

Recurrent Wheezing During the First 3 Years of Life in a Birth Cohort of Moderate-to-Late Preterm Infants

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ABSTRACT

Background. Data addressing short- and long-term respiratory morbidity in moderate-late preterm infants is limited. We aim to determine the incidence of recurrent wheezing and associated risk and protective factors in these infants during the first 3 years of life.

Methods. Prospective, multicenter birth cohort study of infants born at 32⁺⁰ to 35⁺⁰ weeks' gestation and followed for 3 years to assess the incidence of physician-diagnosed recurrent wheezing. Allergen sensitization and pulmonary function were also studied. We used multivariate mixed-effects models to identify risk factors associated with recurrent wheezing.

Results: 977 preterm infants were enrolled. Rates of recurrent wheezing during year (Y)1 and Y2 were similar (19%) but decreased to 13.3% in Y3. Related hospitalizations significantly declined from 6.3% in Y1 to 0.75% in Y3. Independent risk factors for recurrent wheezing during Y2 and Y3 included: day care attendance, acetaminophen use during pregnancy and need for mechanical ventilation. Atopic dermatitis on Y2 and male sex on Y3 were also independently associated with recurrent wheezing. Palivizumab prophylaxis for RSV during the first year of life, decreased the risk of recurrent wheezing on Y3. While there were no differences in rates of allergen sensitization, pulmonary function tests (FEV_{0.5}) were significantly lower in children who developed recurrent wheezing.

Conclusions. In moderate-to-late premature infants, respiratory symptoms associated with lung morbidity persisted during the first 3 years of life and were associated with abnormal pulmonary function tests. Only anti-RSV prophylaxis exerted a protective effect in the development of recurrent wheezing.

Keywords: recurrent wheezing; preterm birth; risk factors; birth cohort; lung function, allergen sensitization

INTRODUCTION

Asthma is the most common chronic condition in children worldwide, with a prevalence of 11.6% in children aged 6–7 years, ranging from 6.8% in India to 21.7% in Oceania, with a prevalence in Western Europe of 9.6-9.9%¹⁻². The reported incidence of recurrent wheezing during the first year of life is significant, varying from 15% in Europe to 24% in Latin America³.

In parallel, the rates of prematurity continue to raise, ranging from 9% to 12% in high and low-middle income countries respectively⁴. Infants of lower gestational age, specifically those born between 30 and 35 weeks' gestation, have an increased risk in the neonatal and perinatal period of respiratory morbidity compared with term infants^{5,6}. The available data suggests that preterm birth may increase the risk of childhood asthma related to a lower lung function⁷⁻⁹. Few studies however, have addressed the short and long-term incidence of recurrent wheezing and related hospitalizations along with allergen sensitization and pulmonary function in unselected moderate-to-late preterm infants with no other comorbidities^{10,11}.

In this context, we designed a birth cohort study to determine the incidence of respiratory morbidity and the associated risks and protective factors during the first 3 years of life in otherwise healthy moderate-to-late premature infants.

METHODS

This was a multicenter, prospective, non-interventional birth cohort study in which moderate-to-late premature infants were longitudinally evaluated from birth and during the first 3 years of life (SAREPREM study). Moderate preterm birth was defined as infants born from 32⁺⁰ to 33⁺⁶ weeks' gestation, and late preterm as those infants born at 34⁺⁰ and 35⁺⁰ weeks' gestation^{10,11}.

Fifteen pediatric hospitals in Spain participated in the study (**Table S1**). Interim results for the first year have been previously reported¹² and the complete data for the study including the second and third years are included in the present report. The study protocol was approved by the Ethics Committees, and all the procedures followed the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from parents/caregivers before inclusion in the study, and patient data confidentiality was maintained according to the Spanish Data Protection Act.

Study design and patients

From October 15, 2006, through April 14, 2008, neonates born between 32⁺⁰ and 35⁺⁰ weeks' gestation with no additional comorbidities, were enrolled within the first 14 days of life and before discharge. Infants were then followed periodically during the first 3 years (Y) of life. Neonates with congenital or chronic diseases were excluded from the study¹².

