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ORIGINAL ARTICLE

Respiratory morbidity, atopy and asthma at school age in preterm infants aged 32–35 weeks

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Abstract

Little is known about respiratory morbidity and asthma risk in preterm infants (PTIs) with a gestational age (GA) over 32 weeks. This was a prospective study carried out from birth to 7–8 years, comparing two groups: (a) PTIs (GAs 32 weeks + 1 day to 35 weeks + 0 days, without comorbidities) and (b) full-term infants (FTIs; GA ≥ 37 weeks). Risk and protective factors for bronchiolitis and asthma were identified. A total of 232 children (116/group) were included. Sixty-six (56.9%) PTIs and 43 (37.1%) FTIs presented bronchiolitis ($p = 0.002$). Recurrent wheezing was 52 (44.8%) on PTIs versus 36 (31.0%) on FTIs ($p = 0.03$). Asthma at school aged was 27 (23.3%) on PTIs and 8 (6.9%) on FTIs ($p = 0.020$). Asthma risk factors were only detected in group A.

Conclusion: PTIs had a higher prevalence of bronchiolitis, recurrent wheezing and asthma; risk factors for asthma are the following: older siblings, allergic father, atopic dermatitis and antibiotic treatment in the first 3 years of life and prematurity itself, which also acted as protective factor for atopic dermatitis.

What is known:

- *In recent decades, there has been a significant increase in the birth of premature babies and consequently, also in the pathologies secondary to the prematurity: a greater number of complications and disorders related to the development and maturation of many organs and systems, especially the respiratory system. Several studies, especially in full-term infants and very preterm infants, have tried to elucidate the risk factors that may influence the development of persistent or chronic respiratory problems such asasthma, but little is known about the aetiology of these disorders in the late or moderate preterm infants. Inthis group of children, the role played by certain factors (early use of antibiotics, chorioamnionitis, smokeexposure, paternal asthma, etc.) on late respiratory morbidity, or asthma, is inconclusive.*
- *Moderate-to-late preterm infants are more predisposed to developing recurrent wheezing/asthma and should adopt control measures.*

What is new:

- *Our work provides data related to little-understood aspects of respiratory diseases in this group of late or moderate preterm infants (gestational age between 32 weeks plus 1 day and 35 weeks plus 0 days), by monitoring their evolution from birth to 7–8 years of age, compared with another group of full-term newborns. We aimed to establish the prevalence of bronchiolitis and recurrent wheezing in these children during their first years of life.*
- *The prevalence of school-aged asthma and the risk factors for contracting it were also investigated.*

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Keywords Prematurity · Asthma · Atopy · Risk factors · Bronchiolitis · Recurrent wheezing

Abbreviations

BDT	Bronchodilator test
BMI	Body mass index
CIs	Confidence intervals
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
FEV_1/FVC	Tiffeneau–Pinelli index
FTIs	Full-term infants
GINA	Global Initiative for Asthma
GA	Gestational age
ISAAC	International Study of Asthma and Allergies in childhood
IgE	Immunoglobulin E
IVF	In vitro fecundation
mAPI	Modified asthma predictive index
MEF25–75	Maximal expiratory flow rate at 25–75% o f forced vital capacity
N	Number of responses
NBs	Newborns
OR	Odds ratio
ppb	Parts per billion
PTIs	Preterm infants
RSV	Respiratory syncytial virus
SD	Standard deviation
TAPQOL	Preschool Children's Quality of Life Questionnaire

Introduction

Currently, 11% of newborns (NBs) are premature [1], predominantly those of later gestational age (GA): 84% are between 32 and 36 weeks [1]. Several studies carried out over many years have tried to determine the risk factors that may influence the development of chronic respiratory diseases such as asthma in the early stages of life [2–16]. In this sense, prematurity itself could be a risk factor. Most of these studies were undertaken in full-term infants (FTIs) and very preterm infants [17, 18], but only a few have been carried out in late or moderate preterm infants [2, 19–22]. As such, it is unknown whether the outcomes in the latter are more like FTIs or if they are more similar to immature preterm infants. This study aimed to determine the prevalence of asthma at 6–8 years of age, as well as the factors which may protect against it, in a group of moderate-to-late NBs delivered between 32 weeks + 1 day and 35 weeks + 0 days. It was initially part of a Spanish multicentric study (SAREPREM) whose results were published in 2015 [20].

