

Late Preterm Birth and Risk of Developing Asthma

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Objective To evaluate the association between gestational age at birth (late preterm vs term) and risk for physician-diagnosed asthma.

Study design We conducted a retrospective cohort study using the Third National Health and Nutrition Examination Survey (1988-1994) linked natality files. The study included children age 2-83 months from singleton births, born late preterm (n = 537) or term (n = 5650). Using survival analysis, we modeled time to diagnosis of asthma; children with no asthma diagnosis were censored at the age of their survey interview. We used Cox proportional hazard regression to estimate hazard ratios and 95% confidence intervals for gestational age and asthma risk, adjusting for maternal age, maternal education, parental history of asthma/hay fever, maternal smoking history during pregnancy, race/ethnicity, and sex of the child.

Results Adjusted analysis showed that physician-diagnosed asthma was modestly associated with late preterm birth (hazard ratio, 1.3; 95% confidence interval, 0.8-2.0), but this association was not statistically significant ($P = .30$).

Conclusions Our study found that late preterm birth was not associated with a diagnosis of asthma in early childhood. (*J Pediatr* 2010; ■: ■-■).

Nearly three-quarters of preterm infants born in the United States are born late preterm (birth between 34 weeks and 36 weeks, 6 days of gestation).^{1,2} These infants often are considered “functionally mature” because they are of similar size and weight at birth as infants born at term. Infants born late preterm also have less severe neonatal complications and long-term neurologic sequelae than infants born before 34 weeks of gestation.^{3,4} However, infants born late preterm are still developmentally and physiologically immature, and some studies have shown that they are at 3-fold greater risk for death and 7-fold greater risk for morbidity during infancy than infants born at term.^{5,6} In 2005, a National Institutes of Health expert workshop addressing the care and outcomes associated with late preterm birth⁷ concluded that children born late preterm were at increased risk for several adverse short-term outcomes, including more early education-related deficiencies than children born at term.⁸⁻¹¹

Although infants born late preterm have been shown to be at greater risk for early respiratory morbidities than infants born at term, whether these infants also might be at greater risk for long-term respiratory problems has not been determined. Epidemiologic studies performed in the United States, Canada, Italy, and the United Kingdom have shown that infants born late preterm (variously defined as 34-36, 33-36, and 35-36 weeks of gestation) have approximately 4- to 9-fold greater risk for respiratory morbidity during birth hospitalization and the neonatal period compared with infants born at term.^{4,12-14} Although preterm birth is generally an established risk factor for long-term respiratory problems, such as asthma,¹⁵ the association between late preterm birth and asthma has not yet been studied.

Between 1980 and 2005, the prevalence of asthma in US children ages 0-17 years increased by 147% (from 3.6% to 8.9%).¹⁶ Asthma also is the leading cause of emergency room admissions in US children under 15 years old, and the cost of emergency room treatment for these children has been estimated at more than \$5 billion per year.^{16,17} Given the increasing prevalence of both late preterm birth and asthma in US children, we sought to determine whether late preterm birth is a risk factor for physician-diagnosed asthma in US children age 2-83 months.

Methods

We conducted a retrospective cohort study using data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) linked to US birth certificate data. This linked data set was compiled by the National Center for

cHR	Crude hazard ratio
CI	Confidence interval
HR	Hazard ratio
LMP	Last menstrual period
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PH	Proportional hazard

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Health Statistics (NCHS)/Centers for Disease Control and Prevention. NHANES III is a nationally representative cross-sectional survey designed to assess the health and nutritional status of US adults and children. It uses a multistage probability sampling design to select noninstitutionalized members of the US civilian population, age 2 months and older. Young children, adults age 65 years and older, non-Hispanic blacks, and Mexican-Americans are oversampled to improve the reliability and precision of the health measurements of these subgroups.¹⁸ Further details on NHANES III sampling procedures have been published elsewhere.¹⁸ We restricted our analysis to 6189 singleton children born at 34–41 completed weeks of gestation, age 2–83 months at the time of survey participation whose parent or guardian granted consent to link the child's birth certificate data to NHANES III survey responses.¹⁹

