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Population-Based Study on Association between Birth Weight and Risk of Asthma: A Propensity Score Approach

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INTRODUCTION

Asthma is the most common chronic illness in childhood and is a major cause of morbidity in adults, affecting 4–17% of children and 7.7% of adults in the US.^{1–3} Nearly 30 million Americans and 300 million people globally are estimated to be affected by asthma.⁴ At present, there are no overall signs of a declining trend in asthma prevalence; rather, asthma continues to increase in many parts of the world.^{3–5}

The etiology of asthma has been considered multifactorial and includes genetic, epigenetic, developmental, and environmental factors, along with their complex interactions. To date, the epidemiologic associations between many of these risk factors and risk of asthma have been inconsistent and are likely to be so in the future, resulting in different interpretations and applications of the existing literature. Although the primary source of this inconsistency may be explained by the heterogeneity of asthma itself,⁶ much of this inconsistency can be attributed to the differences of asthma studies. For example, controlled trials are not always logistically and ethically feasible. Thus, investigations to identify the risk factors for asthma tend to rely on observational studies, which often have significant challenges to address covariate imbalance in comparison groups due to non-random assignment of exposure and other covariates. Therefore, advancement of asthma research is in need of continuous development and application of different research methods to address caveats of observational studies. As an example, we recently proposed to apply a propensity score

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approach in asthma epidemiology research when a controlled clinical trial is infeasible, such as studying the association between neighborhood environment and risk of asthma.⁷

As an extension of this previous work, our objective for this study was to assess the association between birth weight and risk of asthma. Although conceptually, pregnancy may be a critical period of development of airways, and poor intrauterine growth could result in suboptimal development of airways and lung, the literature on the association between low birth weight and risk of asthma have been inconsistent with studies supporting^{8–22} and disputing^{23–33} such an association. This inconsistency is primarily due to heterogeneity of asthma itself, different study designs, study populations, and ascertainment of exposure (birth weight) and outcome variables (asthma status), and inadequate control of covariate imbalance. This study is the first population-based birth cohort study using predetermined criteria for asthma based on comprehensive medical record review (not self or parental report) and applying a propensity score approach to address covariate imbalance between groups of children with and without low birth weight. We investigated the association between low birth weight and risk of asthma in a birth cohort born between 1976 and 1979 using a propensity score approach.

METHODS

This study protocol was approved by the Institutional Review Boards at Mayo Clinic and Olmsted Medical Center.

Study Design and Setting

The study was a retrospective, population-based cohort study. This study followed children born in Rochester, MN between January 1, 1976 and December 31, 1979 to determine risk of asthma during the first 7 years of life (from 1976 to 1983) among children with low birth weight (<2500 g) and those with normal birth weight (> 2500 g). The study setting has been previously reported in detail.^{34,35} Briefly, Rochester, MN is the centrally located seat of Olmsted County, and greater than 60% of the county population resides within the city limits. With the exception of a higher proportion of the working population employed in the health-care industry, characteristics of the city of Rochester and Olmsted County populations are similar to those of the U.S. white population.³⁶ Population-based epidemiology research is possible in this setting because medical care is virtually self-contained within the community and is delivered by only two medical centers that have maintained a common medical record system with their large affiliated hospitals and clinics for the past 90 years through the Rochester Epidemiology Project.^{37–39}

Study Subjects

Study subjects were from a population-based birth cohort, which has been previously described.^{40,41} Briefly, all subjects born in Rochester, MN between January 1, 1976, and December 31, 1979, were identified using computerized birth certificate information obtained from the Minnesota Department of Health, Division of Vital Statistics.

Ascertainment of Asthma (dependent variable)

The criteria for identifying asthma cases have been previously described and are delineated in Table 1.^{35,36} Asthma status was determined by performing comprehensive medical record reviews and applying predetermined criteria for asthma (Table 1).

Exposure Status (independent variable)

The exposure status of interest in this study was birth weight (low vs. normal birth weight) regardless of gestational age. Low birth weight was defined as less than 2500 g, and normal

birth weight was defined as 2500 g or more. We compared the cumulative incidence of asthma between low birth weight and normal birth weight groups during the first seven years of life.

Other Covariates and Confounders

A variety of information on these children was also obtained from the children's birth certificates and medical records, including gestational age, gender, race, age of parents at birth, educational level of parents at birth, parental marital status, family history of atopic disease, smoking during pregnancy, number of prenatal visits, and complications of pregnancy, labor, and delivery. We utilized these variables to formulate a propensity score as described below to address covariate imbalance between low vs. normal birth weight groups.

