ORIGINAL ARTICLE

Antenatal Determinants of Bronchopulmonary Dysplasia and Late Respiratory Disease in Preterm Infants

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Abstract

Rationale: Mechanisms contributing to chronic lung disease after preterm birth are incompletely understood.

Objectives: To identify antenatal risk factors associated with increased risk for bronchopulmonary dysplasia (BPD) and respiratory disease during early childhood after preterm birth, we performed a prospective, longitudinal study of 587 preterm infants with gestational age less than 34 weeks and birth weights between 500 and 1,250 g.

Methods: Data collected included perinatal information and assessments during the neonatal intensive care unit admission and longitudinal follow-up by questionnaire until 2 years of age.

Measurements and Main Results: After adjusting for covariates, we found that maternal smoking prior to preterm birth increased the odds of having an infant with BPD by twofold ($P = 0.02$). Maternal smoking was associated with prolonged mechanical ventilation and respiratory support during the neonatal intensive care unit admission. Preexisting hypertension was associated with a twofold ($P = 0.04$) increase in odds for BPD. Lower gestational age and birth weight *z*-scores were associated with BPD. Preterm infants who were exposed to maternal smoking had higher rates of late respiratory disease during childhood. Twenty-two percent of infants diagnosed with BPD and 34% of preterm infants without BPD had no clinical signs of late respiratory disease during early childhood.

Conclusions: We conclude that maternal smoking and hypertension increase the odds for developing BPD after preterm birth, and that maternal smoking is strongly associated with increased odds for late respiratory morbidities during early childhood. These findings suggest that in addition to the BPD diagnosis at 36 weeks, other factors modulate late respiratory outcomes during childhood. We speculate that measures to reduce maternal smoking not only will lower the risk for preterm birth but also will improve late respiratory morbidities after preterm birth.

Keywords: prematurity; maternal smoking; bronchopulmonary dysplasia; hypertensive disorders of pregnancy; preeclampsia

Despite improvements in perinatal care, preterm children remain at high risk for mortality and significant respiratory morbidities owing to the development of bronchopulmonary dysplasia (BPD) (1). BPD is the chronic lung disease of prematurity that develops in infants who require respiratory support at birth owing to immaturity of the preterm lung (2). BPD occurs in roughly 45% of infants born at less than or equal to 29 weeks of gestation with birth weights between 400 and 1,500 g, with approximately 10,000–15,000 new cases reported each year (1, 3, 4). The incidence of BPD has not changed over the

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At a Glance Commentary

Scientific Knowledge on the Subject: Despite improvements in perinatal care, preterm infants remain at high risk for developing bronchopulmonary dysplasia (BPD) and late respiratory disease during childhood. Antenatal factors that contribute to the development of BPD and late respiratory problems during infancy are incompletely understood. In addition, the relationship between risk for BPD and late respiratory sequelae are uncertain.

What This Study Adds to the Field: Data derived from this prospective, longitudinal multicenter study show that maternal smoking and preexisting hypertension increase the odds for developing BPD after preterm birth and that maternal smoking is strongly associated with increased odds for late respiratory morbidities during early childhood. These findings suggest that in addition to BPD diagnosis at 36 weeks corrected age, other factors modulate late respiratory outcomes during childhood.

past few decades, reflecting improved survival of extremely preterm infants who are at highest risk for BPD (5).

BPD is also associated with significant neonatal intensive care unit (NICU)-related complications, including the prolonged need for mechanical ventilation, respiratory support, and oxygen therapy; longer duration of hospitalization; and higher rates of nonrespiratory comorbidities, such as retinopathy of prematurity and brain injury (5, 6). After NICU discharge, infants with BPD often require frequent hospital readmissions and have high rates of emergency room or physician visits for recurrent respiratory exacerbations, infections, and reactive airway disease. Sustained abnormalities of lung function, poor exercise tolerance, and the need for chronic respiratory medications throughout childhood and adolescence are also increased in former preterm infants (7, 8). Past studies have shown that over 50% of preterm infants subsequently require rehospitalizations or chronic respiratory medications after NICU discharge, including preterm infants without a formal diagnosis of BPD (8). Controversies persist regarding how best to define BPD and whether bearing this diagnosis at 36 weeks postmenstrual age (PMA) adequately reflects the late risk for lung disease during childhood and into adult life (9–11).

Although postnatal factors, such as hyperoxia, mechanical ventilation, prolonged patency of the ductus arteriosus, sepsis, inflammation, and others, increase the risk for BPD, epidemiologic studies have further identified important roles for antenatal factors as well (12–19). Adverse antenatal factors, such as chorioamnionitis, preeclampsia, preexisting hypertensive disorders, obesity, and others, have been variably associated with an increased risk for BPD (11, 15–22). Maternal smoking has also been linked with an increased rate of preterm birth (23, 24). In addition, past studies further suggest that maternal smoking is associated with a higher risk for lung disease in children (25–27).

Recently, participants in an NHLBI-sponsored workshop discussed the importance of prenatal and early postnatal influences on lung growth and development on subsequent respiratory function and disease throughout childhood (11). This workshop further highlighted major gaps in understanding of how environmental and maternal factors can impact late respiratory outcomes during early childhood, and that the exact relationships between prenatal exposures and early postnatal events on the subsequent development of late respiratory disease during infancy, especially after preterm birth, remain uncertain. Because an increasing number of studies have shown that preterm birth alone is associated with late respiratory disease in childhood, links between the diagnosis of BPD at 36 weeks corrected age and persistent chronic lung disease during infancy and beyond remain unclear.

