

The Relationship Between Birth Weight and Childhood Asthma

A Population-Based Cohort Study

Don D. Sin, MD, MPH; Sheldon Spier, MD; Larry W. Svenson, BSc; Don P. Schopflocher, PhD; Ambikaipakan Senthilselvan, PhD; Robert L. Cowie, MD; S. F. Paul Man, MD

Background: Because obesity promotes inflammation and imposes mechanical constraints to the airways, a high birth weight may be a risk factor for asthma in childhood. However, to our knowledge, few studies have examined this potential relationship.

Objective: To determine the relationship between high birth weight and risk of emergency visits for asthma during childhood.

Design: Population-based cohort study.

Setting: Alberta, Canada.

Participants: All neonates born at term (≥ 37 weeks) between April 1, 1985, and March 31, 1988, in Alberta (N=83 595). We divided the cohort into birth-weight categories: low (< 2.5 kg), normal (2.5-4.5 kg), or high (> 4.5 kg). The cohort was observed prospectively for 10 years.

Main Outcome Measure: Comparison of risk of emergency visits for asthma over 10 years across the birth-weight categories.

Results: Neonates born with a high birth weight had a significantly increased risk of emergency visits for asthma during childhood compared with neonates born with a normal birth weight (relative risk [RR], 1.16; 95% confidence interval [CI], 1.04-1.29). The relationship between birth weight and emergency visits for asthma beyond a birth weight of 4.5 kg was linear, such that every increment of 0.10 kg in birth weight was associated with an additional 10% (95% CI, 2%-19%) increase in the risk of emergency visits for asthma. Other factors associated with an elevated risk for emergency asthma visits during childhood included male sex (RR, 1.26; 95% CI, 1.22-1.30), aboriginal status (RR, 1.20; 95% CI, 1.11-1.29), and low-income status (RR, 1.11; 95% CI, 1.06-1.16).

Conclusions: A high, but not low, birth weight is a risk factor for increased emergency visits during childhood. The risk increases linearly beyond a birth weight of 4.5 kg.

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From the Pulmonary Division, the Department of Medicine (Drs Sin and Man), and Public Health Sciences (Mr Svenson and Dr Senthilselvan), University of Alberta, Edmonton; the Departments of Pediatrics (Dr Spier) and Medicine (Dr Cowie), University of Calgary, Alberta; and the Health Surveillance Branch, Alberta Health and Wellness, Edmonton (Mr Svenson and Dr Schopflocher).

CHILDHOOD ASTHMA IS A common chronic condition that is increasing in prevalence and severity, particularly among those younger than 5 years.¹ Indeed, between 1987 and 1997, there was a 57% increase in the asthma hospitalization rate among those younger than 5 years.² Interestingly, during this same interval, there was a substantial increase in the birth weight of neonates born in the Western world and an increased incidence of childhood obesity.³ While there is a paucity of studies evaluating lung function in high-birth-weight neonates, based on data from older children,⁴ increased body fat might be expected to produce lung function impairments in neonates that could increase their risk of asthma. One plausible explanation for the increased prevalence of early

childhood asthma is the temporal increase in birth weight in the community.

We conducted a large population-based cohort study with the following aims: (1) to determine if low or high birth weight modifies the risk of childhood asthma independent of the effects of prematurity; (2) to describe the shape of the relationship between birth weight and childhood asthma; and (3) to determine if factors such as age, sex, race, and income status were also related to childhood asthma.

METHODS

DATA SOURCE

We identified all live births occurring in Alberta, Canada, between April 1, 1985, and March 31, 1988, using the Alberta Health Care

Insurance Plan registry (N=96 359). This registry contains information on sex, birth weight, gestational age of the neonate, and data concerning mother's age, race, marital status, and area of residence. We excluded 7627 children (7.9%) because their birth weight or gestational age was not recorded in the Alberta Health Care Insurance Plan registry. We also excluded children born at a gestational age of less than 37 weeks (n=5137) to eliminate the influence of prematurity on the relationship between birth weight and risk of asthma. Neonates born at term (N=83 595) were observed for 10 years after their birth.