Materials and methods

This was a prospective, longitudinal and observational study carried out from birth to 6–8 years in two groups of children born in a tertiary hospital: group A consists of PTIs born at a GA between 32 and 35 weeks, with no comorbidities, and group B consists of FTIs (GA exceeding 37 weeks). The project was approved by the Ethics Committee at the Hospital Clínico Universitario in Valencia (Spain), and all patients' guardians signed a letter of informed consent.

Patient inclusion and exclusion criteria

All the children born at the Hospital Clínico Universitario, Valencia, Spain, between October 2006 and April 2008 with a GA between 32 weeks + 1 day and 35 weeks + 0 days (group A), or at 37 weeks or more (group B), were included. All NBs with chronic lung disease (including bronchopulmonary dysplasia), airway, lung and/or gastrointestinal malformations, congenital heart disease, chromosomopathies, immunodeficiencies, chronic neurological, renal and/or gastrointestinal diseases or any other condition that might be associated with an increased risk of respiratory morbidity were excluded.

Study design

The children were followed-up at seven visits (every 6 months up to 3 years of age, with a final visit at 7–8 years).

Variables and follow-up protocol

Respiratory morbidity

At each visit, demographic (sex, gestational age, mother's age, father's age), anthropometric (birth weight, weight, size and body mass index) and socio-environmental variables (number of siblings, caregiver presence, child care assistance, maternal/paternal smokers, urban/rural environment, immunisations) were recorded; the family and personal background (allergy or asthma), as well as episodes of atopy and respiratory disease experienced by each child (acute bronchiolitis and recurrent wheezing), were also noted (Table 1). The children's guardians completed the Spanish version of the Preschool Children's Quality of Life (TAPQOL) questionnaire [23] and, on the last visit, the Spanish version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [24].

Acute bronchiolitis was defined as the first infectious process of the lower respiratory tract in children younger than 2 years, manifested as bronchospasm and respiratory distress.

Recurrent wheezing was defined as three or more episodes of tachypnoea, dyspnoea or wheezing per year. Asthma is defined as persistent or recurrent broncho-obstructive symptoms (cough, wheezing and/or dyspnoea) with a good response to bronchodilators, along with an affirmative answer to the ISAAC questionnaire [24] question: "*Have you had any wheezing in the past 12 months*?" The existence of an obstructive spirometry pattern, positive bronchodilator test (BDT) result, exhaled fraction of nitric oxide (FeNO) exceeding 25 ppb and atopy were positive indicators, but not required for a diagnosis of asthma.

Complementary tests

Pulmonary function At the last visit at 7–8 years of age, all the children underwent forced spirometry with a BDT (Master V5.1 Spirometer, Viasys Healthcare, Würzburg, Germany). According to the Global Initiative for Asthma GINA [25], an obstructive spirometry pattern is diagnosed when the forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) are less than 80%; the FEV_1/FVC (Tiffeneau–Pinelli index) is less than 80–85%, and the maximal expiratory flow rate at 25–75% of the FVC (MEF25–75) is less than 65% of the predicted value. The BDT was considered positive when there was a 12% increase in the FEV_1 compared with baseline, or it was 9% of its predicted value after administration of 400 μg salbutamol[25].

Eosinophilic bronchial inflammation Eosinophilic bronchial inflammation was assessed by determining FeNO with a portable device (online electrochemical method, NIOX MINO®, Aerocrine Sweden). Values exceeding 25 ppb were considered indicative of inflammation [26].

Allergy Skin prick testing was performed on all the children for 18 different respiratory allergens with a positive control (10 mg/mL histamine) and a negative control (glycerol-saline carrier solution). Papule diameters exceeding 3 mm with respect to the diluent control, or equal to or exceeding that obtained with histamine, were considered positive.

Biological samples

In all cases, at the last visit of the study, a peripheral blood sample was obtained to analyse the blood count, renal function and immunoglobulin E (IgE). In bronchiolitis that required hospital care (emergency or admitted), respiratory syncytial virus (RSV) was analysed in respiratory secretion samples.

Statistical analysis

Frequencies were estimated with 95% confidence intervals (95% CIs), and the mean, median, quartiles and standard deviations (SDs) were obtained for continuous variables. Prenatal, neonatal and postnatal variables were studied using descriptive and bivariate analysis (Pearson correlation coefficients, chi square and ANOVA tests). A simple analysis of the qualitative variables was done using frequency tables and quantitative variables with descriptive statistics (*N*, minimum and maximum values, mean and SD). Multivariate logistic mixed-models with random effects were created to identify independent risk factors associated with the outcomes of interest: bronchiolitis, recurrent wheezing and asthma, and the odds ratios (ORs) and 95% CI were estimated.