To better understand antenatal risk factors associated with the development of BPD and late respiratory disease during early childhood after premature birth, and to examine the relationship between the diagnosis of BPD and respiratory disease after NICU discharge, we completed a prospective longitudinal study of a cohort of preterm infants. We collected extensive perinatal data and performed serial assessments during NICU admission and longitudinal follow-up by questionnaire to evaluate the potential contributions of antenatal factors that increase the risk for BPD, modulate the clinical severity of BPD, and contribute to persistent respiratory disease throughout early infancy. We further examined the relationship between the current diagnosis of BPD at 36 weeks PMA and subsequent respiratory morbidities during early childhood.

Methods

Study Population

All data were obtained between July 2006 and November 2016 as part of a prospective observational research protocol that was reviewed and approved by the institutional review boards of the respective sites. Written informed consent was received from the parents or guardians of all participants. The study population consisted of subjects enrolled in a prospective study of premature infants at risk for BPD (NHLBI grant HL085703). Participants were preterm infants from five centers who had a gestational age less than or equal to 34 weeks, birth within the previous 7 days, and a birth weight between 500 and 1,250 g.

Study Design

Data were prospectively collected and managed using a REDCap database hosted at the University of Colorado Denver (28). BPD status and severity were assessed at 36 weeks PMA using a modification of the National Institutes of Health workshop definition (3) with application of the oxygen reduction test (29). For some analyses, comparisons were made regarding the presence or absence of BPD, which was defined as children having either no or mild BPD versus those diagnosed with moderate or severe BPD. Birth weight *z*-scores were calculated by the methods of Oken and colleagues (30). Maternal smokers were self-identified at the initial patient assessment. A newborn was considered as small for gestational age if the birth weight *z*-score was below the 10th percentile for sex and gestational age. For subjects with a small number of missing variables (three or fewer), their medical records were assumed to be complete, and the missing values were imputed, except for the following variables, which were not changed: corticosteroids, pregestational diabetes, antibiotic use, maternal fever, or tocolytic medications. Variables with missing values for all other records were left as unknown. The number of events restricted our number of predictors in the model to 20, which were selected on the basis of *a priori* clinical knowledge. We excluded four subjects

with three or more missing variables from the analysis rather than attempting to impute a large proportion of missing information for a given subject. Follow-up surveys were administered at 6-month intervals to examine respiratory health over the first 2 years of life, which included questions regarding environmental exposures to secondhand smoke and to pets. A child was considered to have a diagnosis of late respiratory disease if any of the following events occurred over the first 2 years of life: one or more respiratory hospitalizations; use of inhaled steroids, inhaled bronchodilators, and/or diuretics; and a physician's diagnosis of asthma, reactive airway disease, or a BPD exacerbation.

Statistical Analysis

Chi-square tests, Fisher's exact tests, and Wilcoxon signed-rank tests were used to assess associations across BPD and late respiratory outcome status for categorical and continuous variables, respectively. A logistic regression model was fitted using an outcome of moderate or severe BPD at 36 weeks PMA. Perinatal risk factors and potential confounders were identified *a priori* on the basis of clinical importance and were restricted to an appropriate number based on the number of events (*see* Table 1) (31). To facilitate clinical interpretation, signs were reversed for birth weight *z*-score, maternal age, and gestational age. A similar logistic regression was fitted modeling the diagnosis of late respiratory disease using a reduced set of the covariates from the prior model. Interactions of maternal smoking with all other covariates were tested. Two logistic regressions were fitted on the diagnosis of late respiratory disease using dichotomized BPD and the classification of BPD severity as the only predictors. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Characteristics of the 587 infants enrolled across sites are stratified by BPD status (Table 1). The median birth weight and gestational age were 930 g and 27 weeks, respectively. Most of the mothers in this study were non-Hispanic (79%) and white (77%). Smoking was reported by 14% of mothers (Table 2). The diagnosis of BPD disease severity included mild (n = 214 [36.5%]), moderate (n = 119 [20.3%]), and severe (n = 123 [21.0%]) categories. Applying a dichotomized diagnosis of BPD status, 242 (41.2%) infants developed moderate or severe BPD, and 345 (58.8%) infants did not develop BPD (n = 131 [22.3%]) or developed only mild disease

Table 1. Subject Characteristics by Bronchopulmonary Dysplasia Status

	All Subjects (*n* = *587*)	No or Mild BPD (*n* = *345*)	Moderate or Severe BPD (*n* = *242*)	*P* Value*
Birth weight, g	930 (758 to 1,080)	1,000 (855 to 1,125)	800 (680 to 970)	<0.01
Birth weight *z*-score	−0.24 (−0.82 to 0.29)	−0.24 (−0.94 to 0.29)	−0.25 (−0.69 to 0.29)	0.20
Birth weight strata, g				
500–749 (n = 136)	136 (23%)	46 (13.3%)	90 (37.2%)	<0.01
750–999 (n = 220)	223 (37.7%)	123 (35.7%)	100 (41.3%)	0.16
1,000–1,250 (n = 219)	228 (38.6%)	176 (51%)	52 (21.5%)	<0.01
Small for gestational age	158 (26.7%)	92 (26.7%)	66 (27.3%)	0.87
Birth length, cm	35 (32.5 to 37)	35.5 (34 to 37.2)	33 (31.5 to 35.6)	<0.01
Head circumference, cm	24.5 (23 to 26)	25.05 (24 to 26.5)	23.5 (22 to 25)	<0.01
Gestational age, wk	27 (26 to 28)	27 (26 to 29)	26 (24 to 27)	<0.01
Maternal age, yr	28 (23 to 32)	28 (23 to 33)	28 (23 to 31)	0.14
Male sex	299 (50.6%)	164 (47.5%)	135 (55.8%)	0.05
Maternal race				
Asian	7 (1.2%)	4 (1.2%)	3 (1.2%)	0.93
Black or African American	119 (20.1%)	77 (22.3%)	42 (17.4%)	0.14
Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)	—
White	457 (77.3%)	262 (75.9%)	195 (80.6%)	0.18
Other	1 (0.2%)	0 (0%)	1 (0.4%)	—
Unknown	3 (0.5%)	3 (0.9%)	0 (0%)	0.15
Maternal ethnicity				
Hispanic or Latino	119 (20.1%)	73 (21.2%)	46 (19.0%)	0.52
Not Hispanic or Latino	467 (79.0%)	271 (78.6%)	196 (81.0%)	0.47
Multiple gestations	143 (24.2%)	87 (25.2%)	56 (23.1%)	0.56
Antenatal corticosteroids	487 (82.4%)	289 (83.8%)	198 (81.8%)	0.42
Cesarean section delivery	408 (69.0%)	250 (72.5%)	158 (65.3%)	0.06
Intubated in delivery room	363 (61.4%)	180 (52.2%)	183 (75.6%)	0.02
Intubated in NICU	122 (20.6%)	74 (21.4%)	48 (19.8%)	0.11
Surfactant in delivery room	460 (77.8%)	239 (69.3%)	221 (91.3%)	<0.01
PDA medical treatment	245 (41.5%)	120 (34.8%)	125 (51.7%)	<0.05
PDA surgical ligation	74 (12.5%)	21 (6.1%)	53 (21.9%)	<0.01
IVH grade 3 or 4	24 (4.1%)	8 (2.3%)	16 (6.6%)	0.01
Threshold ROP	47 (8.0%)	8 (2.3%)	39 (16.1%)	<0.01

