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## Environmental exposures and respiratory morbidity among very low birth weight infants at 1 year of life

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### Abstract

**Introduction**—Preterm infants have a substantially increased risk of developing respiratory illnesses. The goal of this study was to consider the impact of modifiable postnatal exposures on respiratory morbidity among a cohort of very low birth weight (VLBW) infants.

**Objectives**—(1) Assess the rates of respiratory morbidity and exposure to indoor respiratory triggers in a population of VLBW infants at 1 year; (2) determine the association between exposures and respiratory morbidity.

**Methods**—We enrolled 124 VLBW infants into a prospective cohort study. Parents were called at 1 year to assess respiratory outcomes and environmental exposures. We used bivariate and multivariate analyses to assess the relationship between environmental exposures and acute care for respiratory illnesses.

**Results**—At 1 year, 9% of infants had physician-diagnosed asthma, 47% required 1 acute visit and 11% required hospitalisation for respiratory illness. The majority of infants (82%) were exposed to at least one indoor respiratory trigger. Infants living with a smoker (61% vs 40%) and infants exposed to pests (62% vs 39%) were more likely than unexposed infants to require acute care for respiratory problems. In a multivariate regression controlling for demographics, birth weight, bronchopulmonary dysplasia, and family history of asthma or allergies, both living with a smoker (OR 2.62; CI 1.09 to 6.29) and exposure to pests (OR 4.41; CI 1.22 to 15.94) were independently associated with the need for acute care for respiratory illnesses.

**Conclusions**—In this sample, respiratory morbidity and exposure to triggers were common. VLBW infants may benefit from interventions that decrease exposure to respiratory triggers.

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Asthma remains one of the most common chronic conditions of childhood.<sup>1</sup> Children born premature have a substantially increased risk of developing asthma and other respiratory illnesses,<sup>2–14</sup> particularly in the first years of life.<sup>7,15,16</sup> The increased risk is even more pronounced for very low birth weight (VLBW) infants (birth weight <1500 g).<sup>17,18</sup> In addition, within the first few years of age, VLBW infants are far more likely than other infants to be hospitalised for and die from acute lower respiratory tract infections.<sup>19,20</sup> This is particularly pertinent since, over the past 20 years, there has been an increase in survival of low birth weight infants.<sup>21</sup>

Little is known about the prevalence of exposure to indoor respiratory triggers and its impact upon the respiratory health of VLBW infants. Indoor environmental exposures such as environmental tobacco smoke (ETS),<sup>18</sup> mold<sup>22–24</sup> and pests<sup>25–27</sup> are associated with an increased risk of respiratory symptoms among mixed birth weight cohorts of children. Several prenatal<sup>28,29</sup> and perinatal<sup>30</sup> factors are associated with asthma in later life. In addition, there is some evidence that postnatal exposures among VLBW infants, including smoking in the household,<sup>33,31</sup> are predictors of respiratory morbidity.

We analysed data from a longitudinal study of VLBW infants to consider the impact of modifiable postnatal exposures on respiratory morbidity. Our objectives were to: (1) assess the rates of respiratory morbidity and exposure to indoor respiratory triggers among VLBW infants at 1 year of life; and (2) determine the association between postnatal exposures and respiratory morbidity.

## Methods

### Study population

We conducted a prospective cohort study of VLBW infants discharged from the neonatal intensive care unit (NICU) in Rochester, New York. From May 2003 to July 2006 we recruited a convenience sample of infants born <1500 g from the NICU, just prior to infant discharge, at times that a recruitment nurse was available. Because some infants were discharged before we approached them about the study, we enrolled a few infants (n = 24) from the neonatal follow-up clinic, where all NICU-discharged infants are seen at 6–9 months corrected age. There were 364 infants <1500 g discharged from the NICU during this timeframe; 195 were approached for enrolment; and 158 agreed to participate (response rate 81%). Our recruitment goal was 150.

At the time of enrolment, we asked caregivers to complete a questionnaire inquiring about the family's sociodemographic background, the infant's prenatal smoke exposure and medical data. We also reviewed medical charts from the infant's NICU admission.

When the infant turned 1 year of age, we conducted telephone surveys with parents to inquire about the infant's respiratory health and risk factors for developing respiratory problems. Parents were asked about the infant's use of acute medical services for respiratory problems, current respiratory symptoms, prescribed medication for asthma or respiratory problems, daycare attendance, smokers in the home and various indoor environmental exposures. The completion rate for the 1-year assessment was 86%, with 22 infants lost to

follow-up. Infants lost to follow-up were similar to enrolled infants in terms of gender, prenatal exposures, and BPD diagnosis, but were more likely to be black and covered by Medicaid insurance (45% vs 18%; and 75% vs 36%).

For this study, we included only one infant per family. From 10 twin pairs and one set of triplets, we randomly selected one infant for a final sample of 124.

