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Secondhand Smoke Exposure in Preterm Infants With Bronchopulmonary Dysplasia

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Summary

Objectives—Preterm infants and children with bronchopulmonary dysplasia (BPD) often experience significant respiratory morbidities during the first two years of life. Second hand smoke (SHS) has been demonstrated to lead to respiratory morbidities in the general population. The objectives of this study were to assess the prevalence/impact of SHS on preterm infants and children with BPD.

Methods—Subjects ($n = 352$) were recruited from the Johns Hopkins BPD outpatient clinic between January 2008 and August 2012. Second hand smoke exposure and respiratory morbidities were assessed through questionnaires and chart review.

Results—Twenty-eight percent of preterm infants with BPD were exposed to SHS in the home setting, despite having significant lung disease. SHS was associated with multiple measures of socio-economic status, including lower household income ($P < 0.001$), lower caregiver education level ($P = 0.013$), and having public versus private insurance ($P = 0.002$). We found no difference in acute care use or chronic symptoms with SHS exposure. We observed trends that preterm infants who were exposed to SHS were more likely to be prescribed inhaled corticosteroids ($P = 0.054$) and were weaned off of supplemental oxygen over 2 months later ($P = 0.13$) than infants not exposed to SHS.

Conclusion—SHS exposure in preterm infants with BPD is common, even in those receiving supplemental oxygen and respiratory medications. Although there were no associations between respiratory outcomes and self-reported SHS exposure, trends toward increased use of inhaled steroids and a longer duration of supplemental oxygen use were noted. Further work is needed to determine more accurate means of assessing SHS risk in this vulnerable population.

Keywords

bronchopulmonary dysplasia; chronic lung disease; prematurity; secondhand smoke; environmental tobacco smoke

INTRODUCTION

Due to advances in neonatology, a larger proportion of infants born prematurely (<37 weeks gestation) are surviving.¹ Many of these survivors are at increased risk for long-term sequelae of prematurity, including developmental delays, cerebral palsy, hearing or vision deficits, and chronic respiratory disease in the form of bronchopulmonary dysplasia (BPD).^{2,3} BPD can present with admixtures of several different phenotypic elements, including small airway disease (symptoms of wheezing, coughing, and/or steroid responsiveness), lung hypoplasia (poor pulmonary reserve with or without hypoxia and/or hypercarbia), and pulmonary vascular disease (manifesting as pulmonary hypertension).⁴

The effects of BPD can be life-long, but are frequently more severe during early childhood with approximately 50% of infants requiring re-hospitalization in the first 2 years of life.⁵⁻⁷ Infants with BPD frequently require home supplemental oxygen and multiple medications, including diuretics, inhaled corticosteroids, anti-reflux agents, and agents for pulmonary vasodilation. They also may require more frequent visits to their pediatricians as well as subspecialists for acute exacerbations and treatment of chronic symptoms. The net result is a substantial burden of disease for these infants and children, their caregivers, and society. It is essential to identify modifiable risk factors to improve outcomes for these infants.

Among infants and children within the general population, secondhand smoke (SHS) exposure is causally related to lower respiratory tract infections, cough, wheezing, onset of wheezing, and decreased lung function.⁸ In preterm infants, prospective studies have found similar adverse outcomes associated with SHS. Specifically, living with a smoker was found to be associated with 2.6-fold increased risk of an acute care visit for respiratory symptoms in 124 very low birth weight (VLBW: <1,500 gm) infants,⁹ maternal smoking was found to be associated with recurrent wheezing in 525 preterm (<33 weeks gestation) infants,¹⁰ and smoking in the household was found to be associated with increased risk of wheezing at age 8 years in 384 VLBW infants.¹¹ However, studies in preterm infants also have shown differing results with regards to SHS exposure. Another study of 715 VLBW infants found no association between SHS and wheezing or re-hospitalization.¹²

To determine whether a relationship existed between SHS and increased respiratory interventions and worse respiratory outcomes in a population of preterm infants limited to those only with BPD, we examined the effects of SHS in 352 infants seen in our specialty outpatient BPD clinic. We also sought to estimate the prevalence of SHS exposure in preterm infants with lung disease. We hypothesized that exposure to secondhand smoke in the home environment would lead to worse respiratory outcomes in preterm infants and children who attended an outpatient BPD clinic. Specifically, we examined outcomes related to acute care use (e.g., hospitalizations), small airway disease (e.g., use of inhaled corticosteroids and/or β -agonists), and poor pulmonary reserve (duration of oxygen supplementation in the home).