Definition of abbreviations: BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NICU = neonatal intensive care unit; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity.

Descriptive statistics [count (percent) or median (interquartile range)] are displayed for the demographics of the study population, stratified by bronchopulmonary dysplasia severity. Univariate comparisons were made across bronchopulmonary dysplasia severity outcomes.

**P* value denotes comparison of last two columns.

Table 2. Maternal Complications by Bronchopulmonary Dysplasia Status

	All Subjects (*n* = 587)	No or Mild BPD (*n* = 345)	Moderate or Severe BPD (*n* = 242)	*P* Value*
Preexisting diabetes	22 (3.7%)	15 (4.3%)	7 (2.9%)	0.33
Gestational diabetes	40 (6.8%)	27 (7.8%)	13 (5.4%)	0.24
Preexisting hypertension	67 (11.3%)	37 (10.7%)	30 (12.4%)	0.55
Prolonged rupture of membranes	107 (18.1%)	64 (18.6%)	43 (17.8%)	0.86
Chorioamnionitis	110 (18.6%)	61 (17.7%)	49 (20.2%)	0.38
Preeclampsia	154 (26.1%)	98 (28.4%)	56 (23.1%)	0.17
Antepartum hemorrhage	67 (11.3%)	33 (9.6%)	34 (14.0%)	0.09
Maternal smoking	80 (13.5%)	35 (10.1%)	45 (18.6%)	<0.01
Maternal alcohol use	13 (2.2%)	6 (1.7%)	7 (2.9%)	0.35
Maternal substance abuse	50 (8.5%)	27 (7.8%)	23 (9.5%)	0.47

Definition of abbreviation: BPD = bronchopulmonary dysplasia.
Descriptive statistics [count (percent)] are presented for maternal complications calculated for the entire study population, stratified by bronchopulmonary dysplasia severity. Univariate comparisons were made across bronchopulmonary dysplasia severity outcomes.
**P* value denotes comparison of last two columns.

(n = 214 [36.5%]). More infants with moderate and severe BPD had severe intraventricular hemorrhage ($P = 0.01$) and more often were treated with surgical ligation of a patent ductus arteriosus ($P < 0.01$) than those with no or mild BPD (Table 1).

A univariate analysis between antenatal events and dichotomized BPD status yielded a significant relationship between maternal smoking and the development of BPD after preterm birth ($P < 0.01$) (Table 2). Of those children who developed moderate or severe BPD, 18.6% had mothers who smoked during pregnancy. Of those who developed mild or no BPD, 10.1% had mothers who smoked during pregnancy. None of the other antenatal events were significantly associated with BPD.

A multiple linear logistic regression was fitted to the diagnosis of BPD (Table 3) (*c*-index, 0.77). There was a significant association between maternal smoking and BPD severity. After adjusting for covariates, we found that mothers who smoked while pregnant increased their odds of having an infant with moderate or severe BPD by 2.02-fold (95% confidence interval (CI), 1.09–3.74; $P = 0.02$). Preexisting maternal hypertension was associated with a 2.11 times increase in the odds of BPD severity (95% CI, 1.05–4.24; $P = 0.04$). Children of white mothers had a 1.85-times increase in the odds of BPD severity at 36 weeks than those of other races (95% CI, 1.11–3.08; $P = 0.02$). As expected, lower gestational age (weeks) (odds ratio [OR], 1.89; 95% CI, 1.65–2.17; $P < 0.01$) and lower birth weight *z*-scores (OR, 2.40; 95% CI, 1.66–3.46; $P < 0.01$) were also significantly associated with an increase in BPD severity. Cesarean section delivery was associated with a lower odds (OR, 0.63; 95% CI, 0.40–0.99; $P = 0.05$). The ORs from the model are ranked graphically in Figure 1. Interactions of maternal smoking with all other covariates

Table 3. Model Results of Logistic Regression for Bronchopulmonary Dysplasia Status