Statistical Analysis

We previously described the propensity score in detail.⁷ Briefly, the main rationale for the propensity score is that this methodological approach is making the comparison groups (i.e., the status of birth weight in this study) more comparable (by reducing covariate imbalance through matching the propensity score) in assessing its association with outcomes (i.e., asthma status in this study). Making the comparison groups more analogous is the main reason for randomization of a clinical trial, which may be difficult, if not impossible, to accomplish in a clinical study. The propensity score is a conditional probability that a subject would have low vs. normal birth weight given all observed covariates. It can be mathematically expressed as: $e(x) = \Pr(z=1|x)$, where $e(x)$ is the propensity score, z is an exposure or treatment (i.e., $z=1$ as a principal treatment or exposure vs. $z=0$ as a comparative one), and x is a vector of covariates. In this study, the main exposure status of interest was the binary variable z indicating whether a subject was born with low birth weight ($z=1$) vs. normal birth weight ($z=0$). The conditional distribution of covariates, $x|e(x)$, is the same for the group of subjects assigned to the principal exposure (i.e., those who had low birth weight, $z=1$) and the group for the comparative one (i.e., those who had normal birth weight, $z=0$).^{42,43} Assignment to the exposure, z , can be considered a "random process" if independence of the assignment to exposure z and outcome measure can be assured given the propensity score $e(x)$. Thus, subjects with a given propensity score will have similar covariate (x) distribution between the group with the principal exposure or treatment and those with the comparative one. The propensity score for each subject is obtained by fitting a logistic regression model that includes the independent variable (i.e., low vs. normal birth weight) as an outcome variable and all pertinent covariates as predictor variables.

In this study, we formulated the propensity scores for birth weight using 16 covariates. We matched the propensity scores for children having low birth weight (<2500 g) with those for children having normal birth weight (≥2500 g) within a caliper of 0.2 standard deviation of logit function of propensity scores (i.e., exact matching).⁴⁴ Two matching schemes, as described, were then applied to obtain the matched data set. In the matched data set, we have equal numbers of children who were born as low birth weight and normal birth weight (i.e., 1:1 matching). We assessed covariate imbalance before and after matching for each method.

After assembling the matched dataset with regard to the propensity score, the cumulative incidence rates of asthma among subjects with low vs. normal birth weight were calculated using the Kaplan-Meier curve. A log-rank test was used to examine statistical significance in differences in cumulative incidence of asthma. The censoring events included development of asthma, emigration, death, and end of the study period (December 31, 1983), whichever occurred first. The total person-years of observation included the total time from birth to the

censoring events described above. A Cox proportional hazard model was applied to assess the association between birth weight as a predictor variable and cumulative incidence of asthma as outcome variable. Statistical significance was tested at a two-sided alpha error of 0.05. The analysis was performed using the SAS software package (SAS Institute, Cary, NC).

RESULTS

Characteristics of Subjects

During the period 1976 to 1979, a total of 3970 children were born to mothers who were residents of the city of Rochester at the time of their delivery. Eleven children died at birth, yielding 3959 children in the birth cohort for follow-up. Of these 3959 children (mean follow-up of 4.9 person-years), 33 (0.8%) died—all without a previous diagnosis of definite or probable asthma. However, we did not include 26 children who did not have pertinent information from our analysis. Thus, there were 3933 children considered in our study. Of these 3933 children who met study eligibility, a total of 214 children met criteria for asthma between 1976 and 1983, and 193 (4.9%) had low birth weight. Of the 193 children born with low birth weight, 109 children were matched to the same number of children born with normal birth weight by using an exact matching approach. The demographic characteristics of the birth cohort are shown in Table 2.

Analysis of Covariate Imbalance

We assessed covariate imbalance before and after matching within a caliper using the 109 matched pairs of children born with low and normal birth weight. The results are summarized in Tables 2 and 3. The results in Table 2 show that there was significant covariate imbalance in the number of prenatal visits, complications related to labor, induction of labor, maternal age at delivery, and marital status of the parents between low vs. normal birth weight groups. After matching with regard to propensity scores as described in Table 3, the covariate imbalance was reduced in such a way that there were no statistically significant differences between the two groups with regard to the variables subject to covariate imbalance. These results suggest that matching with the propensity score reduced covariate imbalance between the comparison groups in such a way that made the low vs. normal birth weight group more comparable.