Study outcomes and definitions

Follow-up during the three study years was accomplished in 7 visits: visit #1, at enrollment within the first 2-4 weeks of life; and visit #2 at 5-6 months of age. Subsequent visits were scheduled every 6 months until 3 years of age (visit #7; Y3) (**Figure S1**). Respiratory morbidity and risk factors for respiratory illnesses were explored over time based on the 2 main outcomes of interest: a) *acute wheezing episodes*: defined as episodes of lower respiratory tract infection with tachypnea, dyspnea, and wheezing or fine crackles on auscultation, with or without fever; and b) *related hospital admissions*. Wheezing episodes were classified as a) *infrequent wheezing* or b) *recurrent wheezing* based on the number of wheezing episodes diagnosed by a physician in a given year: < 3 (infrequent) or ≥ 3 (frequent), as described¹¹. In addition, further analyses were conducted based on the presence and frequency of wheezing episodes during the 3-year follow-up as: a) *no wheezing*; b) *transient wheezing*: recurrent wheezing during Y1 and/or Y2, but not in Y3; c) *early persistent wheezing*: recurrent wheezing during Y1 that persisted throughout Y3; and d) *late wheezing*: no wheezing episodes in Y1, but development of recurrent wheezing in Y3.

Parameters evaluated

Baseline information was collected at enrollment (visit #1) using standardized questionnaires based on the ISAAC study, and included perinatal history, physical examination, family history of asthma/atopy and maternal tobacco use¹³. During the perinatal period we also collected the need and duration of mechanical ventilation. From visits #2 through #7, in addition to a physical examination, information regarding respiratory lung morbidity and epidemiologic variables were also collected using standard questionnaires including: day care attendance (defined as attendance to day care at least 3 times a week in the previous year), breastfeeding, second hand smoke exposure, and presence of atopic diseases such as atopic dermatitis and allergic rhinitis. Last, during the final visit at Y3 (visit #7), allergy and pulmonary function tests were performed. For allergy testing, skin prick testing was performed and included the following allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, dog and cat dander, *Alternaria spp.*, and pollen from olive, *Parietaria judaica*, and *Phleum pratense*. A mean diameter of at least 3 mm was

considered positive¹⁴. Pulmonary function testing was also performed in the centers with available spirometry using a Jaeger MasterScope spirometer (Carefusion, Hoechberg, Germany) or a Datospir-600 spirometer (Sibel Group, Barcelona, Spain), according to ERS/ATS guidelines¹⁵. The following spirometry values were collected: forced vital capacity (FVC), forced expiratory volume at 0.5 seconds (FEV_{0.5}), and forced expiratory flow, mid-expiratory phase (FEF₂₅₋₇₅). Z-scores were calculated based on the Stanojevic's equations^{16,17}.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) unless otherwise specified. Frequencies were estimated with 95% confidence intervals (CI) using the Wilson formula. The Chi-square test was used to analyze the occurrence of the respiratory outcomes of interest in relation to gestational age. ANOVA and the Kruskal-Wallis test were used as appropriate for comparisons. Identification of risk factors independently associated with outcomes of care was explored using multivariable mixed-effects models with random effects. Odds ratios (OR) and 95% CI were estimated. The corresponding probability values were adjusted for multiple comparisons.

RESULTS

Cohort characteristics and incidence of wheezing.

We enrolled a total of 977 preterm infants in the study: 766 (78.4%) completed all follow-up visits during Y1, 707 (72.4%) in Y2, and 670 (68.8%) in Y3. There were no significant differences in baseline characteristics between patients who completed the first vs. the second and third year of follow-up. (**Table 1**).

During the study period, the number of infrequent wheezing episodes was comparable and occurred in 28.8% (95% CI: 25.1- 31.5) of infants during the first year, in 34.9% (21.9 - 28.2) during the second year, and in 27.2% (23.9 - 30.7) during the third year ($p = 0.23$; **Table 2**). A significant decrease in the number of children with recurrent wheezing was observed in Y3: (13.3% [10.9 - 16.1]) compared with Y2 (18.9% [16.2 - 22.1]; $p < 0.01$) and Y1 (18.8% [16.2 - 21.7]).

According to the development of transient, early persistent or late wheezing during the study period, children were stratified in different phenotypic profiles as shown in Figure 1, which summarizes the natural history of wheezing in this cohort. Transient wheezing (Y1 and Y2) occurred in 21.8% of the cohort, while 13.7% presented early persistent or late recurrent

wheezing. Analysis of the incidence of wheezing events per week of gestational age (32, 33, 34 and 35 weeks) did not reveal significant differences (**Table 3**).