Results

A total of 232 children were included in the study (116 PTIs and 116 FTIs), and all of them were followed-up to the endpoint at 7–8 years of age Table 1; 14 children (6%), all PTIs, received palivizumab. Acute bronchiolitis was present in 66 (56.9%) children from group A and 43 (37.1%) from group B ($p = 0.002$). In the first 3 years of life, PTIs had a higher rate of hospital admissions (respiratory distress or need for supplemental oxygen) than FTIs (48.7% versus 5.2%; $p = 0.013$), had more respiratory infections and took more antibiotics (53.4% versus 44.8%; $p < 0.001$). RSV screening was performed in all children requiring hospital care (emergency or admitted) for bronchiolitis; 56 (48.7%) were PTIs and 14 (12.1%) were FTIs; only 3 (2.6%) FTIs (and no PTIs) were positive for RSV ($p < 0.001$). In groups A and B, 52 (44.8%) and 36 (31%) children, respectively, had recurrent wheezing up to 5 years of age ($p = 0.03$), and the severity of these episodes was similar, requiring maintenance treatment in 90.4% of the PTIs and 83.3% of the FTIs (no statistical differences).

At the last visit, from the eight questions on the ISAAC survey for asthma, the following were affirmatively answered and were statistically different between the groups:

1. Has your child ever had wheezing or whistling in the chest at any time in the past? 22 (18.9%) PTIs and 11 (9.5%) FTIs ($p = 0.039$)
2. Has your child had wheezing or whistling in the chest in the past 12 months? 27 (23.3%) PTIs and 8 (6.9%) FTIs ($p < 0.001$)
3. How many attacks of wheezing had your child in the past 12 months? One to three attacks, 23 (19.8%) PTIs and 5 (4.3%) FTIs ($p = 0.029$)
4. In the past 12 months, had your child's chest sounded wheezy during or after exercise? 17 (14.6%) PTIs and 7 (6%) FTIs ($p = 0.031$)

Table 1 Demographic, anthropometric and clinical characteristics of preterm and full-term infants

