ORIGINAL ARTICLE

Risk factors for bronchiolitis, recurrent wheezing, and related hospitalization in preterm infants during the first year of life

Eduardo G. Pérez-Yarza[1,2,3,a], Antonio Moreno-Galdó[4,a], Octavio Ramilo[5], Teresa Rubí[6], Amparo Escribano[7], Antonio Torres[8], Olaia Sardón[1,3], Concepción Oliva[9], Guadalupe Pérez[10], Isidoro Cortell[11], Sandra Rovira-Amigo[4], Maria D. Pastor-Vivero[12], Javier Pérez-Frías[13], Valle Velasco[14], Javier Torres-Borrego[15], Joan Figuerola[16], Maria Isabel Barrio[17], Gloria García-Hernández[18], Asunción Mejías[5], on behalf of the SAREPREM 3235 investigators*

[1]Division of Pediatric Respiratory Medicine, Hospital Universitario Donostia-Instituto Biodonostia, San Sebastián, Spain; [2]Biomedical Research Centre Network for Respiratory Diseases (CIBERES), San Sebastián, Spain; [3]Department of Pediatrics, University of the Basque Country (UPV/EHU), San Sebastián, Spain; [4]Pediatric Pulmonary Unit, Department of Pediatrics, Obstetrics, Gynecology and Preventive Medicine, Hospital Universitario Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain; [5]Division of Infectious Diseases, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA; [6]Pediatric Pulmonary Section, Hospital Torrecárdenas, Almería, Spain; [7]Pediatric Pulmonary Unit, Hospital Clínico Universitario, Universidad de Valencia, Valencia, Spain; [8]Department of Pediatrics, Hospital San Juan de la Cruz, Úbeda, Spain; [9]Pediatric Pulmonary Unit, Hospital Universitario Nuestra Señora de la Candelaria, Tenerife, Spain; [10]Pediatric Pulmonary Section, Hospital Universitario Virgen Macarena, Universidad de Sevilla, Sevilla, Spain; [11]Pediatric Pulmonary Section, Hospital Universitario La Fe, Valencia, Spain; [12]Pediatric Pulmonary Section, Hospital Clínico Universitario Virgen de la Arrixaca, Universidad de Murcia, Murcia, Spain; [13]Pediatric Pulmonary Unit, Hospital Materno-Infantil, Málaga, Spain; [14]Pediatric Pulmonary Unit, Hospital Clínico Universitario, Tenerife, Spain; [15]Pediatric Pulmonary and Allergy Unit, Hospital Reina Sofía, Córdoba, Spain; [16]Pediatric Pulmonary Section, Hospital Universitario Son Espases, Palma de Mallorca, Spain; [17]Pediatric Pulmonary Section, Hospital Universitario La Paz, Madrid, Spain; [18]Pediatric Pulmonary and Allergy Unit, Hospital Universitario 12 de Octubre, Madrid, Spain

To cite this article: Pérez-Yarza EG, Moreno-Galdó A, Ramilo O, Rubí T, Escribano A, Torres A, Sardón O, Oliva C, Pérez G, Cortell I, Rovira-Amigo S, Pastor-Vivero MD, Pérez-Frías J, Velasco V, Torres-Borrego J, Figuerola J, Barrio MI, García-Hernández G, Mejías A, on behalf of the SAREPREM 3235 investigators. Risk factors for bronchiolitis, recurrent wheezing, and related hospitalization in preterm infants during the first year of life. *Pediatr Allergy Immunol* 2015: **00**.

Keywords
bronchiolitis; bronchitis; premature birth; risk factors; wheezing

Correspondence
Antonio Moreno-Galdó, Pediatric Allergy and Pulmonology Unit, Hospital Materno-infantil Vall d'Hebron, Pg. Vall d'Hebron 119-129, 08035 Barcelona, Spain
Tel.: +34 626 774 330
Fax: +34 934 893 171
E-mail: amoreno@vhebron.net

[a]These authors contributed equally to this work.

The details of SAREPREM 3235 investigators are given in Appendix

Accepted for publication 23 May 2015

DOI:10.1111/pai.12414

Abstract

Background: Airway diseases are highly prevalent in infants and cause significant morbidity. We aimed to determine the incidence and risk factors for respiratory morbidity in a Spanish cohort of moderate-to-late preterm (MLP) infants prospectively followed during their first year of life.

Methods: SAREPREM is a multicenter, prospective, longitudinal study. Preterm infants born at 32–35 weeks of gestation with no comorbidities were enrolled within 2 weeks of life and followed at 2–4 weeks, 6, and 12 months of age. Multivariate mixed-models were performed to identify independent risk factors associated with (i) development of bronchiolitis, (ii) recurrent wheezing, or (iii) related hospital admissions.

