Moderately Preterm Children Have More Respiratory Problems during Their First 5 Years of Life Than Children Born Full Term

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Rationale: Pulmonary outcomes of moderate preterm children (MP) are unknown.

Objectives: To investigate the prevalence of respiratory symptoms during infancy and at preschool age of MP compared with full-term (FT) and early preterm children (EP) and to determine factors associated with respiratory symptoms of MP at school age.

Methods: Prospective cohort study. Outcome variables: number of rehospitalizations caused by respiratory problems, prevalence of respiratory symptoms determined by ISAAC Questionnaires, and factors associated with respiratory symptoms determined by univariate and multivariate analyses.

Measurements and Main Results: A total of 988 MP, 551 EP, and 573 FT children were included. The number of hospitalizations caused by respiratory problems during the first year of life was doubled in MP compared with FT (6% vs. 3%; P < 0.001). At preschool age, compared with FT, MP reported more cough or wheeze during a cold (63% vs. 50%; P < 0.001); cough or wheeze without a cold (23% vs. 15%; P = 0.001); nocturnal cough (33% vs. 26%; P = 0.005); dyspnea (8% vs. 4%; P = 0.011); and use of medication (inhaled steroids, 9% vs. 6%; P = 0.042) (antibiotics, 12% vs. 7%; P = 0.002). Factors associated with respiratory symptoms at 5 years among MP were respiratory problems, eczema, rehospitalization in infancy, passive smoking in infancy, family history of asthma, and higher social class. Multivariate analyses showed the same results except for rehospitalization in infancy.

Conclusions: MP have more respiratory symptoms than FT during early childhood. Factors associated with respiratory symptoms at school age are early respiratory problems, family history of asthma, higher social class, and passive smoking.

Keywords: preterm birth; child; follow-up; respiratory tract; respiratory treatment

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Moderate preterm children have more rehospitalizations because of respiratory symptoms during the first year of life and more cough, wheeze, and dyspnea at the age of 4 and 5 years than children born full-term. The symptoms result in greater medication use, and in more school absenteeism. Factors associated with respiratory symptoms at school age are early respiratory problems, family history of asthma, higher social class, and passive smoking.

What This Study Adds to the Field

Being born moderately preterm puts children at risk for continuing respiratory symptoms during the first 4 to 5 years after birth.

Pulmonary outcome of early preterm children (EP) (born before 32 wk gestational age) has been extensively studied. Chronic respiratory morbidity is a common outcome of neonatal intensive care, particularly in children who develop bronchopulmonary dysplasia, and in EP without bronchopulmonary dysplasia (1–4). The residual respiratory problems of EP include cough and wheeze, which may be associated with abnormal lung function, including airway obstruction, airway hyperresponsiveness to direct stimuli and exercise, and hyperinflation (5–8). The previously mentioned problems mostly improve with age and somatic growth, but in some children they are persistent (9, 10).

In contrast to the pulmonary problems of EP, pulmonary outcomes of moderate preterm children (MP) are largely unknown, although this group is much larger. According to data from the 2008 European Perinatal Health Report (11) and the 2009–2010 United States Birth Reports (12, 13), the prevalence of preterm births in the European Union ranged from 5.5% (Ireland) to 11.4% (Austria) and was 12.2% of all births in the United States. This means that about half a million babies are born preterm in both Europe and the United States every year, and that 70–85% of them are born moderately preterm. MP birth is internationally often defined as being born after 32 but before 36 or 37 weeks gestation.

It is generally thought that MP children do not encounter respiratory problems later in life, because they seem relatively healthy compared with EP infants at birth and need little or no respiratory support in the neonatal period. Their problems directly after birth usually include mild and transient respiratory distress, usually because of transient tachypnea of the newborn (14, 15). Respiratory distress syndrome is the most common cause of severe respiratory problems requiring mechanical ventilation in MP, although its incidence is much lower than in EP.
(15–17). However, respiratory problems may persist at least in infancy: several studies have found that rehospitalization rates because of respiratory symptoms are two to three times greater for MP compared with full-term (FT) children (18–20).