Influence of Birth Weight on Asthma Incidence

There were 3740 children born with normal birth weight and 193 children born with low birth weight. Of the 193 subjects born with low birth weight, 13 developed asthma (6.7%); whereas, of the 3740 subjects born with normal birth weight, 201 subjects developed asthma (5.4%) ($p=0.42$) based on unmatched analysis.

After exact matching with propensity scores which generated 109 matched pairs (55% of the original cohort with low birth weight), 9 of the 109 subjects born with low birth weight developed asthma (8.3%); whereas, 8 of 109 children born with normal birth weight developed asthma (7.3%) ($p=0.746$). The results are depicted in Figure 1. We compared these results with those based on a nearest propensity score matching which resulted in matching for 161 infants with low birth weight (i.e., 161 pairs, 83% of the original cohort with low birth weight). The cumulative incidence rates of asthma were 6.8% for low birth weight and 6.2% for normal birth weight with a chi-square p -value of 0.82. The log-rank p -value for the association between low birth weight and risk of asthma was 0.681, not statistically significant either.

DISCUSSION

Our population-based study results show that low-birth weight was not causally associated with risk of subsequent development of childhood asthma in the 1976 to 1979 Rochester birth cohort during the first seven years of life.

Recognizing that observational studies on birth weight and asthma can be confounded by numerous measured and unmeasured genetic and environmental factors (i.e., covariate imbalance), our study made an attempt to address covariate imbalance. We showed that propensity score matching properly reduced covariate imbalance to make the comparison more suitable. For example, multiple pregnancy was significantly more common among children born with low birth weight compared to those with normal birth weight (24% vs. 1.3%, $p<0.001$); however, after propensity score matching, the imbalance was significantly reduced (7.3% vs. 11.0%, $p=0.35$). Similarly, gestational age was significantly different among children born with low birth weight compared to those with normal birth weight (35.9 ± 4.3 vs. 40.3 ± 1.8 , $p<0.001$); but after propensity score matching, the imbalance was reduced (38.0 ± 3.0 vs. 38.1 ± 3.1 , $p=0.52$). Therefore, the propensity score matching made the comparison of asthma risk between children born with low vs. normal birth weight more suitable by addressing the covariate imbalance of measured and potentially unmeasured variables. The results based on exact matching by propensity scores showed no significant difference in the cumulative incidence of asthma between children with low birth weight and those with normal birth weight (8.3% vs. 7.3%, respectively, $p=0.746$). We compared these results based on exact matching with those based on nearest matching which generated a higher proportion of matched pairs (83%). The results were similar to the original results based on exact matching (log-rank p -value = 0.681). The results based on unmatched analysis showed similar findings (6.7% vs. 5.4%, respectively, $p=0.42$). We do not believe this lack of association between birth weight and risk of asthma was solely due to lack of statistical power. Our post-study power calculation for the matched analysis based on a two-sided log-rank test indicates that given the sample size, we will have 80 and 90% power to detect the effect size of 1.52 and 1.62 of hazard ratio, respectively, which are similar to (or smaller effect sizes than) the previously reported ones (i.e., hazard ratios: 1.45– 1.84).^{45,46} Also, the Kaplan-Meier curve did not show any patterns of differences in cumulative incidence of asthma during the first seven years of life between children with low birth weight and those with normal birth weight. The ascertainment of asthma is completely independent of determination of exposure status (birth weight) since the two variables were determined by two independent studies. Also, although the overall cumulative incidence of asthma in the original cohort was slightly lower than that in the cohort for the propensity score matched analysis, the difference was not statistically significant (5.4% vs. 8.0%, $p=0.07$), suggesting the cohort for the matched analysis by propensity score had a similar risk of asthma to the original cohort. Therefore, our overall study results might not suggest a causal association between birth weight and risk of asthma during the first seven years of life.