Results: Overall, 977 preterm infants were included, and 766 (78.4%) completed follow-up. Of those, 365 (47.7%) developed bronchiolitis during the first year, 144 (18.8%) recurrent wheezing, and 48 (6.3%) were hospitalized. While low birthweight, day care attendance (DCA) and school-age siblings were significantly and independently associated with both the development of bronchiolitis and recurrent wheezing, lower maternal age increased the risk for bronchiolitis and respiratory-related hospitalizations. Lastly, mechanical ventilation was associated with a higher risk of bronchiolitis and history of asthma in any parent increased the likelihood of developing recurrent wheezing.

Conclusions: In this study, several non-modifiable parameters (family history of asthma, low birthweight, need for mechanical ventilation) and modifiable parameters (young maternal age, DCA, or exposure to school-age siblings) were identified as significant risk factors for the development of bronchiolitis and recurrent wheezing during the first year of life in MLP infants.

The prevalence of bronchiolitis, recurrent wheezing, and other diseases of the small airways in infants and children is high and carries significant morbidity. According to studies conducted in the United States (1) and Australia (2), up to 50% of children will have an episode of wheezing by 6 years of age. In the *International Study of Wheezing in Infants,* the prevalence of infrequent and recurrent wheezing during the first year of life was 18.6% and 15%, respectively, in Europe, and 26.8% and 23.7% in Latin America (3).

Studies conducted to date in term infants have characterized the different phenotypes of recurrent airway disease (4, 5), presence of risk factors (6, 7), and lung function abnormalities related to each disease phenotype (8, 9). Limited data suggest that there is an overall increase of neonatal and perinatal lung morbidity directly related to the gestational age (GA) and low birthweight (LBW), including the development or recurrent wheezing (10–12). Nevertheless, the majority of studies have focused on premature infants <32 weeks GA, very LBW infants (<1500 g), or children with significant perinatal lung history such as hyaline membrane disease or bronchopulmonary dysplasia (12, 13). Studies addressing the frequency and risk factors for the development of lung disease during the first year of life in moderate-to-late preterm infants (MLP; 32–35 weeks GA) with no other comorbidities are lacking.

The aim of this study was to determine the incidence of respiratory morbidity and the associated risk and protective factors during the first year of life in a Spanish birth cohort of infants born at 32–35 weeks of gestation.

Materials and methods

SAREPREM is a multicenter, prospective, observational study of MLP infants involving 15 pediatric hospitals in Spain. The study protocol was approved by the Ethics Committees, and the study was carried out following the Declaration of Helsinki principles. Patient data remained confidential according to Spanish law. The infants' parents or guardians signed a written informed consent before study participation.

Patients and methods

We conducted a prospective observational study involving a convenience sample of MLP infants from October 15, 2006 to April 14, 2008. Premature infants born between 32 weeks +1 day and 35 weeks +0 days of GA with no comorbidities were enrolled in the study within the first 14 days of life and before hospital discharge. The census of all newborns admitted to the neonatal units was reviewed daily to identify the study participants. Patients were excluded if they had a history of (i) chronic lung disease: bronchopulmonary dysplasia, cystic fibrosis, interstitial lung disease, pulmonary hypertension, and/or primary ciliary dyskinesia; (ii) malformations of the upper airway, lung, and/or gastrointestinal malformations; (iii) congenital heart disease; (iv) chromosomal abnormalities; (v) chronic neurologic, renal, and/or gastrointestinal diseases; (vi) primary or secondary immunodeficiencies; and (vii) any other condition that might be associated with an increased risk of respiratory morbidity.

Table 1 Summary of procedures and variables recorded in the three visits scheduled during the first year of life of SAREPREM cohort

Protocol and variables	Visit 1 0–4 weeeks	Vistit 2 6 months	Visit 3 12 months
Perinatal history	✓		
Family history*	✓		
Respiratory morbidity in the period (questionnaire)		✓	✓
Physical examination	✓	✓	✓
History of respiratory symptoms in the period		✓	✓
Diagnosed diseases in the period (outcomes of interest: bronchiolitis/ wheezing/hospital admissions)		✓	✓
Epidemiologic variables/ liftestyles†		✓	✓

*Qustionnaire based on the ISSAC study and included documentation of family history of atopy, asthma, rhinitis, and atopic dermatitis, maternal smoking during pregnancy, presence of pets, parent's educational level and type of housing (rural and urban).
†Epidemiologic variables included; tobacco smoke exposure, presence of pets, number of siblings, day care attendance, and history and duration of breastfeeding.