Both in the general population and in EP risk factors for continuing pulmonary problems have been studied (21–24). In the general population risk factors for asthma or wheezing illnesses include genetic and environmental factors, such as lower birth weight, smoking during pregnancy (or later), male sex, exposure to allergens in early infancy, attendance of day care, and history of parental asthma. The influence of family income and viral infections is under debate (25–27). In EP, the most consistent factors are male sex (21), mechanical ventilation (23), small for gestational age (22), history of asthma in the family (22), lower social class (21, 23), smoking during pregnancy (24), smoking in the house during the first year of life (24), and severe respiratory problems in the first year of life (21, 23).

In contrast, the (risk) factors for continuing respiratory problems in MP have not been studied separately. Therefore, the aim of the study was (1) to investigate the prevalence of respiratory symptoms during the first year of life after the neonatal period; (2) to determine the prevalence of continuing respiratory symptoms, such as wheeze, cough and shortness of breath, and medication use at both 4 and 5 years of age in MP compared with both FT and EP children; and (3) to determine which factors are associated with respiratory symptoms at school age in MP. Some of the results of this study have been previously reported in the form of an abstract (28).

METHODS

Study Population
The Longitudinal Preterm Outcome Project (Lollipop) is a large prospective cohort study on growth, development, and general health of preterm children. The study's main focus is on MP, born between 32 and 36 weeks gestation. The Lollipop cohort consists of a community-based sample of EP and MP (born before 36 wk gestation) and a random sample of FT children seen at Preventive Child Health Care Centers (PCHCs), enriched with a sample of EP from neonatal intensive care units. Dutch PCHCs monitor 90–95% of all children at regular intervals from birth until 4 years of age in a service that is free of charge. Cohort size was based on estimates of data needed to compile growth charts for Dutch preterm children. In this paper we present the results of the assessment of the children's respiratory symptoms during the first year of life, at the age of 4 years (43–49 mo), and at 5 years (58–62 mo) and consequences of these symptoms, such as hospitalization, medication use, and school absenteeism.

Thirteen PCHCs participated in the Lollipop study. Together they monitored 45,446 children, (i.e., 25% of a complete yearly cohort of children in the Netherlands). Eight PCHCs identified the records of all children that were born between January 1st and December 31st 2002, and five PCHCs those of all children born between June 1st 2002 and May 31st 2003. The participating PCHCs sampled all children born before 36 +0 weeks gestation without major congenital malformations, congenital infections, or syndromes. After each second preterm child sampled, the next term-born child (gestational age 38 to 41 +0 weeks) from the same birth cohort without the previously mentioned exclusion criteria, was drawn from the same records as a control subject. The PCHCs sampled a total of 2,758 children for the study. Five neonatal intensive care units sampled an additional 548 EPs, born between January 1 and December 31, 2003, and alive at discharge, for the study.

Procedure
Parents were invited by mail to participate with their child in the study, 4 weeks before the scheduled PCHC visit at 45–49 months. Parents received an information leaflet on the study, an informed consent form, and several questionnaires. These were collected at the visit by the PCHC physician. Parents of children who did not appear for their regular visit were invited again, and if necessary reminded by telephone or by home-visit (following routine PCHC procedures). A total of 2,517 children (79% of those eligible) were included in the study, of which 698 were EP (80% of those eligible); 1,145 were MP (81% of those eligible); and 674 were FT (74% of those eligible). After inclusion, all available data from PCHC records and all hospital records were collected in a controlled manner. Compared with participating children, the nonparticipating children had a greater proportion of low socioeconomic status (SES) and were more often immigrant (low SES, 40.4% vs. 28.9%; non-Dutch, 15.6% vs. 5.4%; both, P < 0.001). Sex and small for gestational age did not differ significantly between the two groups.

Parents who had completed data at age 4 received another set of questionnaires when the child reached the age of 5 years. Seventy-one percent of these parents participated in the 5 years assessment. There was no difference in the percentage of children with respiratory symptoms at age 4 between the participating and not-participating group. We did not collect data on the percentage of infants that remained with the same PCHC from birth until time of enrollment but in general if the family moves, PCHC records move with them. The Dutch PCHC system is based on a nationally standardized recording system with exchange of records between organizations where needed. Furthermore, parents supplied information in a general questionnaire on all hospitals the child had been admitted to after birth, and we traced the records from all these hospitals, covering the entire Netherlands.

The University Medical Center Groningen Ethics Committee gave approval for this study. Written informed consent was obtained from all parents.