### **Respiratory morbidity**

We collected data regarding healthcare utilisation for respiratory problems by parent report of the number of times and date of each instance that the infant “needed a visit to the doctor or emergency department because of wheezing or breathing problems” and “needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms”. We compiled these data to determine if an infant required any acute care for respiratory problems during the first year after NICU discharge. We chose this as our primary outcome variable because it is less subjective than other measures, less subject to recall bias, and represents a high-cost event to the healthcare system. We also inquired about prophylaxis against respiratory syncytial virus (RSV) by asking parents if the infant had ever received Synagis (palivizumab). We described this as a monthly injection given during the RSV season.

We assessed infant respiratory symptoms by parent report of the number of days over the prior 2 weeks the infant had experienced coughing, wheezing, or trouble breathing during the day and at night, and the number of times the infant required use of a bronchodilator to relieve these symptoms. Infants experiencing daytime symptoms on >4 days, or nighttime symptoms on 2 nights during the past 2 weeks were classified as having persistent symptoms in accordance with National Heart, Lung, and Blood Institute guidelines.<sup>32</sup> We used this classification regardless of whether the child had been diagnosed with asthma in order to systematically collect information regarding symptom severity. Parents also were asked if their infant had been diagnosed with asthma by a physician, if the infant was taking medication for asthma or breathing problems, and if so, the name of the medication and how often it was taken. To assure accuracy of parent-reported data regarding asthma diagnosis and acute care for respiratory illnesses, we reviewed medical records for a convenience sample of 20% (n = 25) of subjects. These subjects were representative of the study population.

### **Environmental exposures**

At follow-up, we inquired about the number of smokers living in the infant's home and the rules about smoking in the home, which correlates with cotinine levels.<sup>33</sup> Caregivers were asked if the infant attended daycare and to report all the places their infant spent a significant amount of time. They were then asked to report (yes/no) if there was any of the following at each location: “noticeable dampness, moisture, or mold”, “pets with fur”, “a wood stove used”, and “had or wanted to have an exterminator or used any chemicals in the past year to control for pests”. Since home inspections were not performed for this study, we collected this information from parents to assess risk for allergen and irritant exposure. We considered each of these exposures separately to determine their influence on respiratory morbidity.

## Sociodemographic and health variables

Demographic variables included gender, race, ethnicity, and insurance. We asked caregivers if there was a family history of asthma or allergies (yes/no), and the amount the mother smoked during pregnancy; we considered the infant to have prenatal smoke exposure if the mother smoked any amount. We obtained gestational age, birth weight, oxygen use, gastroesophageal reflux and bronchopulmonary dysplasia (BPD) diagnosis from the NICU chart. According to standard definitions, we considered infants to have BPD if they received oxygen at 36 weeks' postmenstrual age.

## Analysis

We performed analyses using SPSS version 15.0 (Statistical Product and Service Solutions 15.0; SPSS Inc, Chicago, Illinois). We used chi-square and multivariate logistic regression analyses to assess the relationship between environmental exposures and respiratory morbidity. A two-sided alpha  $<0.05$  was considered statistically significant.

## Results

We collected longitudinal data on 124 infants. Table 1 shows their demographic and birth characteristics. Birth weight ranged from 530 to 1495 g, and 32% had BPD. There was no difference in mean birth weight (1117 vs 1106 g) or gestational age (29 vs 28.6 weeks) among enrolled infants and the general population of VLBW infants discharged from the NICU during the same timeframe. However, enrolled infants had a longer length of stay (62.4 vs 51.3 days) and more days with oxygen therapy (38.3 vs 22.5 days) compared to the overall NICU population from which they were drawn, suggesting a more complicated respiratory course.

Table 2 describes the prevalence of respiratory morbidity at 1 year. Acute care for breathing problems was common with 47% requiring acute care for a respiratory illness at least once since NICU discharge (11% required hospitalisation; 46% had emergency department or office visits). By the time of the 1-year follow-up, 9% had been diagnosed with asthma. The medical record reviews yielded consistent results for acute care for respiratory illness (confirmed in 92% of cases) and asthma diagnosis (confirmed in 88%).

At the time of the follow-up call, 26% of infants experienced persistent symptoms of wheeze, cough, or heavy breathing during the prior 2 weeks, and 11% used an inhaled bronchodilator for symptom relief. Of note, the majority of infants (86%) received Synagis. There was no difference in the proportion of infants requiring acute care for respiratory illness by whether or not the infant had received Synagis (no, 53%; yes, 46%).

We next examined the prevalence of environmental exposures (table 3). The majority of infants (82%) were exposed to at least one indoor respiratory trigger, including pets with fur (56%), living with 1 smoker (33%), and household triggers including mold/mildew (14%), wood stove (13%) and pests (13%). Infants living with a smoker were more likely to require acute care for respiratory problems than were unexposed infants (61% vs 40%). There also was a trend for greater use of acute care for respiratory problems among infants exposed to mold/mildew and pests.

