Respiratory Symptoms at Age 8 Years in a Cohort of Very Low Birth Weight Children

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The childhood respiratory consequences of very low birth weight (birth weight ≤ 1,500 g) are incompletely understood, especially since the introduction of recent changes in neonatal care. To assess prevalence, trends, and risk factors for respiratory symptoms, the authors followed to age 8 years a cohort of 384 very low birth weight children from six regional neonatal intensive care units in Wisconsin and Iowa who were born between August 1, 1988, and June 30, 1991. A control group of 154 Wisconsin schoolchildren was also assembled. Respiratory symptoms in the past 12 months and history of asthma (“asthma ever”) were reported by parents on a questionnaire used in the International Study of Asthma and Allergies in Childhood (ISAAC). Control group prevalence resembled ISAAC prevalence worldwide and in Canada, but respiratory symptoms were twice as common among very low birth weight children. With advent of the availability of pulmonary surfactants, the prevalence of wheezing at age 8 decreased from 50% to 16% (p = 0.002) among children with bronchopulmonary dysplasia, but it increased from 14% to 38% among those with milder neonatal respiratory disease. Bronchopulmonary dysplasia, family history of asthma, smoking in the household, and patent ductus arteriosus were predictive of wheezing in the previous 12 months. Antenatal steroid therapy had a borderline-significant protective association with wheezing (odds ratio = 0.56, 95% confidence interval: 0.29, 1.1). There were interaction effects between several of the predictors. Am J Epidemiol 2001;154:521–9.

Low birth weight (≤ 2,500 g) and very low birth weight (≤ 1,500 g) children have been found to have increased prevalence of chronic respiratory symptoms and decreased respiratory function (1–6). In 1992, Kitchen et al. (7) reported that in their study respiratory problems were present at age 2 years but receded by age 8 years. Other studies, however, found that respiratory signs and symptoms persisted well into school age (2, 4, 5). All of these studies enrolled very low birth weight children born in an era when neonatal care differed fundamentally from that of the present. Recent advances in neonatal care include the availability of exogenous surfactants and frequent use of antenatal and postnatal steroid therapy. In a clinical trial, Sell et al. (8) showed asthma symptoms to be less frequent at age 1 year among children randomized to receipt of surfactants. Speer and Silverman, in a review of respiratory outcomes, called for “carefully conducted prospective follow-up programs linked to a perinatal database” where “data must be relevant to the modern era of neonatal intensive care” (1, p. 155).

Our study, the Newborn Lung Project, followed from birth a regional cohort of very low birth weight children born between August 1, 1988, and June 30, 1991, in Iowa and Wisconsin. In our extensive perinatal data, we found increasing survival of very low birth weight neonates across the time period, concurrent with increasing surfactant and steroid use (9). We also found that the incidence of bronchopulmonary dysplasia increased when pulmonary surfactant was released as an investigational new drug and abated after surfactants became generally available. There was some evidence that the severity of bronchopulmonary dysplasia was lower for infants born during this latter time period.

As one of our long-term follow-up measures, we administered to parents, when their children were 8 years old, a brief questionnaire addressing asthma symptoms that was developed for the International Study of Asthma and Allergies in Childhood (ISAAC).
Allergies in Childhood (ISAAC). This questionnaire has been validated in several studies (10, 11) and has been completed by the parents of 257,800 6- to 7-year-olds worldwide (98 study centers in 38 countries). In North America, data were collected at two sites in Canada (Hamilton and Saskatoon) (12). The Canadian group included 5,755 children. Data from the United States were not available for this age group. To establish whether the prevalence of respiratory symptoms in our geographic area resembles the ISAAC results worldwide and in Canada, we administered the ISAAC questionnaire to students from several classrooms at a school in the Madison, Wisconsin area.

The purpose of our present report is to: 1) document the prevalence of asthma symptoms at age 8 years among the very low birth weight children and compare the prevalence of symptoms with results reported from the ISAAC (12) worldwide and in Canada; 2) assess whether the prevalence of asthma symptoms at age 8 differs between children born prior to August 1, 1989; children born between August 1, 1989, and July 31, 1990, when surfactant was released as an investigational new drug; and children born after August 1, 1990, when surfactant therapy was generally available; and 3) assess baseline and known asthma risk factors for parent-reported asthma and wheezing at age 8.

