contrast to many previous studies, we used birthweight for gestational age and sex to define our exposure as opposed to simple birthweight-based cutoffs and restricted our sample to term infants to remove the effect of prematurity from the association. We were also able to control for a broad range of confounders in our analysis. The outcome of our study was derived from diagnosis codes assigned by physicians and not parent report. The algorithm used to determine the presence of asthma from ICD codes in the administrative data had a sensitivity of 89% and a specificity of 72% for identifying asthma as per standardized diagnostic criteria from a chart review in a sample of Ontario children (17). The relatively low specificity probably contributed to the high cumulative incidence of asthma over the first 18 years of life in our sample. In 2017, the Canadian Chronic Disease Surveillance System reported an asthma prevalence of 14.7% for children and youth aged 1 to 19 years (32). The asthma prevalence in Nova Scotia is above the Canadian average (33). It should be noted that the 30.2% in the current study represent the cumulative incidence of ever having had asthma over the first 18 years of life, which is not directly comparable to the prevalence in a given year. The children identified as having asthma in the present study probably represent a mix of children with true asthma and children with asthma-like respiratory symptoms who were investigated for the presence of asthma. The misclassification would most likely have been non-differential and would, therefore, have resulted in an underestimation of the true association. Antenatal and neonatal care at the time our cohort was born (1989-1993) was different from today's care in some aspects, and therefore, our findings may not

be applicable to children born during this decade. Lastly, there is the potential for residual confounding due to the use of maternal pre-pregnancy weight instead of BMI, which may have also lead to an attenuation of the association.

In summary, our study found that SGA in term infants may not be associated with asthma in childhood in the absence of smoking in pregnancy. We also found no association between LGA and asthma. Future studies should examine the interaction between SGA and smoking dose to clarify their roles in the development of asthma in childhood.

TABLES

Table 1: Sociodemographic and clinical characteristics by birthweight for gestational age category (complete cases, n = 32,867). Values are presented as percentages or mean with standard deviation as appropriate.
Abbreviations: *AGA* appropriate for gestational age, *LGA* large for gestational age, *Q* quintile, *SGA* small for gestational age

	Total	**AGA** 78%	**SGA** 10%	**LGA** 12%
Maternal age [years]	27.4 (5.0)	27.3 (5.0)	26.7 (5.0)	28.3 (5.1)
Married or common-law [%]	83	83	76	87
Area-level household income [%]				
Q1 (lowest)	20	20	23	18
Q2	22	22	23	21
Q3	21	21	21	20
Q4	20	20	18	22
Q5 (highest)	17	17	14	19
Rural residence [%]	42	42	41	44
Parity [%]				
1	45	45	57	32
2	35	35	27	41
3	14	14	11	18
≥ 4	5.6	5.3	3.9	9.5
Maternal asthma [%]	3.0	3.0	3.6	2.5
Pre-pregnancy weight status [%]				
Normal weight	70	71	78	55
Overweight	16	15	12	21
Obese	14	13	9.8	24
Smoking during pregnancy [%]	29	29	51	14
Caesarean section [%]	19	18	21	26
Infant male sex [%]	51	51	50	52
Breast feeding at discharge [%]	55	56	46	59

Table 2: Asthma incidence rates and hazard ratios with 95% confidence intervals for the association of birthweight for gestational age and smoking in pregnancy with asthma in childhood, adolescence, and young adulthood.
* adjusted for smoking in pregnancy, maternal age, parity, area-level household income, rural residence, maternal asthma, and pre-pregnancy weight status.
Abbreviations: *AGA* appropriate for gestational age, *CI* confidence interval, *HR* hazard ratio, *LGA* large for gestational age, *SGA* small for gestational age

	Asthma incidence (100 person-years^{-1})	**Unadjusted** HR [95% CI]	**Adjusted** HR [95% CI]
Birthweight for gestational age			
AGA	2.05	Reference	Reference
SGA	2.32	1.15 [1.06, 1.18]	1.07 [1.02, 1.14]
LGA	1.92	0.94 [0.89, 0.99]	0.96 [0.91, 1.02]
Smoking in pregnancy			
No	1.94	Reference	Reference
Yes	2.37	1.20 [1.16, 1.25]	1.17 [1.12, 1.22]

Table 3: Asthma incidence, adjusted hazard ratios and 95% confidence intervals by birthweight for gestational age category and smoking during pregnancy (adjusted for maternal age, parity, area-level household income, rural residence, maternal asthma, pre-pregnancy weight status), and measures of additive interaction between birthweight for gestational age and smoking.
[a] exact value: 0.002; [b] exact value: 1.003
Abbreviations: *AGA* appropriate for gestational age, *AP* Attributable proportion due to interaction, *CI* confidence interval, *HR* hazard ratio, *LGA* large for gestational age, *PY* person years, *RERI* Relative excess risk due to interaction, *SGA* small for gestational age