Lung morbidity and related hospitalizations

Similar to the decrease observed in the number of episodes of physician diagnosed recurrent wheezing, the number of hospital admissions due to a respiratory illness showed a progressive and significant decline over the 3 years of follow-up: from 6.3% in Y1, to 2.4% in Y2 and 0.75% in Y3 ($p < 0.001$; Table 2). The small percentage of children that were hospitalized, precluded conducting further multivariable analyses for this outcome.

Risk factors for recurrent wheezing during the second and third year of life.

We used univariate followed by multivariable analysis to explore the relationship between various prenatal, perinatal and postnatal factors and the development of recurrent wheezing during the second and third years of life (**Tables 4 and 5**). Both unadjusted and adjusted analysis revealed that acetaminophen use during pregnancy (≥ 1 dose per quarter) and day care attendance were associated with physician diagnosed recurrent wheezing during the second and third years of life (**Table 4 and 5**). On the other hand, young chronologic age at the beginning of the respiratory season (defined as < 10 weeks of age), and need for mechanical ventilation during the neonatal period were associated in unadjusted analysis with recurrent wheezing in the second year of life. Mechanical ventilation remained significant adjusted for other covariates. Atopic diseases were also evaluated. Allergic rhinitis was significantly associated with recurrent wheezing in Y2 and Y3 but it was not included in multivariate analysis because of the small number of cases. On the other hand, atopic dermatitis was significantly associated with recurrent wheezing in Y2 in both unadjusted and adjusted analyses.

During Y3, male sex remained significantly associated with increased risk of recurrent wheezing in adjusted analyses, but not contact with farm animals, that was significant only in univariate analyses (**Table 4**). Last, prophylaxis against respiratory syncytial virus (RSV) with palivizumab was administered in the first year of life to 117 infants (15.1% of the first-year cohort) and showed an independent and protective effect in relation to the development of recurrent wheezing in Y3, in both univariate and multivariable analyses.

Allergy, pulmonary function testing and recurrent wheezing

To explore the possible associations between aeroallergens and respiratory morbidity, skin prick testing was performed in 472 (70%) children who completed the 3 years of follow-up, 67 with recurrent wheezing and 405 without. Of the 67 children with recurrent wheezing, 7 (10.5%) tested positive for at least 1 allergen while 27 (6.7%) with no wheezing tested positive, with no significant differences between the two groups.

Spirometry was performed at 3 years of age in 289/670 (43%) children who completed all study visits. Of these, 187 (64.7%) had accurate data to be included in further analysis. Mean ($\pm$ SD) Z score with 95% CI of FVC was: -0.36 ± 0.91 [-0.23 to -0.49], FEV_{0.5}: -0.98 ± 1.07 [-0.83 to -1.13] and FEF_{25-75%}: -0.79 ± 1.05 [-0.64 to -0.96]. Children who developed recurrent wheezing at any time during the study (z-score -1.5 vs. -1 ; $p = 0.01$) and at 3 years (z-score -1.7 vs. -1 ; $p < 0.05$) had lower FEV_{0.5} values than children who did not develop recurrent wheezing. No significant associations were found between prenatal and postnatal tobacco exposure and parameters of lung function (Table S2).

DISCUSSION

The main goal of this study was to determine the incidence of respiratory morbidity, the associated risk and protective factors, and the allergen sensitization and pulmonary function during the first 3 years of life in a Spanish birth cohort of otherwise healthy moderate-to-late preterm infants. Of all the factors evaluated, administration of acetaminophen during pregnancy and day care attendance were consistently associated with development of recurrent wheezing, while prophylaxis with anti-RSV monoclonal antibodies showed a protective effect. Pulmonary function tests remained abnormal at year 3 in children with recurrent wheezing at any time during the study, reflecting their long-term respiratory vulnerability.

We previously reported a 19% incidence of recurrent wheezing in this cohort during the first year of life, with results comparable to other studies conducted in Europe in premature infants¹¹. In addition, and using strict definitions such as the need for physician-diagnosed wheezing, we found a progressive reduction in the frequency of wheezing episodes during the 3 study years and in hospitalizations for respiratory-related diagnoses¹⁸. Most children who developed recurrent wheezing during the first year of life were categorized as transient wheezers, while only 21% of wheezing episodes persisted through the third year. In fact, the majority (63.5%) of children who developed recurrent wheezing at 3 years of age

developed wheezing after the first year. Nevertheless, the incidence of wheezing in these preterm infants remained high during the third year of life, reflecting their increased risk for respiratory morbidity⁵.