DIAGNOSIS OF ASTHMA

From the physicians' claims database, we identified all physician encounters occurring in the emergency departments for which asthma was the principal diagnosis (as deemed by a physician) during the first 10 years of the children's lives. We used *International Classification of Diseases, Ninth Revision, Clinical Modification* code 493.x to capture asthma encounters.

STATISTICAL ANALYSIS

The children in our cohort were grouped according to the birth weight reported in the Alberta Health Care Insurance Plan registry. Birth weights were categorized as follows: low (<2.5 kg), high (>4.5 kg), and normal (2.5-4.5 kg). χ^2 Tests were used for comparison of sex, aboriginal status, and low-income status between birth-weight categories. Analysis of variance and post hoc comparisons (the Tukey studentized range test) were used to test the differences in gestational and maternal ages between birth-weight categories. We used a Poisson regression analysis using birth-weight categories as the independent variable and emergency visits as the dependent variable. To fit the data into a Poisson equation, person-years were log transformed and included in the model as an offset.⁵ To the baseline model that included only birth-weight categories and risk for asthma emergency visits, we added, one by one, maternal age, gestational age, sex of the child, low-income family, and race. We divided race into aboriginal and nonaboriginal subjects. Low-income families were defined as those that had a combined annual (single) family income of less than Can \$27 210. This constitutes approximately 10% of Alberta families and is the threshold the provincial government uses to determine financial assistance for health care premiums.⁶

To determine the exact shape of the relationship between birth weight and risk of emergency visits for childhood asthma, we also plotted histograms of the frequency distribution for asthma emergency visits using birth weight as the independent variable. We then obtained an estimate of these distributions using smooth interpolation methods to achieve a good fit with minimal restriction on the functional form of this relationship. Finally, we performed a logistic regression analysis to determine the relationship between high birth weight and risk of emergency visits for childhood asthma. A 2-tailed $P < .05$ was considered statistically significant. All analyses were conducted using SAS statistical software, version 7.0 (SAS Institute Inc, Cary, NC). Data are presented as mean $\pm$ SD unless otherwise indicated.

RESULTS

SOCIODEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

There were 88 732 children born in Alberta between April 1, 1985, and March 31, 1988, with valid birth-weight data. Of these children, 5137 were born premature (<37 weeks'

Table 1. Demographic Characteristics of Children Born With Low, High, and Normal Birth Weights*

Characteristic	Birth Weight		
	Normal (2.5-4.5 kg)	Low (<2.5 kg)	High (>4.5 kg)
No. of subjects	80 466	1735	1394
Female sex	48.9	59.5	28.5
Age, mean $\pm$ SD			
Gestational, wk	39.6 $\pm$ 1.2	38.5 $\pm$ 1.3	40.3 $\pm$ 1.1
Maternal, y	27.0 $\pm$ 4.8	26.7 $\pm$ 4.8	27.8 $\pm$ 4.7
Aboriginal status	4.9	4.3	9.3
Low-income status	14.5	18.6	13.6

*Data are given as percentage of each group unless otherwise indicated. $P = .001$ for the difference between groups for all characteristics, except number of subjects.

gestational age), leaving 83 595 term neonates for follow-up; these children were then followed up for 10 years. The mean birth weight for these children was 3.44 ± 0.48 kg, and the mean gestational age was 39.6 ± 1.2 weeks. Girls constituted 48.8% of the cohort (n=40 794); 4.8% (n=3976) of the children were aboriginal, and 14.6% (n=12 205) were born into a low-income family. The mean maternal age was 27.0 ± 4.8 years. During follow-up, 5413 (6.5%) of the children had at least 1 emergency visit for asthma. The total number of emergency visits was 15 634.