	AGA		**SGA**		**LGA**	
Smoking in pregnancy	Incidence per 100 PY	HR [95% CI]	Incidence per 100 PY	HR [95% CI]	Incidence per 100 PY	HR [95% CI]
No	1.96	Reference	2.00	1.02 [0.93, 1.10]	1.85	0.94 [0.88, 1.00[b]]
Yes	2.31	1.14 [1.09, 1.19]	2.65	1.29 [1.19, 1.39]	2.30	1.13 [0.98, 1.29]
RERI [95% CI]		-		0.13 [0.01, 0.26]		0.04 [-0.11, 0.21]
AP [95% CI]		-		0.10 [0.00[a], 0.19]		0.04 [-0.12, 0.16]

FIGURES

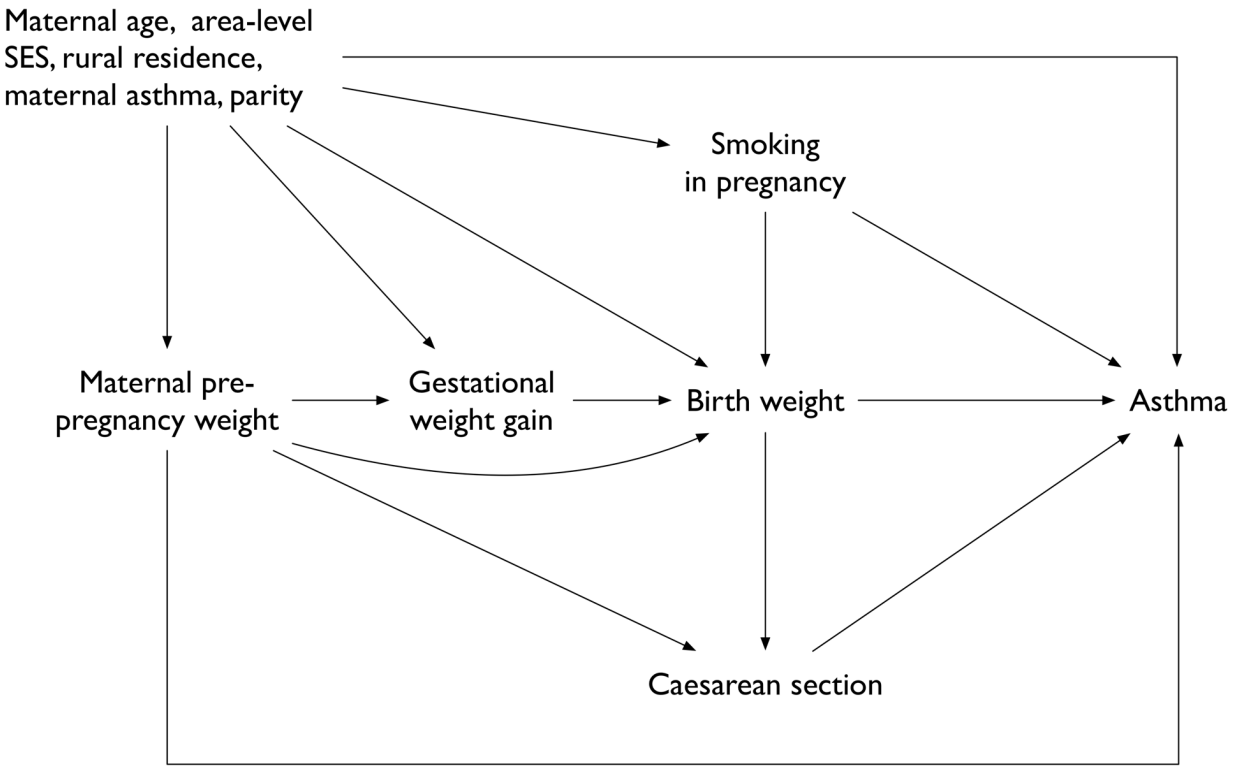

Figure 1: Directed acyclic graph with the hypothesized relationships between the birthweight for gestational age and asthma and the potential confounders and mediators.