The increasing trends in low birth weight and asthma over recent decades and their positive ecological correlation provide sufficient reason to clarify their relationship.^{47,48} However, heterogeneity of baseline or exposure status (i.e., covariate imbalances) is a major source of inconsistency in the results from previous studies. It should be recognized that all previous literature on the association between birth weight and asthma has relied on observational studies, as randomized clinical trials are ethically impossible. Thus, the association between low-birth weight and asthma can be confounded by numerous measured and unmeasured genetic and environmental factors and addressing covariate imbalance is crucially important. The ideal study addressing this covariate imbalance would be the co-twin pair study, since the twin-pair matched analysis controls genetic and environmental factors associated with

risk of asthma. There are three recent co-twin studies of which the primary study aims were to assess the association between birth weight and asthma.^{13,15,25} The Finish study by Rasanen et al. showed no association between birth weight and risk of asthma by ICD code during adolescent age,²⁵ whereas the Swedish study by Villamor et al. showed inconsistent results, i.e., a modest positive association between low birth weight and risk of asthma by ICD code in monozygotic twins (OR: 1.58, 95%CI: 1.06–2.58) and a negative association in dizygotic twins with statistical insignificance.¹⁵ Another recent co-twin study showed a significant association between low birth weight and risk of asthma based on unmatched analysis. However, matched analysis results showed that birth weight was unassociated with risk of asthma in twin pairs with less than 37 weeks of gestation in both monozygotic (OR: 2.26, 95%CI: 0.60–8.55, $p=0.23$) and dizygotic twins (OR: 1.66, 95%CI: 0.65–4.26, $p=0.29$).¹³ This was true for the twin pairs with 37 weeks or older gestational age in both monozygotic and dizygotic twins. Thus, the co-twin studies do not consistently support the causal association between birth weight and asthma. In addition, the literature that specifically addresses the potential biological plausibility for the association between birth weight and asthma is significantly lacking, apart from the literature that suggests increased risk of chronic lung diseases among extreme premature infants with chronic lung injuries and a transient small airway effect (wheezing), which may improve with catch-up growth. For example, atopy status is a well-recognized risk factor for asthma, but low birth weight has been shown to be associated with neither risk of atopy nor atopic dermatitis or allergic rhinitis.^{49–51} Therefore, the existing data may not fully support a causal relationship between low birth weight and risk of asthma. Our study results support this lack of causal association.

The main strength of our study includes a population-based longitudinal birth cohort study, epidemiologic advantages including a self-contained health care environment with a unified medical record system for research, use of the Kaplan-Meier method for assessment of the cumulative incidence of asthma at different ages during the first seven years of life, ascertainment of asthma by applying predetermined asthma criteria through a comprehensive medical record review, and reasonable statistical power. However, there are also inherent limitations in our study because of its retrospective design. Further, some potential confounders were not included in the model for formulating propensity score, e.g., breastfeeding. However, inclusion of these variables is unlikely to affect our study results given the negative study findings (i.e., failure to reject null hypothesis). Moreover, our study population was predominantly Caucasian (97%); thus our results may not be generalizable to populations of other races or ethnicity. However, at the cost of generalizability (i.e., external validity), internal validity can be enhanced, minimizing the confounding effect of ethnicity on the study results.

Our findings show that low birth weight is not associated with a subsequent risk of developing childhood asthma. We suggest that the propensity score approach may be a useful method to reduce covariate imbalance in observational studies concerning asthma epidemiology.

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FIGURE 1.

Kaplan-Meier plot of the cumulative incidence of asthma between low birth weight group (< 2500 g) and normal birth weight group (≥ 2500 g) during the first seven years of life (p=0.746 based on log-rank test)

Table 1**Criteria for Asthma**

Patients were considered to have definite asthma if a physician had made a diagnosis of asthma or if each of the following three conditions were present (see list below). Patients were considered to have probable asthma if the first two of the following three conditions were present.

- 1** History of cough with dyspnea and/or wheezing or history of cough and/or dyspnea plus wheezing on examination
- 2** Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent
- 3** Two or more of the following:
 - Sleep disturbance by nocturnal cough and wheeze
 - Nasal polyps
 - Blood eosinophilia higher than 300/uL
 - Positive wheal and flare skin tests or elevated serum IgE
 - History of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing one FEV1^a or FVC^b <70% predicted and another with at least 20% improvement to an FEV1^a of higher than 70% predicted or methacholine challenge test showing 20% decline in FEV1^a
 - Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions are present:

- Pulmonary function tests that showed FEV1^a to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ α 1-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

^aFVC, forced vital capacity

^bFEV1, forced expiratory volume in 1 second

Table 2

Demographic and Birth-Related Data of the 1976–1979 Rochester Birth Cohort and Associations with Asthma Incidence Before Matching with Propensity Score (n=3933)