	PTI	FTI	Statistical validity
Ethnicity	Caucasian, $N = 103$ (88.8%) Gypsy, $N = 5$ (4.3%)	Caucasian, $N = 113$ (97.4%) Gypsy, $N = 3$ (2.6%)	NS
	Arabic, $N = 4$ (3.4%)	Arabic, $N = 0$	
	Chinese, $N = 1$ (0.9%)	Chinese, $N = 0$	
	Other, $N = 3$ (2.6%)	Other, $N = 0$	
Maternal age	Age mean, 32.2 years SD = 4.2 years	Age mean, 32.7 years SD, 4.5 years	NS
Smoking mother during pregnancy	$N = 35$ (30.2%)	$N = 47$ (40.5%)	NS
Allergic mother	$N = 20$ (17.2%)	$N = 21$ (18.1%)	NS
Asthmatic mother	$N = 9$ (7.8%)	$N = 18$ (15.5%)	NS
Smoking father during pregnancy	$N = 37$ (31.9%)	$N = 47$ (40.5%)	NS
Allergic father	$N = 7$ (6%)	$N = 21$ (18.1%)	$p = 0.005$
Asthma father	$N = 2$ (1.7%)	$N = 12$ (10.3%)	$p = 0.006$
Allergic family	$N = 27$ (23.3%)	$N = 36$ (31%)	NS
Asthmatic family	$N = 11$ (9.5%)	$N = 27$ (23.3%)	$p = 0.005$
In vitro fecundation	$N = 39$ (33.6%)	$N = 6$ (5.2%)	$p < 0.001$
Multiple pregnancy	$N = 46$ (39.7%)	$N = 0$	$p < 0.001$
Gestational diabetes; preeclampsia; chorioamnionitis	$N = 18$ (15.5%)	$N = 3$ (2.6%)	$p = 0.001$
	$N = 19$ (8.2%)	$N = 3$ (2.6%)	$p = 0.002$
	$N = 5$ (4.3%)	N, 0	$p = 0.024$
Type of birth	Vaginal, $N = 42$(36.2%); caesarean section, $N = 72$ (62.1%); instrumented, $N = 2$ (1.7%)	Vaginal, $N = 94$ (81%); caesarean section, $N = 0$; instrumented, $N = 22$ (19%)	$p < 0.001$
Apgar score	Mean 9/10; SD 1/0.2	Mean 9/10; SD 1.2/0.5	NS
Month of birth	April (14.7%); January (12.9%); October (11.2%)	April (17.2%); March (16.4%); October (12.9%)	NS
Birth weight	Mean 1941.65 g; SD 383.83 g	Mean 3377.38 g; SD 405.29 g	$p < 0.001$
Neonatal disease (jaundice; sepsis; oxygen therapy)	$N = 35$ (30.2%); $N = 1$ (0.9%); $N = 33$ (28.4%)	$N = 4$ (3.4%); $N = 0$; $N = 3$ (2.6%)	$p < 0.001$
Transient tachypnoea/pneumonia/hyaline membrane	$N = 13$ (11.2%) $N = 1$ (0.9%) $N = 2$ (1.7%)	$N = 3$ (2.5%) $N = 0$ $N = 0$	$p < 0.001$
Invasive mechanical ventilation	$N = 23$ (19.8%)	$N = 0$	$p < 0.001$
Noninvasive mechanical ventilation	$N = 27$ (23.3%)	$N = 0$	$p < 0.001$
Breastfeeding/bottle feeding	$N = 38$ (32.7%)/$N = 51$ (44%)	$N = 87$ (75%)/$N = 23$ (19.8%)	$p < 0.001$
Duration of (lactation 36 months)	$N = 3$ (2.6%)	$N = 6$ (5.2%)	$p < 0.001$
Older brothers	$N = 22$ (19%)	$N = 70$ (60.3%)	$p < 0.001$
Rural/urban environment	$N = 23$ (19.8%)/$N = 93$ (80.2%)	$N = 34$ (29.3%)/$N = 82$ (70.7%)	NS
Weight gain exceeding three percentiles	$N = 12$ (10.3%)	$N = 3$ (2.6%)	$p < 0.001$
Day care	$N = 92$ (79.3%)	$N = 101$ (87.1%)	NS
Immunisations, including pneumococcus	$N = 109$ (94%)	$N = 95$ (81.9%)	$p < 0.001$
Palivizumab	$N = 14$ (12.1%)	$N = 0$	$p < 0.001$
Egg allergy	$N = 4$ (3.4%)	$N = 0$	p, 0.044
Atopic dermatitis in infant/6–8 years old	$N = 35$ (30.2%)/$N = 9$ (7.8%)	$N = 52$ (44.8%)/$N = 34$ (29.3%)	$p = 0.021/p < 0.001$
No antibiotics during first 3 years	$N = 62$ (53.4%)	$N = 52$ (44.8%)	NS
Final study age (6/7/8 years)	$N = 16$ (13.8%); $N = 19$ (16.4%); $N = 81$ (69.8%)	$N = 4$ (3.4%); $N = 0$; $N = 112$ (96.6%)	$p < 0.001$
Body mass index at study end-point	Mean 16.5; SD = 2.3	Mean 17.7; SD = 1.7	$p < 0.001$

PTIs, preterm infants; *FTIs*, full-term infants; *NS*, not significant

Based on an affirmative answer to question 2, which is used by validation studies to define asthma [27], the prevalence of asthma in our study was higher in group A (27 children; 23.3%) than that in group B (8 children; 6.9%; $p < 0.001$).

The mean spirometric values were normal in both groups (Table 4; Fig. 1), although overall, they were higher in FTIs and the difference reached statistical significance for FEV_1 ($p = 0.001$); accounting for the SDs (Table 4) were 27 PTIs (23.3%) and 8 FTIs (6.9%) which presented an obstructive spirometry pattern coincided with those considered asthmatic by the ISAAC criteria; the BDT was positive in 31 (88.6%) of the 35 asthmatic children, 27 (77.1%) PTIs and 8 (22.8%) FTIs. FeNO exceeding 25 ppb was predominant in PTIs ($N = 27$, 23.3%) compared with the FTIs ($N = 8$, 6.7%; $p < 0.001$) and coincided with those with an obstructive spirometric pattern also diagnosed with asthma. There was also a significant correlation ($p = 0.019$) between elevated FeNO and atopic dermatitis: 23 (85.7%) PTIs and 4 (14.3%) FTIs.