Parameter	Odds Ratio	95% Confidence Interval	*P* Value
Decreasing birth weight *z*-score, 1 SD	2.40	1.66–3.46	<0.01
Male sex	1.37	0.92–2.03	0.12
Maternal race: white	1.85	1.11–3.08	0.02
Maternal ethnicity: Hispanic or Latino	0.70	0.42–1.17	0.17
Decreasing gestational age, wk	1.89	1.65–2.17	<0.01
Maternal smoking status	2.02	1.09–3.74	0.02
Antenatal corticosteroids	0.90	0.51–1.59	0.71
Multiple gestations	1.50	0.92–2.44	0.10
Cesarean section delivery	0.63	0.40–0.99	0.05
Preexisting diabetes	0.92	0.32–2.65	0.87
Gestational diabetes	1.23	0.56–2.67	0.61
Preexisting hypertension	2.11	1.05–4.24	0.04
Prolonged rupture of membranes	0.86	0.50–1.48	0.59
Chorioamnionitis	0.87	0.51–1.48	0.60
Preeclampsia	0.97	0.55–1.70	0.92
Antepartum hemorrhage	1.13	0.62–2.05	0.69
Decreasing maternal age, yr	1.01	0.98–1.05	0.57
Maternal alcohol consumption	0.97	0.20–4.70	0.97
Maternal drug use	0.94	0.44–2.02	0.88
Tocolytics	1.08	0.72–1.63	0.71

Risk factors for bronchopulmonary dysplasia: parametric estimates, Wald 95% confidence intervals, and *P* values derived from the logistic regression analysis modeling bronchopulmonary dysplasia severity.

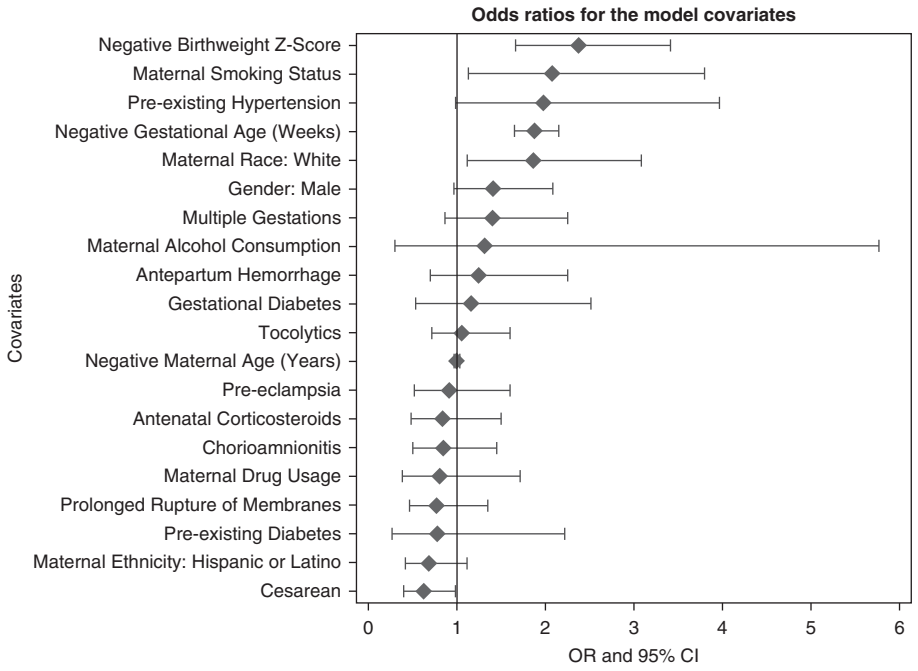

Figure 1. Odds ratios (ORs) with 95% confidence intervals (CIs) for model covariates from the logistic regression analysis modeling bronchopulmonary dysplasia severity.

were tested, and none yielded significant associations with smoking status, including degree of prematurity.

To further investigate the impact of maternal smoking, univariate analyses between postnatal NICU events and maternal smoking status were performed (Table 4). The requirement for continuous positive airway pressure at 36 weeks PMA was marginally greater in infants from maternal smokers and nonsmokers ($P = 0.06$). For mothers who smoked during pregnancy, 11.3% of their children required continuous positive airway pressure at 36 weeks PMA, whereas only 5.7% of children whose mothers did not smoke required the treatment. The median number of days on mechanical ventilation for a child of a maternal smoker was greater than that for infants born from nonsmoker mothers (14 vs. 6 d; $P = 0.04$). As a sensitivity analysis, we evaluated whether the association with smoking remained between the four-category BPD variable (none, mild, moderate, and severe). The risk was similar between the groups that were combined (*see* online supplement). When we used an ordinal model for multinomial data (four-category BPD), maternal smoking remained significant after adjusting for the other covariates (OR, 1.7; 95% CI, 1.03–2.81; $P = 0.04$). We evaluated many potential interactions with the smoking variable, but none of the interactions reached statistical significance (*see* online supplement). Variables were selected for inclusion in the model on the basis of *a priori* knowledge of clinical importance.

Follow-up surveys were used to examine risk factors for continuing respiratory problems. Five hundred thirty-seven of the 587 children (91.5%) completed one or more surveys. Of these, 223 completed all four, 134 completed three, 110 completed two, and 70 completed only one. Of 537 children with at least one survey, 372 infants (69.3%) had late respiratory disease during early childhood, as defined above. There were 13 children (2.4%) whose respiratory diagnosis could not be computed, owing to missing questions. Similar BPD rates (44% vs. 41%), maternal ages (mean, 27.2 vs. 27.8 yr), and gestational ages (mean, 26.6 vs. 27.0 wk) were observed for the subjects who had a missing respiratory diagnosis. More of the subjects with missing respiratory diagnoses than those with respiratory diagnosis information were smokers (22% vs. 13%; $P = 0.04$). By univariate analysis, there were significant differences in gestational age ($P < 0.01$) and maternal age ($P = 0.01$) between those who had a late respiratory

Table 4. Postnatal Neonatal Intensive Care Unit Events by Maternal Smoking Status