The characteristics of children with low, high, and normal birth weights are described in **Table 1**. Most female neonates were born with a low birth weight; the least were born with a high birth weight. Although maternal age was similar between these birth-weight groups, children with low birth weights were more likely to come from a family with a low income compared with those with normal or high birth weights. In contrast, aboriginal children were more likely to have high birth weights compared with nonaboriginal children.

BIRTH WEIGHT AND EMERGENCY VISITS FOR CHILDHOOD ASTHMA

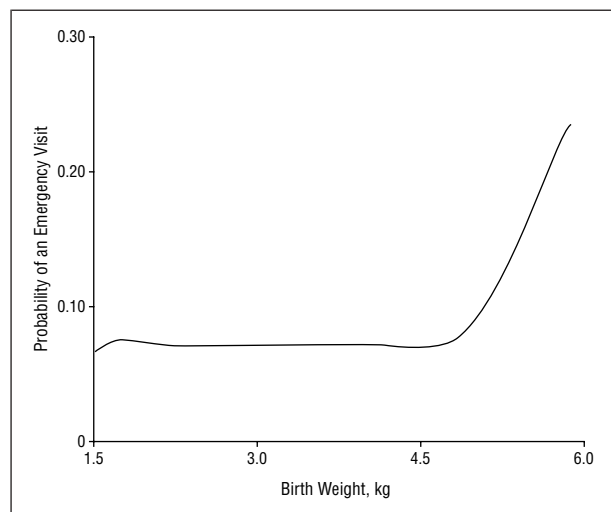
Compared with children with a normal birth weight, those with a high birth weight had a higher risk of emergency visits for asthma within the first 10 years of their lives (**Table 2**). When we controlled for gestational age, sex, maternal age, aboriginal status, and low-income status, a high birth weight was significantly associated with an increased risk of emergency visits for childhood asthma (relative risk [RR], 1.16; 95% confidence interval [CI], 1.04-1.29) compared with a normal birth weight ($P = .01$). This was a linear relationship, such that those with the highest birth weight had the greatest risk of experiencing emergency visits for asthma (**Figure**). For every 0.10-kg increase in birth weight above 4.5 kg, there was an additional 10% (95% CI, 2%-19%) increase in the risk of experiencing an emergency visit over 10 years. Adjustments for gestational age, sex, maternal age, aboriginal status, and low-income status did not change this relationship (RR increase of 10% [95% CI, 2%-19%] for every 0.10-kg increment in birth weight >4.5 kg). In con-

Table 2. Analysis of Sociodemographic Factors Associated With Emergency Visits for Childhood Asthma

Factor	Emergency Visit*	
	Crude Rate per 10 000 Person-years	Adjusted Relative Risk†
Birth weight		
Normal (2.5-4.5 kg)	185.9 (182.9-188.8)	1.0
Low (<2.5 kg)	195.4 (174.6-216.2)	1.00 (0.90-1.11)
High (>4.5 kg)	243.9 (218.0-269.8)	1.16 (1.04-1.29)
Sex		
Girls	136.2 (132.6-139.8)	1.0
Boys	235.5 (230.9-240.0)	1.26 (1.22-1.30)
Race		
Nonaboriginal subjects	187.2 (184.2-190.2)	1.0
Aboriginal subjects	183.1 (170.0-196.4)	1.20 (1.11-1.29)
Income level		
Normal	185.0 (181.8-188.1)	1.0
Low	199.0 (191.1-206.9)	1.11 (1.06-1.16)

*Data in parentheses are 95% confidence intervals.

†Adjusted for sex, gestational age, maternal age, aboriginal status, and low-income status using multivariate Poisson regression analysis.



