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Risk of Asthma in Late Preterm Infants: A Propensity Score Approach

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Abstract

Background—The risk of asthma, specifically in former late preterm infants, has not been well defined. Covariate imbalance and lack of controlling for this has led to inconsistent results in prior studies.

Objective—Determine the risk of asthma in former late preterm infants using a propensity score approach.

Methods—The study was a population-based birth cohort study. Study subjects were all children born in Rochester, Minnesota, between 1976 and 1982. Asthma status during the first seven years of life was assessed by applying predetermined criteria. The propensity score was formulated using 15 covariates by fitting a logistic regression model for late preterm birth versus term birth. We applied the propensity score method to match late preterm infants (34 0/7 to 36 6/7 weeks gestation) to term infants (37 0/7 to 40 6/7 weeks gestation) within a caliper of 0.2 standard deviation of logit of propensity score.

Results—Of the eligible 7,040 infants, 5,915 children had complete data. Before propensity score matching, late preterm infants had a higher risk of asthma (20 of 262, 7.6%) compared to full-term infants (272 of 5,653, 4.8%)($p=0.039$). There was significant covariate imbalance between comparison groups. After matching with propensity scores, we found that former late preterm infants had a similar risk of asthma to the matched full-term infants (6.6% vs. 7.7%, respectively, $p=0.61$), and the result were consistent with covariate-adjustment, Cox regression models controlling for significant covariates ($p=0.57$).

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Conclusion—A late preterm birth history is not independently associated with childhood asthma, as the reported risk of asthma among former late preterm infants appears to be due to covariate imbalance.

Keywords

asthma; epidemiology; risk; late preterm infants; propensity score

INTRODUCTION

Asthma is the most common chronic illness among children, affecting 9.6–13% of children.^{1,2} 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 The total incremental cost of asthma to society was estimated to be \$56 billion,⁴ suggesting that asthma is a significant medical and economic burden to society.

In addressing birth-related risk factors for asthma, the impact of premature birth must be considered because 1 in 8 infants is born premature in the United States, and the majority of these infants are born between 34 0/7 and 36 6/7 weeks of gestational age, otherwise referred to as late preterm (LPT) infants.⁵ Risk of developing asthma in former premature infants is consistently greater than term birth infants.^{6,7} However, most previous studies include all preterm infants born less than 37 weeks into one category, which likely skews the association towards a higher risk of asthma in former preterm infants and inadequately addresses the risk of asthma among more mature infants, such as LPT infants.^{8,9} Several studies have assessed the risk of asthma in the LPT population, and the results have been inconsistent.^{6,10–15} This inconsistency might be stemming from heterogeneity of asthma, but much of this inconsistency is resulting from covariate imbalance and unmeasured confounders, which is a major caveat of observational studies because random assignment of exposure (e.g., premature delivery or neighborhood environment) and all pertinent covariates are unavailable or unmeasured. For example, several risk factors for preterm birth have been identified which include: maternal smoking during pregnancy, African-American race, lower socioeconomic status, and maternal asthma.¹⁶ These same risk factors have also been linked to an increased risk of developing asthma.¹⁷ Therefore, to address this concern, we recently proposed to apply a propensity score approach in asthma epidemiology research when a controlled clinical trial is infeasible, such as studying the association between neighborhood environment and risk of asthma.¹⁸ Since random assignment of term vs. LPT birth is infeasible, we applied a propensity score approach to assess the relationship between LPT birth and risk of asthma. To further address the limitations of previous studies, we conducted a population-based birth cohort study minimizing sampling error.

