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Predictors of Wheezing in Prematurely Born Children

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Abstract

Objective: To examine the degree to which neonatal illness severity, post-neonatal health problems, child characteristics, parenting quality as measured by the HOME Inventory, and maternal characteristics related to the development of wheezing in prematurely born children over the first 27 months after term.

Design: Longitudinal predictive study.

Setting: Infants were recruited from two NICUs, one in southeast and one in Midwest.

Participants: One hundred thirteen (113) preterm infants who weighed less than 1500 gm or required mechanical ventilation and their mothers.

Main outcome measures: The presence of wheezing was obtained from maternal report at 2, 6, 9, 13, 18, 22, and 27 months. Wheezing was considered to be medically significant if the child was using bronchodilators or pulmonary anti-inflammatory medications.

Results: Sixty eight (68) percent of the children had wheezing at least one age; 47% of the children were also taking bronchodilators or pulmonary anti-inflammatory medications and thus had medically significant wheezing.

Conclusion: Post-neonatal health problems and the social environment appear to be more important in developing wheezing in prematurely born children than neonatal medical complications.

Keywords

Wheezing; Premature Infants; Risk; Overweight

Asthma is the most common chronic illness of children (Yawn, Wollan, Kurland, & Scanlon, 2002). One group of children at particular risk for wheezing and asthma is premature infants (Berz et al., 2007; Gessner & Chimonas, 2007; Greenough et al., 2005;

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Milner, Stein, McCarter, & Moon, 2004; Siltanen, Savilahti, Pohjavuori, & Kajosaari, 2004), but only limited prospective research has examined how neonatal and post-neonatal factors relate to the development of wheezing in prematures. According to the developmental science perspective (Cairns, Elder, & Costello, 1996; Miles & Holditch-Davis, 2003), children's health and development are outcomes of their continuous, reciprocal interactions with their environment. The child and environment form a complex system, made up of elements that are also systems, such as the mother and child (Cairns et al., 1996; Miles & Holditch-Davis, 2003). Thus, the development of wheezing is due to interactions among characteristics of the infant, such as age and other illnesses, and factors in the infant's environment including parenting quality and can be best understood by exploring the effects of multiple aspects of the child and environment at the same time. The purpose of this study, therefore, was to examine environmental and medical factors related to the development of wheezing in prematurely born children over the first 27 months after term. Although this paper focuses on wheezing, definitions of wheezing and asthma used in previous studies overlap, and the predictors of wheezing and asthma were quite similar so literature on both wheezing and asthma will be reviewed.

Callout 1

Predictors of Wheezing and Asthma

The incidence of wheezing and asthma is related to neonatal illness severity. Birthweight of less than 2500 grams has been related to transient wheezing occurring before 4 years of age but not to persistent wheezing or wheezing beginning at later ages (Kurukulaaratchy, Waterhouse, Matthews, & Arshad, 2005), and birth weight less than 1500 grams was related to an increased rate of asthma diagnoses (Brooks, Byrd, Weitzman, Auinger, & McBride, 2001; Gessner & Chimonas, 2007). Premature infants with oxygen dependence at 36 weeks or longer mechanical ventilation had a higher incidence of asthma by 12 months corrected age than other premature infants (Greenough et al., 2005; Grischkan et al., 2004; Koivisto et al., 2005). Some investigators have found that small for gestational age (SGA) premature infants had lower rates of asthma (Grischkan et al., 2004), whereas others have found no differences in the asthma rates of SGA and average-sized prematures (Bardin, Piuze, & Papageorgiou, 2004; Gessner & Chimonas, 2007).

The incidence of wheezing and asthma are also related to post-neonatal health problems. Children with allergies are more likely to develop asthma than other children (Kocabas et al., 2005; Kurukulaaratchy, Matthews, & Arshad, 2004; Nafstad, Brunekreef, Skrondal, & Nystad, 2005), but prematurely born children with wheezing were less likely to have allergies than fullterms (Siltanen et al., 2004). Children with more respiratory infections in the first year of life, including lower respiratory tract infections, respiratory syncytial virus (RSV) infections, or croup, were at higher risk of asthma at 3 to 10 years of age than other children (Gessner & Chimonas, 2007; Korppi, Piippo-Savolainen, Korhonen, & Remes, 2004; Kurukulaaratchy et al., 2004; Lee et al., 2007; Nafstad et al., 2005). Obesity increased asthma risk in school-aged children and adolescents (Flaherman & Rutherford, 2006; Grischkan et al., 2004; Mai, Gaddlin, Nilsson, & Leijon, 2005; Saha, Riner, & Liu, 2005). Some investigators have found that being large for gestational age at birth increased asthma risk in fullterms (Flaherman & Rutherford, 2006; Sin et al., 2004) although other investigators did not (Taveras et al., 2006). No investigators have examined the impact of excess weight gain on wheezing risk in premature infants or toddlers.