MATERIALS AND METHODS

The Newborn Lung Project is a multicenter study of all neonates with birth weights less than 1,501 g who were born between August 1, 1988, and June 30, 1991, and were admitted to one of six neonatal intensive care units in Wisconsin and Iowa. The institutional review boards of the participating study centers approved the protocol.

Population

Between August 1, 1988, and June 30, 1991, 1,024 very low birth weight neonates were admitted before 24 hours of age to six regional neonatal intensive care units covering a contiguous geographic area of Wisconsin and Iowa. The births represent three time periods with differing surfactant availabilities: period I, infrequent sporadic randomized clinical trials (up to July 31, 1989); period II, investigational new drug (August 1, 1989–July 31, 1990); and period III, general availability (August 1, 1990–June 30, 1991). During the investigational new drug period, surfactant was administered according to strict guidelines dependent on whether the drug was given prophylactically or therapeutically and on the infant’s birth weight and blood gases. Treatment during this period was limited to a maximum of two doses. After surfactants became generally available, they were given to a greater proportion of infants and sooner after birth in greater numbers of doses. We have previously described these changes in our cohort (9). Antenatal and postnatal steroid use also increased across the three time periods in our region (9).

Searches of state death certificates and follow-up clinic records were performed to identify children who had died after hospital discharge. Of the 802 children who survived to age 8 years, the parents of 625 had agreed to potential follow-up and provided recontact information prior to the child’s discharge from the neonatal intensive care unit. Those parents agreeing to recontact comprised the target group for follow-up; they were representative of the surviving children with regard to a wide range of clinical characteristics, including birth weight and fraction of inspired oxygen at 24 hours (table 1). Attempts were made to contact all 625 parents who had agreed to follow-up, and 437 were located when their children were aged 5 years, with 13 refusing participation. ISAAC questionnaires were sent at age 8 years, with 384 being returned. Table 1 shows a comparison of the group that returned questionnaires with the group of 625 targeted for follow-up. The ISAAC responders were very similar to those in the other two groups with regard to all clinical characteristics. Data on ISAAC items are given in table 2.

In light of the wide geographic variation in respiratory symptoms found by ISAAC (12), we assembled a local control group to validate that the prevalence of respiratory symptoms in Wisconsin was similar to worldwide and Canadian prevalences. For this purpose, we used information provided by parents of six classrooms of third graders and two classrooms of fourth graders at a suburban Madison, Wisconsin school during the 1999-2000 and 2000-2001 school years. Of the parents of 185 potential control children, 154 (83 percent) responded to the ISAAC questionnaire. The age range of these children was 8–10 years, with a mean of 9.2 years.

Data collection

During each child’s initial hospitalization, parents were approached for informed consent to perform a baseline interview and to abstract medical records. At this time, a recontact address was requested. Birth weight, gender, and race were recorded. The presence of patent ductus arteriosus and the administration of antenatal and postnatal steroid and surfactant therapy were ascertained. Gestational age was determined by the method of Ballard et al. (13). Respiratory records were photocopied, and severity of respiratory distress in the first 72 hours was scored on a scale of 0–100 by the method of Palta et al. (14). For 171 infants with readable pulmonary radiographs taken between days 25 and 35 of life, each such radiograph was independently scored on the scale of Weinstein et al. (15) by a radiologist and a neonatologist who were masked as to infant identity and clinical characteristics. The overall score for each infant is the average of the readings across all radiographs, averaged over the two readers. Average scores of 2 (linear reticular opacities, centrally located) or higher were considered to indicate bronchopulmonary dysplasia. Previous analyses showed that this level corresponds to an Edwards radiographic score of 3, which has been employed as an indicator of bronchopulmonary dysplasia in several clinical trials (16). The remaining radiographs all showed minimal abnormalities scored below level 2 and were considered to indicate mild respiratory disease.

Among the 213 neonates without readable radiographs, 40 had another indication of respiratory disease (use of supplemental oxygen or assisted ventilation between days 25 and 35 of life or at 36 weeks’ postconceptional age, or
Asthma at Age 8 in Very Low Birth Weight Children

Abnormal levels of blood gases between days 25 and 35 of life. These neonates were classified according to our previously published bronchopulmonary dysplasia severity score (17), which is scaled 0–100. A score greater than 20 is considered to indicate bronchopulmonary dysplasia (n = 13); a score above 0 but less than or equal to 20 is considered to indicate mild respiratory disease (n = 27). The cutpoint of 20 was found to be comparable to a radiographic score of 2 in our previous analysis (17).