Postnatal NICU Events (*n* = 587)	Smokers (*n* = 80)	Nonsmokers (*n* = 507)	*P* Value
Pneumonia	10 (12.5%)	48 (9.5%)	0.40
Necrotizing enterocolitis	10 (12.5%)	56 (11.0%)	0.70
Sepsis	16 (20%)	93 (18.3%)	0.72
Threshold retinopathy	9 (11.3%)	38 (7.5%)	0.25
Days of CPAP	12.5 (4.5–23)	14 (6–29)	0.13
Required CPAP at 36 wk PMA	9 (11.3%)	29 (5.7%)	0.06
Days of MV	14 (2–40)	6 (2–21)	0.04
Required MV at 36 wk PMA	7 (8.8%)	23 (4.5%)	0.44
Length of stay in NICU	91.5 (74–118)	85 (70–110)	0.11
Discharged on oxygen	48 (60.0%)	293 (57.8%)	0.71
Mortality	2 (2.5%)	6 (1.2%)	0.35
Total oxygen days (includes 1-yr follow-up)	73 (39.5–110.5)	73 (43.5–98)	0.68

Definition of abbreviations: CPAP = continuous positive airway pressure; MV = mechanical ventilation; NICU = neonatal intensive care unit; PMA = postmenstrual age.
Descriptive statistics [count (percent) or median (interquartile range)] and univariate comparisons are presented for postnatal neonatal intensive care unit events, stratified by maternal smoking status.

diagnosis and those who did not (Table 5). There was a higher percentage of children with a late respiratory diagnosis who were from black or African American parents ($P < 0.01$) than those without a diagnosis. There was a lower percentage of white children who were diagnosed with a late respiratory diagnosis than those who were not ($P < 0.01$). Children of mothers who smoked during pregnancy were more likely to develop a respiratory disorder ($P = 0.02$) (Table 6). Pregnancies complicated by chorioamnionitis had a higher rate of children with a late respiratory diagnosis than those that did not ($P = 0.03$). Children who were given a surfactant in the delivery room were more likely to develop a respiratory disorder ($P < 0.01$), and those with threshold retinopathy of prematurity had a higher diagnosis rate ($P = 0.01$).

Of the children diagnosed with a respiratory disease in the first 2 years of life, 45% had moderate or severe BPD (Table 5). Similarly, of the children who were not diagnosed with a respiratory disease, 69% had no or mild BPD. A logistic regression was fitted for respiratory diagnosis over the first 2 years of life with dichotomized BPD as a predictor (c-index, 0.57). Children with moderate or severe BPD had a 1.82-fold increase in the odds of a respiratory diagnosis during the first 2 years of life (95% CI, 1.22–2.72; $P < 0.01$). In addition, a logistic regression was fitted for a respiratory diagnosis over the first 2 years of life with the four-category BPD as a predictor (c-index, 0.63). Children with severe BPD had a 5.0-fold increase in the odds of a respiratory diagnosis compared with those without BPD during the first 2 years of life (95% CI, 2.54–9.68; $P < 0.01$). Children with moderate BPD had a 1.64-fold increase in the odds of a respiratory diagnosis (95% CI, 0.95–2.83; $P = 0.08$), and children with mild BPD had 1.9-fold increase in the odds of a respiratory diagnosis compared with those without BPD (95% CI, 1.15–3.01; $P = 0.01$). In comparison with infants with no or mild BPD, infants with moderate or severe BPD had significantly more emergency room visits, hospitalizations, and respiratory medication use during the first 2 years of life (Table 7). Importantly, of those infants diagnosed with moderate or severe BPD, 22% had no clinical evidence of late

Table 5. Subject Characteristics by Respiratory Diagnosis Status

	No Respiratory Diagnosis (*n* = *152*)	Respiratory Diagnosis (*n* = *372*)	*P* Value
Birth weight, g	970.5 (815 to 1,092.5)	910 (756 to 1,085)	0.14
Birth weight *z*-score	−0.399 (−1.04 to 0.24)	−0.215 (−0.76 to 0.29)	0.06
Birth weight strata, g			
500–749	29 (19.1%)	87 (23.4%)	0.28
750–999	57 (37.5%)	140 (37.6%)	0.98
1,000–1,250	66 (43.4%)	145 (39.0%)	0.35
Small for gestational age	52 (34.2%)	89 (23.9%)	0.02
Birth length, cm	35.45 (33 to 37)	35 (32 to 37)	0.03
Birth head circumference, cm	25 (23.5 to 26.5)	24.5 (23 to 26)	<0.01
Gestational age, wk	27 (26 to 29)	27 (25 to 28)	<0.01
Maternal age, yr	29 (25 to 33)	28 (22 to 32)	0.01
Male sex	71 (46.7%)	192 (51.6%)	0.31
Maternal race			
Asian	3 (2.0%)	4 (1.1%)	0.42
Black or African American	18 (11.8%)	92 (24.7%)	<0.01
Hawaiian or Pacific Islander	0 (0%)	0 (0%)	—
White	130 (85.5%)	273 (73.4%)	<0.01
Other	0 (0%)	1 (0.3%)	—
Unknown	1 (0.7%)	2 (0.5%)	0.868
Maternal ethnicity			
Hispanic or Latino	30 (19.7%)	69 (18.5%)	0.75
Not Hispanic or Latino	122 (80.3%)	302 (81.2%)	0.81
Multiple gestations	37 (24.3%)	98 (26.3%)	0.63
Antenatal corticosteroids	124 (81.6%)	312 (83.9%)	0.75
Cesarean section delivery	104 (68.4%)	262 (70.4%)	0.65
Intubated in delivery room	85 (55.9%)	239 (64.2%)	0.06
Intubated in NICU	34 (22.4%)	76 (20.4%)	0.87
Surfactant in delivery room	103 (67.8%)	308 (82.8%)	<0.01
PDA medical treatment	62 (40.8%)	149 (40.1%)	0.92
PDA surgical ligation	16 (10.5%)	48 (12.9%)	0.23
IVH grade 3 or 4	6 (3.9%)	15 (4.0%)	0.96
Threshold ROP	4 (2.6%)	37 (9.9%)	0.01
BPD severity			
None or mild	105 (69.1%)	205 (55.1%)	<0.01
Moderate or severe	47 (30.9%)	167 (44.9%)	<0.01
Oxygen use at discharge, yes (%)	90 (59.2%)	209 (56.2%)	0.53