[1]The development of wheezing in premature infants is due to the interactions among infant characteristics and factors in the infant's environment including parenting quality.

Wheezing and asthma also are related to child characteristics. In particular, in studies of both fullterm and premature infants before 10 years of age, boys have been found to be at greater risk of wheezing and asthma than girls (Berz et al., 2007; Gessner & Chimonas, 2007; Greenough et al., 2005; Grischkan et al., 2004; Higgins, Wakefield, & Cloutier, 2005; Koivisto et al., 2005; Kurukulaaratchy et al., 2005; Milner et al., 2004; Saha, Riner, & Liu, 2005; Wright, Stern, Kauffmann, & Martinez, 2006). Minority children, particularly African Americans, have been found to have higher rates of asthma in population-based studies and studies of prematurely born children (Akinbami, Rodes, & Lara, 2005; Arif, Borders, Patterson, Rohrer, & Xu, 2004; Berz et al., 2007; Grischkan et al., 2004; Higgins et al., 2005; McDaniel, Paxson, & Waldfogel, 2006; Milner et al., 2004; Ramsey, Celedon, Sredl, Weiss, & Cloutier, 2005; Saha et al., 2005). Being born by cesarean birth was also associated with an increased risk of asthma, particularly in premature infants (Debley, Smith, Redding, & Critchlow, 2005; Gessner & Chimonas, 2007; Kero et al., 2002), because of lower exposure to maternal vaginal and fecal flora during delivery.

Finally, developing wheezing and asthma has been related to maternal characteristics and parenting. Mothers with low socioeconomic status (SES), as indicated by low education, low income, living in rented housing, or being unmarried, are usually found to be more likely to have children with asthma (Berz et al., 2007; Gessner & Chimonas, 2007; Greenough et al., 2005; Higgins et al., 2005; Kurukulaaratchy et al., 2004; Milner et al., 2004), but Yawn et al. (2002) found that higher SES children were more likely to be diagnosed with asthma. Health problems and asthma in particular are more common in infants experiencing less positive parenting and greater punitiveness, possibly because of the stress (Klinnert et al., 2001; Mantymaa et al., 2003).

However, most studies of wheezing or asthma risk have been conducted in fullterm infants or older children. Studies of risk for wheezing in prematures have been focused primarily on neonatal illnesses or child characteristics (Debley et al., 2005; Greenough et al., 2005; Grischkan et al., 2004; Koivisto et al., 2005). Post-neonatal health problems, maternal characteristics, and parenting have been examined mainly in population-based studies or studies of fullterms. Yet according to the developmental science perspective, these factors need to be examined along with more infant-focused factors. Environmental factors and post-neonatal health problems may be more accessible to nursing interventions than neonatal illnesses or child characteristics. In order for nurses to better target preventive efforts, identifying the multitude of factors related to the development of wheezing in premature infants is needed. Thus, the purpose of this study was to examine environmental and medical factors related to developing wheezing in prematurely born children over the first 27 months after term. Specifically, we determined the degree to which neonatal illness severity (birthweight, being small for gestational, length of mechanical ventilation), post-neonatal health problems (allergies, upper respiratory tract infections, pneumonia, weight for height), child characteristics (gender, race, cesarean delivery), parenting quality, and maternal characteristics (marital status, education) were related to wheezing.

Methods

Participants

The participants in this study were 113 infants and mothers who were enrolled in a larger study of biological and social risks of prematures (Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Holditch-Davis, Schwartz, Black, & Scher, 2007). All infants were born before 35 weeks gestation and were high risk for developmental problems due to either a birthweight less than 1500 grams or a requirement for mechanical ventilation or continuous positive airway pressure. The infants were recruited from two tertiary hospitals: 60 from a southeastern perinatal center with a rural/small town population and 53 from an urban

midwestern children's hospital. Infants with congenital problems affecting development (such as Down Syndrome) were excluded, but infants with postnatal neurological insults were eligible. To allow time for infants to manifest wheezing not directly due to neonatal respiratory problems, only infants from the larger study with data for at least 6 months after term were included in this report. The demographic characteristics of the sample are given in Table 1. Infants from the two hospitals and their mothers did not differ on any demographic variable except that more multiple births and first births were recruited from the southeastern hospital (Holditch-Davis et al., 2004). The 21 infants and mothers who were lost to follow-up before 6 months differed significantly from the 113 infant-mother dyads in this report only in that the mothers of drop-outs were younger (mean of 23.7 years versus 28.8 years).

Variables for Analysis

All data were collected using ages corrected for prematurity.

