Original Article

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

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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 with 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 of 8), the study findings help clinicians counsel parents with late preterm infants for risk of asthma, and both clinicians and parents avoid unnecessary evaluations or interventions for late preterm infants.

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: The objective of this study was to 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, Minn, between 1976 and 1982. Asthma status during the first 7 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 of gestation) to term infants (37 0/7 to 40 6/7 weeks of gestation) within a caliper of 0.2 standard deviation of logit of propensity score.

RESULTS: Of the eligible 7040 infants, 5915 children had complete data. Before propensity score matching, late preterm infants had a higher risk of asthma (20 of 262, 7.6%) compared with full-term infants (272 of 5653, 4.8%) ($P = .039$). 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, $P = .61$), and the result was consistent with covariate-adjustment Cox regression models controlling for significant covariates ($P = .57$).

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. **(J Allergy Clin Immunol Pract 2015;■:■-■)**

Key words: *Asthma; Epidemiology; Risk; Late preterm infants; Propensity score*

Asthma is the most common chronic illness among children, which affects 9.6% to 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] which suggests 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, who otherwise are referred to as late preterm (LPT) infants.[5] Risk of developing asthma in former premature infants is consistently greater than that in 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 toward 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 (eg, premature delivery or neighborhood environment) and all pertinent covariates are unavailable or

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Abbreviations used
LPT- Late preterm
PSA- Propensity score approach
RCT- Randomized clinical trial

unmeasured. For example, several risk factors for preterm birth have been identified that 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 (PSA) in asthma epidemiology research when a controlled clinical trial is infeasible, such as studying the association between neighborhood environment and risk of asthma.[18] Because random assignment of term versus LPT birth is infeasible, we applied a PSA 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] The characteristics of the Rochester, Minn, population were similar to those of the US 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, Mich (250/100,000), during the study period.[24]

Study subjects

Study subjects were from the population-based birth cohort, which has been previously described.[19,25,26] 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 to 36 6/7 weeks of gestation. Term was defined as $\geq$ 37 0/7 weeks of gestation.

Asthma ascertainment

The criteria for identifying asthma cases have been previously described and are noted in Table I.[20,21] These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.[18,21,27] 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. The 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, because most probable asthma cases became definite asthma over time.[18,21,27]

TABLE I. 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 3 conditions was present. *Probable asthma*: Subjects were considered to have probable asthma if only the first 2 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/μL
• 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

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