Multivariate analysis allowed us to identify risk factors associated with outcomes of care. Among them, day care attendance was consistently associated with recurrent wheezing in all study years, and also acetaminophen use during pregnancy which was also significantly associated with recurrent wheezing during the second and third years of life, but not on year 1¹². The association of both day care attendance and acetaminophen exposure during pregnancy/early childhood and the occurrence of respiratory disorders in children has been previously reported in selected cohorts and meta-analyses^{3,19-26}. Nevertheless, our results in an unselected large cohort of otherwise healthy premature infants emphasize the impact of preventable risk factors in the development on long-term respiratory morbidity.

Different studies support the role of RSV infection during infancy in the development of recurrent wheezing. An observational case-control study from Japan, showed that preterm infants who received anti-RSV prophylaxis had a significant reduction in the incidence of recurrent wheezing at 3 years²⁷ and 6 years²⁸ of age, with no impact in the development of atopic asthma. In a placebo-controlled trial conducted in moderate-late preterm Dutch infants (32-35 weeks' gestation), palivizumab prophylaxis led to a reduction in the development of recurrent wheezing at 1 year of follow-up¹¹, and of any wheezing at 6 years of follow-up, but it did not influence the incidence of asthma diagnosed by a physician at 6 years of age²⁹. Our results also showed that at 3 years of follow-up, children who received RSV prophylaxis had a 66% reduction in rates of recurrent wheezing compared with the non-treated group. This effect was not observed during the first¹¹ or second years of follow-up.

Last, in our study atopic dermatitis was associated with recurrent wheezing, emphasizing the need to understand the complex interactions between endogenous and external factors in the genesis on reactive airway disease. Interestingly, the majority of infants who developed wheezing did not require hospitalization, yet independent of the severity, lung function was reduced at follow-up in these children, reflecting their high respiratory vulnerability.

Our study has limitations, most of them inherent to the study design and/or methodology. Pulmonary function was only performed in some centers and results might be biased. These centers however, are the reference center for the pediatric population in their areas, with ample expertise with this technology. Various epidemiologic factors analyzed

relied on parental self-reporting, such as acetaminophen use, and hence there is potential recall bias. Although the sample size was sufficient to analyze the main study outcome (development of recurrent wheezing) conclusions regarding other outcomes should be interpreted with caution.

In summary, by conducting a prospective birth cohort study, using strict criteria for the main clinical outcome, performing allergy and pulmonary function testing, and adjusting analyses for different covariates, we believe we add another piece of information demonstrating the increased lung vulnerability of otherwise healthy moderate-to-late premature infants.

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Table 1. Baseline characteristics of infants enrolled during the first 2 weeks of life and who completed the first year of follow-up included in the second- and third-year analysis

		First year†	Second year	Third year	p-value
		<i>n</i> = 766	<i>n</i> = 707	<i>n</i> = 670	
Maternal age (years; mean ± SD)		31.8 ± 5.5	32.0 ± 5.3	31.9 ± 5.3	0.920
Sex, n (%)	Male	435 (56.8%)	404 (57.1%)	386 (57.6%)	0.952
	Female	331 (43.2%)	303 (42.9%)	284 (42.4%)	
Birth weight (g; mean ± SD)		1957.3 ± 393.8	1961.1 ± 397.6	1962.6 ± 393.2	0.966
Low birth weight, n (%)		149 (19.5%)	140 (19.8%)	133 (19.9%)	0.978
Length at birth (cm; mean ± SD)		44.1 ± 2.9	44.1 ± 2.9	44.1 ± 2.9	0.943
Gestational age (weeks; mean ± SD)		33.7 ± 0.9	33.7 ± 0.9	33.7 ± 0.9	0.853
Gestational age, n (%)					0.955
	32 weeks	164 (21.4%)	146 (20.7%)	132 (19.7%)	
	33 weeks	211 (27.5%)	194 (27.4%)	187 (27.9%)	
	34 weeks	391 (51%)	367 (51.9%)	351 (52.4%)	
Quarter of birth, n (%)					0.999
	Jan-Mar	281 (36.7%)	255 (36.1%)	240 (35.8%)	
	Apr-Jun	132 (17.2%)	126 (17.8%)	116 (17.3%)	
	Jul-Sep	103 (13.4%)	98 (13.9%)	96 (14.3%)	
	Oct-Dec	250 (29.9%)	228 (32.2%)	218 (32.5%)	
Type of pregnancy, n (%)					