METHODS

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

Study design and setting

The study was designed as a population-based retrospective birth cohort study, which followed the Rochester Birth Cohort of children born between 1976 and 1982 until December 31, 1983. The study design has been described previously in detail.^{19,20} Characteristics of the Rochester, MN, population were similar to those of the U.S. Caucasian population, with the exception of a higher proportion of the working population employed in the health care industry.²¹ Health care is geographically self-contained within the region. If a patient grants the authorization (95% compliance), under the auspices of the Rochester Epidemiology Project (REP),^{22,23} each patient is assigned a unique identifier; all clinical diagnoses are electronically indexed, and information from every episode of care is contained within detailed patient-based medical records; essentially, all medical care settings and providers are linked. Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to other communities. The incidence rate of asthma in Rochester was 238 cases per 100,000 persons, which is comparable to those in other communities such as Tecumseh, Michigan, (250/100,000) during the study period.²⁴

Study subjects

Study subjects were from the population-based birth cohort, which has been previously described.^{25–27} Briefly, all children born in Rochester between January 1, 1976, and December 31, 1982, were identified using computerized birth certificate information obtained from the Minnesota Department of Health, Division of Vital Statistics. Gestational age was determined from birth certificates. LPT was defined as 34 0/7 – 36 6/7 weeks of gestation. Term was defined 37 0/7 weeks of gestation.

Asthma ascertainment

The criteria for identifying asthma cases have been previously described and noted in Table 1.^{20,28} These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.^{21,29,30} In brief, the medical record must indicate a history of wheezing, recurrence of wheezing, and supporting signs or symptoms of asthma, such as nocturnal symptoms and responsiveness to albuterol. Predetermined criteria for asthma were applied to ascertain asthma status through comprehensive medical record review, which did not entirely rely on a physician's diagnosis of asthma. Survival time of asthma for each child is defined as time from birth to the first occurrence of asthma. Children without evidence of asthma during this observation period are censored at the last follow-up time. Definite and probable asthma cases were considered to be asthmatics, since most probable asthma cases became definite asthma over time.^{21,29,30}

Covariates

Additional information was gathered on covariates via birth certificates and medical records, which were used for formulating propensity scores discussed below. Relevant covariates were included based on each having a known or potential impact on late preterm birth and/or asthma, as several have been shown to be associated with both conditions. The covariates included were: gender, ethnicity, size for gestational age, twin gestation, age of parents at birth, maternal educational level at birth, single parent, family history of atopic disease,

smoking during pregnancy, and complications of pregnancy, labor and delivery, and required hospitalization. The list of covariates is summarized in Tables 2 and 3.

Statistical Analysis

We have previously described the use of the propensity score in detail.¹⁸ Briefly, the propensity score is a conditional probability that a subject would be born as an LPT infant (vs. term infant), given all observed unit covariates. It can be mathematically expressed as:

$$e(x) = Pr(z=1|x)$$

where $e(x)$ is the propensity score, z is an exposure status (i.e., $z_i=1$ as a principle treatment or exposure vs. $z_i=0$ as a comparative one), and x is a vector of covariate(s).

The propensity score was formulated using the covariates listed in Tables 2 and 3 (except asthma) by fitting a logistic regression model, which predicted LPT birth versus term birth. We used propensity scores to match LPT infants to term infants within a caliper of 0.2 standard deviations of the logit function of the propensity scores (i.e., exact matching)³¹, which left only term infants who met this matching criteria. We compared covariate imbalance before and after matching the comparison groups. After matching LPT and term infants with regard to propensity score, the cumulative incidence rates of asthma for LPT and term infants were calculated using the Kaplan-Meier curve. To compare the propensity score approach and the conventional covariate-adjustment regression method, multivariate Cox proportional hazard regression models were used to test statistical significance in the difference of the hazard of asthma between the comparison groups (LPT infants vs. term infants) included in Table 2 (ie, the full cohort with complete data), controlling for the same covariates used for constructing the propensity scores. The censoring events included emigration, death, and end of the study period (December 31, 1983), whichever occurred first. The total person-years of observation were the time from birth to the censoring events described above. Two Cox regression models were calculated based on the full cohort. Model 1 included only covariates satisfying Greenland's and Dales's entering criteria (α level of 0.2).^{32–35}, while model 2 included only significant variables from univariate analysis results. The analyses were performed by using the SAS software package (SAS Institute, Cary, NC).