Measures
Patient characteristics including gestational age and factors possibly associated with pulmonary symptoms at preschool age in MP were obtained from questionnaires and medical records. We expressed gestational age in completed weeks of gestation. Gestational age was confirmed with early ultrasound measurements in more than 95% of cases. In the remaining cases only clinical estimates based on last menstrual date were available and compared with clinical estimates of gestational age after birth. Children whose gestational age could not be confirmed without reasonable doubt were excluded.

Outcome variables were respiratory symptoms and number of rehospitalizations caused by respiratory problems in the first year of life after the neonatal period and the prevalence of respiratory symptoms at the age of 4 and 5 years. Respiratory symptoms were measured as questions of the (adapted) International Study of Asthma and Allergies in Childhood (ISAAC) Questionnaire (http://isaac.auckland.ac.nz/index.html). The International Study of Asthma and Allergies in Childhood is a worldwide epidemiologic research program established in 1991 to investigate asthma, rhinitis, and eczema in children. The ISAAC Questionnaire measures the prevalence and severity of asthma-like symptoms, rhinitis, and eczema. There was a slight difference between the lay-out of the two questionnaires at ages 4 and 5 concerning daytime wheezing. At age 4, parents could also report daytime cough, and the use of inhalation medication and antibiotics, whereas they could not at age 5.

Possible risk factors for respiratory symptoms at age 5 that we investigated included small for gestational age (<10th percentile); male sex; mechanical ventilation after birth; family history of asthma; one or more school-aged siblings; mother smoking while pregnant; passive smoking during the first year of life; breastfeeding less than 3 months; day care attendance during the first year of life; respiratory problems during the first year of life; rehospitalization because of respiratory problems in the first year of life; hospitalization because of respiratory syncytial virus (RSV); eczema during the first year of life; and lower social class (i.e., lower education of father and mother and/or low income).

Statistical Analysis
First we used descriptive statistics to provide the characteristics of our sample. Second, we compared the prevalence of respiratory symptoms and rehospitalizations for respiratory symptoms in MP during the first year of life with EP and FT control subjects using chi-square tests. We then repeated the analyses adjusting for month and year of birth using
multivariate logistic regression analysis. We performed these analyses in the same order for respiratory symptoms at age 4 and 5. The reported P values are the results of the analyses adjusted for differences in month and year of birth. In case the P value was different from the analysis without adjustment for differences in month and year of birth, we mentioned this in a footnote to the table concerned.

Third, we performed univariate logistic regression analyses to determine which factors were associated with respiratory symptoms at school age among MP. Each factor that showed an association in the univariate analyses with a significance at P less than 0.20 was included in a subsequent multivariate logistic model (enter method). All calculations were done using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY). All tests were two-sided and differences between groups were considered to be significant at P less than 0.05.

RESULTS

The characteristics of the three gestational groups are described in Table 1. The percentage of boys and the percentage of children with smoking mothers were higher in the MP group compared with both other groups. Not all questionnaires of eligible children were returned: the results of 551 (79%) EP, 988 (86%) MP, and 573 (85%) FT could be analyzed.

Table 2 summarizes the prevalence of respiratory symptoms, hospitalizations, and eczema during the first year of life. The number of hospitalizations because of respiratory problems during the first year of life was doubled in MP compared with FT. Furthermore, compared with FT, parents of MP reported more respiratory symptoms and more eczema during the first year of life. Compared with EP, MP had fewer reported hospitalizations because of respiratory problems (except for those caused by RSV, which occurred with equal frequency in both groups), and fewer respiratory symptoms, but more eczema during the first year of life.

Table 3 summarizes the prevalence of continuing respiratory symptoms, such as wheeze, cough and shortness of breath, and respiratory medication use at 4 years. Compared with FT controls, MP had more frequent reported cough or wheeze during a cold; cough or wheeze without a cold; shortness of breath; and use of medication, such as inhaled steroids and antibiotics at 4 years of age. As expected, EP had significantly more daytime wheeze and medication use than MP at this age. The use of inhaled corticosteroids and antibiotics especially was greater in the EP.

Table 4 describes the respiratory symptoms (and their consequences) at 5 years of age. At this age, MP had more reported wheeze, cough, asthma, treatment for respiratory symptoms, and school absenteeism than FT. The differences between EP and MP were not significant statistically after adjustment for differences in month and year of birth. Without adjustment for these factors only the prevalence of wheezing differed significantly. The differences between the daytime wheezing reported at ages 4 and 5 may be because of a difference in the wording of the questions at these ages: at age 4, the parents could differentiate between cough and wheeze at daytime, at age 5 they could not make this distinction.