Presence of wheezing—The presence of wheezing was obtained from a child health history. At 2, 6, 9, 13, 18, 22, and 27 months, the mother reported whether her child had experienced any of 10 listed health problems, including wheezing or asthma, since the previous contact. She also listed any medications the child was currently receiving. The investigators considered wheezing to be medically significant if the mother reported that the child was using any medications that the investigators later classified as pulmonary anti-inflammatory medications or bronchodilators. Otherwise, the child was considered to have mild wheezing. Children could change back and forth from no wheezing to mild wheezing or medically significant wheezing.

Child characteristics and illness severity—Days of mechanical ventilation, gestational age, birthweight, whether the infant was SGA, cesarean delivery, and gender were obtained from the neonatal medical record. The length of mechanical ventilation was skewed (mean 11.0, *SD* 18.4), so infants with 1 day or less of ventilation were scored as receiving 1 day, and the logarithm (base 10) of each subject's days of ventilation was used in analyses. Forty-six infants had chronic lung disease, but chronic lung disease was correlated (Spearman correlation = .65) with longer mechanical ventilation so ventilation length was used instead of chronic lung disease in analyses.

Child race was scored as either white or minority from the demographic questionnaire that the mothers completed at each contact. (One minority infant was Asian; the rest were African American.) Allergies, upper respiratory tract infections (listed as colds, croup, or cough), and pneumonia or RSV infection--were three health problems listed on the child health history. Infant post-neonatal health problems were obtained by maternal report on this history. Seven dichotomous allergy and seven dichotomous upper respiratory infection variables (presence of allergies or upper respiratory infections from hospital discharge to 2 months, between 2 and 6 months, between 6 and 9 months, between 9 and 13 months, between 13 and 18 months, between 18 and 22 months, and between 22 and 27 months) and one dichotomous pneumonia variable (occurrence of pneumonia or RSV any time in the first 13 months) were used in analyses. The pneumonia and RSV variable was limited to the first 13 months because previous investigators indicated that having these illnesses in the first year increased asthma risk (Korppi et al., 2004), and these illnesses occurred too infrequently in this sample to be sampled at 3-6 month intervals.

Height and weight were obtained at each in-person contact (2, 6, 9, 18, and 27 months). Infants were weighed on a battery-operated, electronic scale with a capacity of 20 kilograms and accuracy within 10 gm. Length was measured on a height measuring board, which was

accurate to the nearest 0.1 cm. The equipment was portable and was taken into the home. Weight in kilograms divided by length (cm^2) was calculated, and the mean values at early ages (2, 6, 9 months) and at later ages (18, 27 months) were used in analyses. Forty-nine of the 107 infants with measurements were above the 90^{th} percentile on weight-for-length ratio for premature infants and toddlers (Guo, Wholihan, Roche, Chumlea, & Casey, 1996) at the early ages, and 22 of 72 were above the 90^{th} percentile at older ages.

HOME—The HOME inventory (0-3 version) consists of 45 items in six sub-scales and is designed to identify children who are at risk for developmental delay due to a lack of appropriate stimulation in the home environment (Caldwell & Bradley, 1980). Each item is scored as present or absent; the score equals the number of present items. The HOME is administered using maternal interview and observation. The first author trained research assistants at both sites until they achieved 90% inter-rater reliability. Test-retest reliability for the total scale over 6-months was .76-.77 (Holditch-Davis, Tesh, Goldman, Miles, & D'Auria, 2000). Two HOME sub-scales were used in this report: sub-scale I, Maternal Emotional and Verbal Responsivity, which measures the mother's sensitivity to child cues, and sub-scale II, Acceptance of the Child's Behavior, which measures the mother's avoidance of use of punishment and restriction. Internal consistency of sub-scale I for this sample was .90 at 6 months and .69 at 18 months; sub-scale II was .77 at 6 months and .58 at 18 months. These sub-scales were correlated with other measures of parenting quality (Holditch-Davis et al., 2000; Tesh & Holditch-Davis, 1997).

Maternal characteristics—Maternal characteristics of years of education and marital status were recorded on the demographic questionnaire that the mothers completed at enrollment.

Procedures

The institutional committee for protection of human subjects at each institution approved the study. Infants were enrolled when their medical conditions were no longer critical (not mechanically ventilated or in an immediate life-threatening situation) if an additional hospital stay of at least 1 week was anticipated and informed consent was obtained from the mothers. Immediately after enrollment, mothers completed questionnaires on demographic characteristics. Infant medical records were reviewed weekly until hospital discharge.

Follow-up at home was conducted at 6 and 18 months corrected for prematurity, and the HOME Inventory was administered. The mothers also completed questionnaires (demographics, health history). Questionnaires were also administered by mail (13 and 22 months) or during hospital visits (2, 9, and 27 months) using the same procedures. Height and weight measurements were obtained during home and hospital visits. Mothers were paid $10 each time they completed questionnaires. The infant was given a small gift at the end of each home visit.