Variable	Normal birth weight (n=3740)	Low birth weight (n=193)	p-value*
Sex			0.06
Male	1915 (51.2%)	95 (58%)	
Gestation age in weeks (mean, SD^a)	40.3±1.8	35.9±4.3	<0.001
Marital status			0.02
Married	3460 (92.5%)	170 (88.1%)	
Not married	280 (7.5%)	23 (11.9%)	
Race			0.39
Caucasian	3549 (95%)	186 (96.4%)	
Others	187 (5%)	7 (3.6%)	
Educational status of mother			0.12
High school or less	210 (2.6%)	9 (4.9%)	
Some college	1158 (31.8%)	72 (38.9%)	
College graduate	1132 (31.1%)	59 (31.9%)	
Graduate degree or above	1143 (31.4%)	45 (24.3%)	
Unknown	115 (33.0%)	8 (4.1%)	
Multiple pregnancy			<0.001
No	3693 (98.7%)	147 (76.2%)	
Yes	47 (1.3%)	46 (23.8%)	
Number of prenatal visits (Mean, SD^a)	10.8±2.65	7.9±3.48	<0.001
Age of mother at birth (Mean, SD^a)	26.4±4.6	25.7±4.4	0.03
Age of father at birth (Mean, SD^a)	28.6±5.0	28.3±4.8	0.53
Complication not related to pregnancy			0.40
No	3543 (95.1%)	180 (93.8%)	
Yes	182 (4.9%)	12 (6.3%)	
Complication related to labor			<0.001
No	2550 (68.5%)	80 (41.7%)	
Yes	1171 (31.5%)	112 (58.3%)	
Induction ever			0.012
No	2939 (79.2%)	164 (86.8%)	
Yes	771 (20.8%)	25 (13.2%)	
Asthma			0.42
No	3539 (94.6%)	180 (93.3%)	
Yes	201 (5.4%)	13 (6.7%)	
Family history of atopic disease			0.37
No	3544 (94.8%)	180 (93.3%)	
Yes	196 (5.2%)	13 (6.7%)	
Smoking at pregnancy			0.44
No	3537 (94.6%)	180 (93.3%)	

Variable	Normal birth weight (n=3740)	Low birth weight (n=193)	p-value*
Yes	203 (5.4%)	13 (6.7%)	

* p-values less than 0.05 were considered statistically significant.

^aSD=Standard deviation

Table 3

Demographic and Birth-Related Data of the 1976–1979 Rochester Birth Cohort and Associations with Asthma Incidence After Exact Matching with Propensity Score (n=218)

	Normal birth weight (n=109)	Low birth weight (n=109)	p value
Sex			0.89
Male	59 (54.1%)	60 (55.0%)	
Gestation age in weeks (mean, SD^a)	38.1±3.1	38.0±3.0	0.52
Marital status			0.65
Married	107 (98.2%)	106 (97.2%)	
Not married	2 (1.8%)	3 (2.8%)	
Race			0.52
Caucasian	105 (96.3%)	103 (95.1%)	
Others	4 (3.7%)	6 (4.9%)	
Educational status of mother			0.89
High school or less	7 (6.4%)	7 (6.4%)	
Some college	42 (38.5%)	37 (33.9%)	
College graduate	36 (33.0%)	41 (37.6%)	
Graduate degree or above	24 (22.0%)	24 (22.0%)	
Multiple pregnancy			0.35
No	97 (89.0%)	101 (92.7%)	
Yes	12 (11.0%)	8 (7.3%)	
Number of prenatal visits (Mean, SD^a)	9.2±2.6	9.1±3.0	0.98
Age of mother at birth (Mean, SD^a)	25.6±4.0	25.9±4.1	0.48
Age of father at birth (Mean, SD^a)	28.0±4.4	28.1±4.6	0.99
Complication not related to pregnancy			1.00
No	102 (93.6%)	102 (93.6%)	
Yes	7 (6.4%)	7 (6.4%)	
Complication related to labor			0.42
No	60 (55.0%)	54 (49.5%)	
Yes	49 (45.0%)	55 (50.5%)	
Induction ever			0.85
No	92 (84.4%)	91 (83.5%)	
Yes	17 (15.6%)	18 (16.5%)	
Asthma			0.80 [*]
No	101 (92.7%)	100 (91.7%)	
Yes	8 (7.3%)	9 (8.3%)	
Family history of atopic disease			0.80
No	101 (92.7%)	100 (91.7%)	
Yes	8 (7.3%)	9 (8.3%)	
Smoking at pregnancy			0.80
No	101 (92.7%)	100 (91.7%)	
Yes	8 (7.3%)	9 (8.3%)	

*
p-value was calculated using chi-square test

^aSD=Standard deviation