METHODS

Study Sample

All subjects (n = 352) were recruited from the Johns Hopkins Bronchopulmonary Dysplasia (BPD) Clinic between January 2008 and August 2012. Patients are referred to the clinic by area neonatal intensive care units on the basis of prematurity and having respiratory disease. Subjects were recruited by a data coordinator if they met the inclusion criteria, which included¹ a diagnosis of BPD by the staffing pediatric pulmonologist,² born at 34 weeks of gestation, and³ clinical data for review before the age of 2 years. 98% of parents or legal guardians approached did give consent. This study was approved by the Johns Hopkins University Institutional Review Board.

Demographics

Birth weight percentile was derived from published US norms.¹³ The presence/absence of gastrostomy tubes and respiratory support were ascertained at the first BPD clinic encounter through chart review. The 134 subjects receiving respiratory support at home included 127 children on supplemental oxygen via nasal cannula and seven children on home mechanical ventilation. Inhaled corticosteroid use was defined as any use prior to 2 years of age based on chart review. Insurance coverage (private vs. public) was obtained from billing records. Race/ethnicity and primary caregiver education level were self-reported. Median household income was derived from 2000 U.S. Census tract data. Dates of initial discharge and first BPD clinic encounter were ascertained through chart review.

Secondhand Smoke

Secondhand smoke (SHS) exposure was ascertained through asking whether anyone in the household smokes on questionnaires completed by caregivers at every visit (n = 306) and through chart review if questionnaire data were not available (n = 46). There was no difference in the frequency of reported smokers in the household on questionnaire data (28.4%) versus chart review (23.9%; $P = 0.52$). For analyses involving demographics, clinical outcomes, and time to wean off of home supplemental oxygen, SHS exposure was defined as a fixed exposure, thus if an infant had SHS exposure at any time point, he/she was considered exposed. For analyses involving respiratory morbidities, SHS exposure was defined as a time-varying exposure, specifically reported on a specific questionnaire linked to outcomes reported on that clinic visit, thus infants could have had changing SHS exposure status with time.

Respiratory Morbidities

Respiratory morbidities were assessed using yes/no questions on questionnaires completed by caregivers. Primary outcomes included emergency department visits, hospital admissions, systemic steroid use, and antibiotic use for respiratory reasons since the last BPD clinic visit (or since initial hospital discharge if assessed at the first BPD clinic visit). Secondary outcomes included the presence/absence of trouble breathing, rescue beta-agonist use, activity limitations, and nighttime symptoms. A total of 642 questionnaires were completed for 296 subjects prior to the age of 2 years with 5% of all questions left blank by

caregivers. There was no difference in the frequency of questionnaires completed between SHS and non-SHS exposed subjects ($P = 0.89$).

Statistical Methods

Demographic frequencies and clinical outcomes stratified by SHS exposure were compared using chi-square and t tests (Tables 1 and 2). Kaplan–Meier methodology was used to analyze the time at which subjects on home supplemental oxygen were weaned off oxygen stratified by SHS exposure (Fig. 1). Of the 131 subjects who received supplemental oxygen at home, for 102 subjects the date of oxygen discontinuation is known, and 73 out of 102 did receive overnight polysomnography as part of assessment for readiness to discontinue supplemental oxygen. For the remaining 29 subjects where the date of oxygen discontinuation is unknown, 18 were on oxygen at the time of analysis, and 11 were lost to follow-up prior to oxygen discontinuation; for all of these subjects their data were censored. The relationship between reported secondhand smoke exposure and respiratory morbidities at each clinical visit was assessed using logistic regression adjusted for the age of the subject at the time of questionnaire completion as well as socioeconomic status (estimated household income and insurance status)(Table 3). We did not adjust for primary caregiver education status owing to missing data. As caregivers may have completed questionnaires at several clinic visits, the logistic regressions accounted for this using Generalized Estimating Equations (GEE) methodology (clustered by subject).¹⁴ STATA IC 11 (StataCorp LP, College Station, TX) was used for all statistical analyses. P values <0.05 were considered statistically significant.