RESULTS

Characteristics of subjects

During the period 1976 to 1982, a total of 7,463 children were born to mothers who were residents of the city of Rochester at the time of their delivery. Twenty-one children died at birth, yielding 7,442 children in the birth cohort for follow-up. An additional 402 infants born less than 34 weeks gestation were excluded. This left 7,040 children in our study (median follow-up of 3.8 person-years). Of these 7,040 children who met the study eligibility, 333 were born LPT (4%) (6,707 children were full-term infants) and 341 (4.8%) children met the criteria for asthma. Of the 7,040 eligible children, 5915 children had complete data (5673 term infants and 262 LPT infants) and 259 subjects were exact-matched

to term infants within the caliper and 3 were unmatched due to failure to match with controls within the caliper. Although we applied a caliper suggested by the literature,³¹ we tried different calipers, but different calipers did not make a significant difference (0.1SD for 258 and wild for 262 matched cases). The demographic characteristics of the birth cohort who had complete data are shown in Table 2. The median (range) follow-up duration was 5.1 years (0–8).

Analysis of Covariate Imbalance

We assessed covariate imbalance before and after matching, using the 259 matched pairs. The results are summarized in Tables 2 and 3. The results in Table 2 show that there was significant covariate imbalance in complication not related to pregnancy, complication related to labor, size for gestational age, multiple gestation, family history of atopic disease, and maternal smoking between LPT and term infants. After matching with regard to propensity scores as described in Table 3, the covariate imbalance was reduced in a way that there were no statistically significant differences between the two groups. These results suggest that matching with propensity score reduced covariate imbalance between the comparison groups in a way making the LPT and term birth groups more comparable (similar to randomization in an experimental study).

Influence of late preterm birth on asthma incidence

There were 6,707 children born term compared to 333 LPT births. However, there were 5,915 children that had complete data. After exact matching with propensity scores, 17 of the 259 LPT subjects developed asthma (6.6%), whereas 20 of 259 children born at term developed asthma (7.7%) ($p=0.61$). The results are depicted in the Kaplan-Meier curve with a p -value of 0.585 from log-rank test (Figure 1). As a comparison, of the 333 LPT infants, 27 developed asthma (8.1%), whereas 314 of the 6,707 term infants developed asthma (4.7%) ($p=0.0045$) based on a univariate analysis of asthma incidence rate. When we limit our analysis to the birth cohort with complete data, 20 of 262 LPT infants (7.6%) developed asthma whereas 272 of 5653 term infants (4.8%) developed asthma ($p=0.039$). The results, based on multivariate Cox regression models, including only covariates satisfying p -value < 0.2 (Model 1), showed that the hazards ratio (HR) for asthma in LPT as compared to term was 1.09 (95% CI 0.70–1.70, $p=0.71$). In Model 2 that included only significant covariates (size for gestational age, multiple gestation, complication not related to pregnancy, complication related to labor, family history of atopic disease, and maternal smoking during pregnancy), the HR was 1.13 (95% CI 0.75–1.70, $p=0.56$).

DISCUSSION

In our population-based birth cohort study using the propensity score approach (PSA) to reduce covariate imbalance, we found there was no significant difference in risk of asthma between LPT and term infants. PSA might be a useful tool for research concerning asthma epidemiology where random assignment of exposure is not feasible.

We believe the finding of no association between LPT and risk of asthma in our study is not due to lack of statistical power. For example, the literature showed the effect size for the

association between LPT and risk of asthma was 0.94–4.7.^{6,10,12–14,36} Given the sample size (n=300 for each group), we had 80% power to detect an HR of 2.06. Thus, our study had adequate statistical power to address the study aims. In addition, the results based on multivariate Cox regression models, a more conventional approach to this type of data analysis (used in previous studies), also support the study findings by PSA. This consistency in the results, despite changing the analytic approaches, would indicate that addressing the covariate imbalance is critical when assessing the risk of asthma in former LPT infants. Because of the potential difficulty to diagnose asthma in younger children (<5 years), we restricted the analysis to those who had a follow-up at least 5 years of age (range: 5–7 years). The results on the relationship between late-preterm infancy and the risk of asthma remain unchanged (p=0.61 for PS analysis and p=0.71 for covariate-adjustment Cox regression model on the full cohort) suggesting the results were consistent and independent of a follow-up period of the birth cohort.