Data Analyses

Alpha was set at .05 for two-tailed tests. The likelihood of having medically significant wheezing, mild wheezing, or neither at each age was analyzed using generalized estimating equations (GEE; Zeger, Liang, & Albert, 1988), an extension to the proportional odds model (Stokes, Davis, & Koch, 2000). The GEE approach is a flexible procedure capable of analyzing ordinal longitudinal categorical data and easily accommodates missing and mistimed values, as occurred in this study. As a repeated measures regression model, it can assess the relationship between an ordinal categorical outcome measure and continuous and categorical covariates. Parameterization of GEE includes population (fixed) effects (the effect of age and static and time-varying covariates). Time was modeled as a continuous

explanatory variable, and the repeated measures within a subject were treated as being correlated. Our GEE models tested for the linear and quadratic effects of post-menstrual age, the effects of the covariates, and any pairwise interactions among the environmental and medical variables as well as between these variables and age. In the GEE approach, missing data are assumed to be missing completely at random, and the predicted trends are not affected. An odds ratio was estimated for each predictor.

Because the ages of the children at the contacts varied slightly, the actual age of the child at the time of each contact was used in analyses. Age was adjusted so that the intercepts equaled the cumulative log odds of having medically significant or mild wheezing at 29 weeks post-menstrual age, roughly the mean gestational age of the sample. The groupings of neonatal illness severity, post-neonatal health problems, child characteristics, parenting quality, and maternal characteristics were candidate covariates. Two variables were measured at all ages: the presence of allergies and the presence of upper respiratory infections. For all other covariates, a single value was used for each infant. The model selection strategy was performed in multiple stages. First, models of the relation of the wheezing variable within each grouping of predictors were fitted and reduced using backward selection at $p = .15$. Then, we tested a combined model that included all individual variables significant at $p < .15$. Interactions of these variables with age, and pairwise interactions among these variables were tested separately. A group-wise test of the interactions was performed at $p < .10$, and individual interactions were only tested if the group met this criterion. Backward elimination was used for the remaining variables until a final mixed model with each variable having $p < .05$ was obtained. (Higher *p*-levels were used in the preliminary analyses to avoid prematurely eliminating a variable, resulting in a Type II error.) Overall, our procedure simplified the model and led to inferences that some effects were either zero or not large enough to be detected.

Results

Table 2 shows the percent of infants reported to have wheezing at each age. About 47% of the children were reported to have medically significant wheezing by 27 months corrected age. The mean age of the children at the first report of significant wheezing was 53 weeks or about 12 months. There were three patterns of medically significant wheezing: 10.6% of children had a report of medically significant wheezing at one age and no other report of wheezing, 11.5% had significant wheezing at one age along with mild wheezing at one or more ages, and 24.8% of children had recurrent medically significant wheezing (10.6% at two ages, 7.1% at three, 5.3% at four, 0.9% at five, 0.9% at six). In addition, 21.2% of the children had mild wheezing at one or more ages but no medically significant wheezing. Only 31.9% of the children had no reports of wheezing at any age. Only eight children had medically significant wheezing at 2 months (one with significant wheezing at only that age and the rest with wheezing at other ages) so very few children showed transient medically significant wheezing that was likely to be due exclusively to neonatal respiratory problems.

CALLOUT 2

Medical and Environmental Effects on Wheezing

Tables 1 and 3 present the descriptive statistics for the medical and environmental variables. The parenting variables and maternal characteristics were inter-correlated ($r = .25$ to .40) but uncorrelated with the child variables except for race (correlated with all maternal variables, *r*

[2]A high percentage of prematurely born children were reported to have medically significant wheezing (47%) or mild wheezing (21%) in the first 27 months.

= −.35 to −.56) and cesarean delivery (r = .23 with education). Child variables showed only isolated correlations (birthweight with mechanical ventilation, early and late weight/length^2, and cesarean delivery; mechanical ventilation with pneumonia; SGA with URIs and cesarean delivery; allergies with URIs; and early weight/length^2 with pneumonia, cesarean delivery, and late weight/length^2).

In preliminary GEEs, we examined the relationship of the variables within each group of predictors with wheezing (see Table 4). For the backward elimination model with the neonatal illness variables, mechanical ventilation was related to the development of wheezing although at p > .05. Three of the post-neonatal health problems--URIs, allergies, and weight to length^2 ratio at early ages--were associated with a greater probability of having wheezing. Race was the only child characteristic related to wheezing; minority children were more likely to develop wheezing. One parenting variable (HOME sub-scale II) and one maternal characteristic (marital status) were also related to the development of wheezing. Lower scores on HOME subscale II (greater punitiveness) and unmarried mothers were associated with a greater risk for wheezing.