Prematurity (32–35 weeks GA) was a risk factor for asthma: there was a significant correlation between GA and the FEV_1 and Tiffeneau–Pinelli index parameters which indicates on obstructive spirometric pattern. Prophylaxis with palivizumab in PTIs was a protective factor against an obstructive spirometry pattern at 7–8 years of age. The total PTIs that received palivizumab were16.2% with an obstructive pattern compared with 83.8% who did not receive it ($p < 0.001$). IgE and eosinophil values in peripheral blood were similar in both groups, with only slight insignificant increases in IgE values in FTIs. There were no statistically significant relationships between these values and the GA.

During the infant period, 30.2% of the PTIs ($N = 35$) and 44.8% of the FTIs ($N = 52$; $p = 0.021$) were diagnosed with atopic dermatitis, whereas at 7–8 years of age, 7.8% of the PTIs and 29.3% of the FTIs ($p < 0.001$) had the same diagnosis. Moreover, atopic dermatitis did not increase the risk of recurrent wheezing. Of those who presented recurrent wheezing, 42.3% ($N = 22$) of the PTIs and 47.2% ($N = 17$) of the FTIs were atopic ($p = 0.03$). The skin prick test for aeroallergens was positive in a total of 12.5% ($N = 29$) of all the children (5.2%, $N = 6$ in group A and 19.8%, $N = 23$ in group B; $p = 0.001$). There were no statistically significant relationships between asthma, allergic sensitisation or eosinophilia.

The risk factors for bronchiolitis in PTIs were the following: female gender ($p = 0.020$), allergic mother ($p = 0.019$), maternal age over 32 years ($p = 0.022$), day care attendance ($p = 0.040$), urban environment ($p = 0.050$), low birth weight ($p = 0.020$) and July–December birth month ($p = 0.020$). For FTIs, they were maternal asthma ($p < 0.001$) and smoking father during pregnancy ($p = 0.003$). In both groups (PTIs/FTIs), they were atopic dermatitis ($p = 0.030/p = 0.027$) and having older siblings ($p = 0.016/p < 0.001$). The protective factors for PTIs were the following: in vitro fecundation (IVF; $p = 0.050$), multiple pregnancy ($p = 0.020$), non-smoking father during pregnancy ($p = 0.01$), breastfeeding ($p = 0.013$) and a weight gain of less than two percentiles in the first year of life ($p = 0.010$). For FTIs, only IVF was found to be a protective factor ($p = 0.001$; Tables 2 and 3).

There were no risks or protective factors for asthma in FTIs, but in PTIs, the risk factors were the following: having