RESULTS

Demographics and SHS exposure

The population recruited for this study was predominantly non-white (67.9%) and born at a mean gestational age of 26.5 ± 2.4 weeks with a mean birth weight percentile adjusted for gestational age of 40.2 ± 22.8 .

We found that 28% of caregivers of premature infants with BPD reported that someone in their household smoked. In our study SHS exposure was highly correlated with measures of lower socio-economic status, including lower estimated household income ($P < 0.001$), healthcare coverage through public insurance ($P = 0.002$), and lower caregiver education level ($P = 0.013$)(Table 1). There was no difference in secondhand smoke exposure rates between whites and non-whites ($P = 0.91$).

Clinical Outcomes

Clinical outcomes determined during the initial NICU hospitalization, including the timing of initial discharge from the hospital ($P = 0.63$) or the decision to discharge a subject with supplemental oxygen/mechanical ventilation ($P = 0.57$) (Table 2) were not influenced by a history of SHS exposure in the home environment, suggesting that many children on respiratory support are exposed to SHS in the home setting.

Several clinical outcomes measured after the initial NICU hospitalization was associated with SHS exposure in the home environment. Infants and young children exposed to SHS tended to be prescribed inhaled corticosteroids prior to 2 years of age at a higher rate (85.7%) than those not exposed to SHS (76.4%; $P = 0.054$). Furthermore, infants exposed to SHS in the home environment were generally seen at an earlier age in BPD clinic (6.6 ± 2.6 months) compared to those not exposed to SHS (8.0 ± 6.5 months; $P = 0.057$), however the reasons for an earlier assessment in the SHS exposed infants were not readily apparent.

Oxygen Use

We assessed whether SHS exposure may lead to decreased pulmonary reserve by assessing when preterm infants discharged to home on supplemental oxygen were weaned off oxygen using Kaplan–Meier methodology (Fig. 1). There was a trend towards a delay in weaning off of supplemental oxygen in subjects exposed to SHS (median age: 13.6 months) versus those not exposed (median age: 10.8 months; log rank $P = 0.13$).

Respiratory Morbidities

Out of the 352 subjects in the study population, 296 had completed at least one questionnaire assessing for respiratory morbidities prior to 2 years of age. On average subjects completed 2.2 ± 1.4 questionnaires (range: 1–8). Respiratory morbidities and SHS exposure status were reassessed on every questionnaire, thus SHS exposure is linked to outcomes and can change for a subject over time. We tested for the association between respiratory morbidities and SHS exposure using regression models clustered by subject to account for caregivers who completed more than one questionnaire at different clinic visits prior to 2 years of age. We did not find any association between SHS exposure and any of the respiratory morbidities that we tested for in the study population, including re-hospitalization and bag-onist use (Table 3). The robustness of our results was checked with the inclusion of sex, inhaled corticosteroid use, and age at first visit as covariates. No association between SHS and respiratory morbidities was seen with the inclusion of these potential confounders.

DISCUSSION

Our data indicates that a substantial number (28%) of preterm infants with BPD are exposed to secondhand smoke in the home setting, despite having significant lung disease and in many cases being on supplemental oxygen. Other studies of preterm infants have reported similar SHS exposure rates anywhere from 6% to 37%.^{9–12} As is similar to the general population SHS exposure is associated with multiple measures of socio-economic status in our preterm population, including household income, caregiver education level, and insurance status. Unexpectedly, we saw no difference in acute care use or chronic symptoms between infants exposed to SHS versus those not exposed, but this does not preclude the possibility of injury to the developing lung with SHS exposure.