Definitions

'Acute bronchiolitis' was defined as the first episode of lower respiratory tract infection associated with tachypnea, dyspnea, and wheezing or fine crackles on auscultation after a brief period of upper respiratory infection with or without fever. 'Acute wheezing episode' was considered as an episode of lower respiratory tract infection with tachypnea, dyspnea, and wheezing or fine crackles on auscultation. 'Infrequent wheezing' was defined as 1–2 episodes of wheezing per year diagnosed by a physician and 'recurrent wheezing' if ≥3 episodes per year were diagnosed by a physician.

Variables and follow-up protocol

The complete SAREPREM study comprises seven visits for each study participant. The present report includes the data regarding the development of respiratory morbidity during the first year of life, that is, three visits. Schedules, procedures, and variables recorded in each visit are summarized in Table 1. Virology testing was performed per standard of care using a direct fluorescent antibody assay, which identified the following respiratory viruses: respiratory syncytial virus (RSV), adenovirus, influenza virus, parainfluenza virus (PIV), and human metapneumovirus (HMPV).

Table 2 Baseline characteristics of infants enrolled during the first two weeks of life and comparisons between those who completed the 3 study visits and those who were lost to follow-up during the first year

	Complete follow-up 1st year n = 766	Lost to follow-up at 1 year n = 211	p-value
Maternal age (years; mean ± s.d.)	31.8 ± 5.5	30.6 ± 5.9	0.006
Gender, n (%)			
Male	435 (56.8)	95 (45)	0.003
Female	331 (43.2)	116 (55)	
Birthweight (grams; mean ± s.d.)	1957.3 ± 393.8	1983.4 ± 442.7	0.438
Low weight at birth, n (%)	149 (19.5)	53 (25.1)	0.088
Length at birth (cm; mean ± s.d.)	44.1 ± 2.9	44.2 ± 3.0	0.606
Gestational age (weeks, mean ± s.d.)	33.7 ± 0.9	33.9 ± 0.8	0.006
Gestational age, n (%)			
32 weeks	164 (21.4)	29 (13.7)	0.002
33 weeks	211 (27.5)	46 (21.8)	
34 weeks	391 (51.0)	136 (64.5)	
Quarter of birth, n (%)			
Jan–Mar	281 (36.7)	88 (41.7)	0.253
Apr–Jun	132 (17.2)	27 (12.8)	
Jul–Sep	103 (13.4)	33 (15.6)	
Oct–Dec	250 (29.9)	63 (29.9)	
Type of pregnancy, n (%)			
Single	422 (55.1)	110 (53.9)	0.826
Multiple	344 (44.9)	94 (46.1)	
Type of delivery, n (%)			
Normal vaginal	275 (35.9)	81 (40.3)	0.499
Assisted vaginal	41 (5.4)	9 (4.5)	
C-section	449 (58.7)	111 (55.2)	
Need for mechanical ventilation, n (%)			
Yes	67 (8.8)	16 (8.2)	0.910
No	696 (91.2)	179 (91.7)	
Need for CPAP, n (%)			
Yes	178 (23.3)	47 (23.4)	1.000
No	587 (76.7)	154 (76.6)	
Need for oxygen therapy, n (%)			
Yes	220 (28.9)	55 (27.8)	0.829
No	542 (71.1)	143 (72.2)	
Maternal atopy, n (%)			
Yes	316 (41.3)	50 (23.7)	<0.001
No	450 (58.7)	161 (76.3)	
Maternal asthma, n (%)			
Yes	95 (12.4)	20 (9.5)	0.295
No	671 (87.6)	191 (90.5)	
Paternal atopy, n (%)			
Yes	213 (27.8)	47 (22.3)	0.128
No	553 (72.2)	164 (77.7)	
Paternal asthma, n (%)			
Yes	59 (7.7)	16 (7.6)	1.000
No	707 (92.3)	195 (92.4)	
Maternal tobacco use during pregnancy, n (%)			
Yes	185 (24.2)	31 (16.5)	0.030
No	579 (75.8)	157 (83.5)	
Acetaminophen use during pregnancy, n (%)			
≥1 × 3-mo	185 (24.7)	36 (19.9)	0.208
0–1 × 3-mo	565 (75.3)	145 (80.1)	

s.d., standard deviation; CPAP, continuous positive airway pressure; mo, months.

Statistical procedures

Sample size was calculated according to the primary outcome variable: recurrent wheezing. The expected frequency was estimated to be between 15% and 20%. Thus, a sample size of 784–984 children was required to identify 15–20% of children who will develop recurrent wheezing at $\alpha = 0.05$, and a precision of 3%.