Final Model Predicting Wheezing from Medical and Environmental Factors

We then tested a combined GEE model that included all individual variables with $p < .15$ on the preliminary analyses; pairwise interactions among these variables and of each variable with age were also tested. Figure 1 shows the results with significant covariates held constant at their means. The probability of medically significant wheezing increased from term age through 27 months (from about a 10% probability to slightly less than 20% probability), while the probability that the children would not have wheezing decreased. The likelihood of having mild wheezing also increased but at a slower rate from about 14% to 22%.

Table 5 shows the results of the final reduced model. In addition to the age effect, mechanical ventilation, allergies, URIs, weight to length^2 ratio at early ages, sub-scale II of the HOME Inventory (avoidance of punitiveness), and marital status were related to wheezing. Children with longer mechanical ventilation, with allergies, with URIs, greater weight for length in the first year, lower scores on HOME sub-scale II, and unmarried mothers were more likely to have wheezing. The odds ratios indicated that gaining 52 weeks in age increased the odds of having wheezing by about 50%. An increase in 1 in log mechanical ventilation (the difference between 1 and 10 days or between 10 and 100 days) was associated with 1.6 times the odds of wheezing. Children with allergies had 2.8 times the odds of wheezing as children without allergies, and children with URIs had 2.9 times the odds of wheezing. An increase in 1 in the weight to length^2 ratio (roughly the difference between the smallest and the heaviest infant) was associated with four times the risk of wheezing. A decrease in 1 point in the HOME sub-scale II score was associated with 1.3 times the odds of wheezing. Having an unmarried mother was associated with 2.4 times the odds of wheezing. There were no significant interactions.

Discussion

Similar to the results of other studies (Gessner & Chimonas, 2007; Greenough et al., 2005; Milner et al., 2004; Siltanen et al., 2004), we found that mothers reported that a high percentage of prematurely born children had medically significant wheezing (47%) or mild wheezing (21%) in the first 27 months after term. Children who experienced longer mechanical ventilation, were older, had allergies or more frequent upper respiratory tract infections, had greater weight for length in the first year, or had mothers who were more punitive or unmarried were more likely to be reported to have wheezing. Studies of fullterms and population-based studies have had similar results (e.g., Berz et al., 2007; Grischkan et

al., 2004; Korppi et al., 2004; Kurukulaaratchy et al., 2004; Nafstad et al., 2005; Saha et al., 2005), but this is one of the very few studies in which multiple factors were examined in prematures (Gessner & Chimonas, 2007; Siltanen et al., 2004).

The incidence of recurrent medically significant wheezing in this study, 24.8%, was similar to rates reported by other investigators. In studies using parental report, 19%-33% of prematures had asthma by 8-15 years (Nixon, Washburn, Schechter, & O'Shea, 2007; Palta et al., 2001; Saigal et al., 2001), and 16-34% of fullterms had wheezing by 3 years (Berz et al., 2007; Traveras et al., 2006). Using physician diagnoses, investigators found 20%-43% of prematures had wheezing or asthma (Brooks et al., 2001; Greenough et al., 2005; Siltanen et al., 2004). In our study, another 43% of infants had medically significant wheezing at one age or mild wheezing.

Other studies on wheezing or asthma risk in prematures have been focused primarily on the effects of neonatal illnesses or child characteristics (Debley et al., 2005; Greenough et al., 2005; Grischkan et al., 2004, Koivisto et al., 2005). Yet the only neonatal illness related to wheezing in our analyses was longer mechanical ventilation. Infants experiencing longer mechanical ventilation or chronic lung disease are known to be more likely to have respiratory illnesses in the first 2 years of life (Chien, Tsao, Chou, Tang, & Tsou, 2002; Koivisto et al., 2005).

Most of the predictors of wheezing we identified were similar to those identified in studies of fullterms and in population-based studies. Like other investigators, we found the rate of wheezing increased with age (Akinbami et al., 2005; Arif et al., 2004; Saha et al., 2005). However, we did not follow our children into school-age so we do not know whether this trend will continue. Wheezing diagnosed before 4 years does not necessarily continue to be problem in later childhood and has different predictors than chronic asthma (Kurukulaaratchy et al., 2005; Siltanen et al., 2004), so whether our predictors would be useful for predicting asthma is unknown. Therefore, prospective longitudinal research is needed to examine the course of early wheezing in preterm infants and how it evolves from infancy to school-age.