The absence of significant associations between poor respiratory outcomes and SHS exposure status compared to other studies^{9,10} may be secondary to misclassification of SHS exposure or factors in medical care that mitigate poor outcomes. With regards to

misclassification, the clinical question of asking whether a smoker lives in the home may not capture the exposure accurately. Families may be underreporting whether smoking occurs, or they may be engaging in behaviors that minimize SHS exposure to their infants, such as smoking outdoors or smoking in a different room than the infant. We also found some differences in clinical care that might mitigate the expected respiratory morbidities with SHS exposure between infants who were exposed to SHS compared to those who were not. Specifically, SHS exposed children with BPD were more likely to be prescribed inhaled corticosteroids compared to children not exposed to SHS ($P = 0.054$). This observation suggests that the increased use of inhaled corticosteroids may mitigate symptoms of small airway disease in these children that would otherwise be exacerbated by SHS exposure. In addition, although preterm infants are being discharged from neonatal intensive care units at the same mean age regardless of potential SHS exposure in the home, infants who are exposed to SHS tended to be seen in BPD clinic 1.3 months earlier than those not exposed to SHS ($P = 0.057$). Our data do not permit us to determine whether the NICU, the patient's primary care provider, or the family requested appointments within an earlier timeframe. More rapid access to a subspecialty clinic where education can occur and medications/oxygen can be titrated may improve outcomes, thus contributing to the lack of observed differences in acute care use or chronic symptoms by SHS status.

Although we did not observe differences in respiratory morbidities, we observed that infants exposed to SHS tended to be weaned off oxygen over 2 months later than infants not exposed ($P = 0.13$). This delay in weaning from oxygen is not necessarily related to differences in access to subspecialty care as infants exposed to SHS tended to present to BPD clinic at a mean younger age as previously mentioned. A study in neonatal mice found that SHS exposure caused impaired postnatal alveolar growth. This study suggests that SHS may impair lung growth and limit pulmonary reserve during a critical period of postnatal lung development.¹⁵ Although, it is unclear whether SHS exposure has a similar effects on the lungs of young children with BPD, further studies may be warranted.

Our study's strengths include a well-characterized population of preterm infants with BPD with longitudinal data collection.^{16–19} As mentioned previously, our study's largest limitation is the potential misclassification of SHS exposure. Ultimately, misclassification using this common means ascertaining SHS exposure may lead to poorly targeted interventions to limit SHS exposure. Future research should examine whether other subjective questions (e.g., smoking rules in the home or whether the primary caregiver smokes) or objective data from biomarkers (e.g., saliva cotinine) may be more accurate means of characterizing risk from SHS. Another limitation is that given the retrospective nature of our data collection as well as potential recall biases/social desirability, we cannot comment on causality between SHS and selected outcomes. Also, our population is recruited from a tertiary care center clinic, thus they may all have access to therapies that reduce the impact of SHS. Conversely, subjects attending our subspecialty clinic may have more severe lung disease than other preterm infants and SHS may not substantially impact the course of severe disease; we believe this may be one reason why other studies of preterm infants (with and without BPD) did observe outcome differences with SHS, and our study of preterm infants only with BPD did not.^{9,10} Lastly, there may be unmeasured confounders in our data

that are not accounted for, including aspects of socio-economic status, breastfeeding, and the presence of other siblings in the household.

In conclusion, we observed that SHS exposure is unfortunately common (28%) in high-risk preterm infants, including even those on home supplemental oxygen or mechanical ventilation (26.1% exposed to SHS). The absence of association of poor respiratory outcomes with SHS exposure may represent misclassification of SHS status with the clinical question asking caregivers whether someone in the home smokes. Further work is needed to determine more accurate ways of assessing the risk that SHS poses to this vulnerable population. Research is also needed to determine whether the judicious use of inhaled corticosteroids as well as encouraging family members to smoke outside if they cannot quit, are effective interventions for mitigating the effects of SHS on frequency of acute care visits and/or presence of chronic symptoms in this vulnerable population. Nevertheless, healthcare providers should continue to screen for and educate caregivers of preterm infants on the risks of SHS exposure.

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Fig. 1.