Frequencies were estimated with 95% confidence intervals (CI). Mean, median, quartiles, and standard deviation were obtained for continuous variables. Multivariate logistic mixed-models with random effects were performed to identify independent risk factors associated with the outcomes of interest: (i) recurrent wheezing, (ii) development of bronchiolitis, and (iii) related hospital admissions. Odds ratios (OR) and 95% CI were estimated. The corresponding probability values were adjusted in the subgroup analysis and adjusted for multiple comparisons.

Results

A total of 977 children were enrolled in the study, and 766 (78.4%) completed the three follow-up visits. Of those, 435 (56.8%) were males and 331 females (43.2%). The mean gestational age was 33.7 ± 0.9 weeks, and the mean birthweight was 1957 ± 394 g. The descriptive characteristics of the study population are shown in Table 2, where demographic and clinical data were compared between infants who completed the three study visits vs. those that were lost to follow-up during the first year. Except for a slightly younger maternal age (MA), less frequency of maternal atopy, and a greater proportion of neonates born at 34 weeks of GA in the group of infants who were lost to follow-up, the rest of the parameters were similar between the two groups.

Incidence of bronchiolitis, recurrent wheezing, and need for hospitalization

Univariate and multivariable analyses were conducted to determine which factors were associated with the outcomes of interest.

Of the 766 infants who completed the first year of follow-up, 365 (47.7%) experienced an episode of acute bronchiolitis. Overall, 401 (52.3%) did not experience any episodes of wheezing, 221 developed infrequent wheezing (28.8% [25.1–31.5]), and 144 reported recurrent wheezing (18.8% [16.2–21.7]). During this first year, 48 children required hospital admission for bronchiolitis (6.3% of the whole cohort; 13.2% of those with acute bronchiolitis). Viral testing was performed in 46 (95.8%) of those hospitalized: respiratory syncytial virus (RSV) was identified in 27 (58.7%), influenza virus in two patients (4.4%), and human metapneumovirus in one patient (2.2%). Viral testing did not yield any positive results in 16 infants (34.8%). Twenty-three percent (11/48) of the hospitalized infants required admission to the pediatric intensive care unit (PICU) and two (4.2%) required mechanical ventilation.

Univariate analysis was used to examine the relationship between various factors and the three study outcomes stratified by the period of exposure (prenatal, perinatal, and postnatal). Data are shown in Table 3. Unadjusted analysis revealed that younger MA, male gender, mechanical ventilation at birth, and day care attendance were significantly associated with the development of bronchiolitis. On the other hand, parental history of asthma, day care attendance (DCA), and both prenatal and postnatal contact with farm animals were risk factors for developing recurrent wheezing. Lastly, parental history of atopy and need for mechanical ventilation were the significant factors associated with increased risk for hospitalization (Table 3).

A total of 117 (15.1%) infants received prophylaxis with palivizumab. There were no differences in the development of bronchiolitis, the rate of hospitalizations, or development of recurrent wheezing compared to those who did not (Table 3).

Independent risk factors for increased respiratory morbidity

We included in the multivariate models variables that were independently associated with outcomes of care in the univariate analysis, plus other variables of clinical interest often reported in the literature. Of those, younger MA, history of atopy in any parent, and DCA were found to be the independent predictors for most outcomes (Table 4):

1 Bronchiolitis: Adjusted for all other covariates, MA (OR [95% CI]: 1.04 [1.02–1.07]; p = 0.002), LBW (1.54 [1.04–2.27]; p = 0.032), mechanical ventilation (2.04 [1.16–3.59]; p = 0.013), DCA (2.30 [1.50–3.53]; p = 0.0001), and school-age siblings (1.48 [1.04–2.11]; p = 0.030) increased the risk for developing bronchiolitis.
2 Recurrent wheezing: Risk factors for developing recurrent wheezing during the first year of life were LBW (OR = 1.71, 95% CI: 1.06–2.76, p = 0.027), history of asthma in either parent (OR = 1.94, 95% CI: 1.14–3.30, p = 0.015), day care attendance (OR = 3.73, 95% CI: 2.30–6.03, p < 0.001), and the presence of school-age siblings (OR = 1.72, 95% CI: 1.10–2.71, p = 0.018).
3 Hospital admissions for bronchiolitis: In multivariate analyses, only one factor was found to be a significant risk factor associated with the need for hospital admission: lower MA (OR = 1.06, 95% CI: 1.01–1.36; p = 0.033) (Table 4).

Discussion

The main goal of this prospective birth cohort study was to identify the incidence and risk factors associated with respiratory disease in preterm infants born at 32–35 weeks of gestational age. We found several modifiable and not modifiable parameters to be independently associated with outcomes of care. Of those LBW, DCA and school-age siblings were consistently associated with the development of bronchiolitis and recurrent wheezing while lower MA increased the risk for bronchiolitis and subsequent related hospitalizations.