	Single	422 (55.1%)	394 (55.7%)	375 (56%)	0.941
	Multiple	344 (44.9%)	313 (44.3%)	295 (44%)	
Type of delivery, n (%)					
	Normal vaginal	275 (35.9%)	255 (36.1%)	240 (35.9%)	
	Assisted vaginal	41 (5.4%)	37 (5.2%)	39 (5.8%)	0.992
	C-section	449 (58.7%)	414 (58.6%)	390 (58.3%)	
Mechanical ventilation,					
	Need for n (%) / duration (h)	67 (8.8%) / 65 [3-240]	61 (8.7%) NA	54 (8.1%) NA	0.883 NA
Need for CPAP, n (%)					
		178 (23.3%)	166 (23.5%)	153 (22.9%)	0.960
Need for supplemental oxygen, n (%)					
		220 (28.9%)	203 (28.9%)	191 (28.6%)	0.994
Parental history of atopy, n (%)					
		418 (54.6%)	383 (54.2%)	376 (56.1%)	0.746
Parental history of asthma, n (%)					
		141 (18.4%)	131 (18.5%)	124 (18.5%)	0.998
Maternal tobacco use during pregnancy, n (%)					
		185 (24.2%)	171 (24.3%)	155 (23.2%)	0.866
Acetaminophen use during pregnancy, n (%)					
	≥ 1× 3-mo	185 (24.7%)	166 (24%)	159 (24.2%)	
	0-1 ×3-mo	565 (75.3%)	526 (76%)	498 (75.8%)	0.935

SD: standard deviation; CPAP: continuous positive airway pressure; mo: months.

†Data published as interim results of the first year⁹

Table 2. Incidence of recurrent wheezing and hospitalizations during the three years of follow-up

	First year (<i>n</i> = 766)	Second year (<i>n</i> = 707)	Third year (<i>n</i> = 670)	<i>p</i>-value
No wheezing, <i>n</i> (%[95% CI])	401 (52.3% [48.8-55.9])	397 (56.2% [52.5-59.8])	399 (59.6% [55.8-63.2])	-
Infrequent wheezing, <i>n</i> (%[95% CI])	221 (28.8%[25.1-31.5])	176 (34.9% [21.9-28.2])	182 (27.2% [23.9-30.7])	0.231
Recurrent wheezing, <i>n</i> (%[95% CI])	144 (18.8% [16.2-21.7])	134 (19.0% [16.2-22.0])	89(13.3% [10.9-16.1])	0.006
Hospital admissions†, <i>n</i> (%[95% CI])	48 (6.3% [4.6-8.0])	17 (2.4% [1.5-3.8])	5 (0.75% [0.3-1.7])	<0.001

Infrequent wheezing= 1 or 2 episodes per year; Recurrent wheezing= 3 or more episodes per year. CI, confidence interval. † due to respiratory condition (bronchiolitis or pneumonia)

Table 3. Incidence of wheezing according to gestational age (GA) at birth

	GA 32	GA 33	GA 34	GA 35	Total	P- value
First year (n = 766)						
No wheezing	88 (53.7%)	110 (52.1%)	169 (54.3%)	39 (48.8%)	406 (53.0%)	0.282
Infrequent wheezing	46 (28.0%)	62 (29.4%)	77 (24.8%)	31 (38.8%)	216 (28.2%)	
Recurrent wheezing	30 (18.3%)	39 (18.5%)	65 (20.9%)	10 (12.5%)	144 (18.8%)	
Second year (n = 707)						
No wheezing	77 (52.7%)	108 (55.7%)	170 (58.4%)	42 (55.3%)	397 (56.2%)	0.871
Infrequent wheezing	38 (26.0%)	47 (24.2%)	69 (23.7%)	22 (28.9%)	176 (24.9%)	
Recurrent wheezing	31 (21.2%)	39 (20.1%)	52 (17.9%)	12 (15.8%)	134 (19.0%)	
Third year (n = 670)						
No wheezing	81 (61.4%)	100 (53.5%)	175 (62.5%)	43 (60.6%)	399 (59.6%)	0.354
Infrequent wheezing	35 (26.5%)	60 (32.1%)	72 (25.7%)	15 (21.1%)	182 (27.2%)	
Recurrent wheezing	16 (12.1%)	27 (14.4%)	33 (11.8%)	13 (18.3%)	89 (13.3%)	