Kaplan–Meier plot with time to wean off of home supplemental oxygen. Subjects who were exposed to SHS tended to wean off of oxygen later than those not exposed ($P = 0.13$).

TABLE 1

Study Sample Demographics

Mean ($\pm$ SD) (range)	Study sample	No SHS exposure ever	Any SHS exposure	P value
N	352	254	98	–
Demographics				
Sex (% male)	58.5	61	52	0.13
Gestational age (weeks)	26.5 $\pm$ 2.4	26.5 $\pm$ 2.4	26.4 $\pm$ 2.1	0.68
	22.7–34.0	22.7–34.0	23.0–32.0	
Birth weight (grams)	890 $\pm$ 363 (380–2,510) (n = 341)	893 $\pm$ 384 (380–2,510) (n = 243)	883 $\pm$ 305 (455–2,065)	0.81
Birth weight percentile (%)	40.2 $\pm$ 22.8 (1–95) (n = 341)	39.2 $\pm$ 23 (1–90) (n = 243)	42.6 $\pm$ 22.6 (3–95)	0.21
Race/ethnicity (% non-white)	67.9	67.7	68.4	0.91
Socio-economic characteristics				
Public insurance (% yes)	59.9	53.2	77.6	<0.001
Estimated household income (\$'000)	46.1 $\pm$ 17.2 (11.1–101.4)	47.8 $\pm$ 16.5 (11.1–101.4)	41.6 $\pm$ 18.3 (11.1–98.9)	0.002
Primary less than high school	6.7	2.7	17	
Caregiver high school graduate	20.5	18.5	25.5	
Education some college	31.4	29.1	37.3	0.013
College degree	14.3	17.9	5.1	
Level (%) any post-graduate education	16.2	19.2	8.5	

TABLE 2

Clinical Outcomes by Smoke Exposure

Mean ($\pm$ SD) (range)	Study sample	No SHS exposure ever	Any SHS exposure	P value
N	352	254	98	—
Clinical outcomes				
Age at initial discharge (months)	4.2 $\pm$ 2.6 (0.23–24.5) (n = 350)	4.2 $\pm$ 2.8 (0.23–24.5) (n = 252)	4.1 $\pm$ 2.1 (0.59–13.6)	0.63
Age at first pulmonary clinic visit (months)	7.6 $\pm$ 5.8 (1.9–51.2)	8.0 $\pm$ 6.5 (1.9–51.2)	6.6 $\pm$ 2.6 (2.5–17.0)	0.057
Respiratory support (% yes) ^a	38.1	39.0	35.7	0.57
Inhaled corticosteroid use prior to 2 years of age (% yes)	79.0	76.4	85.7	0.054

^a Supplemental oxygen and/or mechanical ventilation at home.

TABLE 3

Adjusted Odds Ratios of Respiratory Morbidities With Secondhand Smoke Exposure

	Number of forms (number of subjects)	No SHS exposure ever (% yes)	Any SHS exposure (% yes)	Adjusted odds ratio (95% C.I.) ^a	Adjusted OR <i>P</i> value
Primary outcomes					
Emergency department	590	18.2	15.4	0.89	0.71
	278			(0.49–1.62)	
Hospitalization	589	10.9	8.2	0.78	0.53
	279			(0.36–1.69)	
Steroid use	583	22.5	18.5	0.81	0.50
	277			(0.44–1.49)	
Antibiotic use	590	25.0	27.3	1.16	0.52
	279			(0.74–1.84)	
Secondary outcomes					
Trouble breathing	593	33.5	35.5	1.14	0.60
	280			(0.70–1.84)	
Rescue medication use	586	24.9	19.4	0.65	0.16
	277			(0.35–1.18)	
Activity limitations	577	12.0	12.8	1.03	0.93
	275			(0.53–2.01)	
Caregiver awake at night	594	15.5	17.1	1.16	0.64
	279			(0.62–2.16)	

^aLogistic regressions clustered by subject and adjusted for age in months at the time of visit, estimated household income, and insurance status. Only data obtained prior to 24 months of age was utilized.