Mothers were questioned about a history of physician-diagnosed asthma in the following relatives of the infant: parents and siblings, aunts and uncles, and grandparents. This information was summarized as family history of asthma in any first- or second-degree relative (18).

### TABLE 1. Comparison of participants and nonparticipants at baseline and at age 8 years in a study of very low birth weight children born in Wisconsin and Iowa between August 1, 1988, and June 30, 1991

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>8-year group (n = 384)</th>
<th>Target group (n = 625)</th>
<th>Survivors (n = 802)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data available for all survivors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time period of birth* (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period I</td>
<td>33</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Period II</td>
<td>36</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Period III</td>
<td>31</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Mean birth weight (g)</td>
<td>1,111 (251)†</td>
<td>1,115 (260)</td>
<td>1,125 (256)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>53</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>95</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>African-American</td>
<td>2.3</td>
<td>5.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Other</td>
<td>2.3</td>
<td>4.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Multiple birth (%)</td>
<td>29</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Mean fraction of inspired oxygen at 24 hours</td>
<td>0.38 (0.22)</td>
<td>0.39 (0.23)</td>
<td>0.39 (0.22)</td>
</tr>
<tr>
<td>Median no. of days in the neonatal intensive care unit</td>
<td>57</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>44–78</td>
<td>43–80</td>
<td>40–79</td>
</tr>
<tr>
<td><strong>Data available for all children in target group and at least 85% of survivors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gestational age (weeks)</td>
<td>29 (2.6)</td>
<td>29 (2.7)</td>
<td>29 (2.7)</td>
</tr>
<tr>
<td>Mean respiratory distress severity score (on a scale of 0–100)</td>
<td>30 (27)</td>
<td>30 (27)</td>
<td>29 (27)</td>
</tr>
<tr>
<td>Patent ductus arteriosus (%)</td>
<td>39</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Infant received antenatal steroids (%)</td>
<td>24</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Infant received postnatal steroids (%)</td>
<td>13</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Infant received surfactant (%)</td>
<td>30</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Mild respiratory disease at 25–35 days of life‡</td>
<td>22</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia§</td>
<td>32</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td><strong>Data available for those target group children with a baseline maternal interview (n = 568)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of asthma (%)</td>
<td>26</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Mother’s education at birth (mean score¶)</td>
<td>3.3 (1.3)</td>
<td>2.9 (1.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Data available for 8-year group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal(s) in household (%)</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking in household (%)</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Period I refers to children born between August 1, 1988 and July 31, 1989; period II refers to children born between August 1, 1989 and July 31, 1990 (investigational new drug period for surfactant); period III refers to children born between August 1, 1990 and June 30, 1991 (surfactant therapy generally available).

† Defined as a radiographic score showing milder abnormalities or a bronchopulmonary dysplasia severity score between 1 and 20 for infants without radiographs.

‡ Defined by a radiographic score ≥2 from days 25–35 of life (linear reticular opacities, centrally located) or a bronchopulmonary dysplasia severity score >20 (on a scale of 0–100) for infants without radiographs.

¶ 1 = less than high school, 2 = high school, 3 = business or occupational school, 4 = some college, 5 = college graduate, 6 = postcollege.
Parents were recontacted when the child was 5 years of age, and a telephone interview was conducted (17–19). Relevant to the present investigation, information on smoking in the household and the presence of animals (pets or farm animals) was ascertained.

The ISAAC questionnaire was mailed to parents in the fall of the study year in which the child reached age 8. Nonresponders were contacted by telephone. Parents of control children were administered the ISAAC questionnaire by telephone.

Statistical methods

Statistical analyses were carried out with the SAS package (20) on a Sun SPARC station 10 (Sun Microsystems, Inc., Palo Alto, California). Descriptive statistics were produced as means, standard deviations, and percentages (with 95 percent confidence intervals) as appropriate.

In accordance with the aims of the study (see Introduction), the following analyses were conducted. 1) The percentage prevalences of parent-reported history of asthma (“asthma ever”) and respiratory symptoms in the past 12 months were computed for very low birth weight children and for controls and were compared with those of the worldwide and Canadian samples by 95 percent confidence intervals. 2) The same outcomes were compared between the three time periods by overall chi-squared tests and chi-squared tests for trend for the 2 × 3 table. 3) Logistic regression models were used to assess associations of parental report of “asthma ever” and “wheezing in the last 12 months” with baseline and household characteristics.