The incidence of at least one episode of wheezing during the first year of life (47.7%) was clearly higher than the prevalence

Table 3 Univariate analysis of study outcomes according to period of exposure

n = 766	Bronchiolitis in the first year of life n = 365 (47.7%)			Development of recurrent wheezing n = 144 (18.8%)			Need for hospitalization n = 48 (6.3%)		
	Risk factor present	Risk factor not present	p-value	Risk factor present	Risk factor not present	p-value	Risk factor present	Risk factor not present	p-value
Prenatal and Parental factors									
Acetaminophen use (≥1 × quarter/<1 × quarter)	88 (47.6)	267 (47.2)	1.000	35 (18.9)	106 (18.8)	0.960	10 (5.4)	38 (6.7)	0.520
Maternal tobacco use (Yes/No)	93 (50.3)	271 (46.8)	0.460	33 (17.8)	111 (19.2)	0.690	11 (5.9)	37 (6.4)	0.828
Maternal age (Mean; s.d.)*	31.2 (5.5)	32.4 (5.4)	**0.002**	31.4 (5.6)	31.9 (5.4)	0.330	30.4 (5.1)	31.9 (5.5)	0.051
Contact with animals (Yes/No)	100 (50.2)	262 (46.4)	0.401	51 (25.6)	92 (16.3)	**0.005**	17 (8.5)	31 (5.5)	0.130
Parental history of asthma (Yes/No)	78 (55.3)	287 (45.9)	0.054	36 (25.5)	108 (17.3)	**0.023**	10 (7.1)	38 (6.1)	0.650
Parental history of atopy (Yes/No)	209 (50.0)	156 (44.8)	0.176	80 (19.1)	64 (18.4)	0.790	33 (7.9)	15 (4.3)	**0.041**
Perinatal factors									
Gender (male/female)	222 (51.0)	143 (43.2)	**0.038**	89 (20.5)	55 (16.6)	0.170	27 (6.2)	21 (6.3)	0.940
Low birthweight for GA (Yes/No)	79 (53.0)	286 (46.3)	0.170	35 (23.5)	109 (17.7)	0.100	11 (7.4)	37 (6.0)	0.390
Semester of birth (Jul–Dec/Jan–Jun)	169 (47.9)	196 (47.4)	0.966	67 (19.0)	77 (18.6)	0.900	22 (5.3)	26 (7.4)	0.240
Age at the beginning of RSV season (<10 weeks/≥10 weeks)	141 (48.1)	224 (47.3)	0.895	86 (18.2)	58 (19.8)	0.570	24 (8.2)	24 (5.1)	0.080
Mechanical ventilation (Yes/No)	41 (61.2)	323 (46.4)	**0.029**	15 (22.4)	129 (18.5)	0.440	8 (11.9)	40 (5.7)	**0.032**
Postnatal factors									
Breastfeeding (≥90 days /<90 days)	133 (47.8)	227 (48.5)	0.921	52 (18.7)	91 (19.4)	0.800	13 (4.7)	35 (7.5)	0.130
Day care attendance (Yes/No)	82 (60.7)	283 (44.8)	**0.001**	47 (34.8)	97 (15.4)	**<0.001**	5 (3.7)	43 (6.8)	0.170
Household members (>4/≤4)	85 (47.2)	278 (47.9)	0.935	40 (22.2)	104 (17.9)	0.190	12 (6.7)	36 (6.2)	0.820
School-age siblings (Yes/No)	138 (52.3)	222 (45.6)	0.094	59 (22.3)	82 (16.8)	0.750	21 (8.0)	27 (5.5)	0.200
Prophylaxis with palivizumab (Yes/No)	50 (42.7)	315 (48.7)	0.278	19 (16.2)	125 (19.3)	0.430	10 (8.5)	38 (5.9)	0.270
Contact with farm animals (Yes/No)	111 (49.3)	254 (46.9)	0.601	54 (24.4)	90 (16.6)	**0.017**	17 (7.6)	31 (5.7)	0.340

*Comparison of maternal age between groups with and without bronchiolitis, with and without recurrent wheezing, with and without need for hospitalization. GA, gestational age. Data given as n (%) except for maternal age [mean (s.d.)]. Bold values represent statistically significant risk factors.