A spline interpolation curve demonstrating the relationship between risk of having at least 1 emergency visit for asthma and birth weight during the first 10 years of life.

trast, we did not observe a significant relationship between low birth weight and risk of emergency visits for childhood asthma in children born at full term (RR, 1.00; 95% CI, 0.90-1.11) ($P = .97$). In a secondary analysis, we excluded emergency visits occurring within the first 2 years of life. The findings from the secondary analysis were similar to those from the main analysis (RR for high-birth-weight neonates, 1.17 [95% CI, 1.04-1.31]; and RR for low-birth-weight neonates, 1.07 [95% CI, 0.95-1.20]).

OTHER IMPORTANT PREDICTORS OF EMERGENCY VISITS FOR ASTHMA

Table 2 shows the crude and adjusted rates for emergency visits for childhood asthma in those with low, normal, and high birth weights across sex, income status, and aboriginal status. Boys consistently had a higher risk

than girls for emergency visits for asthma. Similarly, aboriginal children had a higher risk for emergency visits for asthma. A similar but less striking relationship was observed for those children born in a family with a low income.

COMMENT

This large population-based study of childhood asthma and birth weight produced some important and novel observations. First, we observed that children born with a high birth weight (>4.5 kg) had the greatest incident risk of emergency visits for asthma. Second, the association between birth weight and emergency visits for childhood above a birth weight of 4.5 kg was linear such that those neonates having the highest birth weight had the greatest risk for asthma emergency visits. Although more boys and aboriginal children were found within the high-birth-weight category, adjustments for these and other confounding factors did not materially change this relationship. Third, a low birth weight was not an independent predictor of emergency visits for asthma during childhood.

The mechanism by which high birth weight results in an elevated incidence of emergency visits for childhood asthma is not well understood. However, it is known that heavy neonates at birth tend to remain obese throughout childhood and into adolescence.⁷⁻¹⁰ This association is particularly pronounced when the birth weight is greater than 4.5 kg, such that the risk of continued obesity is 3 to 4 times that of those in lower-birth-weight categories.¹⁰ Because adiposity adversely affects lung function by decreasing expiratory flow rates and inducing premature closure of peripheral airways,⁴ obese children are more likely to develop asthma symptoms than age-matched normal-weight kids. Moreover, obesity can decrease respiratory muscle function and increase the work and energy cost of breathing, leading to worsening of asthma symptoms.¹¹⁻¹³ The proinflammatory state related to obesity may also contribute to the asthma burdens in the obese population. Biomedical experiments have demonstrated that adipocytes up-regulate the production of various proinflammatory cytokines, including leptin, interleukin 6, and tumor necrosis factor α , that can localize to the pulmonary system and exacerbate airway inflammation.¹⁴ Adipocytes may also increase the production and activation of mast cells in large airways, predisposing airways to bronchospasm.¹⁵

There remains considerable controversy surrounding the role of low birth weight in childhood asthma. Although some studies¹⁶⁻¹⁸ suggest that low birth weight is a significant risk factor for the development of childhood asthma, others¹⁹⁻²³ do not. Part of the confusion may be related to the possible confounding effect of gestational age. Because prematurity and low birth weight are intrinsically linked,²³ the independent contribution of low birth weight to the development of childhood asthma has not been fully established. An advantage of our study was that by excluding all premature neonates (gestational age, <37 weeks), we were able to determine the role of low birth weight without significant confounding by gestational age. Our observations are, therefore, consistent with

the concept that low birth weight by itself does not predict incidence or severity of asthma later in childhood.¹⁹

Our observation that boys have a higher incidence of asthma emergency visits compared with girls is consistent with that of previous reports.^{24,25} Although the exact mechanism is not known, several studies^{25,26} suggest that female neonates have proportionately larger airways relative to their lung size than do male neonates, resulting in increased expired flow rates and airway conductance. We also found that aboriginal children had a higher risk of emergency asthma visits during childhood than nonaboriginal children. Although, from our study, we could not determine why this pattern of health care use for asthma was present among aboriginal children, a previous study²⁷ suggests that aboriginal neonates have a substantially higher risk of early childhood infections, which may damage their airways early in life, predisposing them to the development of asthma during childhood. An alternate explanation is that aboriginal children may not be seeking or receiving optimal primary care in the community, leading to a heavy reliance on immediate rescue care in emergency departments.