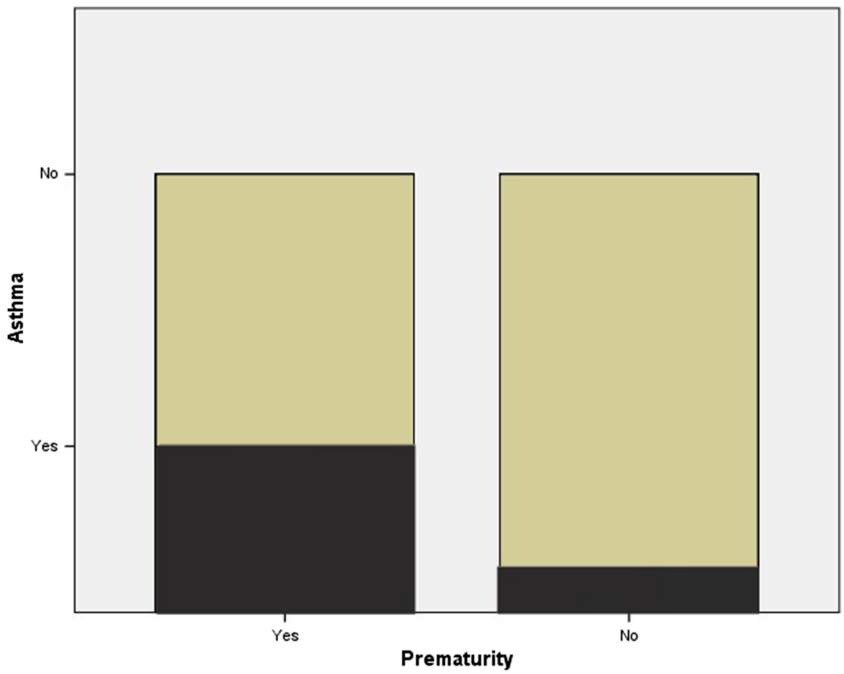

Fig. 1 Prevalence of asthma in preterm and full-term infants

an older siblings (OR = 4.77, 95% CI = 2.24–10.16, $p < 0.001$), an allergic father (OR = 3.60, 95% CI = 1.58–8.20, $p = 0.040$), atopic dermatitis at school age (OR = 3.30, 95% CI = 1.64–6.65, $p = 0.020$), atopic dermatitis in infancy (OR = 2.41, 95% CI = 1.11–5.2, $p = 0.020$), antibiotic treatment in the first 3 years of life (OR = 2.36, 95% CI = 1.25–4.47, $p = 0.005$) and Caucasian ethnicity (OR = 177, 95% CI = 1.05–2.98, $p = 0.030$) (Tables 2 and 3). The only factor that was protective against asthma in the PTIs was a weight gain of three percentiles or more in the first year of life (OR = 0.65, 95% CI = 0.45–0.99, $p = 0.030$) (Tables 2 and 3).

The overall TAPQOL score, at age 7–8, was low in both PTIs and FTIs (19.9 and 17.7 points, respectively), indicating that both groups had a good quality of life; there were no significant differences between asthmatics and non-asthmatics. Children with recurrent wheezing achieved worse results in the respiratory assessment scales, but there were no differences on the other scales.

Discussion

The prevalence of bronchiolitis, recurrent wheezing and asthma at 7–8 years was significantly higher among 32–35-week GA PTIs than among FTIs.

Research on the risk factors for both early or late respiratory morbidity has been the subject of multiple studies, most of them in children born at term and without previous respiratory disease [4, 6, 8]; studies in PTIs usually analyse very preterm cases [17, 18]. It is known that up to one-third of FTIs will present recurrent wheezing linked to respiratory infections, during their first 3 years of life [28] and contrary to original beliefs, Colin et al. [2] reported that after birth, the respiratory vulnerability of 32–36-week GA children is closer to that of PTIs with a GA of less than 32 weeks than that of FTIs.

Our data echo those of this latter study [2], with 47% ($N = 109$) of all the children being diagnosed with bronchiolitis; more than half of them were PTIs (56.9%, $N = 66$; mean GA of 34 weeks + 6 days) and about one-third (37.1%, $N = 43$) were FTIs (mean GA of 39 weeks + 6 days). There was a significant relationship between bronchiolitis and prematurity, with a higher prevalence in 32–35-week GA NBs than in FTIs, similar to that reported in preterm infants born at a GA of less than 32 weeks [2]. The hospital admission rate due to bronchiolitis was also higher in PTIs ($N = 56$, 48.7%) than in FTIs ($N = 6$, 5.2%, $p = 0.013$), but we were unable to determine if this was due to greater severity or because doctors are more cautious in this risk group. In contrast, the majority of FTIs with bronchiolitis ($N = 37$, 86%) were treated at home. PTIs also tended to be diagnosed with bronchiolitis earlier

Table 2 Multivariate analysis of risk and protective factors for bronchiolitis and asthma in preterm infants

	Bronchiolitis		Asthma	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Older siblings	OR = 5.8, CI = 1.11–2.08	$p = 0.016$	OR = 4.77, CI = 2.24–10.16	$p < 0.001$
Allergic mother	OR = 2.1, CI = 1.07–4.1	$p = 0.019$	No risk or protective factor	
Female gender	OR = 2, CI = 1.2–3.15	$p = 0.020$	No risk or protective factor	
Urban environment	OR = 1.7, CI = 1.15–2.4	$p = 0.050$	No risk or protective factor	
Atopic dermatitis in infancy	OR = 1.6, CI = 1.2–2.3	$p = 0.030$	OR = 2.41, CI = 1.11–5.2	$p = 0.020$
Caucasian ethnicity	OR = 1.58, CI = 1.20–2.10	$p = 0.001$	OR = 1.77, CI = 1.05–2.98	$p = 0.030$
Maternal age (over 32 years)	OR = 1.56, CI = 1.17–2.06	$p = 0.022$	No risk or protective factor	
Low birth weight	OR = 1.56, CI = 1.17–2.01	$p = 0.020$	No risk or protective factor	
Birth month (July–December)	OR = 1.56, CI = 1.17–2.07	$p = 0.020$	No risk or protective factor	
Day care	OR = 1.4, CI = 1.0–1.9	$p = 0.040$	No risk or protective factor	
Antibiotic treatment in the first 3 years of life	No risk or protective factor		OR = 2.36, CI = 1.25–4.47	$p = 0.005$
Non-smoking father during pregnancy	OR = 0.65, CI = 0.49–0.85	$p = 0.01$	No risk or protective factor	
In vitro fecundation	OR = 0.59, CI = 0.45–0.76	$p = 0.050$	No risk or protective factor	
Multiple pregnancy	OR = 0.43, CI = 0.25–0.73	$p = 0.020$	No risk or protective factor	
Breastfeeding	OR = 0.37, CI = 0.17–0.822	$p = 0.013$	No risk or protective factor	
Weight gain of less than two percentiles in the first year of life	OR = 0.37, CI = 0.2–0.67	$p = 0.010$	No risk or protective factor	
Allergic father	No risk or protective factor		OR 3.60, CI = 1.58–8.20	$p = 0.040$
Atopic dermatitis at school age	No risk or protective factor		OR = 3.30, CI = 1.64–6.65	$p = 0.020$
Weight gain equal or greater than thee percentiles in the first year of life	No risk or protective factor		OR = 0.65, CI = 0.45–0.99	$p = 0.030$