Table 4 Multivariate analysis of variables related to respiratory outcomes and hospitalization

	Bronchiolitis		Recurrent wheezing		Hospitalization	
Predictors	OR [95% CI]	p-value	OR [95% CI]	p-value	OR [95% CI]	p-value
Prenatal and parental factors						
Acetaminophen ≥ 1 × trimester	1.01 [0.70–1.45]	0.953	0.89 [0.55–1.43]	0.623	0.75 [0.34–1.67]	0.482
Maternal tobacco use	1.11 [0.77–1.61]	0.565	0.75 [0.45–1.24]	0.261	0.87 [0.40–1.88]	0.717
Maternal age	**1.04** [1.02–1.07]	**0.002**	1.02 [0.99–1.06]	0.204	**1.06** [1.01–1.36]	**0.033**
Contact with animals	1.21 [0.69–2.11]	0.509	1.89 [0.94–3.78]	0.072	1.81 [0.63–5.23]	0.273
Parental history of atopy	1.35 [0.96–1.89]	0.086	1.05 [0.67–1.65]	0.835	1.78 [0.86–3.70]	0.120
Parental history of asthma	1.40 [0.91–2.16]	0.127	**1.94** [1.14–3.30]	**0.015**	1.00 [0.44–2.30]	0.997
Perinatal						
Gender (male)	1.35 [0.99–1.85]	0.054	1.26 [0.84–1.89]	0.268	1.10 [0.58–2.08]	0.784
Low birthweight for GA	**1.54** [1.04–2.27]	**0.032**	**1.71** [1.06–2.76]	**0.027**	1.33 [0.62–2.83]	0.461
Semester of birth	0.98 [0.71–1.34]	0.884	0.93 [0.62–1.42]	0.749	1.44 [0.75–2.76]	0.272
Need for mechanical ventilation	**2.04** [1.16–3.59]	**0.013**	1.11 [0.55–2.24]	0.780	2.17 [0.88–5.38]	0.093
Postnatal						
Breastfeeding (> 90 days)	0.92 [0.66–1.27]	0.599	0.87 [0.56–1.35]	0.541	0.69 [0.33–1.44]	0.324
Day care attendance	**2.30** [1.50–3.53]	**0.0001**	**3.73** [2.30–6.03]	**0.000**	0.51 [0.18–1.42]	0.198
Household members (>4)	1.05 [0.70–1.56]	0.828	1.19 [0.72–1.96]	0.508	0.86 [0.38–1.93]	0.709
School-age siblings (>1)	**1.48** [1.04–2.11]	**0.030**	**1.72** [1.10–2.71]	**0.018**	1.86 [0.94–3.68]	0.073
Prophylaxis with palivizumab	0.67 [0.43–1.06]	0.087	0.83 [0.44–1.59]	0.581	0.74 [0.30–1.83]	0.519
Contact with animals	0.95 [0.55–1.64]	0.852	0.85 [0.43–1.70]	0.648	1.02 [0.35–2.98]	0.964

Bold values represent statistically significant risk factors.

reported in Europe (34.4%), while the incidence of recurrent wheezing was only slightly increased (18.8% vs. 15.0%) (3). Although not completely comparable due to differences in study design and the definitions of respiratory morbidity, other studies performed in high-risk infants, mostly born prematurely with very LBW, have reported a higher incidence of wheezing, ranging from 38.9% to 65% (14–16).

On the other hand, our results are similar to that reported in the control group of a recent randomized clinical trial in whom the incidence of any wheezing and recurrent wheezing in infants born at 33–35 weeks of GA who received placebo were 47% and 20.9%, respectively (17). In addition, in agreement with our findings, a systematic review of respiratory morbidity in preterm infants born between 32 and 36 weeks of gestation suggested that the respiratory vulnerability in this group during the following years is higher than what was originally thought. In that study, the authors showed that preterm infants present a higher rate of lower respiratory tract infections, increased incidence of wheezing, impaired lung function, increased rates of hospital readmission, and longer hospital stays (18).

We found younger MA, LBW, need for mechanical ventilation during the neonatal period, day care attendance, and school-age siblings to be independently associated with the development of bronchiolitis. The latter two factors have been also found to increase the risk of respiratory morbidity in infants from the general population (3). We also found that parental history of asthma, LBW, school-age siblings, and DCA were risk factors for the development of recurrent wheezing during the first year of life. Of those, DCA was found to be the most significant risk factor, which is in agreement with previous studies conducted in term (3, 19) and preterm infants (20).On the other hand, we did not find differences in respiratory morbidity between infants that had been breastfed for less or more than 90 days. This lack of association could be explained by the small sample size compare to other studies such as that conducted by Oddy et al. who reported that breastfeeding between 1 and 4 months of age could reduce respiratory morbidity during the first year of life (21). Surprisingly, we did not find a relationship between cigarette smoking during pregnancy and respiratory disease, contrary to other reports in the literature (22, 23). According to previous studies, tobacco use during pregnancy is associated with both respiratory diseases and infection. In our study, only 24.2% of the mothers reported smoking during pregnancy. Unfortunately, information about tobacco use was entirely based on self-reported information and thus is not entirely reliable (24) for drawing definitive conclusions.