GA: gestational age. Differences within year calculated with Chi² test

Table 4. Univariate analysis of factors associated with recurrent wheezing

		Second year <i>n</i> = 707			Third year <i>n</i> = 670				
		Risk factor present		<i>P</i>	OR (95% CI)	Risk factor present		<i>P</i>	OR (95% CI)
		No Wheezing	Wheezing			No Wheezing	Wheezing		
		<i>n</i> = 573	<i>n</i> = 134			<i>n</i> = 581	<i>n</i> = 89		
Prenatal and Parental factors									
Acetaminophen use (≥1 × quarter)		124 (21.6%)	42 (31.3%)	0.016	1.66 (1.09 – 2.52)	127 (21.8%)	32 (35.9%)	0.005	1.95 (1.21 – 3.14)
Maternal tobacco use		137 (23.9%)	34 (25.4%)	0.740	1.08 (0.70 – 1.66)	138 (23.7%)	17 (19.1%)	0.330	0.76(0.43 – 1.33)
Maternal age (Mean ± SD)		32.0 ± 5.3	31.7 ± 5.6	0.510		31.83 ± 5.3	32.45 ± 4.89	0.290	
Respiratory infections in pregnancy		96 (16.7%)	30 (22.4%)	0.159	1.43 (0.9 – 2.27)	107 (18.4%)	20 (22.5%)	0.445	1.28 (0.75 – 2.20)
Contact with animals		148 (25.8%)	38 (28.3%)	0.570	1.13 (0.74 – 1.72)	145 (24.9%)	33 (37.1%)	0.020	1.77 (1.10 – 2.83)
Parental history of asthma		106 (18.5%)	25 (18.6%)	0.970	1.01 (0.62 – 1.64)	316 (54.4%)	60 (67.4%)	0.020	1.73 (1.08 – 2.78)
Parental history of atopy		303 (52.9%)	80 (59.7%)	0.150	1.32 (0.90 – 1.93)	98 (16.9%)	26 (29.2%)	0.005	2.03(1.23 – 3.37)
Perinatal factors									
Sex (Male)		326 (56.9%)	78 (58.2%)	0.780	1.05 (0.72 – 1.54)	323 (55.6%)	63 (70.8%)	0.007	1.92 (1.19 – 3.12)
Low birth weight for GA		114 (19.9%)	26 (19.4%)	0.890	0.97 (0.60 – 1.56)	117 (20.1%)	16 (18.0%)	0.630	0.87(0.49 – 1.55)
Semester of birth	Jul-Dec	315 (55.0%)	66 (49.2%)	0.230	1.26 (0.86 – 1.83)	314 (54.0%)	42 (47.2%)	0.230	1.32(0.84 – 2.06)
	Jan-Jun	258 (45.0%)	68 (50.7%)			267 (45.9%)	47 (52.8%)		
Age at the beginning of RSV season (<10 weeks)		210 (36.6%)	62 (46.3%)	0.040	1.49 (1.02 – 2.18)	226 (38.9%)	37 (41.6%)	0.630	1.12(0.71 – 1.76)
Mechanical ventilation		43 (7.5%)	18 (13.4%)	0.026	1.92 (1.07 – 3.45)	46 (7.9%)	8 (9.0%)	0.740	1.14(0.52 – 2.51)
Postnatal factors									
Breastfeeding (≥90 days)		205 (35.8%)	50 (37.3%)	0.970	1.01(0.68 – 1.49)	207 (35.6%)	39 (43.8%)	0.170	1.36(0.87 – 2.15)
Day care attendance		285 (49.7%)	91 (67.9%)	<0.001	2.30 (1.52 – 3.49)	444 (76.4%)	78 (87.6%)	0.030	2.09 (1.05 – 4.16)
Household members (>4)		133 (23.2%)	25 (18.6%)	0.270	0.76 (0.47 – 1.23)	123 (21.2%)	19 (21.3%)	0.940	0.98(0.57 – 1.69)