There are several previous studies that have investigated the association between LPT and risk of asthma, and the results of these studies are difficult to compare with ours. Previous studies had a few important limitations. For example, the definition of LPT or gestation age compared was different from ours. Our study used the strict definition of LPT (34 0/7 – 36 6/7 weeks of gestation), whereas the studies by Dombkowski et al⁶ and Rasanen et al¹⁴ evaluated the risk of asthma in infants with 33–36 weeks of gestation as compared to term, and the study by Raby et al¹⁰ compared infants born between 36–38.5 weeks of gestation to term infants. Thus, the inconsistency in using defined gestational age categories in these studies could potentially lead to difficulty in understanding what gestational ages may be at an increased risk of asthma. In addition, studies conducted by others did use the standard definition of LPT birth.^{12,13,36} These studies found a positive association of LPT birth with risk of asthma. However, after adjusting for pertinent covariates, only the study by Escobar et al¹³ showed a significant positive association, while others did not, suggesting the importance of addressing covariate imbalance between comparison groups. Furthermore, the majority of the previous studies were based on parental report of a physician diagnosis of asthma in their child or diagnostic or administrative search codes such as ICD-9 codes as compared with predetermined criteria for asthma in our study, which did not entirely rely on a physician diagnosis of asthma or parental self-report. Our previous studies as well as the literature showed asthma might be under-identified by parental self-report or by physician diagnosis.^{37–40} Finally, asthma is a very heterogeneous disease, and the risk of developing the disease is multifactorial. In order to assess a single additional risk factor, adequate control of known risk factors or confounders is critical. Known risk factors for developing asthma include: maternal smoking during pregnancy, family history of atopic disease, and lower socioeconomic status. These three variables are also known to contribute to preterm birth.^{41–43} Our study was able to account for these known risk factors as well as other important covariates. One of the important advantages of PSA is ability to address unmeasured covariates or confounders as shown in RCT, since the conceptual basis of PSA is mimicking RCT, i.e., a quasi RCT. Given the multifactorial nature of asthma risk factors and difficulty to measure all pertinent risk factors, this is an important advantage of PSA.

While our study has added valuable insight into the association of LPT birth and asthma, there were a few limitations. We were unable to assess respiratory status at birth. Oxygen

exposure and respiratory support at birth have been linked to an increased association with asthma.¹³ The current practice for newborn resuscitation of a preterm infant has changed over the past three decades, with significant changes regarding the use of oxygen at delivery. Without resuscitation information on this historical cohort, drawing conclusions that are relevant to current practice may be difficult. Another limitation pertains to the method of pregnancy dating. The study population was born in 1976–1982, which was prior to the use of modern ultrasound techniques. Pregnancy dating was based primarily on clinician's estimate derived from the mother's self-reported last menstrual period (LMP) in conjunction with initial clinical assessment such as birth weight. Characteristics of subjects indicate a higher percent of SGA infants born at term than LPT (6.9% vs. 3.6%) and more LGA infants born LPT than term (25.6% vs. 9.0%). While this method of dating may lead to misclassification bias, currently the American College of Obstetrics and Gynecology recommends using the LMP date, if known, and defaults to an ultrasound-derived due date when there is a difference between the two methods of >7 days in the first trimester or >10 days in the second trimester. This current recommendation may allow a potential misclassification bias but is likely to be non-differential and reflects some of the difficulty inherent to studying LPT infants. Additional limitation is our asthma criteria as there is no gold standard for diagnosing asthma. While our predetermined criteria for asthma has unique strengths and merits (i.e., providing incidence date of asthma, high reliability and construct validity, and track record of being utilized for asthma research), it could result in misclassification of asthma status. However, it is likely to be non-differential misclassification without regard to exposure status (late preterm vs. term newborn). Our study has important strengths in addressing the study aim. It is a population-based birth cohort study. Our study setting is a self-contained health care environment with the unique medical record linkage system under the auspices of the REP. Despite the limitations, we defined asthma status based on predetermined criteria and comprehensive medical record review instead of billing code (ICD codes).