The factors most strongly associated with respiratory symptoms at 5 years among MP in univariate analyses were respiratory problems during the first year and a positive family history of asthma (Table 5). Also, a history of eczema in the first year, rehospitalization for pulmonary symptoms during the first year, and passive smoking in the first year increased the risk of respiratory problems. Lower social class was protective.

Multivariate logistic regression analyses showed the same results except for rehospitalization during the first year. No increased risk was found for the following factors: children born small for gestational age, male sex, older siblings, children of mothers smoking during pregnancy, children breastfed for less than or equal to 3 months, children who had been treated with mechanical ventilation during the neonatal period, and day care attendance during the first year.

DISCUSSION

This large prospective community-based study demonstrated that among MP both the prevalence of respiratory symptoms and rehospitalizations for respiratory problems during the first year of life and the occurrence of symptoms at preschool age were greater than in FT and more similar to EP. The factors most strongly associated with respiratory symptoms at 5 years of age among MP were a positive family history of asthma, respiratory problems during the first year, a history of eczema during the first year, passive smoking during the first year, and higher social class.

We found that the incidence of respiratory symptoms during the first year and the rehospitalization rate for respiratory problems was greater among MP infants than among FT counterparts. Other studies have also found that rehospitalization rates are two to three times greater for late preterm (34–36 wk gestational age) compared with term infants (18). Especially the risk of hospitalization because of respiratory viruses, such as RSV, is often suggested (27, 29). In our cohort the hospitalization for proved RSV was low, but four times higher for MP compared with FT. One study from California noted that the largest group of infants readmitted to the hospital because of a respiratory illness during the first month of life consisted of infants born at 35 weeks gestation (19).

We found that MP at preschool age had more respiratory problems leading to more absence from school than FT. These findings are new. In 2010, Colin and coworkers (14) reviewed studies on the respiratory morbidity of moderate and late preterm infants and found that essentially no information beyond the first year of life was available. Results from the Millennium Cohort Study suggest that there is a continued risk of respiratory problems into infancy and childhood for moderate to late preterm children (20). They reported that respiratory morbidity increases with decreasing gestational age. We found that the

<table>
<thead>
<tr>
<th>TABLE 1. CHARACTERISTICS OF THE PARTICIPANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Preterm (I) (n = 551)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Gestational age (median, range)</td>
</tr>
<tr>
<td>Birth weight (median, range)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Mother smoking during pregnancy</td>
</tr>
<tr>
<td>Asthma in family</td>
</tr>
<tr>
<td>(first + second degree)</td>
</tr>
<tr>
<td>Small for gestational age*</td>
</tr>
</tbody>
</table>

Definition of abbreviation: NS = not significant.
* Below 10th percentile for gestational age.
prevalence of doctor-diagnosed asthma was higher in EP and MP compared with FT, and found no difference between EP and MP for respiratory problems at age 5. Boyle and coworkers (20) also reported that asthma and wheezing are increasingly prevalent with increasing prematurity, with particularly high odds of having these outcomes in children born very preterm. They found, at 5 years, that the condition most commonly requiring medication was asthma. In contrast, we found no differences between EP and MP in these outcomes, but this may have been because of lack of statistical power.

We also examined possible (risk) factors for respiratory problems at preschool age for MP. We found a limited set of “predictors”: having a positive history of eczema, a positive family history of asthma, respiratory problems during the first year of life, passive smoking during the first year, and being from a higher social class. These factors are mostly in agreement with those found in the general population and with those found in EP children. However, in most other studies more predictors were identified.

First, in the general population, different longitudinal patterns of wheeze are described, such as transient wheeze, atopic and non-atopic persistent wheeze with for each group different risk factors. Transient wheeze was associated with maternal smoking during pregnancy (30), male sex, the presence of older siblings, day care attendance (31–33), and the absence of atopy (30, 32–34). Persistent wheeze or asthma at school age was associated with male sex, post-term delivery, inhaled medication, high wheezing frequency, wheeze apart from colds, high number of respiratory tract infections, low parental education, and eczema (35).