In contrast to other reports, we did not find that the semester of birth, or chronological age in weeks at the beginning of the RSV season increased the risk for both the development of bronchiolitis and the need for related hospitalizations (22, 25), which could be partially explained considering that we divided the time of birth in semesters (Jan–Jun and July–Dec) rather than month of birth.

RSV is the leading cause of hospitalization in infants worldwide, with at least 3.4 million children <5 years requiring hospitalization for RSV-associated lower respiratory tract infections (LRTI) each year (26). In Spain, previous studies have shown that the rate of hospital admission for RSV is approximately 3.5% in infants, and as high as 15–20% in <32 weeks of GA preterm neonates (27). In our study, 6.2% of premature infants required hospitalization for bronchiolitis,

and RSV infection was identified as the causal pathogen in more than half of those (56.3%), a rate similar to that reported in other studies (25, 28). Case–control studies conducted by the Spanish IRIS study group (29) found independent risk factors for RSV-related hospitalizations in preterm infants born between 33 and 35 weeks of gestational age. Of those factors, chronological age ≤10 weeks at the start of the RSV season, school-age siblings, and smoking during pregnancy were confirmed in subsequent studies (22) leading to specific recommendations for the use of palivizumab. In contrast, and possibly due to differences in study design (case–control vs. a birth cohort study), we only found younger MA to increase the risk of hospitalization. We also explored the possible effect of prophylaxis with palivizumab in our cohort, but in contrast to previous reports (22, 30), we did not find differences in the frequency of bronchiolitis, hospitalization rates, or wheezing in premature infants who received or not anti-RSV prophylaxis. This could be partially explained by the fact that a small group of infants received prophylaxis (15% of the whole cohort) and few infants were hospitalized in our cohort (n = 48, 6.3%) with RSV infection identified in only 27, thus not allowing a fair comparison with those studies.

Our study has limitations, some of which are inherent to the study design, as no direct comparison with a cohort of term infants was conducted. Various epidemiologic factors were self-reported by the parents, which may lead to inaccuracy in some cases. On the other hand, our methodology allowed for very thorough prospective data collection and analysis. The sample size was sufficient to analyze the main study outcome (development of recurrent wheezing), but possibly underpowered for the other additional outcomes, which warrant future prospective studies possibly including international sites. Lastly, viral testing was not systematically performed at bronchiolitis or recurrent wheezing diagnosis; however, 95.8% of infants who required hospitalization for respiratory-related problems underwent viral testing.

Conclusions

We showed that the incidence of respiratory morbidity in premature infants born between 32 and 35 weeks of gestational age during the first year of life was significant. Both unmodifiable (family history of asthma, LBW, need for mechanical ventilation) and, more importantly, modifiable parameters (young MA, DCA, or exposure to school-age siblings) were identified as significant risk factors for the development of bronchiolitis and recurrent wheezing during the first year of life. Targeted interventions to prevent or limit the development of respiratory morbidity and the associated costs should be a high priority for both moderate and late premature infants.

Acknowledgments

The authors acknowledge the collaboration of Alce Ingeniería (Las Rozas, Madrid, Spain) in the development of the project support systems and statistical analysis, and the editorial support of Dr Blanca Piedrafita of Medical Statistics Consulting (Valencia, Spain) in the writing of this manuscript.