Definition of abbreviations: BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NICU = neonatal intensive care unit; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity.
Descriptive statistics [count (percent) or median (interquartile range)] and univariate comparisons for the study demographics, stratified by respiratory diagnosis over the first 2 years of life.

Table 6. Prenatal Factors by Respiratory Diagnosis Status

Maternal Complications	No Late Respiratory Diagnosis	Late Respiratory Diagnosis	*P* Value
Preexisting diabetes	3 (2%)	19 (5.1%)	0.11
Gestational diabetes	7 (4.6%)	30 (8.1%)	0.18
Preexisting hypertension	19 (12.5%)	46 (12.4%)	0.89
Prolonged rupture of membranes	26 (17.1%)	72 (19.4%)	0.51
Chorioamnionitis	20 (13.2%)	79 (21.2%)	0.03
Preeclampsia	46 (30.3%)	95 (25.5%)	0.25
Antepartum hemorrhage	14 (9.2%)	47 (12.6%)	0.30
Maternal smoking	11 (7.2%)	55 (14.8%)	0.02
Maternal alcohol use	3 (2.0%)	8 (2.2%)	0.90
Maternal substance abuse	7 (4.6%)	37 (9.9%)	0.05

Descriptive statistics [count (percent)] and univariate comparisons are presented for antenatal events, stratified by respiratory diagnosis over the first 2 years of life.

respiratory disease after NICU discharge during early childhood. Of infants without BPD, 34% were not diagnosed with late respiratory disease postdischarge. The odds associated with mild BPD were slightly higher than the odds for moderate BPD, although this difference was not significant ($P = 0.62$).

A multiple linear logistic regression was fitted on respiratory diagnosis using a subset of predictors from the previous model of BPD status (Table 8) (c-index, 0.66). A subset of the predictors included for the BPD outcome was used for modeling late respiratory diagnosis owing to the differences in event rate. Included variables were selected *a priori* on the basis of clinical importance. There was a significant association between mothers smoking during pregnancy and children with a respiratory diagnosis during the first 2 years of life ($P = 0.02$) (Table 6). After adjusting for covariates, we found that children of mothers who had smoked had increased odds of a respiratory diagnosis of 2.18 (95% CI, 1.07–4.44; $P = 0.03$). Children of white mothers had a 0.51-fold decrease in the odds of late respiratory disease compared with those of other races (95% CI, 0.30–0.87; $P = 0.01$). Lower gestational age (OR, 1.15; 95% CI, 1.01–1.30; $P = 0.04$) was significantly associated with an increase in the odds of a late respiratory diagnosis. Children of mothers who had multiple gestations had a 1.68-fold increased odds of late respiratory disease (95% CI, 1.02–2.77; $P = 0.04$). Children of mothers who had preexisting diabetes or gestational diabetes had a 2.53-fold increase in odds of a late respiratory diagnosis compared with those who did not (95% CI, 1.16–5.54; $P = 0.02$). Lower maternal age (OR, 1.04; 95% CI, 1.00–1.08; $P = 0.03$) was significantly associated with an increase in the odds of a late respiratory diagnosis. All other covariates had insignificant ORs. The ORs from the model are ranked graphically in Figure 2. Figure 3 displays the common ORs from the full model predicting BPD status stacked with the OR from this model. Finally, children with late respiratory disease were more frequently exposed to passive smoking in the household than those without late respiratory disease (Table 9). In addition, exposure to household pets was less common in children with late respiratory disease.

Discussion

To better understand the contribution of antenatal factors to the development of BPD and late respiratory disease during early childhood, we performed a prospective longitudinal study of preterm infants that included extensive data collection of perinatal, NICU, and postdischarge information. We report a striking

Table 7. Relationship of Bronchopulmonary Dysplasia Status to Late Respiratory Disease

	No or Mild BPD	Moderate or Severe BPD	*P* Value
Number of surveys completed	3 (2–4)	3 (2–4)	0.31
Last survey completed, age, mo	24 (18–24)	24 (18–24)	0.94
Number of children with one or more emergency department visits	167 (48.4%)	142 (58.7%)	0.01
Number of children with one or more emergency department visits for respiratory reasons	120 (34.8%)	106 (43.8%)	0.10
Number of children with one or more hospitalizations	96 (27.8%)	98 (40.5%)	<0.01
Number of children with one or more hospitalizations for respiratory reasons	64 (18.6%)	75 (31.0%)	<0.01
Diuretic use	5 (1.4%)	13 (5.4%)	0.01
Bronchodilator use	87 (25.2%)	99 (40.9%)	<0.01
Inhaled steroid use	46 (13.3%)	58 (24.0%)	<0.01
Age when successfully taken off oxygen, d	59 (32–107.5)	180 (98.5–326)	<0.01

Definition of abbreviation: BPD = bronchopulmonary dysplasia.
Data are presented as count (percent) or median (interquartile range).