Our study suggests that covariates associated with preterm birth, such as maternal smoking during pregnancy and family history of atopic disease, might account for the apparent association between late preterm birth and asthma. Given the large number of LPT infants born in the United States and the increased risk of asthma among significantly premature infants, our study findings have the implications on clinical practice. Clinicians can counsel parents who have LPT infants about the risk of asthma and both clinicians and parents avoid unnecessary evaluations and interventions related to LPT infancy status. In addition, our consistent and robust study results are particularly helpful to clinicians as the information lessens their burdens to address controversial research results around many risk factors for asthma.

In summary, a late preterm birth history is not independently associated with the risk of childhood asthma. Given the significant number of late preterm infants born annually and the large number of children affected by asthma, this information is useful for clinicians in counseling parents who have children with a late preterm birth history. The PSA is a valuable tool in addressing covariate imbalance in observational studies for asthma.

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Abbreviations

LPT	late preterm
PSA	propensity score approach

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Highlights Box

What is already known about this topic?

- A history of late preterm birth has been reported to be associated with an increased risk of asthma, but the literature has been inconsistent and inadequately addressed covariate imbalance.

What does this article add to our knowledge?

- Late preterm infants do not have an increased risk of childhood asthma compared to term infants, and the previously reported association was accounted for by the known confounders for asthma and preterm delivery.

How does this study impact current management guidelines?

- Given the large number of children born in late preterm (1 out of 8), the study findings help clinicians counsel parents with late preterm infants for risk of asthma, and both clinicians as well as parents avoid unnecessary evaluations or interventions for late preterm infants.

Figure 1.
Cumulative incidence of asthma in the matched cohort

Table 1**Asthma Criteria**

To meet the criteria, at least items #1 and #2 must be present. Definite 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:

Probable asthma: Subjects were considered to have probable asthma if only the first two conditions were present:

- 1** History of cough with wheezing and/or dyspnea OR history of wheezing with cough and/or dyspnea on examination
- 2** Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and
- 3** Two or more of the following:
 - Sleep disturbed by nocturnal cough and wheeze
 - Nonsmoker (14 y or older)
 - Nasal polyps
 - Blood eosinophilia >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 or forced vital capacity < 70% predicted and another with at least 20% improvement to an FEV1 of >70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV1
 - Favorable clinical response to bronchodilator

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

- Pulmonary function tests that showed FEV1 to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG < 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications

The following diseases excluded the patient from study if they occurred before the incidence date:

- Bullous emphysema or pulmonary fibrosis on chest radiograph
- Alpha1-antiprotease phenotype ZZ alpha1-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

Table 2

Baseline Characteristics of Birth Cohort (before propensity score matching)