In step 3, hospital of admission and time period of birth were included as indicator variables in all models, as were bronchopulmonary dysplasia and mild respiratory disease at age 25–35 days. The latter two variables were considered predictors of primary interest. Other risk factors were family history of asthma, mother’s education, gestational age, birth weight, patent ductus arteriosus, exposure to antenatal and postnatal steroids, surfactant therapy, severity of respiratory distress, presence of animal(s) in the household, and smoking in the household. Model-building proceeded by backward elimination, requiring \( p < 0.05 \) for significance, starting with a model that contained all variables and interactions. Main effects were retained if their interaction was significant. After a final model was obtained, variables associated univariately with either outcome at \( p < 0.15 \) were reentered and rechecked for significance (at \( p < 0.05 \)). Wald chi-squared tests were used to assess the significance of variables in the models, except that variables represented by two or more indicator categories and their interactions were tested by likelihood ratio tests.

Since a significant interaction effect was found between time period and bronchopulmonary dysplasia/respiratory disease at age 25–35 days, time trends for “wheezing in the last 12 months” were tested separately for the three respiratory disease categories.

RESULTS

Prevalence of parent-reported asthma and symptoms

Table 2 shows the prevalence of key symptoms in the preceding 12 months as well as parental report of “asthma ever” obtained by the ISAAC questionnaire for birth periods combined. Worldwide and Canadian prevalences from the ISAAC report (12) are shown for comparison, as is the prevalence in our control group. Pooled prevalence among very low birth weight infants was statistically significantly higher than worldwide prevalence for all symptoms except “sleep disturbed by wheezing.” The pooled prevalence among very low birth weight children was also significantly higher than the Canadian prevalence for most symptoms, the exceptions being “sleep disturbed by wheezing,” “speech limited by wheezing,” and “dry cough.” Prevalence in our control group fell between the worldwide and Canadian

For the table:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Very low birth weight children (age 8 years)</th>
<th>Wisconsin controls (ages 8–10 years)</th>
<th>Worldwide (ages 6–7 years)</th>
<th>Canada (ages 6–7 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( (n = 384) )</td>
<td>( (n = 154) )</td>
<td>( (n = 257,800) )</td>
<td>( (n = 5,755) )</td>
</tr>
<tr>
<td></td>
<td>( % )</td>
<td>( 95% ) CI*</td>
<td>( % )</td>
<td>( 95% ) CI</td>
</tr>
<tr>
<td>Asthma ever†</td>
<td>19</td>
<td>15, 23</td>
<td>14</td>
<td>8.7, 20</td>
</tr>
<tr>
<td>12-month prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>26</td>
<td>22, 30</td>
<td>14</td>
<td>8.2, 19</td>
</tr>
<tr>
<td>Sleep disturbed by wheezing‡</td>
<td>4.4</td>
<td>1.4, 6.5</td>
<td>1.9</td>
<td>0.4, 4.1</td>
</tr>
<tr>
<td>Speech limited by wheezing</td>
<td>4.7</td>
<td>2.6, 6.8</td>
<td>1.9</td>
<td>0.4, 4.1</td>
</tr>
<tr>
<td>Wheezing with exercise</td>
<td>17</td>
<td>13, 20</td>
<td>11</td>
<td>6.1, 16</td>
</tr>
<tr>
<td>Dry cough during night</td>
<td>27</td>
<td>23, 32</td>
<td>21</td>
<td>14, 27</td>
</tr>
<tr>
<td>Four or more wheezing attacks</td>
<td>8.9</td>
<td>6.0, 12</td>
<td>6.5</td>
<td>2.6, 10</td>
</tr>
</tbody>
</table>

* ISAAC, International Study of Asthma and Allergies in Childhood; CI, confidence interval.
† Four children had blank entries on the ISAAC questionnaire for this question, leading to a total sample size of 380.
‡ Sleep was disturbed by wheezing on one or more nights per week.
prevalences for “asthma ever” and three of the symptoms. Prevalences of “four or more wheezing attacks” and “wheezing with exercise” were slightly but not significantly above the Canadian prevalence, while that of “speech limited by wheezing” was slightly below the worldwide prevalence.

Prevalences are shown for the very low birth weight children by birth period in table 3. The only statistically significant difference in prevalence of respiratory symptoms between birth periods occurred for “sleep disturbed by wheezing at least once a week,” which was highest for children born in period II.