In a multivariate logistic regression analysis (table 4) controlling for demographic characteristics, birth weight, BPD and family history of asthma or allergies, living with a smoker (OR 2.62; 95% CI 1.09 to 6.29) and exposure to pests (OR 4.41; 95% CI 1.22 to 15.94) were independently associated with need of acute care for respiratory illness in the first year.

Birth weight also was included in the model as a continuous variable; there was no association between birth weight and need for acute care ( $p = 0.692$ ). Separate models including wood stove, mold/mildew, and pets with fur did not show significant associations between the exposures and acute care.

We reanalysed the data for the subgroup of children who did *not* have BPD ( $n = 85$ ). Among these infants, 39% required acute care for a respiratory illness at least once since NICU discharge, 9% had been diagnosed with asthma, and 26% reported persistent symptoms during the prior 2 weeks. Further, we found a similar relationship between environmental exposures and need for acute care for respiratory illness as seen in the full sample (data not shown).

## Discussion

In this sample of VLBW infants, respiratory morbidity in the first year of life was common, with almost half of the infants requiring acute care for respiratory problems at least once. In addition, many of these infants experienced persistent respiratory symptoms, and almost 10% had been diagnosed with asthma. This is consistent with prior studies demonstrating an elevated risk of respiratory illness among VLBW infants,<sup>14</sup> and suggests that this risk continues despite modern advances in neonatal care.

We found that exposure to environmental triggers was prevalent in this cohort. One-third of the children lived in a home with a smoker, and more than 10% were exposed to pests. These exposures appear to put VLBW infants at elevated risk for respiratory morbidity; children living with a smoker and children exposed to pests had significantly elevated odds of requiring acute care for respiratory problems compared to children without these exposures. Consistent with other studies,<sup>34–36</sup> we found that the subgroup of children without BPD were at risk for respiratory illness, and environmental exposures also seem to play a role for this group.

Other studies in mixed-age cohorts have considered the impact of postnatal exposures on respiratory illness in early childhood. In one study of infants at high risk for asthma, exposure to cockroach allergen increased the risk of persistent cough at 12 months of age.<sup>25</sup> In another study, mold exposure was associated with wheeze and persistent cough in the first year of life.<sup>22</sup> Others have shown a positive association between exposure to house dust mite and cat allergens during infancy and development of sensitisation in early childhood.<sup>37–39</sup> It has been suggested that the response to allergen exposure in infancy may vary depending on whether or not there is a family history of atopy.<sup>37,40–42</sup> In contrast, data suggest that exposure to endotoxin and other microbial agents may reduce the risk of atopy and asthma in some populations.<sup>43–46</sup>

Palta *et al*, as part of the Newborn Lung Project, followed from birth a cohort of VLBW children and found that, among 8-year-old children with no family history of asthma, household smoking predicted wheezing in the prior 12 months.<sup>31</sup> Elder *et al* found that maternal smoking was an independent risk factor for wheeze in a population of infants born <33 weeks.<sup>3</sup> We similarly found an increased risk of respiratory illness among smoke-exposed infants, independent of other factors. This is particularly pertinent since young infants living with smokers are at risk of ETS exposure in their homes not only through the air, but also through dust and surfaces in the home. Thus simply smoking outside will not completely protect an infant from ETS contamination.<sup>47</sup>

Significant evidence is now available to suggest that asthma is precipitated by complex interactions between specific exposures and genes during critical time periods.<sup>48</sup> The first year of life for a VLBW infant presents a window during which exposures may have a critical influence. Animal studies suggest that exposure of the premature lung to oxidant stress for relatively brief periods is sufficient to cause airway remodelling and smooth muscle changes that predispose towards airway reactivity with subsequent environmental challenges.<sup>49-52</sup> While we were not able to evaluate for interaction effects in our study due to limited sample size, it is possible that oxygen and/or smoke exposure sensitised the premature infant's airways to yield a more reactive response to allergen exposure.

Some efforts to reduce exposure to indoor respiratory triggers have been successful in improving respiratory health in older groups of asthmatic children.<sup>53,54</sup> Specifically, significant correlations have been found between reductions in cockroach allergen and decreases in asthma-related morbidity.<sup>50</sup> However other studies of environmental interventions for children at risk for asthma have not yielded clear benefit.<sup>55</sup> Thus it is not clear which interventions to prevent exposures for the population of VLBW infants would effectively improve respiratory outcomes.