School-age siblings	200 (34.9%)	51 (38.0%)	0.360	1.20 (0.81 – 1.79)	212 (36.5%)	35 (39.3%)	0.620	1.13(0.71 – 1.79)
Prophylaxis with palivizumab	90 (15.7%)	19 (14.2%)	0.660	0.89 (0.52 – 1.51)	101 (17.4%)	7 (7.9%)	0.020	0.40 (0.18 – 0.90)
Contact with animals	152 (26.5%)	41 (30.6%)	0.340	1.22 (0.81 – 1.84)	148 (25.5%)	31 (34.8%)	0.060	1.56 (0.97 – 2.51)
Atopic dermatitis	156 (27.2%)	50 (37.3%)	0.021	1.59 (1.07 – 2.36)	167 (28.7%)	32 (35.9%)	0.207	1.39 (0.87 – 2.22)
Allergic rhinitis	16 (2.8%)	10 (7.5%)	0.020	2.81 (1.24 – 6.33)	17 ((2.9%)	9 (10.1%)	0.003	3.73 (1.61 – 8.66)
Postnatal tobacco exposure	309 (53.9%)	65 (48.5%)	0.728	0.92 (0.63 – 1.34)	279 (48.0)	44 (49.4%)	0.646	1.14 (0.73 – 1.78)

GA: gestational age. RSV; respiratory syncytial virus; Data given as n (%) except for maternal age (mean $\pm$ standard deviation [SD])

Table 5. Multivariate analysis of variables related to recurrent wheezing

Predictors	Second year			Third year		
	OR	[95% CI]	<i>p</i> -value	OR	[95% CI]	<i>p</i> -value
Prenatal and parental factors						
Acetaminophen $\geq 1 \times$ trimester	1.73	(1.06-2.82)	0.029	1.86	(1.10-3.14)	0.021
Maternal tobacco use						
(< 10 cig/day)	1.05	(0.54-2.04)	0.884	--		
(>10 cig/day)	1.66	(0.72-3.85)	0.237	--		
Maternal age	0.99	(0.95-1.03)	0.579			
Contact with animals	1.21	(0.56-2.65)	0.629	1.83	(0.79-4.26)	0.159
Parental history of atopy	1.34	(0.83-2.16)	0.235	1.69	(0.96-2.97)	0.068
Parental history of asthma	0.71	(0.38-1.29)	0.259	1.76	(0.97-3.21)	0.064
Perinatal factors						
Sex (male)	1.04	(0.62-1.49)	0.869	2.2	(1.28-3.57)	0.036
Low birth weight for gestational age	1.16	(0.69-1.97)	0.573	--		
Semester of birth	1.41	(0.91-2.18)	0.129	--		
Need for mechanical ventilation	2.01	(1.01-3.99)	0.046	1.17	(0.49-2.80)	0.718
Postnatal factors						
Breastfeeding (> 90 days)	0.87	(0.54-1.39)	0.552	--		
Day care attendance	2.42	(1.53-3.85)	0.0002	2.59	(1.21-5.52)	0.014
Household members (>4)	0.76	(0.42-1.39)	0.369	--		
School-age siblings (>1)	1.40	(0.86-2.28)	0.181	--		
Prophylaxis with palivizumab	0.85	(0.42-1.71)	0.644	0.40	(0.17-0.96)	0.039
Contact with animals	0.92	(0.43-1.98)	0.834	0.89	(0.35-2.30)	0.940

Atopic dermatitis	1.70	(1.06-2.72)	0.027	1.24	(0.73-2.09)	0.424
Postnatal tobacco exposure	0.88	(0.53-1.48)	0.634	1.01	(0.62-1.65)	0.973

FIGURE LEGEND

Figure 1. Natural history of recurrent wheezing in preterm infants (32-35 weeks' gestational age) during the first 3 years of life. RW: Recurrent wheezing H: Healthy; T: Transient; P: Persistent; L: Late. The numbers following these denote the year of occurrence of the episodes. Transient: recurrent wheezing during the first and/or second persisting the third year. Late: no recurrent wheezing the first year, but recurrent wheezing the third year.

	1st year	2nd year	3rd year	N		
H					No RW 421 (64.5%)	
T1	RW			58	Transient wheezing 142 (21.8%)	
T1-2	RW	RW		64		
T2		RW		50		
P1-2-3	RW	RW	RW	20	Early persistent wheezing 32 (4.9%)	89 (13.7%)
P1-3	RW		RW	12		
L3			RW	38	Late RW 57 (8.7%)	
L2-3		RW	RW	19		

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