Characteristic	Full Term N=5653	Late PreTerm N=262	Total N=5915	p-value
Asthma, n (%)	272 (4.8%)	20 (7.6%)	292 (4.9%)	0.0393
Gestational Age, M (SD)	40.3 (1.4)	35.7 (0.8)	40.1 (1.7)	<0.0001
Female, n (%)	2717 (48.1%)	125 (47.7%)	2842 (48.0%)	0.9110
Size for Gestational Age, n (%)				<0.0001
Small	358 (6.3%)	12 (4.6%)	370 (6.3%)	
Average	4761 (84.2%)	193 (73.7%)	4954 (83.8%)	
Large	534 (9.4%)	57 (21.8%)	591 (10.0%)	
Non-Caucasian, n (%)	322 (5.7%)	12 (4.6%)	334 (5.6%)	0.4443
Twin Gestation, n (%)	75 (1.3%)	27 (10.3%)	102 (1.7%)	<0.0001
Paternal Age at Birth, M (SD)	28.7 (5.1)	28.5 (4.9)	28.7 (5.1)	0.5584
Maternal Age at Birth, M (SD)	26.8 (4.4)	26.6 (4.8)	26.8 (4.4)	0.4167
Single Parent	133 (2.4%)	6 (2.3%)	139 (2.3%)	0.9478
Maternal Education, n (%)				0.3855
College	1887 (33.4%)	78 (29.8%)	1965 (33.2%)	
Some College	1838 (32.5%)	84 (32.1%)	1922 (32.5%)	
High School	1660 (29.4%)	83 (31.7%)	1743 (29.5%)	
Some High School	268 (4.7%)	17 (6.5%)	285 (4.8%)	
Complication - not related to pregnancy, n (%)	311 (5.5%)	27 (10.3%)	338 (5.7%)	0.0011
Birth Induction, n (%)	1237 (21.9%)	69 (26.3%)	1306 (22.1%)	0.0893
Labor Complication, n (%)	1963 (34.7%)	143 (54.6%)	2106 (35.6%)	<0.0001
Maternal smoking during pregnancy	275 (4.9%)	21 (8.0%)	296 (5.0%)	0.0222
Family history of Atopic Disease	265 (4.7%)	21 (8.0%)	286 (4.8%)	0.0141
Known hosp. ever after index	274 (4.8%)	18 (6.9%)	292 (4.9%)	0.1394
Known hosp. asthma beyond 30 days of index	15 (0.3%)	1 (0.4%)	16 (0.3%)	0.7230

* Comparison of baseline characteristics were based on subjects with complete data (without missing data) who were used for propensity score matching analysis

Table 3

Baseline Characteristics of Propensity Score-Matched Cohort

Characteristic	N Missing	Full Term N =259	Late Preterm N=259	p-value
Asthma, <i>n</i> (%)	0	20 (7.7%)	17 (6.6%)	0.61
Gestational Age, <i>M</i> (<i>SD</i>)	0	40.3 (1.4)	35.6 (0.8)	<0.0001
Female, <i>n</i> (%)	0	124 (47.9%)	124 (47.9%)	1
Size for Gestational Age, <i>n</i> (%)	0			0.28
Small		8 (3.1%)	12 (4.6%)	
Average		206 (79.5%)	191 (73.7%)	
Large		45 (17.4%)	56 (21.6%)	
Non-Caucasian, <i>n</i> (%)	0	10 (3.9%)	11 (4.2%)	0.82
Twin Gestation, <i>n</i> (%)	0	31 (12.0%)	27 (10.4%)	0.58
Paternal Age at Birth, <i>M</i> (<i>SD</i>)	0	28.2 (5.3)	28.5 (4.9)	0.45
Maternal Age at Birth, <i>M</i> (<i>SD</i>)		26.3 (4.7)	26.6 (4.8)	0.47
Single Parent	0	5 (1.9%)	6 (2.3%)	0.76
Maternal Education, <i>n</i> (%)	0			0.82
College		73 (28.2%)	76 (29.3%)	
Some College		93 (35.9%)	83 (32.0%)	
High School		76 (29.3%)	83 (32.0%)	
Some High School		17 (6.6%)	17 (6.6%)	
Complication - not related to pregnancy, <i>n</i> (%)	0	25 (9.7%)	26 (10.0%)	0.88
Birth Induction, <i>n</i> (%)	0	55 (21.2%)	68 (26.3%)	0.18
Labor Complication, <i>n</i> (%)	0	142 (54.8%)	141 (54.4%)	0.93
Maternal Smoking During Pregnancy, <i>n</i> (%)	0	20 (7.7%)	18 (6.9%)	0.74
Family history of Atopic Disease, <i>n</i> (%)	0	20 (7.7%)	18 (6.9%)	0.74
Known hosp. ever after index, <i>n</i> (%)	0	20 (7.7%)	18 (6.9%)	0.74
Known hosp. asthma beyond 30 days of index, <i>n</i> (%)	0	0 (0.0%)	1 (0.4%)	0.32