We also found that the risk of wheezing was increased by post-neonatal health problems particularly allergies, upper respiratory infections, and greater weight for length. Other investigators had similar results for allergies and upper respiratory tract infections (Flaherman & Rutherford, 2006; Grischkan et al., 2004; Kocabas et al., 2005; Kurukulaaratchy et al., 2005; Nafstad et al., 2005; Saha et al., 2005). However, unlike other studies (Korppi et al., 2004; Kurukulaaratchy et al., 2004; Lee et al., 2007; Nafstad et al., 2005), we did not find a relationship between wheezing and pneumonia or RSV, probably due to the low incidence of these illnesses in our sample. Only 11 of our infants experienced pneumonia or RSV by 13 months corrected age.

Ours in the first study to find that greater weight for length in infancy is related to wheezing risk in the first 27 months. Premature infants may be at particular risk for excess weight gain in infancy because they are more likely to be formula fed than fullterms, and formula feeding leads to more rapid weight gain in early infancy than breastfeeding (Kramer et al., 2004). Also, mothers may feel pressured by their families, friends, and even health care providers to “fatten up” their tiny prematures. On the other hand, we did not find a relationship between wheezing and greater weight for length in toddlers. Infants in our sample were more likely to be above the 90th percentile on weight for length in infancy than in toddlerhood. Because we followed the children only until 27 months, children who were normal weight for length in infancy but became overweight at 18 or 27 months may not have had enough time to develop wheezing. Our findings do differ from those of Mai et al.

(2005) that very-low-birth-weight infants showing rapid weight gain in the first 6 months after term were less likely to have asthma at 12 years. However, Mai et al. did not examine whether their infants with rapid weight gain ended up with larger weights for length than other infants, nor did they assess wheezing or asthma at earlier ages.

We found that maternal characteristics and parenting were related to wheezing. Like other studies (Berz et al., 2007; Greenough et al., 2005; Higgins et al., 2005; Kurukulaaratchy et al., 2004; Mantymaa et al., 2003; Milner et al., 2004), we found that maternal punitiveness and maternal marital status were related to an increased risk for wheezing. Children of unmarried mothers and children with more punitive mothers were more likely to develop medically significant wheezing. All of the parenting and maternal characteristic variables were inter-correlated, suggesting that there may be an underlying socioeconomic risk for wheezing. The particular variable showing significance may just be an artifact of the particular study. There are two possible explanations for these effects: low SES children are more likely to be exposed to allergens, tobacco smoke, and other environmental triggers of wheezing (Chen, Matthews, & Boyce, 2002; Wood, 2003); or living in poverty and more punitive parenting may be stressors for children that reduce the effectiveness of their immune systems (Chen et al., 2002; Klinnert et al., 2001; Mantymaa et al., 2003). Other investigators have found that the risk of asthma is increased by a chronic, low-grade stress, such as night-time traffic noise (Dulime et al., 1996; Ising, Lange-Asschenfeldt, Lieber, Weinhold, & Eilts, 2003), so the stresses associated with being raised in a low SES household or by a punitive mother might have a similar effect.

Minority children had more wheezing than whites when child characteristics were analyzed separately but not when race was analyzed along with health problems, parenting, and maternal variables. Other investigators found that race is a risk factor for wheezing and asthma (Akinbami et al., 2005; Berz et al., 2007; Grischkan et al., 2004; Higgins et al., 2005; McDaniel et al., 2006; Saha et al., 2005). Our findings suggest that the higher risk of wheezing in prematurely born minorities is due to the increased rate of low SES and higher use of punitive discipline in minority families (McLoyd, 1998), rather than race or culture per se. Population-based studies of fullterms have had opposite findings: the rate of asthma in African Americans was higher than whites even after controlling for SES (Higgins et al., 2005; McDaniel et al., 2006).

On the other hand, we did not find a relationship between wheezing in prematurely born children and many factors associated with wheezing or asthma in the literature. For example, we did not find a relationship between wheezing risk and either being small for gestational age or being born by cesarean delivery. We also did not find a difference in the incidence of wheezing in boys and girls. Most investigators have found that wheezing incidence is higher in boys (Berz et al., 2007; Gessner & Chimonas, 2007; Greenough et al., 2005; Grischkan et al., 2004; Higgins et al., 2005; Koivitso et al., 2005; Kurukulaaratchy et al., 2005; Milner et al., 2004; Saha et al., 2005; Wright et al., 2006; Yawn et al., 2002). However, this finding is not universal (Osman et al., 2007), and different sub-populations of children with wheezing or asthma show different gender distributions. Thus, Webber, Carpiniello, Oruwariye, and Appel (2002) found that boys were more likely to have an asthma diagnosis, but girls were more common in the children with asthma symptoms but without a diagnosis. Clearly additional research is needed in this area.

