Preterm Birth with Childhood Asthma: The Role of Degree of Prematurity and Asthma Definitions

To the Editor:

Preterm birth (PTB) (1) and childhood asthma (2) are major health problems that disproportionally affect urban, poor minorities in the United States. Growing evidence suggests that children born preterm are at increased risk for asthma, but findings are inconsistent across studies (3–5). Of the 30 major studies on the association published worldwide, nearly a third reported null effects, whereas the others reported significant associations, with odds ratios ranging from 1.2 to 4.9 (4). We suspected that inconsistencies in the PTB–asthma association in part reflected differences among studies in three key domains: definitions of asthma (6), degree of prematurity, and the age when asthma was assessed.

We therefore investigated whether the association between PTB and asthma varied by definition of asthma used (e.g., recurrent wheezing vs. asthma, physician diagnosis vs. prescribed medication), degree of prematurity, and age at assessment (0–5 yr vs. 6–9 yr) in the Boston Birth Cohort (BBC). Our study is the first to simultaneously address these three sources of ambiguity in a large, prospective U.S. birth cohort. As an urban, poor, predominantly minority cohort with a high burden of PTB and asthma, the BBC is well-suited to this investigation.

Methods

Our analysis included 2,540 children (age 5.0 ± 2.8 yr) recruited at Boston Medical Center after excluding 161 children because of postterm birth or incomplete data. BBC data collection protocols are described elsewhere (7, 8) and were approved by the appropriate institutional review boards.

Asthma measures were created using electronic medical record data on physician diagnoses and prescriptions documented between October 2003 and September 2013. Eleven measures were created for children assessed between ages 0 and 5 years, and eight measures for children assessed between ages 6 and 9 years (*see* Table E1 in the online supplement).

Gestational age was measured by an algorithm combining the first day of the last menstrual period and data from the <20 weeks' ultrasound (9). Prematurity was defined in conventional categories (PTB [<37 wk, 28.3% of sample] vs. term birth [TB, 37–41 wk, 71.7%]) and refined categories (early preterm [22–31 wk, 8.1%], late preterm [32–36 wk, 20.2%], early term [37–38 wk, 25.7%], and full term [39–41 wk, 44.1%]) (Table E2).

We used multivariate logistic regression to examine the associations between categories of PTB and the asthma measures at ages 0–5 (n = 2,540) and 6–9 (n = 1,072) years. All analyses were performed using Stata 12.0 (College Station, TX).

Results

The prevalence of asthma varied substantially across the asthma measures in both age ranges (7–43% in PTB; 2–25% in TB). However, children born preterm had a significantly higher prevalence ($P < 0.001$) of asthma than children born term on all asthma measures in both age ranges (Figure 1). Models adjusting for covariates showed the same results, with adjusted odds ratios (AORs) ranging from 1.8 (95% confidence interval [CI], 1.5–2.3) to 2.9 (95% CI, 2.1–4.1) ($P < 0.001$) in both age ranges (Table 1).

Compared with full-term children, early preterm children had the highest odds of asthma (AORs 3.2 [95% CI, 2.2–4.5] to 6.2 [95% CI, 3.3–11.6]; $P < 0.001$), and late preterm children had the second highest (AORs 1.5 [95% CI, 1.1–2.2] to 2.5 [95% CI, 1.6–3.8]; $P < 0.05$) (Table 1). These associations were consistent across all asthma measures in both age ranges. Early term children's odds of asthma were not significantly higher than those for full-term children, with the exception of asthma exacerbation at ages 6–9 years (AOR = 1.8 [95% CI, 1.1–3.2]; $P = 0.029$). Given the variable length of follow-up resulting from our rolling enrollment design, we performed an analysis of the subset of children with continuous electronic medical record data from birth (n = 1973). Those analyses demonstrated similar or even higher PTB–asthma associations after adjusting for length of follow-up (Table E3).

Discussion

We found that, although the prevalence of asthma varied by asthma definition, children born preterm were at a higher risk of asthma compared with term children on all measures at ages 0–5 and 6–9 years. We also observed a robust dose–response association between degree of prematurity and all asthma measures in both age ranges. Our results provide strong evidence that PTB is an important risk factor for asthma.

Despite the strengths of the BBC data, this study has potential limitations. First, although electronic medical record data are not affected by recall bias, they may suffer from other errors, such as underdiagnosing because of transcriber/coder's experience. In addition, the BBC sample may limit generalizability of our results; however, the results are highly relevant to urban, poor, minority populations, who have a high prevalence of both asthma and PTB.