**Association of “asthma ever” and “wheezing in the last 12 months” with risk factors**

Descriptive statistics for all risk factors considered are shown in table 1. Table 4 shows the results of fitting predictive models to the two key outcomes, “asthma ever” and “wheezing in the last 12 months.” Family history of asthma and bronchopulmonary dysplasia played major independent roles in predicting “asthma ever.” Smoking in the household had a borderline-significant association with this outcome. Gestational age, while significant by itself, with an odds ratio of 0.87 per week (95 percent confidence interval: 0.78, 0.97), was not significant when bronchopulmonary dysplasia was included in the model. No other risk factors or interactions were significant when added to this model, and mild respiratory disease at age 25–35 days was also not significantly associated with “asthma ever.”

For wheezing in the previous 12 months, the relation between outcome and family history was evident only in households without smoking, and the relation with smoking in the child’s household was evident only among children without a family history of asthma. Patent ductus arteriosus was a significant predictor, and there was an interaction effect between study year and respiratory disease at age 25–35 days ($p = 0.0012$ jointly for the two categories). The protective association of antenatal steroids with “wheezing in the last 12 months” was borderline-significant.

We investigated further the interaction between radiographic bronchopulmonary dysplasia and time period for the outcome “wheezing in the last 12 months.” Table 5 shows the prevalence of wheezing in the previous 12 months by category of respiratory disease at age 25–35 days. There was a statistically significant increase ($p = 0.044$) across time periods in the prevalence of wheezing in the past 12 months among children who had mild respiratory disease at age 25–35 days, while there was a decrease among children with bronchopulmonary dysplasia ($p = 0.002$). There was no trend among children without respiratory disease.

Table 5 also shows changes in key infant characteristics in therapies across time. It is clear that the percentages of infants receiving surfactants and steroids increased dramatically. There was also a decrease in gestational age that was statistically significant among infants with bronchopulmonary dysplasia. Note that the characteristics of infants with mild respiratory disease in the last time period are similar to those of infants with bronchopulmonary dysplasia in the first time period. The former received more surfactants and steroids and had a lower (but not statistically significantly) prevalence of wheezing at age 8. The infants with bronchopulmonary dysplasia in the last two time periods were notably more premature on average than infants in any group during earlier time periods.

**DISCUSSION**

Our study showed a moderately to strikingly higher prevalence of respiratory symptoms among very low birth weight

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**TABLE 3. Prevalence (%) of parent-reported history of asthma (“asthma ever”) and asthma symptoms at age 8 years in a cohort of very low birth weight (≤1,500 g) children born during three time periods with differing availabilities of surfactant, Wisconsin and Iowa, 1996–1998**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Time period of birth*</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period I (n = 126)</td>
<td>Period II (n = 138)</td>
<td>Period III (n = 120)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 95% CI††</td>
<td>% 95% CI††</td>
<td>% 95% CI††</td>
<td></td>
</tr>
<tr>
<td>Asthma ever‡</td>
<td>18 11, 25</td>
<td>19 12, 26</td>
<td>19 12, 26</td>
<td></td>
</tr>
<tr>
<td>12-month prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>28 20, 36</td>
<td>26 19, 33</td>
<td>24 16, 32</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbed by wheezing§</td>
<td>3.2 0.10, 6.2</td>
<td>8.0 3.4, 13</td>
<td>1.7 0.0, 4.0</td>
<td></td>
</tr>
<tr>
<td>Speech limited by wheezing</td>
<td>3.2 0.10, 6.2</td>
<td>7.3 2.9, 11.6</td>
<td>3.3 0.11, 6.6</td>
<td></td>
</tr>
<tr>
<td>Wheezing with exercise</td>
<td>18 11, 24</td>
<td>16 10, 22</td>
<td>16 9.4, 23</td>
<td></td>
</tr>
<tr>
<td>Dry cough during night</td>
<td>26 18, 34</td>
<td>30 23, 38</td>
<td>24 17, 32</td>
<td></td>
</tr>
<tr>
<td>Four or more wheezing attacks</td>
<td>10 5.0, 16</td>
<td>11 5.7, 16</td>
<td>5.0 1.1, 8.9</td>
<td></td>
</tr>
</tbody>
</table>