Finally, several factors may limit the generalizability of this study. The use of a maternal self-report health questionnaire may have affected our findings. In a study by Cane, Ranganatahan, and McKenzie (2000), there was less than 50% agreement between parents' and clinicians' reports of asthma. In our study, maternal reports of wheezing were confirmed by maternal report of child medications, which nurses on our research team classified as

bronchodilators or pulmonary anti-inflammatory medications. Because these medications may also be prescribed for transient wheezing and reactive airway disease, we do not know the medical diagnoses of the children whom we classified with medically significant wheezing. Thus, additional research on the health problems of premature infants that uses medical diagnoses is needed.

Another limitation of our study was the failure to obtain information on a common risk factor for wheezing: parental smoking. Parental smoking is known to increase asthma rates (Berz et al., 2007; Higgins et al., 2005; Murray et al., 2004), and smoking rates are higher in low SES families (Chen et al., 2002; Walker et al., 2004). Thus, some of the increased risk of wheezing in low-income families may have been due to parental smoking. Also, mothers of premature infants are more likely to smoke than mothers of fullterms (Burguet et al., 2004; Gennaro, Dunphy, Dowd, Fehder, & Douglas, 2001). On the other hand, one study found no relationship between maternal prenatal smoking and asthma (Gessner & Chimonas, 2007).

A final limitation was the relatively high number of missing values at some time points. Although 113 infants contributed to the analysis at one or more time points, no time point included more than 98 infants, and as is typical for longitudinal studies, subject attrition increased with time. This tendencey did not seem to be affected by whether the contact was by mail or in person. For this reason we used a statistical technique, the generalized estimating equation (Zeger et al., 1988) in which the predicted trends are not affected missing values and subjects with missing data at one time point can contribute data at a later time.

Implications for Practice

Because prematures have a higher incidence of wheezing and asthma than fullterm infants (Berz et al., 2007; Greenough et al., 2005; Milner et al., 2004; Siltanen et al., 2004), nurses and other health providers need to understand the factors that contribute to developing wheezing and asthma. Our findings provide evidence of the complex processes affecting the development of wheezing in premature infants, although we did not find interactions between variables as expected by the developmental science perspective. Both infant (neonatal and post-neonatal health problems) and environmental factors (maternal marital status) were related to wheezing. Fortunately, many of these factors are potentially amenable to intervention.

CALLOUT 3

Prior to NICU discharge, nurses need to educate parents about the high risk for wheezing in premature infants. Parents need to know what wheezing is (Cane et al., 2000) and the importance of taking a child with wheezing to the pediatrician. Parents should also be instructed to limit the exposure of prematurely born children to respiratory illnesses and potential allergens, not only in the immediate period after discharge but throughout infancy and toddlerhood in order to reduce the incidence of wheezing. In addition, encouraging parents to promote adequate nutrition and growth while avoiding over-feeding may also be beneficial. Weight gain in excess of growth in length in infancy not only leads to increased wheezing in the first few years of life but also is associated with obesity in childhood (Snethen, Hewitt, & Goretzke, 2007).

[3]Ongoing nursing interventions to promote positive parenting and reduce punitiveness might also reduce the incidence or slow the development of wheezing.

After discharge, ongoing nursing interventions to promote positive parenting and reduce punitiveness might also reduce the incidence or slow the development of wheezing because this factor was related to wheezing risk. Parents have more difficulties parenting premature infants than fullterms because of their atypical and immature behaviors and parental distress about the NICU experience (Holditch-Davis et al., 2007; Muller-Nix et al., 2004; Singer et al., 2003). These early problems can lead to ongoing problems with discipline (Miles & Holditch-Davis, 1995). Listening to parental concerns about interactions with their premature infants and providing ongoing support should reduce these concerns. In addition, nurses can suggest the use of positive forms of discipline, such as rewarding appropriate behaviors and use of time out. These strategies should lead to better parenting and a reduction in wheezing in this vulnerable group of infants.

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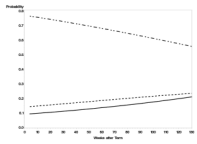

Figure 1.
The model-predicted probabilities of a prematurely born children having medically significant and mild wheezing over age. The covariates are held constant at their means. The solid line shows the predicted probability for medically significant wheezing, the dotted line is mild wheezing, and the line with short and long dashes is no wheezing.

Table 1

Demographic Characteristics of the 113 Premature Infants and Their Mothers.

	Mean	(SD)	Percent
Gestational Age (weeks)	28.8	(2.7)	
Birth Weight in Grams	1221	(430)	
Small for Gestational Age			13.3%
Sex of Child: Male			52.2%
Female			47.8%
Mechanical Ventilation (days)	11.0	(18.4)	
Neurological Insults	2.8	(3.0)	
IVH			22.1%
Percent: Singletons			69.9%
Twins			24.8%
Triplets			5.3%
Maternal Age (years)	28.5	(6.5)	
Married Mothers			57.5%
Maternal Education (years)	13.7	(2.3)	
First-Time Mothers			55.8%
Race: African American			46.0%
White			53.1%
Asian			0.9%

Note: The two hospitals differed significantly in multiple births and percent of first births.