About one in nine of all children and one in six of black infants were born preterm in the United States in 2013 (1). PTB is not

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Author Contributions: X.W. is the principal investigator of the Boston Birth Cohort and has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis in this report. The subject recruitment, follow-up, and data collection were overseen and managed by X.W. and B.S.Z. and were conducted by a team of investigators including C.P., X.H., and D.M.C. H.H., M.E.H., and X.W. conceptualized this study. H.H. assumed primary responsibility for data cleaning and statistical analyses and drafted this manuscript. All the other coauthors provided critical inputs on the study design, data analyses, and interpretation of the study findings. All the authors reviewed the final version of the manuscript and approved submission to the journal for publication.

This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

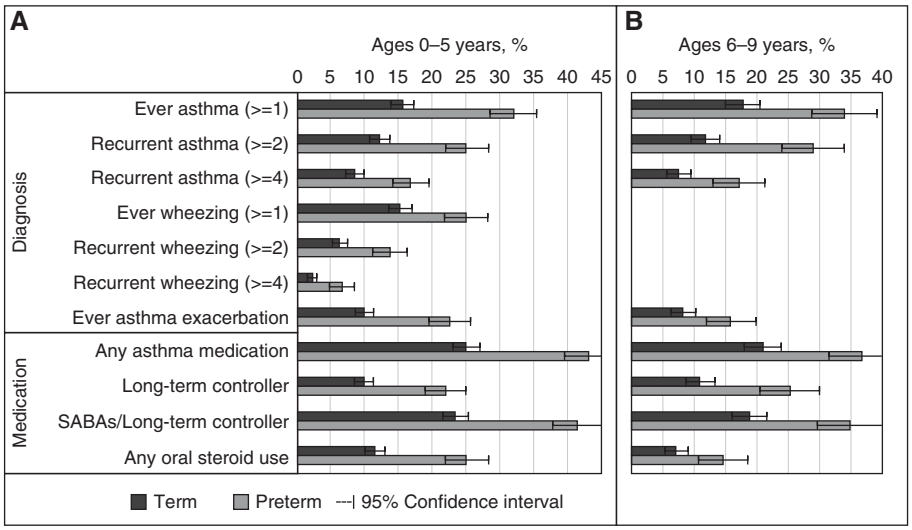

Figure 1. Percentage of childhood asthma among preterm births versus term births, stratified by age group. (*A*) Childhood asthma measures assessed between ages 0 and 5 years. (*B*) Childhood asthma measures assessed between ages 6 and 9 years. The preterm group had a higher percentage of each asthma measure than the term group ($P < 0.001$). For asthma measures: ever asthma (≥1) = had at least one asthma diagnosis from the electronic medical record during the specified ages; recurrent asthma (≥2) = had two or more asthma diagnoses during the specified ages; recurrent asthma (≥4) = had four or more asthma diagnoses during follow-up time; ever wheezing (≥1) = had at least one wheezing diagnosis during the specified ages; recurrent wheezing (≥2) = had two or more wheezing diagnoses during the specified ages; recurrent wheezing (≥4) = had four or more wheezing diagnoses during the specified ages; ever asthma exacerbation = had an asthma exacerbation diagnosis during the specified ages. Please *see* Table E1 for more detailed description of asthma measures. SABAs = short-acting β-agonists.

included in the Asthma Predictive Index (10), but our findings underscore the important role it plays in the development of childhood asthma. Prevention of PTB is thus important not only for reducing well-known PTB-associated mortality and morbidity but also for reducing the burden of asthma, especially the disproportionate burden among urban, poor Americans. ■

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Table 1. Adjusted Odds Ratios of Asthma-related Outcomes across Preterm Birth Categories*