Infants born late preterm were defined as those born between 34 and 36 completed weeks of gestation. Infants born at term were defined as those born between 37 and 41 completed weeks of gestation. NCHS estimates of children's gestational age at birth were obtained from birth certificates and based on the estimated time in weeks from the first day of a mother's last normal menstrual period (LMP) to the date of her infant's birth. If the day of the LMP was missing from a birth certificate but a valid month and year were available, then the NCHS imputed the number of weeks of gestation using a previously completed record with the same computed months of gestation and birth weight category. For 1989–1994, NCHS used a “clinical estimate of gestation” if a mother's LMP was not reported or if the duration of gestation calculated from the LMP was inconsistent with the infant's birth weight.¹⁹ After we excluded 2 of the 6189 NHANES III participants who met our study criteria (one because the child's birth weight was missing and one because the child's asthma status was missing), our final study population comprised 6187 children, including 537 classified as born late preterm and 5650 classified as born at term.

Children's physician-diagnosed asthma status was based on the family reference person's response to the survey question: “Did a doctor ever say that the (child) had asthma?” The family reference person (or head of household) was a respondent age 17 years or older who owned or rented the dwelling unit where the index child lived; for 97% of the children in our study, the family reference person was the mother or father.¹⁸

The potential covariates that we assessed were known or biologically plausible risk factors for both asthma and preterm birth. In developing our conceptual model of the likely pathways for an association between late preterm birth and asthma, we used a model proposed by Jakkola et al¹⁵ in which children born preterm and those with asthma share common genetic and environmental factors. Covariates from birth certificate data were mother's age at the time of the child's birth (categorized as <20 years, 20–34 years, or ≥35 years) and child's sex. Covariates from NHANES III were history of maternal smoking during pregnancy, education level of the head of household (categorized as less than high school, high

school, or more than high school), parental history of asthma or hay fever (yes/no; based on response to the question “Has either of [child's] biological parents ever been told by a doctor that he or she had asthma or hay fever at any age?”), and self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other).¹⁸

Potential effect modifiers and confounders were evaluated by the χ^2 test. We estimated the probability of children not developing asthma by age in months using Kaplan-Meier survival functions. To assess the association between late preterm birth and the prevalence of physician-diagnosed asthma, we used Cox proportional hazard (PH) regression with discrete ties and estimated the crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs).²⁰ We considered time to diagnosis of asthma in months as the survival time/failure event and censored children without physician-diagnosed asthma at their age in months at the time of the interview. We tested the PH assumptions by assessing log-log survival plots and determined that the PH had not been violated. We followed the NHANES analytic guidelines and applied statistical sample weights for examined children to account for both oversampling and unit nonresponse, used SUDAAN (Research Triangle Institute, Research Triangle Park, North Carolina) to adjust for the complex sampling design and to determine appropriate variance estimates,²⁰ and considered a *P* value <.05 to indicate a statistically significant difference.

Results

Table I shows the distribution of sociodemographic characteristics of the study population by duration of gestation (late preterm vs term). Of the 6187 children in the study, 537 (7.6%) were born late preterm and 370 (6.3%) had physician-diagnosed asthma (data not shown). Compared with infants born at term, those born late preterm were more likely to be non-Hispanic black and to have a mother age <20 years, a mother who smoked during pregnancy, and a family reference person with less than a high school education. No differences were noted for parental history of asthma or hay fever among infants born late preterm compared with term infants.

As shown by unadjusted Kaplan-Meier survival curves (**Figure**), at age 24 months, 5% of the children born at term would have developed asthma, compared with 9% of those born late preterm. At age 60 months, 9% of the children born at term would have developed asthma, compared with 11% of those born late preterm.