Table 3 Multivariate analysis of risk and protective factors for bronchiolitis and asthma in full-term infants

	Bronchiolitis		Asthma	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Maternal asthma	OR = 8.3, CI = 2.5–27.45	$p < 0.001$	No risk or protective factor	
Older siblings	OR = 7.47, CI = 2.8–19.9	$p < 0.001$	No risk or protective factor	
Smoking father during pregnancy	OR = 3.2, CI = 1.47–7.06	$p = 0.003$	No risk or protective factor	
Atopic dermatitis during infancy	OR = 2.37, CI = 1.1–5.1	$p = 0.027$	No risk or protective factor	
In vitro fecundation	OR = 0.34, CI = 0.26–0.44	$p = 0.001$	No risk or protective factor	

(before 6 months of age; $N = 27$, 23.3%) than FTIs ($N = 21$, 18.1%; $p = 0.029$). Therefore, GA is a risk factor for bronchiolitis [13, 20] and significantly correlates with its earlier onset.

In our series, more than a third (39.1%) of the children diagnosed with bronchiolitis were born during the RSV epidemic season, although the virus was only detected in three cases, all in FTIs (2.5%).

RSV screening was only performed on children requiring hospital care (emergency or admitted) for bronchiolitis, and there were patients diagnosed with bronchiolitis during the RSV season or not. This may be the reason for the low percentage of positive tests for RSV.

Therefore, unlike other studies [29, 30], we cannot use our data to draw any conclusions regarding RSV risk in PTIs or the potential protective role of palivizumab in preventing RSVs. Palivizumab was not a protective factor for recurrent wheezing; however, those who had received it did not present an obstructive spirometry pattern at 7–8 years of age.

PTIs developed more infections and took more antibiotics than FTIs. PTIs also had a higher prevalence of recurrent wheezing, although there were no differences in severity with respect to FTIs. As in other studies, previous bronchiolitis was a risk factor in both groups [22, 30–32]. Likewise, the prevalence of asthma was significantly higher in PTIs ($N = 27$, 23.3%) than in FTIs ($N = 8$, 6.9%; $p < 0.001$). This figure greatly exceeds the prevalence rates for that age (7–10%) according to the Global Initiative for Asthma (GINA) [25] and the Spanish Guide to Asthma Management (GEMA) [28], but is similar to our findings in the FTI group. The severity of preterm asthmatic patients, inferred from responses to questions 3, 4 and 5 of the ISAAC questionnaire, was also higher in PTIs compared with FTIs ($N = 23$, 19.8% versus $N = 5$, 4.3%; $p = 0.029$).

Most children diagnosed with asthma in either group had recurrent wheezing during childhood (74.1% of PTIs and 87.5% of FTIs; $p < 0.001$); indeed, this risk factor was also described in other studies [3]. The modified Asthma Predictive Index (mAPI) [33] was useful for predicting asthma in all the children in this study; 32/35 asthmatic children (91.4%) had a positive mAPI score ($p < 0.001$). The neonatal weight and lung function variables have been usually the most closely associated with asthma [6–10]. In this study, mean spirometric values obtained at 6–8 years of age were normal in both groups (Table 4), although with a very large SD. Assessing each case separately, 23.3% of PTIs ($N = 27$) and 6.9% of FTIs ($N = 8$) presented an obstructive pattern, coinciding with children diagnosed with asthma by the ISAAC questionnaire. Our results also tally with other studies which show that spirometric measurements at age 8–9 years were lower in children born at 33–34 weeks GA than those born at term. [34–37] GA, and the spirometric parameters indicative of obstruction (Tiffeneau–Pinelli index and FEV_1) also significantly correlated in our study, which may indicate that prematurity contributes to obstruction, in turn promoting the development of asthma in at-risk children.