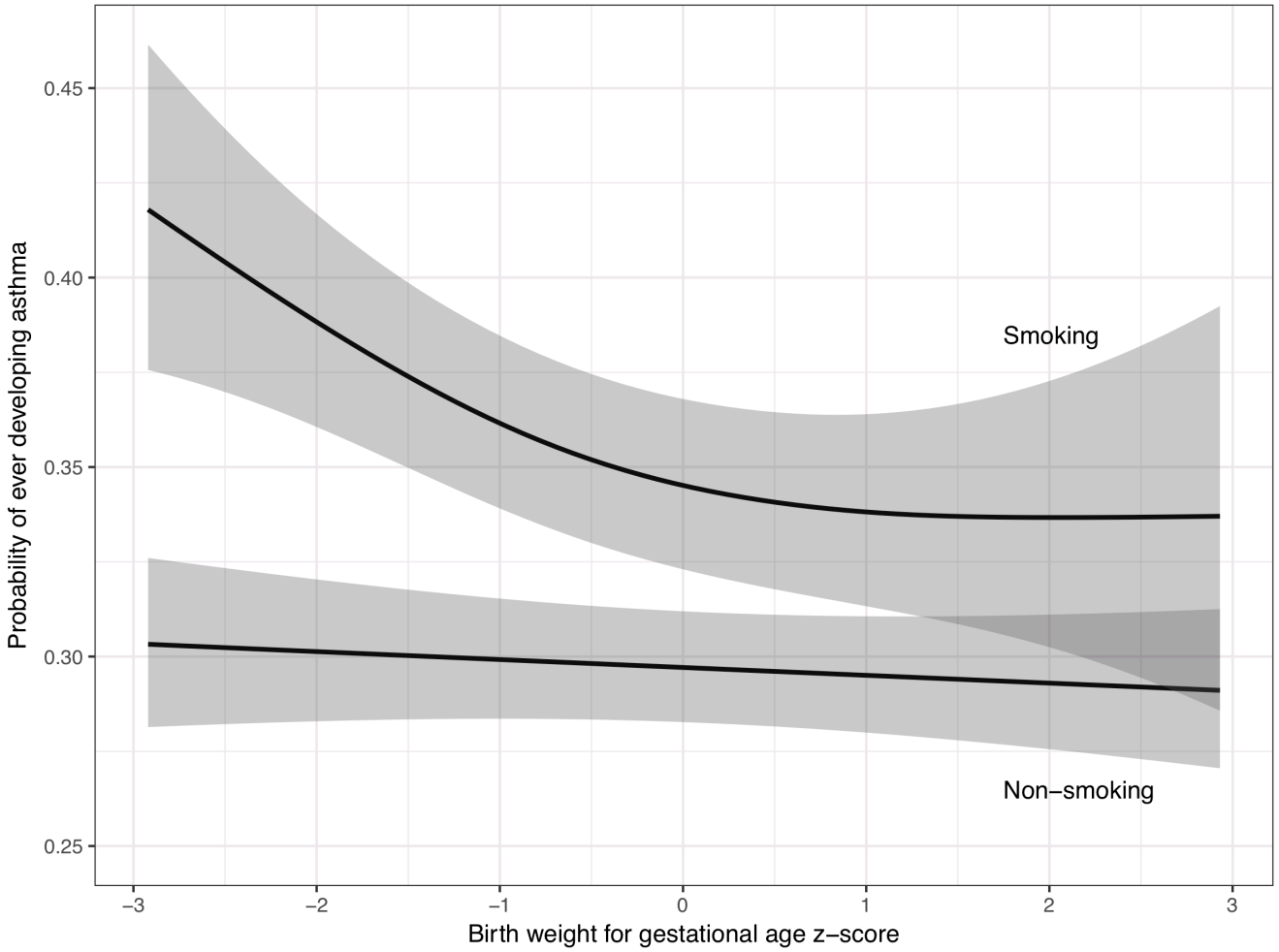

Figure 2: Generalized additive model for the relationship between birthweight for gestational age z-score and asthma risk stratified by smoking status in pregnancy.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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CONTRIBUTORSHIP STATEMENT

Jillian Carter contributed to the design of the study, wrote the initial manuscript draft, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Christy Woolcott contributed to the design of the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Lihui Liu carried out the analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Stefan Kuhle conceptualized and designed the study, carried out the analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

DATA SHARING

The data used in this study are available from the Reproductive Care Program of Nova Scotia and Health Data Nova Scotia, Canada. As these data constitute personal health information, they can only be accessed from within Nova Scotia as per provincial privacy laws. Researchers must submit a data access application to the database custodians and upon approval sign a data sharing agreement.

What is already known on this topic: Low birth weight infants are at a higher risk for asthma in childhood but this association may be modified by smoking in pregnancy. The role of high birth weight in the etiology of childhood asthma is unclear.

What this study adds: In term infants, being born small for gestational age is not associated with asthma in childhood in the absence of smoking in pregnancy. Large for gestational age infants do not have increased risk of asthma.

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