Table 2

Percent of Infants Reported to Have Each Wheezing Variable at Each Age

	N[a]	No Wheezing	Mild Wheezing	Medically Significant Wheezing
2 months	98	83.7%	8.2%	8.2%
6 months	98	69.4%	17.4%	13.3%
9 months	90	63.3%	22.2%	14.4%
13 months	88	60.2%	17.1%	22.7%
18 months	94	54.3%	20.2%	25.5%
22 months	81	64.2%	17.3%	18.5%
27 months	57	59.7%	14.0%	26.3%

[a]The N varies over time because of missing contacts, study withdrawals, and incomplete questionnaires.

Table 3

Descriptive Characteristics of the Medical and Environmental Variables

	N[a]	Mean	(SD)	Percent
Allergies: 2 months	96			3.1%
6 months	97			7.2%
9 months	88			14.8%
13 months	86			8.1%
18 months	91			14.3%
22 months	83			14.5%
27 months	55			21.8%
Upper respiratory tract infections: 2 months	98			36.7%
6 months	98			78.6%
9 months	90			64.4%
13 months	88			77.3%
18 months	94			83.0%
22 months	81			80.3%
27 months	57			86.0%
Pneumonia in first 13 months	111			9.9%
Weight for Length^2: Early Ages	107	1.7	(0.2)	
Later Ages	72	1.6	(0.2)	
Cesarean Delivery	113			54.0%
HOME Sub-Scale I	109	10.0	(0.9)	
Home Sub-Scale II	109	6.5	(1.3)	

[a]The N varies over time because of missing contacts, study withdrawals, and incomplete questionnaires.

Table 4

Relationship of Wheezing to Variables Within Each Group of Medical and Environmental Predictors (Initial and Reduced Models Within Each Group of Variables).

		Initial Model		Reduced Model	
Group	**Predictors**	**Estimate[a]**	**(SE)**	**Estimate[a]**	**(SE)**
Neonatal Illness	Birthweight	0.00	(0.00)		
	Mechanical Ventilation	0.34	(0.28)	0.35#	(0.21)
	Size (Being SGA)	−0.41	(0.50)		
Post-Neonatal Health	Allergies	0.78#	(0.36)	0.93**	(0.32)
Problems	URIs	0.92**	(0.35)	1.05***	(0.28)
	Pneumonia	0.18	(0.46)		
	Early Weight/Length^2	2.58*	(0.88)	2.10**	(0.73)
	Later Weight/Length^2	0.14	(0.91)		
Child Characteristics	Gender (Being Female)	0.12	(0.28)		
	Race (Being Minority)	0.98***	(0.29)	1.02***	(0.28)
	Cesarean Delivery	−0.17	(0.29)		
Parenting	HOME--I (Responsivity)	0.03	(0.13)		
	HOME--II (Acceptance)	−0.39***	(0.11)	−0.39***	(0.10)
Maternal Characteristics	Marital Status	−1.11***	(0.32)	−1.18***	(0.28)
	Maternal Education	−0.03	(0.07)		

[a] Estimates are the natural log of the cumulative odds ratios.

* p < .05.

** p < .01.

*** *p* < .001.

# p < .15.

Table 5

Final Model of Predictors of Wheezing by Medical and Environmental Variables

			Cumulative Odds Ratios[a]	
	Estimate	**SE**	**Estimate**	**Confidence Limits**
Intercept1[b]	−3.918**	1.437		
Intercept2[c]	−2.817*	1.414		
Age (weeks)	0.007*	0.003	1.007	1.001 - 1.013
Mechanical Ventilation	0.461*	0.199	1.586	1.075 – 2.342
Allergies	1.027**	0.321	2.792	1.487 – 5.241
URIs	1.056***	0.264	2.875	1.714 – 4.823
Early Weight/Length^2	1.483*	0.660	4.404	1.209 – 16.049
HOME Sub-Scale II	−0.245*	0.110	0.782	0.631 – 0.970
Marital Status	−0.868**	0.320	0.420	0.224 - 0.785

[a] The odds ratio both for medically significant wheezing versus mild wheezing or no wheezing and for any wheezing versus no wheezing.

[b] Intercept for the cumulative odds of medically significant wheezing versus either mild wheezing or no wheezing.

[c] Intercept for the cumulative odds of any wheezing (medically significant or mild) versus no wheezing.

* $p < .05$.

** $p < .01$.

*** $p < .001$.