Table 8. Model Results of Logistic Regression for Respiratory Diagnosis

Parameter	Odds Ratio	95% Confidence Interval	*P* Value
Decreasing birth weight *z*-score, 1 SD	1.04	0.72–1.50	0.85
Male sex	1.22	0.81–1.83	0.34
Maternal race: white	0.51	0.30–0.87	0.01
Decreasing gestational age, wk	1.15	1.01–1.30	0.04
Maternal smoking status	2.18	1.07–4.44	0.03
Antenatal corticosteroids	1.11	0.62–1.98	0.73
Multiple gestations	1.68	1.02–2.77	0.04
Cesarean section delivery	1.11	0.69–1.80	0.67
Preexisting or gestational diabetes	2.53	1.16–5.54	0.02
Preexisting hypertension	1.15	0.57–2.30	0.70
Prolonged rupture of membranes	0.97	0.55–1.71	0.91
Chorioamnionitis	1.56	0.85–2.83	0.15
Preeclampsia	1.11	0.64–1.92	0.72
Decreasing maternal age, yr	1.04	1.00–1.08	0.03

Risk factors for a respiratory diagnosis over first 2 years of life. Parametric estimates, Wald 95% confidence intervals, and *P* values derived from the logistic regression modeling analysis for a respiratory diagnosis over the first 2 years of life.

association between maternal smoking and the subsequent diagnosis of moderate and severe BPD. After adjusting for covariates, we found that maternal smoking prior to birth increased the odds of having an infant with moderate or severe BPD by 2.02-fold. Maternal smoking was also associated with prolonged need for mechanical ventilation and the use of respiratory support during the NICU admission, as well as with late respiratory disease during infancy.

Additional risk factors for BPD in this cohort also included lower gestational age at birth, lower birth weight *z*-scores, white race, and preexisting maternal hypertension. As shown in Table 3, decreasing birth weight *z*-score was an even better predictor of the development of BPD than maternal smoking. More infants with moderate and severe BPD had severe intraventricular hemorrhage and more often were treated with surgical ligation of a patent ductus arteriosus than were those with no or mild BPD. Overall, these findings suggest that maternal smoking and hypertension increase the risk for developing BPD after preterm birth and that maternal smoking and chorioamnionitis are strongly associated with an increased risk for late respiratory morbidities during early childhood.

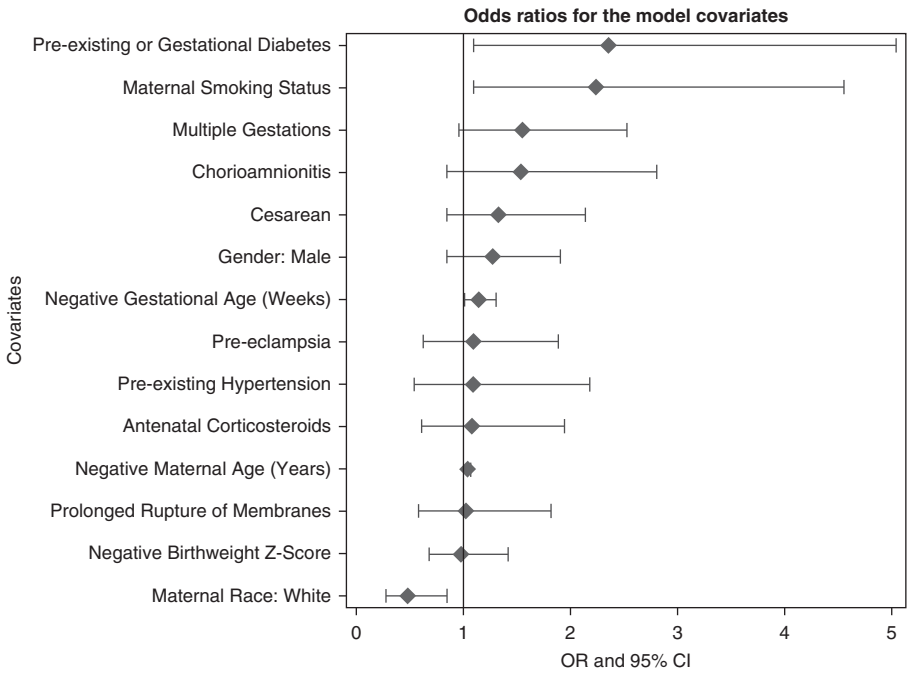

Figure 2. Odds ratios (ORs) with 95% confidence intervals (CIs) for model covariates from the logistic regression analysis modeling respiratory diagnosis over the first 2 years of life.

To address ongoing controversies regarding how well the current National Institutes of Health definition of BPD at 36 weeks PMA reflects the risk for persistent respiratory disease during childhood (10, 11), we further examined the relationship between the diagnosis of moderate or severe BPD and late respiratory outcomes during infancy. In this cohort, infants with BPD had significantly more emergency room visits, hospitalizations, and respiratory medication use during the first 2 years of life than those without BPD. Interestingly, 22% of infants who were diagnosed with moderate or severe BPD at 36 weeks PMA and 34% without BPD had no clinical evidence of late respiratory disease after NICU discharge during early childhood.