Second, in the EP group, male sex, lower gestational age, lengthy mechanical ventilation, oxygen dependency at 36 weeks postmenstrual age, atopic constitution, having older siblings aged less than 5 years, family history of atopy, upper respiratory tract infections, greater weight for length in the first year, living in rented accommodation, lower scores on HOME sub-scale II, (Acceptance of the Child’s Behavior, which measures the mother’s avoidance of use of punishment and restriction), and/or having an unmarried

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**TABLE 2. RESPIRATORY SYMPTOMS, RESPIRATORY REHOSPITALIZATIONS, AND ECZEMA DURING THE FIRST YEAR**

<table>
<thead>
<tr>
<th></th>
<th>Early Preterm (I)</th>
<th>Moderate Preterm (II)</th>
<th>Full Term (III)</th>
<th>P I–II</th>
<th>P II–III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td>(n = 551)</td>
<td>(n = 988)</td>
<td>(n = 572)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of respiratory symptoms</td>
<td>n = 549</td>
<td>n = 978</td>
<td>n = 570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>276 (50%)</td>
<td>566 (58%)</td>
<td>394 (69%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>148 (27%)</td>
<td>225 (23%)</td>
<td>121 (21%)</td>
<td>0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regularly</td>
<td>110 (20%)</td>
<td>163 (17%)</td>
<td>50 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almost always</td>
<td>15 (3%)</td>
<td>24 (2%)</td>
<td>5 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization because of respiratory problems</td>
<td>94 (17%)</td>
<td>62 (6%)</td>
<td>18 (3%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization because of respiratory syncytial virus</td>
<td>17 (3%)</td>
<td>38 (4%)</td>
<td>7 (1%)</td>
<td>NS</td>
<td>0.003</td>
</tr>
<tr>
<td>Eczema</td>
<td>71 (13%)</td>
<td>179 (18%)</td>
<td>80 (14%)</td>
<td>0.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: NS = not significant.
P values with adjustment for differences in month and year of birth.

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**TABLE 3. RESPIRATORY SYMPTOMS AND MEDICATION USE AT 4 YEARS**

<table>
<thead>
<tr>
<th></th>
<th>Early Preterm (I)</th>
<th>Moderate Preterm (II)</th>
<th>Full Term (III)</th>
<th>P I–II</th>
<th>P II–III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questions regarding the past 12 mo</td>
<td>n = 551</td>
<td>n = 984</td>
<td>n = 572</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms associated</td>
<td>n = 551</td>
<td>n = 984</td>
<td>n = 572</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with a cold or chest infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>176 (32%)</td>
<td>354 (36%)</td>
<td>287 (51%)</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sometimes</td>
<td>299 (54%)</td>
<td>506 (51%)</td>
<td>247 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>60 (11%)</td>
<td>90 (9%)</td>
<td>29 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not the past 12 mo, but before</td>
<td>16 (3%)</td>
<td>34 (3%)</td>
<td>9 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms without a cold or chest infection</td>
<td>n = 551</td>
<td>n = 978</td>
<td>n = 570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>391 (71%)</td>
<td>754 (77%)</td>
<td>485 (85%)</td>
<td>NS*</td>
<td>0.001</td>
</tr>
<tr>
<td>Sometimes</td>
<td>141 (26%)</td>
<td>180 (18%)</td>
<td>68 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>6 (1%)</td>
<td>15 (2%)</td>
<td>5 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not the past 12 mo, but before</td>
<td>13 (2%)</td>
<td>33 (3%)</td>
<td>12 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific symptoms</td>
<td>n = 551</td>
<td>n = 978</td>
<td>n = 570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attacks of wheezing</td>
<td>30 (6%)</td>
<td>45 (5%)</td>
<td>18 (3%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Wheezing (daytime)</td>
<td>63 (11%)</td>
<td>69 (7%)</td>
<td>34 (6%)</td>
<td>0.013</td>
<td>NS</td>
</tr>
<tr>
<td>Cough (daytime)</td>
<td>190 (34%)</td>
<td>263 (27%)</td>
<td>113 (20%)</td>
<td>NS*</td>
<td>0.001</td>
</tr>
<tr>
<td>Shortness of breath (daytime)</td>
<td>50 (9%)</td>
<td>76 (8%)</td>
<td>25 (4%)</td>
<td>NS</td>
<td>0.011</td>
</tr>
<tr>
<td>Cough (night)</td>
<td>221 (40%)</td>
<td>318 (33%)</td>
<td>147 (26%)</td>
<td>NS*</td>
<td>0.002</td>
</tr>
<tr>
<td>Shortness of breath (night)</td>
<td>67 (12%)</td>
<td>99 (10%)</td>
<td>35 (6%)</td>
<td>NS</td>
<td>0.014</td>
</tr>
<tr>
<td>Limited exercise capacity</td>
<td>53 (10%)</td>
<td>79 (8%)</td>
<td>34 (6%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td>n = 550</td>
<td>n = 988</td>
<td>n = 573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β₂-Agonist</td>
<td>103 (19%)</td>
<td>133 (13%)</td>
<td>62 (11%)</td>
<td>NS*</td>
<td>0.082</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>76 (14%)</td>
<td>87 (9%)</td>
<td>34 (6%)</td>
<td>0.025</td>
<td>0.042</td>
</tr>
<tr>
<td>Combination β₂/inhaled corticosteroids</td>
<td>6 (1%)</td>
<td>19 (2%)</td>
<td>5 (1%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>105 (19%)</td>
<td>117 (12%)</td>
<td>40 (7%)</td>
<td>0.035</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: NS = not significant.
P values with adjustment for differences in month and year of birth.
*Without adjustment for differences in month and year of birth, the P value was <0.05.
We did not find an association of male sex, having had mechanical ventilation, or being small for gestational age with respiratory symptoms at age 5. Only a small percentage of the MP (6.5%) was mechanically ventilated and only 3% for more than a few days. We hypothesize that a very short period of mechanical ventilation may not have long-lasting consequences. We found no association with severe RSV infection (causing hospitalization) either, but this might also have been caused by relatively small numbers of study subjects. In the univariate and the multivariate analyses, lower social class unexpectedly seemed to have a protective effect. The influence of social class has also been shown to have an increased risk for atopic sensitization (36). Moreover, the somewhat lower participation rate of low SES children may contribute but this is unlikely to explain these differences in full.