Table II presents the proportion of infants with asthma and the results of the crude HRs (cHRs) associated with each characteristic. Approximately 9% of children born late preterm were reported to have physician-diagnosed asthma, compared with 6.0% of those born at term. For each comparison, the group with the lowest proportion of asthma was used as the reference group to calculate the cHR. Children with asthma were more likely to have a mother who gave birth before age 35 years (<20 years:

Table 1. Distribution of characteristics of US children age 2-83 months, by length of gestation (late preterm or term), NHANES III, 1988-1994, linked with US birth certificate files (n = 6187)

Characteristic	Late preterm birth (n = 537), % (95% CI)*	Term birth (n = 5650), % (95% CI)*
Maternal age at birth		
<20 years	21.3 (14.0-31.2)	11.0 (9.6-12.6)
20-34 years	72.6 (62.0-81.1)	80.4 (78.3-82.2)
≥35 years	6.1 (3.9-9.5)	8.6 (7.3-10.2)
Education of family reference person		
<High school	32.9 (26.4-40.0)	22.1 (20.0-24.2)
High school	38.0 (31.0-45.0)	33.6 (31.0-36.4)
≥High school	29.1 (19.5-41.1)	44.3 (40.7-48.1)
Parental history of asthma/hay fever		
Yes	24.3 (18.0-32.0)	24.6 (22.1-26.9)
No	75.7 (68.0-82.0)	75.4 (73.0-77.6)
Maternal smoking during pregnancy		
Yes	34.5 (29.3-40.2)	21.8 (19.5-24.2)
No	65.5 (59.8-70.7)	78.2 (75.8-80.5)
Child's age at interview		
<12 months	12.8 (9.3-17.3)	13.9 (12.9-14.9)
12-23 months	13.0 (9.3-18.0)	16.0 (14.7-17.3)
24-35 months	14.5 (11.6-17.8)	15.5 (14.3-16.7)
36-47 months	12.5 (8.2-18.7)	15.4 (14.2-16.6)
48-83 months	47.2 (37.9-56.7)	39.2 (37.6-41.1)
Race/ethnicity of child		
Non-Hispanic white	42.2 (31.0-54.3)	67.1 (63.3-70.7)
Non-Hispanic black	29.0 (20.6-39.2)	15.4 (13.1-18.1)
Mexican-American	9.8 (6.8-14.0)	8.7 (7.3-10.4)
Other	19.0 (7.3-41.2)	8.8 (6.4-11.9)
Sex of child		
Male	46.8 (36.5-57.3)	53.3 (51.4-55.1)
Female	53.2 (42.7-63.5)	46.7 (44.9-48.6)

*Sample weights applied to proportions and 95% CIs.

cHR, 2.6; 95% CI, 1.2-5.8; 20-34 years: cHR, 2.8; 95% CI, 1.5-5.3), a family reference person with less than a high school education (cHR, 1.9; 95% CI, 1.2-3.0), a parent with a family history of asthma (cHR, 2.6; 95% CI, 2.0-3.6), and a mother who smoked during pregnancy (cHR, 1.9; 95% CI, 1.3-2.8). These children also were more likely to be non-Hispanic black (cHR, 1.6; 95% CI, 1.1-2.2) and male (cHR, 1.4; 95% CI, 1.0-1.9). Late preterm birth showed a modest association with asthma (cHR, 1.5; 95% CI, 1.0-2.3). Multivariate analyses were performed, adjusted for duration of gestation, mother's age at birth, education level of the family reference person, parental history of asthma/hay fever, whether the mother smoked during pregnancy, and child's race/ethnicity and sex. We did not incorporate birth weight as a covariate, because it is highly dependent on gestational age and would be strongly correlated with preterm birth. We included household exposure to environmental tobacco smoke, but later excluded this covariate because it too was highly correlated with maternal smoking and did not change the total indirect and direct effects on asthma risk in our population in the adjusted analysis. The results show that late preterm birth was weakly associated with physician-diagnosed asthma