While recognizing the multifactorial etiologies of BPD, we found that the link between smoking and BPD risk in our study cohort to be striking. Previous studies have shown that maternal smoking is strongly associated with premature birth, low birth weight, and abnormal infant lung function (32, 33). Factors associated with BPD, such as preeclampsia, preexisting maternal hypertension, and demographic factors,

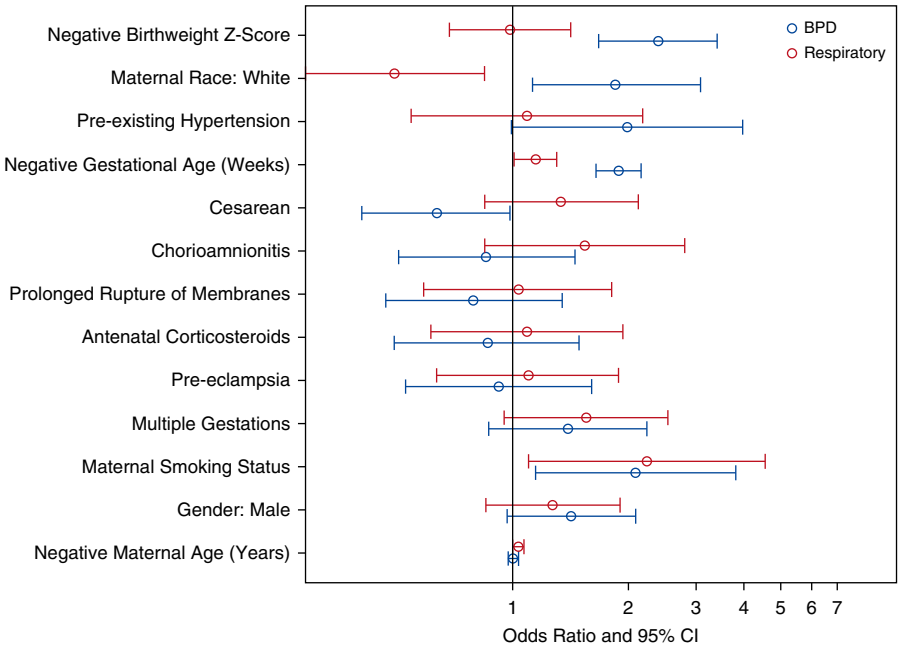

Figure 3. Comparisons of associations between perinatal factors with bronchopulmonary dysplasia (BPD) and late respiratory disease models. CI = confidence interval.

were adjusted for in the model to avoid confounders. Maternal smoking during pregnancy is a known risk factor for impaired childhood lung function and respiratory disease after term birth (34–36). Pooled analyses of several birth cohort studies showed that maternal smoking during pregnancy independently increased the risk of asthma at 4–6 years of age by 39 to 65% (35). Possible mechanisms include increased inflammatory cytokine production, altered placental function, or direct impact on lung development, which disrupts lung structure and function (37, 38). In addition, critical interactions between *in utero* events with asthma susceptibility genes suggest a potential mechanism for gene-by-environment interactions that may contribute to high risk for disease (39). We lack quantitative data to address potential dose–response relationships between the amount of smoking and respiratory outcomes in our population.

Hypertensive disorders of pregnancy, especially preeclampsia, have previously been associated with high risk for BPD after preterm birth. In a small cohort study, the risk for BPD was dramatically increased in the presence of preeclampsia, even after accounting for intrauterine growth restriction (IUGR) (18). This finding has been confirmed in some studies (40) but not in others (41). Our findings extend previous observations by providing further evidence for antenatal events that are strongly associated with respiratory disease in preterm infants throughout early childhood. These data are of further interest because they were obtained from a prospective longitudinal study that included strict characterization of BPD definition and assessment of its severity along with the inclusion of follow-up assessments throughout the first 2 years of life to examine links between BPD severity and respiratory outcomes during infancy.

Mechanisms through which antenatal events contribute to high risk for BPD or late respiratory disease in childhood are at least partly related to placental abnormalities, as observed in hypertensive disorders of pregnancy, preeclampsia, chorioamnionitis, and other disorders (11, 42, 43). Animal studies have shown that prenatal insults can be sufficient to impair lung structure during infancy, even without adverse postnatal stimuli (44–46). Researchers in clinical studies have reported striking associations between placental histopathology and the presence of IUGR, as well as high risk for BPD and BPD with pulmonary hypertension (42, 43). Preterm human infants with IUGR have consistently been shown have a high risk for BPD, providing strong proof regarding the importance of fetal events in the pathobiology of BPD (15, 47). In addition to the presence or absence of BPD at 36 weeks, preterm infants who were born with IUGR remained at high risk for abnormal lung function at school age (48, 49).

Potential limitations of the present study include that maternal smoking was reported

Table 9. Environmental Exposures to Passive Smoking and Pets in Subjects with or without Late Respiratory Diagnosis

	No Late Respiratory Diagnosis	Respiratory Diagnosis	*P* Value
PFT performed	20 (13.2%)	33 (8.9%)	0.14
RSV shots	125 (82.2%)	326 (87.6%)	0.11
Flu shots	130 (85.5%)	324 (87.1%)	0.63
Smoking allowed in child's home	4 (2.6%)	27 (7.3%)	0.04
One or more people in the home smoke	33 (21.6%)	127 (37.7%)	<0.01
Primary caregivers smoke occasionally or daily	42 (27.6%)	129 (38.6%)	0.02
Families with pets	83 (54.6%)	168 (45.2%)	0.05
Families with dogs	64 (42.1%)	145 (39.0%)	0.51
Families with cats	32 (21.1%)	66 (17.7%)	0.38
Families with other pets	13 (8.6%)	27 (7.3%)	0.61

Definition of abbreviations: PFT = pulmonary function testing; RSV = respiratory syncytial virus.

by the patient rather than through biochemical assays for nicotine exposure (50). We have no evidence that underreporting rates differed between study groups in our cohort. In addition, we did not perform pathologic or histologic assessments of the placenta to better define chorioamnionitis or vascular pathology.

In conclusion, we found that maternal smoking and hypertension increased the risk for developing BPD after preterm birth and that maternal smoking is strongly associated with increased risk for late respiratory morbidities during early childhood. Twenty-two percent of infants diagnosed with BPD and 34% of preterm infants without BPD had no clinical signs of late respiratory disease during early childhood, suggesting that factors beyond the BPD diagnosis alone modulate respiratory outcomes in childhood. ■

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