* Period I refers to children born between August 1, 1998 and July 31, 1998; period II refers to children born between August 1, 1989 and July 31, 1990 (investigational new drug period for surfactant); period III refers to children born between August 1, 1990 and June 30, 1991 (surfactant therapy generally available).
†† CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood.
‡‡ Four children had blank entries on the ISAAC questionnaire for this question, leading to a total sample size of 380.
§ Sleep was disturbed by wheezing on one or more nights per week ($p = 0.035$ in chi-squared test for the association between symptom and time period).
TABLE 4. Predictive models* for parent-reported history of asthma (“asthma ever”) and wheezing in the past 12 months for very low birth weight children born in Wisconsin and Iowa, 1996–1998

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Asthma ever</th>
<th>Wheezing in past 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1.7</td>
<td>1.0, 3.1</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>0.56</td>
<td>0.29, 1.1</td>
</tr>
<tr>
<td>Mild respiratory disease† at age 25–35 days‡</td>
<td>1.1</td>
<td>0.5, 2.4</td>
</tr>
<tr>
<td>Period I§</td>
<td>1.1</td>
<td>0.5, 2.4</td>
</tr>
<tr>
<td>Period II</td>
<td>1.1</td>
<td>0.5, 2.4</td>
</tr>
<tr>
<td>Period III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia‡,¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period I§</td>
<td>2.9</td>
<td>1.5, 5.5</td>
</tr>
<tr>
<td>Period II</td>
<td>2.9</td>
<td>1.5, 5.5</td>
</tr>
<tr>
<td>Period III</td>
<td>2.9</td>
<td>1.5, 5.5</td>
</tr>
<tr>
<td>Family history of asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With smoking in household</td>
<td>2.2</td>
<td>1.2, 4.0</td>
</tr>
<tr>
<td>With no smoking in household</td>
<td>2.2</td>
<td>1.2, 4.0</td>
</tr>
<tr>
<td>Smoking in household</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With family history of asthma</td>
<td>1.7</td>
<td>1.0, 3.1</td>
</tr>
<tr>
<td>Without family history of asthma</td>
<td>1.7</td>
<td>1.0, 3.1</td>
</tr>
</tbody>
</table>

* All models included indicator variables for hospital of birth and time period of birth.
† Defined as a radiographic score representing milder abnormalities or a bronchopulmonary dysplasia score between 1 and 20 for infants without radiographs.
‡ p = 0.02 for interaction effect of period with bronchopulmonary dysplasia for wheezing in the past 12 months and p = 0.09 for interaction effect with mild respiratory disease for wheezing in the past 12 months; p = 0.0012 jointly for the two interactions.
§ Period I refers to children born between August 1, 1988 and July 31, 1989; period II refers to children born between August 1, 1989 and July 31, 1990 (investigational new drug period for surfactant); period III refers to children born between August 1, 1990 and June 30, 1991 (surfactant therapy generally available).
¶ Defined by a radiographic score ≥2 from days 25–35 of life (linear reticulate opacities, centrally located) or a bronchopulmonary dysplasia severity score >20 (on a scale of 0–100) for infants without radiographs.

children at age 8 years than among 6- to 7-year-olds worldwide and in Canada, while the prevalence in a control group from Wisconsin fell between these two benchmarks. The excess among very low birth weight children was approximately twofold compared with Wisconsin and worldwide prevalences for wheezing symptoms in the past 12 months, but the excess was less pronounced for parent-reported asthma. There were no notable overall differences in symptom prevalence between children born before and after the introduction of surfactant therapy (except an excess of wheezing during the night among children born during the investigational new drug period for surfactants). However, there was a rather dramatic trend of decreasing symptom prevalence at age 8 years across the three time periods among children who had bronchopulmonary dysplasia at 25–35 days of age. On the other hand, there was an increase in wheezing at age 8 years among children with mild respiratory disease that did not meet the criteria for bronchopulmonary dysplasia at age 25–35 days. While both bronchopulmonary dysplasia and family history of asthma were associated with parent-reported asthma, several additional variables were associated with wheezing in the past 12 months. We point out that there were changes in therapies other than surfactants during the time period in which our cohort accrued. Our previous work (9) indicated that antenatal steroid therapy strongly contributed to increased survival of very low birth weight infants.