	Preterm Birth (<37 wk); Ref = Term (37–41 wk)			Degree of Prematurity; Ref = Full Term (39–41 wk)								
				Early Preterm (22–31 wk)			Late Preterm (32–36 wk)			Early Term (37–38 wk)		
	AOR	95% CI	*P* Value	AOR	95% CI	*P* Value	AOR	95% CI	*P* Value	AOR	95% CI	*P* Value
Outcome at ages 0–5 yr (N = 2,540)												
Diagnosis												
Ever asthma (⩾1)	2.45	(1.98–3.04)	<0.001	5.90	(4.19–8.31)	<0.001	1.70	(1.30–2.23)	<0.001	1.05	(0.80–1.38)	0.718
Recurrent asthma (⩾2)	2.28	(1.81–2.88)	<0.001	4.13	(2.88–5.93)	<0.001	1.70	(1.27–2.28)	<0.001	0.95	(0.70–1.29)	0.763
Recurrent asthma (⩾4)	2.00	(1.52–2.61)	<0.001	4.09	(2.72–6.13)	<0.001	1.54	(1.09–2.19)	0.015	1.17	(0.83–1.66)	0.364
Ever wheezing (⩾1)	1.85	(1.48–2.31)	<0.001	3.15	(2.21–4.49)	<0.001	1.67	(1.26–2.20)	<0.001	1.27	(0.97–1.66)	0.084
Recurrent wheezing (⩾2)	2.29	(1.71–3.09)	<0.001	4.16	(2.66–6.51)	<0.001	1.92	(1.31–2.82)	<0.001	1.21	(0.82–1.79)	0.339
Recurrent wheezing (⩾4)	2.85	(1.83–4.43)	<0.001	6.17	(3.30–11.55)	<0.001	2.12	(1.17–3.82)	0.013	1.20	(0.64–2.26)	0.567
Ever asthma exacerbation	2.48	(1.94–3.17)	<0.001	4.49	(3.08–6.55)	<0.001	2.05	(1.50–2.79)	<0.001	1.14	(0.82–1.57)	0.435
Medication												
Any asthma medication	2.22	(1.83–2.68)	<0.001	5.74	(4.14–7.96)	<0.001	1.68	(1.33–2.12)	<0.001	1.22	(0.97–1.52)	0.088
Long-term controller	2.42	(1.89–3.09)	<0.001	5.82	(4.03–8.39)	<0.001	1.54	(1.12–2.12)	0.008	1.00	(0.72–1.39)	0.988
SABAs/long-term controller	2.26	(1.87–2.74)	<0.001	5.60	(4.03–7.76)	<0.001	1.73	(1.36–2.19)	<0.001	1.21	(0.96–1.52)	0.109
Any oral steroid use	2.45	(1.95–3.08)	<0.001	5.35	(3.76–7.60)	<0.001	1.87	(1.39–2.51)	<0.001	1.18	(0.87–1.59)	0.292
Outcome at ages 6–9 yr (N = 1,072)†												
Diagnosis												
Ever asthma (⩾1)	2.28	(1.66–3.12)	<0.001	4.92	(2.91–8.31)	<0.001	2.04	(1.38–3.01)	<0.001	1.46	(0.98–2.16)	0.062
Recurrent asthma (⩾2)	2.94	(2.08–4.15)	<0.001	5.68	(3.27–9.86)	<0.001	2.46	(1.60–3.80)	<0.001	1.22	(0.76–1.95)	0.409
Recurrent asthma (⩾4)	2.40	(1.57–3.67)	<0.001	3.92	(2.05–7.47)	<0.001	1.97	(1.16–3.36)	0.013	1.10	(0.61–1.98)	0.744
Ever asthma exacerbation	2.05	(1.35–3.12)	<0.001	3.91	(2.04–7.50)	<0.001	2.09	(1.21–3.60)	0.008	1.83	(1.07–3.15)	0.029
Medication												
Any asthma medication	2.05	(1.51–2.77)	<0.001	3.82	(2.28–6.41)	<0.001	1.87	(1.29–2.71)	<0.001	1.31	(0.90–1.90)	0.163
Long-term controller	2.64	(1.84–3.77)	<0.001	3.57	(2.03–6.28)	<0.001	2.26	(1.47–3.49)	<0.001	0.99	(0.61–1.61)	0.972
SABAs/long-term controller	2.17	(1.59–2.96)	<0.001	4.00	(2.37–6.73)	<0.001	2.02	(1.38–2.96)	<0.001	1.35	(0.91–1.99)	0.133
Any oral steroid use	2.16	(1.39–3.36)	<0.001	3.21	(1.68–6.15)	<0.001	1.60	(0.93–2.75)	0.092	0.90	(0.50–1.65)	0.743

Definition of abbreviations: AOR = adjusted odds ratio; CI = confidence interval; Ref = reference; SABAs = short-acting β-agonists.
See Table E1 for description of asthma measures.
*Adjusted for maternal age, race/ethnicity, marital status, education, history of asthma, maternal persistent smoking during the index pregnancy; child sex and age, followed years, and family member smoking.
†Wheezing measures were excluded because of low prevalence during ages 6–9 years.