A major strength of our study is the large sample size, which provided the opportunity to adequately control for the potential confounding effects of gestational age (ie, prematurity), sex, and other important sociodemographic factors to elucidate the independent association between birth weight and incident risk of childhood asthma. Adjustments for prematurity and sex were particularly important because they have been shown to be leading predictors of childhood asthma.^{17,25} Another advantage was that, because of the nature of our study design (a population-based cohort study), we were able to capture nearly all neonates born in Alberta during the study period. This avoided selection bias, which could be present in studies that use a highly selected cohort of patients. Furthermore, while many of the previous studies relied on self-report, we estimated the incidence and severity of asthma using emergency visits as case events. This has the advantage of avoiding recall bias, and allowed us to determine the risk of clinically significant asthma that brings patients to see their physicians for assistance and treatment.

Other childhood conditions may clinically mimic asthma. By relying on physician diagnosis of asthma, there was potential for diagnostic misclassification. However, for this bias to have made a significant difference to our findings, there had to have been a preferential diagnostic bias for asthma in children born with a high birth weight compared with those born with a low or normal birth weight. Because high birth weight has not been previously reported as a putative determinant of childhood asthma, to our knowledge, there is no material reason why clinicians would have preferentially labeled high-birth-weight children as "asthmatics," making this a remote possibility. Another limitation was that we did not capture symptomatic patients who did not have an emergency visit for their asthma. Therefore, our findings cannot be generalized to children who wheeze but do not seek emergency help.

In summary, our study findings indicate that there is a significant relationship between high, but not low,

What This Study Adds

Obesity is a proinflammatory state and adds to the asthma burden in the community. Children born with a high birth weight (>4.5 kg) have close to a 20% increased probability of emergency visits for asthma in the first 10 years of their lives than children born with a normal birth weight. For every 0.10-kg increase in birth weight above 4.5 kg, there is an additional 10% increase in the probability of having an emergency visit for asthma. A high birth weight, therefore, is an important risk factor for childhood asthma.

birth weight and emergency visits for childhood asthma. These data are consistent with other reports²⁸ that indicate that individuals with severe asthma requiring emergency services tend to be more obese than those without asthma. Because there has been a gradual increase in birth weight in North America during the past 20 years,²⁹ our observations may explain why there has been an increased incidence of severe childhood asthma during this time. Future work is needed for determining the mechanism by which high birth weight leads to increased incidence of emergency visits for childhood asthma. Our findings of increased emergency use for asthma among aboriginal children also highlight the need for future studies aimed at reducing the asthma burden in aboriginal communities.

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Corresponding author: Don D. Sin, MD, MPH, 2E4.29 Walter C. Mackenzie Centre, University of Alberta, Edmonton, Alberta, Canada T6G 2B7 (e-mail: don.sin@ualberta.ca).