The ISAAC questionnaire is a simple standardized method for obtaining information on the prevalence of asthma (“asthma ever”) and wheezing symptoms. It has been extensively validated. One report (10) showed a positive predictive value of 0.61 and a negative predictive value of 0.94 (sensitivity and specificity were 0.86 and 0.81, respectively) for “asthma ever” on the ISAAC questionnaire, using physician diagnosis of asthma as the gold standard. Another study (11) used bronchial hyperreactivity as the gold standard. It found sensitivities for ISAAC wheezing and nocturnal wheezing in the past 12 months of 0.65 and 0.54, respectively, with corresponding specificities of 0.62 and 0.84. No effect of season of response was found in a validation study carried out in New Zealand (21).

A great advantage of using the ISAAC questionnaire is the availability of comparison data from around the world. The ISAAC results show great variability in prevalences both across and within regions. As our tables show, the prevalence of asthma symptoms in Canada was found to be somewhat higher than the worldwide average. A more detailed recent report (22) listed results separately for the two study sites, Hamilton and Saskatoon. These results showed that prevalences of symptoms and “asthma ever” in Saskatoon were close to the worldwide averages, while the prevalences in Hamilton were higher. Our control group had symptom prevalences that largely fell between those at these two sites.
Data from ISAAC on 6- to 7-year-olds in the United States are not available. A US population study by Stoddard et al. (23) found that approximately 8 percent of children aged 6–12 years had experienced wheezing in the previous year. Among Seattle, Washington, schoolchildren aged 5–9 years, 11 percent reported physician-diagnosed asthma (24).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>No late neonatal respiratory disease</strong></td>
<td><strong>Time period of birth†</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>period I</td>
<td>period II</td>
</tr>
<tr>
<td></td>
<td>(n = 126)</td>
<td>(n = 138)</td>
</tr>
<tr>
<td>No. of neonates</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>No. with wheezing in past 12 months</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Mean gestational age (weeks)</td>
<td>30.8 (2.1)‡</td>
<td>30.9 (2.3)</td>
</tr>
<tr>
<td>Severity of respiratory distress (mean score on a scale of 0–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. who received antenatal steroids***</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>No. who received surfactant***</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>No. who received postnatal steroids</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

| **Mild respiratory disease at age 25–35 days§** | |
|---|---|---|
| No. of neonates | 29 | 23 | 19 |
| No. with wheezing in past 12 months* | 4 | 14 | 9 |
| Mean gestational age (weeks) | 29.2 (2.6) | 28.6 (2.0) | 28.7 (1.7) |
| Severity of respiratory distress (mean score on a scale of 0–100) | | | |
| No. who received antenatal steroids | 3 | 10 | 4 |
| No. who received surfactant*** | 2 | 6.9 | 13 |
| No. who received postnatal steroids | 1 | 3.5 | 6 |

| **Bronchopulmonary dysplasia¶** | |
|---|---|---|
| No. of neonates | 30 | 53 | 38 |
| No. with wheezing in past 12 months** | 15 | 50 | 28 |
| Mean gestational age* (weeks) | 28.5 (2.6) | 27.5 (2.3) | 27.1 (2.0) |
| Severity of respiratory distress (mean score on a scale of 0–100) | | | |
| No. who received antenatal steroids | 5 | 17 | 16 |
| No. who received surfactant*** | 1 | 3.3 | 27 |
| No. who received postnatal steroids*** | 2 | 6.7 | 13 |

* p < 0.05 for trend; ** p < 0.01 for trend.
† Period I refers to children born between August 1, 1988 and July 31, 1989; period II refers to children born between August 1, 1989 and July 31, 1990 (investigational new drug period for surfactant); period III refers to children born between August 1, 1990 and June 30, 1991 (surfactant therapy generally available).
‡ Numbers in parentheses, standard deviation.
§ Defined as a radiographic score representing milder abnormalities or a bronchopulmonary dysplasia score between 1 and 20 for infants without radiographs.
¶ Defined by a radiographic score ≥2 from days 25–35 of life (linear reticular opacities, centrally located) or a bronchopulmonary dysplasia severity score >20 (on a scale of 0–100) for infants without radiographs.
Prevalence was higher among disadvantaged children enrolled in Head Start programs in Chicago, Illinois, where 14 percent of parents reported physician-diagnosed asthma (3). The ISAAC prevalence of symptoms during the previous 12 months at ages 13–14 years was slightly lower in the United States than in Canada, while the prevalences of “asthma ever” were similar. These results are in general agreement with the findings in our control group.