There are some limitations to this analysis. First, there is a potential for recall bias. However this would not be expected to alter the relationship between exposures and respiratory outcomes. Further, in the sampled medical charts, the reported information was consistently confirmed. Second, we did not have objective measures, such as cotinine samples and dust analyses, to confirm parent-reported exposures. We cannot determine from these data whether the infants are experiencing transient early wheezing or persistent wheezing that will continue beyond the preschool years.<sup>56</sup> The infants lost to follow-up in this study were more likely to be from poor minority backgrounds; however we were able to maintain >85% of the sample. Third, we obtained these longitudinal data from a convenience sample of infants that were ready for discharge at a time that our study nurse was available. Although mean birth weight and gestational age of enrolled infants were similar to the general population of VLBW infants, our enrolment protocol resulted in over-sampling patients with longer hospitalisations and who required more days of supplemental oxygen, which may have caused study infants to be somewhat more susceptible to respiratory illness.

## Implications

This study suggests that VLBW infants are at substantial risk for respiratory illness in the first year of life, and this may be in part attributable to modifiable postnatal exposures. These infants might benefit from environmental interventions early in life that decrease exposure to indoor respiratory triggers. Additional studies are needed to further explore exposures and risk in this population, and ultimately to test interventions to reduce exposures and prevent morbidity.

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**What is already known on this topic**

- Children born premature have a substantially increased risk of developing respiratory illnesses.
- Indoor environmental exposures are associated with an increased risk of respiratory symptoms among young children.

**What this study adds**

- In this sample of very low birth weight (VLBW) infants, respiratory morbidity and exposure to triggers were common.
- We found that both living with a smoker and exposure to pests were independently associated with the need for acute care for respiratory illnesses among this population.
- These findings suggest that VLBW infants may benefit from interventions that decrease exposure to respiratory triggers.

**Table 1****Demographics**

<b>Demographics</b>	<b>Overall (n = 124) (%)</b>
Male	63 (51)
Mean (SD) birth weight, g	1117 (242)
Range: 530–1495	
Mean (SD) gestational age, weeks	29 (2)
Range: 23–34	
Mean (SD) length of NICU stay, days	62.4 (27.8)
Range: 16–145	
BPD	39 (32)
GER	57 (46)
Mean (SD) days on oxygen	38 (31)
Range: 0–134	
Mean (SD) days on ventilator	9.7 (16)
Range: 0–110	
Race	
White	82 (66)
Black	22 (18)
Other	17 (14)
Unknown	3 (2)
Hispanic	5 (5)
Medicaid Insurance	45 (36)
Mean (SD) age at 1-year follow-up, months	13 (2.27)
Range: 10–21	
Parent/family demographics	
Prenatal smoke exposure	24 (19)
Family history of allergies	83 (67)
Family history of asthma	55 (44)

BPD, bronchopulmonary dysplasia; GER, gastro-oesophageal reflux; NICU, neonatal intensive care unit.

**Table 2**  
**Respiratory morbidity at 1 year**

	n (%)
Required acute care for breathing problems since NICU discharge	58 (47)
Required hospitalisation	14 (11)
Required an ED or doctor's visit	57 (46)
Diagnosed with asthma	11 (9)
Prescribed a bronchodilator	31 (25)
Prescribed inhaled steroids	15 (12)
At follow-up, respiratory symptoms over the prior 2 weeks:	
Experienced any wheezing, coughing	37 (30)
Experienced persistent symptoms of wheezing, coughing	32 (26)
Required use of bronchodilator to relieve wheezing/coughing	14 (11)

ED, emergency department; NICU, neonatal intensive care unit.

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**Table 3**  
**Environmental exposures at 1 year**

	Overall n (%)	* Any acute visits among exposed	* Any acute visits among not exposed	p Value
Any exposure	101 (82)	49 (48)	9 (39)	0.491
Pets with fur	70 (56)	33 (47)	25 (46)	1.00
Attendance at daycare	30 (24)	17 (57)	41 (44)	0.293
Living with 1 smoker(s)	41 (33)	25 (61)	33 (40)	0.04
Pests	16 (13)	11 (69)	47 (44)	0.07
Mold/mildew	17 (14)	11 (65)	47 (44)	0.12
Wood stove	16 (13)	10 (62)	48 (45)	0.19

\* Percentage of infants with 1 acute care visits for respiratory problems in the first year of life.

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**Table 4**  
**Factors associated with 1 acute care visit for wheezing/breathing problems**

Characteristics	OR (95% CI)	p Value
Living with 1 smoker	2.62 (1.09 to 6.29)	0.031
Pests	4.41 (1.22 to 15.94)	0.024
Race	1.04 (0.44 to 2.50)	0.926
Family history of asthma or allergies	2.22 (0.80 to 6.10)	0.124
Bronchopulmonary dysplasia	4.32 (1.59 to 11.72)	0.004
Daycare attendance	3.30 (1.20 to 9.08)	0.021

Reference: no smokers in the home, no exposure to pests, white race, no family history of asthma or allergies, not diagnosed with BPD, and no attendance at daycare.

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