Major strengths of our study were the use of data from a large, representative community-based sample including the entire range of preterm gestational ages, which provides more valid estimates of prevalences and the long follow-up period of 5 years. A potential limitation is that we used only questionnaires, hospital discharge letters to general practitioners, and follow-up data from the PCHCs. In contrast to earlier studies, however, we obtained information not only from medical records, but also from other sources.

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directly from the parents leading to more complete information. Furthermore, we could reliably exclude children with major congenital malformations and syndromes.

We used multiple sources to obtain information on the participating children and in general, agreement between these multiple information sources was high. Any errors probably affected all groups, implying some increase in measurement error and thus some underestimation of real differences. Another limitation is that the moderately preterm sample was restricted to children born at gestational ages from 32 $^{+0}$ to 35 $^{+6}$ weeks, thus missing those born at gestational ages from 36 $^{+0}$ to 36 $^{+6}$ weeks. The latter are included in the current definition of late preterm birth, which did not yet exist when we started our project in 2004 (37). This restriction may have led to some overestimation of the impact of being born moderately preterm.

Our findings suggest that knowledge of the family history of the parents and the perinatal history of the child are informative in the management of preterm children. Moreover, not only being born EP, but also moderately preterm puts children at risk for continuing respiratory symptoms during the first 4 to 5 years after birth. MP deserve more comprehensive pulmonary care than they currently receive. A worldwide network of long-term follow-up studies in MP could provide more evidence on this large group.

In future research, it is important to include physiologic data comparing EP, MP, and FT to establish the impact of differences in lung volumes caused by prematurity and/or differences in baseline airway obstruction caused by the development of asthma-like symptoms. Results could be used to develop specific interventions for infants and children born preterm to support them in their course of life toward adulthood.

Conclusions

MP children have more rehospitalizations because of respiratory symptoms during the first year of life and more cough, wheeze, shortness of breath, and medication use at the age of 4 and 5 years than FT children. Compared with EP children, the parents of MP children reported less respiratory problems during early infancy and at age 4 but after adjustment for differences in month and year of birth, these differences were no longer significant except for wheezing. At the age of 5 years, rates of respiratory symptoms between moderate and EP children were similar and both were higher than in term-born children. The symptoms result in higher medication use, and in more school absenteeism. The most important risk factors for continuing respiratory problems in MP children are eczema and/or respiratory problems during the first year of life, passive smoking during the first year, higher social class, and a positive family history of asthma.

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