The excess prevalence of symptoms among very low birth weight children in our study is consistent with the twofold increase found with very low birth weight among 8- to 9-year-olds in Scotland (2). That study included children born in 1984. Another study in New Zealand (25) also found an almost twofold higher prevalence of asthma among very low birth weight children born in 1986. Little has been reported about long-term respiratory symptoms or function after surfactant therapy became generally available. Clinical trials tend to provide data up to the age of 12 months. One trial (26) indicated improvement in airflow-resistant components at age 1 year among surfactant-treated children. Our results indicate that in the group as a whole, there was little change in the prevalence of respiratory symptoms or parent-reported “asthma ever” with the introduction of surfactants. However, there was a dramatic decrease in wheezing symptoms at age 8 among children with bronchopulmonary dysplasia at 25–35 days of age. This decrease was balanced against an increase in symptoms at age 8 among children with mild respiratory disease at age 25–35 days.

We cannot explain the above trends with the data we have available, except to note that neonatal characteristics of infants at different levels of respiratory severity at age 25–35 days have changed dramatically, so that only the most premature infants now display signs of classic bronchopulmonary dysplasia. Most likely, new approaches in neonatal care have shifted infants who would earlier have developed bronchopulmonary dysplasia into less severe categories of neonatal respiratory disease, and may have done so without correspondingly changing long-term outcome. Several studies have shown long-term respiratory symptoms to be associated not only with bronchopulmonary dysplasia but also with prematurity per se (5, 7). Our results show that patent ductus arteriosus, a sign of prematurity, is predictive of wheezing at age 8. There is also evidence that asthma prevalence is increasing in the general population of children (27–29), but this is unlikely to have been a factor in our results, since there was no increase in symptoms among children who were free of respiratory disease at age 25–35 days.

It appears contradictory that wheezing prevalence decreased among infants with classic bronchopulmonary dysplasia, as these infants were increasingly premature. One possible explanation is that, being the most ill, they may have benefitted from receiving the most intense therapy. Note that it is not possible to directly evaluate the effects of therapies in an observational study such as ours, since treatments are administered more often to more severely ill neonates. On the one hand, these neonates have the worst outcomes, because they are the most ill. On the other hand, these same neonates may benefit most from the therapies. Further complicating unbiased comparisons, surfactant therapy is administered very early in life before severity can be reliably quantitated. Administration of antenatal steroids is the only treatment given before the severity of neonatal disease is a factor, and it is the only therapy displaying some association with outcome in our study.

Speer and Silverman (1) hesitate to label wheezing symptoms following prematurity “asthma,” and they point to a lack of association of these symptoms with atopic disease. There is no universally accepted clinical diagnostic criterion for asthma, and assignment of diagnostic categories to wheezing symptoms may have undergone recent shifts (29). Some previous studies (4) indicated that traditional factors associated with asthma may play only a marginal role among children who are already at very high risk of respiratory disease due to prematurity. Our results, in contrast, imply that familial asthma also may account for a proportion of wheezing symptoms and asthma diagnoses among very low birth weight children. This is consistent with another recently published study (25). Family history of asthma was associated with a twofold increase in the odds of parent-reported “asthma ever” overall. We also found family history of asthma and smoking to be predictive of wheezing at age 8. However, family history was associated with wheezing only in households without smoking, and smoking was associated with wheezing only in households without a family history of asthma. These results appear to reflect complex relations between asthma in family members, smoking, and wheezing in the child. A previous study reported failure to identify smoking as a risk factor for wheezing in adults cross-sectionally, as individuals stopped smoking when wheezing symptoms appeared (30). Our study may have failed to fully assess associations with smoking and pets, since these risk factors were ascertained when the children were 5 years old, while symptom prevalence was assessed at age 8.

We did not find the interaction effect between family history and bronchopulmonary dysplasia that we previously reported when employing use of respiratory medication up to age 5 as the outcome (18). Detailed data analyses (not reported here) indicated this to be due to the lower predictive value of classic bronchopulmonary dysplasia, as well as to the different age and outcome criteria in the two analyses.

In summary, our results indicate a continuing increased prevalence of respiratory symptoms among very low birth weight children up to at least the age of 8 years. However, we also see a change in the nature of neonatal respiratory disease that makes long-term outcome more difficult to predict. This change occurred parallel to the introduction of new therapies that led to increased survival. The prevalence of wheezing symptoms also appears to reflect a small subgroup of very low birth weight children who have asthma due to traditional risk factors and genetic causes unrelated to prematurity.

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REFERENCES