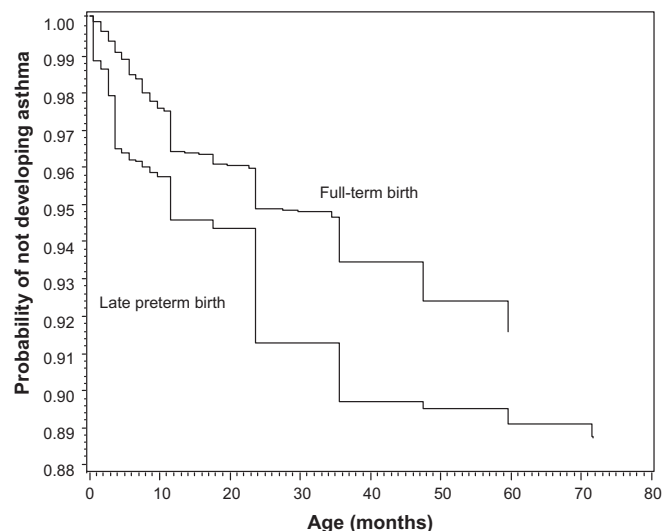


Figure. Kaplan-Meier survival curve illustrating the probability of not developing asthma by age (in months) in infants born late preterm and term, NHANES III, 1988-1994, linked with US birth certificate files.

(adjusted HR, 1.3; 95% CI, 0.8-2.0), but this association was not statistically significant ($P = .30$).

Discussion

Compared with infants born at term, infants born late preterm are more susceptible to respiratory morbidities during their birth hospitalization and neonatal period.^{4,12-14} Our data indicate that late preterm birth was weakly associated with asthma risk in early childhood, but this association was not statistically significant. Other covariates, including male sex, black race, a parental history of asthma/hay fever, less education (head of household), young maternal age, and maternal smoking during pregnancy, remained significant in the model and were stronger predictors of having an asthma diagnosis. These covariates are well-known risk factors for asthma, and these significant associations are consistent with previous research.²¹⁻²³

Our study evaluated the association between late preterm birth (34-36 weeks of gestation) and physician-diagnosed asthma. Although the association between asthma and preterm birth in general has been assessed in previous studies, the findings of these studies have been inconsistent, due in part to inconsistencies in the definitions of preterm birth (eg, <36 weeks, <37 weeks, ≤37 weeks) and asthma (eg, physician-diagnosed asthma, use of asthma medication, symptoms of asthma).^{15,21,24,25} Effect estimates from a meta-analysis of studies on the association between preterm birth and risk for asthma showed that infants born preterm (defined as <37 weeks of gestation) could have up to a 36% greater risk for asthma than infants born at term.¹⁵ No previous study has assessed asthma risk among infants born between 34 and 36 weeks of gestation, however.

Table II. Proportion of US children age 2-83 months with physician-diagnosed asthma, and cHRs for association between late preterm birth and asthma, by selected characteristics, NHANES III, 1988-1994, linked with US birth certificate files

Characteristic	Proportion with asthma	cHR	95% CI
Length of gestation, weeks			
Term	6.0	1.0	Reference
Late preterm	9.1	1.5	1.0-2.3
Maternal age at birth, years			
<20	6.2	2.6	1.2-5.8
20-34	6.7	2.8	1.5-5.3
≥35	2.3	1.0	Reference
Education of family reference person			
<High school	8.7	1.9	1.2-3.0
High school	6.7	1.5	1.0-2.3
≥High school	4.6	1.0	Reference
Parental history of asthma/hay fever			
Yes	11.8	2.6	2.0-3.6
No	4.5	1.0	Reference
Maternal smoking during pregnancy			
Yes	7.7	1.9	1.3-2.8
No	5.5	1.0	Reference
Race/ethnicity of the child			
Non-Hispanic white	5.6	1.0	Reference
Non-Hispanic black	8.6	1.6	1.1-2.2
Mexican-American	6.3	1.1	0.8-1.7
Other	6.7	1.2	0.8-1.9
Sex of the child			
Male	7.2	1.4	1.0-1.9
Female	5.3	1.0	Reference