References

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995: **332**: 133–8.
2. Young S, Arnott J, O'Keeffe PT, Le Souef PN, Landau LI. The association between early life lung function and wheezing during the first 2 yrs of life. *Eur Respir J* 2000: **15**: 151–7.
3. Garcia-Marcos L, Mallol J, Sole D, Brand PL, Group ES. International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. *Pediatr Allergy Immunol* 2010: **21**: 878–88.
4. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003: **111**: 661–75; quiz 76.
5. Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev* 2004: **5**: 155–61.
6. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med* 1999: **159**: 403–10.
7. Rusconi F, Galassi C, Corbo GM, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. *Am J Respir Crit Care Med* 1999: **160**: 1617–22.
8. Palmer LJ, Rye PJ, Gibson NA, Burton PR, Landau LI, Lesouef PN. Airway responsiveness in early infancy predicts asthma, lung function, and respiratory symptoms by school age. *Am J Respir Crit Care Med* 2001: **163**: 37–42.
9. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005: **171**: 231–7.
10. Altman M, Vanpee M, Cnattingius S, Norman M. Neonatal morbidity in moderately preterm infants: a Swedish national population-based study. *J Pediatr* 2011: **158**: 239–44. e1.
11. Hibbard JU, Wilkins I, Sun L, et al. Respiratory morbidity in late preterm births. *JAMA* 2010: **304**: 419–25.
12. Elder DE, Hagan R, Evans SF, Benninger HR, French NP. Recurrent wheezing in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1996: **74**: F165–71.
13. Hulskamp G, Pillow JJ, Dinger J, Stocks J. Lung function tests in neonates and infants with chronic lung disease of infancy: functional residual capacity. *Pediatr Pulmonol* 2006: **41**: 1–22.
14. Greenough A, Maconochie I, Yuksel B. Recurrent respiratory symptoms in the first year of life following preterm delivery. *J Perinat Med* 1990: **18**: 489–94.
15. Halterman JS, Lynch KA, Conn KM, Hernandez TE, Perry TT, Stevens TP. Environmental exposures and respiratory morbidity among very low birth weight infants at 1 year of life. *Arch Dis Child* 2009: **94**: 28–32.
16. Holditch-Davis D, Merrill P, Schwartz T, Scher M. Predictors of wheezing in prematurely born children. *J Obstet Gynecol Neonatal Nurs* 2008: **37**: 262–73.
17. Blanken MO, Rovers MM, Bont L, Dutch RSVNN. Respiratory syncytial virus and recurrent wheeze. *N Engl J Med* 2013: **369**: 782–3.
18. Colin AA, McEvoy C, Castile RG. Respiratory morbidity and lung function in preterm infants of 32 to 36 weeks'

gestational age. *Pediatrics* 2010: **126**: 115–28.
19. Hagerhed-Engman L, Bornehag CG, Sundell J, Aberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. *Allergy* 2006: **61**: 447–53.
20. Hagen EW, Sadek-Badawi M, Palta M. Daycare attendance and risk for respiratory morbidity among young very low birth weight children. *Pediatr Pulmonol* 2009: **44**: 1093–9.
21. Oddy WH, Sly PD, de Klerk NH, et al. Breast feeding and respiratory morbidity in infancy: a birth cohort study. *Arch Dis Child* 2003: **88**: 224–8.
22. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jimenez J, et al. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. *Pediatr Infect Dis J* 2008: **27**: 788–93.
23. Haberg SE, Stigum H, Nystad W, Nafstad P. Effects of pre- and postnatal exposure to parental smoking on early childhood respiratory health. *Am J Epidemiol* 2007: **166**: 679–86.
24. Dietz PM, Homa D, England LJ, et al. Estimates of nondisclosure of cigarette smoking among pregnant and nonpregnant women of reproductive age in the United States. *Am J Epidemiol* 2011: **173**: 355–9.
25. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J* 2004: **23**: 806–14.
26. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010: **375**: 1545–55.
27. Valverde MJ, Korta MJ. Bronquiolitis. In: Andrés Martín A, Valverde Molina V, eds. *Manual de Neumología Pediátrica*. Madrid: Ed. Panamericana, 2011: 205–14.
28. Doering G, Gusenleitner W, Belohradsky BH, Burdach S, Resch B, Liese JG. The risk of respiratory syncytial virus-related hospitalizations in preterm infants of 29 to 35 weeks' gestational age. *Pediatr Infect Dis J* 2006: **25**: 1188–90.
29. Russell T, Crawford M, Woodby L. Measurements for active cigarette smoke exposure in prevalence and cessation studies: why simply asking pregnant women isn't enough. *Nicotine Tob Res* 2004: **6** (Suppl 2): S141–51.
30. Langley GF, Anderson LJ. Epidemiology and prevention of respiratory syncytial virus infections among infants and young children. *Pediatr Infect Dis J* 2011: **30**: 510–7.

Appendix

SAREPREM 3235 Project Investigators:

A. Aldasoro, P. Corcuera y J. Korta (H.U. Donostia, San Sebastián, Spain), J. Bosch, G. Morera y M. Mumany (H.U. Vall d'Hebron, Barcelona, Spain), J. Batlles-Garrido y Y. González-Giménez (H. Torrecárdenas, Almería, Spain), T. Romero y J. Morata (H. Clínico U. de Valencia, Spain), M. Navarro-Merino (H.U. Virgen Macarena, Sevilla, Spain), M. Sanchez-Solis y P. Mondejar Lopez (H. Clínico Universitario Virgen de la Arrixaca, Murcia, Spain), Francisca Gómez-Acebo (H.U. 12 de Octubre, Madrid, Spain).