REFERENCES

1. Asthma hospitalizations and readmissions among children and young adults: Wisconsin, 1991-1995. *MMWR Morb Mortal Wkly Rep.* 1997;46:726-729.
2. Childhood asthma hospitalizations: King County, Washington, 1987-1998. *MMWR Morb Mortal Wkly Rep.* 2000;49:929-933.
3. Tremblay MS, Willms JD. Secular trends in the body mass index of Canadian children. *CMAJ.* 2000;163:1429-1433.
4. Inselma LS, Milanese A, Deurloo A. Effect of obesity on pulmonary function in children. *Pediatr Pulmonol.* 1993;16:130-137.
5. Rosner B. *Fundamentals of Biostatistics.* Belmont, Calif: Wadsworth Publishing; 1995:90-93.
6. Alberta Health and Wellness: premium and rates, 2000. Available at: <http://www.health.gov.ab.ca/coverage/ahcip/subsidies.html#current>. Accessed September 30, 2003.
7. Barker M, Robinson S, Osmond C, et al. Birth weight and body fat distribution in adolescent girls. *Arch Dis Child.* 1997;77:381-383.
8. Duran-Tauleria E, Rona RJ, Chinn S. Factors associated with weight for height and skinfold thickness in British children. *J Epidemiol Community Health.* 1995;49:466-473.
9. Hediger ML, Overpeck MD, McGlynn A, Kuczmarski RJ, Maurer KR, Davis WW. Growth and fatness at three to six years of age of children born small- or large-for-gestational age. *Pediatrics.* 1999;104:e33.
10. Sorensen HT, Sabroe S, Rothman KJ, Gillman M, Fischer P, Sorensen TI. Rela-

- tion between weight and length at birth and body mass index in young adulthood: cohort study. *BMJ*. 1997;315:1137.
11. Ray CS, Sue DY, Bray G, Hansen JE, Wasserman K. Effects of obesity on respiratory function. *Am Rev Respir Dis*. 1983;128:501-506.
 12. Biring MS, Lewis MI, Liu JT, Mohsenifar Z. Pulmonary physiologic changes of morbid obesity. *Am J Med Sci*. 1999;318:293-297.
 13. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci*. 2001;321:249-279.
 14. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. *Int J Obes Relat Metab Disord*. 1998;22:1145-1158.
 15. Mito N, Kitada C, Hosoda T, Sato K. Effect of diet-induced obesity on ovalbumin-specific immune response in a murine asthma model. *Metabolism*. 2002;51:1241-1246.
 16. Wjst M, Popescu M, Trepka MJ, Heinrich J, Wichmann HE. Pulmonary function in children with initial low birth weight. *Pediatr Allergy Immunol*. 1998;9:80-90.
 17. Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States: association with social class, perinatal events, and race. *Am Rev Respir Dis*. 1990;142:555-562.
 18. Weitzman M, Gortmaker S, Sobol A. Racial, social and environmental risks for childhood asthma. *AJDC*. 1990;144:1189-1194.
 19. Matthes JW, Lewis PA, Davies DP, Bethel JA. Birth weight at term and lung function in adolescence: no evidence for a programmed effect. *Arch Dis Child*. 1995;73:231-234.
 20. Gregory A, Doull I, Pearce N, et al. The relationship between anthropometric measurements at birth: asthma and atopy in childhood. *Clin Exp Allergy*. 1999;29:330-333.
 21. Chen J, Millar WJ. Birth outcome, the social environment and child health. *Health Rep*. 1999;10:57-67.
 22. Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. *Am J Respir Crit Care Med*. 1998;158:352-357.
 23. Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. *BMJ*. 1993;306:817-820.
 24. Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA*. 1992;268:3437-3440.
 25. Stocks J, Henschen M, Hoo A, Costeloe K, Dezateux C. Influence of ethnicity and gender on airway function in preterm infants. *Am J Respir Crit Care Med*. 1997;156:1855-1862.
 26. O'Connor GT, Sparrow D, Demolles D, et al. Maximal and partial expiratory flow rates in a population sample of 10- to 11-yr-old schoolchildren: effect of volume history and relation to asthma and maternal smoking. *Am J Respir Crit Care Med*. 2000;162:436-439.
 27. Lowther SA, Shay DK, Holman RC, Clarke MJ, Kaufman SF, Anderson LJ. Bronchiolitis-associated hospitalizations among American Indian and Alaska Native children. *Pediatr Infect Dis J*. 2000;19:11-17.
 28. Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr*. 1998;132:699-703.
 29. Arbuckle TE, Wilkins R, Sherman GJ. Birth weight percentiles by gestational age in Canada. *Obstet Gynecol*. 1993;81:39-48.