Our findings may reflect the need to identify subgroups of infants born late preterm who may be at risk for long-term respiratory outcomes. One subgroup may be infants born late preterm in the presence of maternal morbidity. Several studies have suggested that long-term respiratory outcomes in offspring are initiated early on by the intrauterine environment (ie, fetal programming of the immune system).^{24,26} Transient tachypnea has been shown to occur more frequently in newborn infants with asthmatic mothers than in those with nonasthmatic mothers.²⁷ Infants born preterm or at low birth weight who have respiratory morbidities, such as respiratory distress syndrome, during their birth hospitalization and neonatal period have been shown to be at higher risk for asthma compared with infants born at term.^{28,29} Infants born late preterm with similar respiratory morbidities also may be at increased risk for long-term respiratory problems. Finally, the risk for long-term respiratory problems in children born late preterm may be affected by the type of respiratory therapy received during the neonatal period. Although the risk for respiratory morbidities has been shown to be inversely related to gestational age, the use of antenatal corticosteroids to help speed fetal lung development is not recommended after 34 weeks of gestation unless fetal pulmonary immaturity is present.³⁰ Whether infants born late preterm would benefit from antenatal corticosteroid treatment is not clear. In summary, to better understand which infants born late preterm might be at greater risk of developing long-term adverse respiratory outcomes,

researchers should pay particular attention to these infants' medical history during their birth hospitalization and neonatal period and closely monitor those whose mothers had morbidities associated with an increased risk for adverse respiratory outcomes among offspring.

This study has several strengths. We assessed a long-term respiratory outcome in infants born late preterm. Moreover, the NHANES III linked natality files for children age 2-83 months, thus providing a large representative birth cohort of infants born late preterm and term for multiple years. Second, because this was a retrospective cohort study, we could establish temporality and assess late preterm birth occurring before the diagnosis of asthma. Third, the questionnaire data and the large sample size allowed us to assess the effects of various potential confounders. Finally, because of the complex survey sampling design and weighting of NHANES III, our results can be generalized to the US population.

But despite these strengths, this study also has some limitations. Studies that rely on reports of LMP to estimate gestational age are prone to error.^{31,32} An analysis comparing clinical estimates and LMP estimates of gestational age showed that infants born at 28-36 weeks gestation were prone to misclassification error.³² Thus, in our study, some actual term births may have been misclassified as being born late preterm, which might have biased the results toward the null. In addition, misclassification of asthma status resulting from head of household self-reported physician-diagnosed asthma might have biased our results toward the null. However, one nationally representative study investigating US children's risk for asthma by 3 years of age showed similar odds ratios based on mothers' reports of asthma and those based on medical diagnoses of asthma.²¹ Misclassification also could have occurred in the diagnosis of asthma in infants and younger children, in whom this diagnoses is more likely to be based on subjective criteria compared with older children, in whom it is more likely to be based on clinical test results.³³ Both of these misclassifications, if nondifferential, would bias hazard ratio estimates toward the null. But if infants born late preterm were monitored more closely by a health professional than infants born at term, then these misclassifications might be differential and bias the results away from the null.³⁴ Because infants born late preterm have a 3-fold greater mortality rate compared with infants born at term, another limitation may be that infants born late preterm who survive the neonatal period are healthier infants and more medically similar to infants born at term. Thus, selective survival might have biased our results toward the null. Our analyses were also limited by the variables collected on the birth certificate and as part of the NHANES survey, and as such we were not able to accurately assess the impact of elective deliveries on respiratory outcomes.

Finally, this study is limited by data collected more than 15 years ago. Rates of asthma and late preterm birth have both increased since that time. But if a true (albeit modest) association does exist between late preterm birth and asthma, then this association should not change over time, except perhaps in terms of the magnitude of the association. Thus,

if our earlier data reflect a true association between late preterm birth and asthma, this association could partially explain the recently increasing rates of asthma in children.

Numerous studies show that infants born late preterm have higher morbidity and mortality risk compared with infants born at term.³⁵ Despite the vulnerabilities of this growing population, the long-term health outcomes of infants born late preterm have not yet been comprehensively investigated. In the present analysis, late preterm birth was not an important predictor of asthma risk for children age 2-83 months. Further studies that assess for a "gestational age" dose effect and that help identify the groups at greatest risk for potential long-term respiratory outcomes among infants born late preterm will help health care providers prepare for the medical needs of this population. ■

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