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Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease

To the Editor:

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition (1). The identification of COPD phenotypes may allow stratified treatment approaches that modulate discrete disease mechanisms. Peripheral blood eosinophilia is both a common and repeatable finding in COPD (2). In addition, the presence of a blood/sputum eosinophilia is associated with a significant proportion of COPD exacerbations (3, 4) and a favorable response to systemic steroids (5). However, the role of blood eosinophils in stratifying treatment response to inhaled corticosteroid/long-acting β-agonist combinations is poorly understood.

The FORWARD (Foster 48-Week Trial to Reduce Exacerbations in COPD) study was a randomized, double-blind, parallel group trial that compared 48 weeks of treatment with extrafine beclomethasone dipropionate plus formoterol fumarate (BDP/FF), 100/6 μg pressurized metered-dose inhaler, two inhalations twice a day, versus FF 12 μg pressurized metered-dose inhaler, one inhalation twice a day, in patients with severe COPD with a history of exacerbations (clinical trial registered with www.clinicaltrials.gov [NCT 00929851]). The results of the study have been reported (6) and showed a significant reduction in exacerbation rate (28%) and improvement in lung function with BDP/FF compared with FF treatment.

Here we evaluate the hypothesis that these treatment differences differ according to the baseline blood eosinophil count by performing a *post hoc* analysis on the FORWARD study data.

Methods

The median (quartile 1; quartile 3) baseline blood eosinophil count was 181.6 (110.4; 279.8), and the distribution of counts is shown in Figure E1 in the online supplement. The patients (n = 1,184) were stratified into quartile groups on the basis of the baseline eosinophil count. The clinical characteristics of the study population across the quartiles of baseline blood eosinophils are reported in Table E1. The following endpoints were analyzed: COPD exacerbation rate over the course of 48 weeks, using a negative binomial model for adjusted exacerbation rates, Kaplan-Meier analysis, and Cox proportional hazard model for time to first exacerbation event; change from baseline in predose morning FEV_1 at 48 weeks, using a linear mixed model for repeated measurements; and change from baseline in St. George's Respiratory Questionnaire total score at 48 weeks, using an analysis of covariance model. Further details of the models are provided in the online supplement. Additional analyses using percentage eosinophil count thresholds and considering absolute counts as a continuous variable were also performed. A predictive model (*see* online supplement for details) for future COPD exacerbation rate was estimated, accounting for a variety of baseline factors that may influence exacerbations (7). The effect of baseline blood eosinophil count on adverse events, and in particular pneumonia, was also evaluated.

Results

The adjusted exacerbation rate in patients receiving BDP/FF was similar across the quartiles, ranging from 0.75 to 0.87 events/patient/year. However, there was a pattern of increasing exacerbation frequency with increasing eosinophil count in patients treated with FF, with 1.39 events/patient/year within the highest quartile (≥279.8/μl); a 46% reduction in adjusted exacerbation rate caused by BDP/FF was found in this quartile ($P < 0.001$), with numerically smaller treatment effects in the other quartiles (Figure 1*A*). These results were supported by a similar trend when evaluating the time to first exacerbation event (Figure E2 and Table E2). Exploratory predictive modeling supported these observations and suggested that in patients treated with BDP/FF, the risk for future exacerbations was not influenced by baseline blood eosinophils, in contrast to in patients treated with FF alone (Figure E3).

The treatment difference for the adjusted mean change in predose FEV_1 from baseline to 48 weeks within the highest blood eosinophil quartile was 0.102 L in favor of BDP/FF ($P = 0.001$) (Figure 1*B*). The treatment differences were lower in the other quartiles and retained in the lowest quartile (0.083 L; $P = 0.006$).

Patients receiving BDP/FF within the highest blood eosinophil quartile demonstrated an adjusted mean change in St. George's Respiratory Questionnaire total score from baseline to 48 weeks of −5.6 units compared with +0.3 units in the FF-only group; $\Delta = 5.9$ units in favor of BDP/FF ($P < 0.001$) (Figure 1*C*). Smaller differences were seen in the other quartiles.

Analyses of these outcomes according to percentage baseline eosinophils and eosinophils as a continuous variable identified a similar trend (*see* Tables E3–E5 and online supplement).

No significant differences were observed between BDP/FF and FF alone in adverse events, including pneumonia, across the blood eosinophil quartiles (Table E6).

Discussion

Greater treatment differences in the FORWARD study were observed in patients with eosinophil counts ≥ 279.8/μl compared with lower eosinophil counts. Patients in the highest eosinophil quartile experienced the highest exacerbation rate with FF treatment, and the benefit of additional inhaled corticosteroid

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