Recent studies have continued to assess the relationship between prematurity and subsequent development of recurrent wheezing or/and asthma. Thus, in 2017, Kaczmarczyk et al. [38], studying adults born prematurely, do not appreciate significant differences in the lung function in comparison with adults born to term, although the first ones did show lower values in all parameters as well as more frequent obstructive disorders. In 2018, Leps et al. [37] concluded that a gestational age < 37 weeks is a risk factor of wheezing expressed as 'early-remittent' or 'persistent/relapsing' wheeze.

Total IgE (exceeding 100 U/L) and eosinophilia (exceeding 4%) in peripheral blood are usually associated with atopy, allergic disease, digestive disease (intestinal parasites) or cutaneous disease (atopic dermatitis). It is important to identify atopy early in order to predict atopic march. Several studies have analysed the relationship between allergens, atopy and asthma in children [39–43], and a positive relationship between atopic asthma and prematurity has been found [44]. The mean IgE and eosinophil values in peripheral blood were similar in both our study groups, and there was a positive linear correlation between eosinophilia (exceeding 4%) and elevated IgE, but not with GA. Elevated IgE was a risk factor for asthma, especially in the FTIs.

Interestingly, the number of children diagnosed with atopic dermatitis was significantly higher in FTIs ($p < 0.001$). This may mean that prematurity, independently of GA, is a protective factor against atopic dermatitis and that, as previously

Table 4 Spirometric and FeNO values

	N	Minimum	Maximum	Mean	Standard deviation
	FeNO (ppb)				
Preterm infants	116	3.0	29.0	12.9	5.2
Full-term infants	116	8.0	54.0	16.4	8.7
Total	232	3.0	54.0	14.7	7.4
	FVC, %				
Preterm infants	116	44.5	114.8	85.3	16.6
Full-term infants	116	47.3	127.4	88.3	14.7
Total	232	44.5	127.4	86.8	15.7
	FEV1, %				
Preterm infants	116	49.7	113.1	90.2	13.9
Full-term infants	116	53.8	139.5	96.0	13.0
Total	232	49.7	139.5	93.1	13.8
	MEF, 25–75%				
Preterm infants	116	49.1	155.6	100.4	21.5
Full-term infants	116	45.9	164.5	106.4	20.7
Total	232	45.9	164.5	103.4	21.3
	FEV1/FVC, % (Tiffeneau–Pinelli index)				
Preterm infants	116	79.2	117.3	108.4	8.3
Full-term infants	116	75.7	116.3	112.3	6.7
Total	232	75.7	117.3	110.3	7.8

indicated [40–44], this atopy acts as a risk factor for asthma in PTIs but not in FTIs. In contrast, allergic sensitisation was not a risk factor for asthma in either group. Some studies have shown the presence of a specific IgE during the first year of life is the main (and earliest) marker of subsequent sensitisation to inhalant allergens and the development of allergic respiratory pathology [45, 46]. However, very few children had a sensitisation in our study, and so we cannot draw conclusions based on this information. Regarding FeNO, more children in the preterm group had values exceeding 25 ppb, but this relationship was only significantly correlated with atopy and not with GA.

The only protective factor against asthma in the PTIs was an increase in weight of at least three percentiles, in the first year of life (OR = 0.65, 95% CI = 0.45–0.99, $p = 0.030$), which contrasts with the results of other studies such as those published by Gugten et al. and Sonnenschein et al. [10, 47]. This authors concluded that younger gestational age, smaller size for gestational age and greater infant weight gain were across the full ranges associated with childhood lung function. These associations explain the risk of childhood asthma to a substantial extent.

One of the limitations of the study was its sample size, which is lower than in other studies. However, it should be noted that no study child was lost during the 8 years of follow-up. On the other hand, the study design allowed the data from the PTIs to be compared with that from the FTIs. Given that at the beginning of the study the panel of respiratory viruses we investigated was not analysed in routine practice, only RSV could be studied among the possible viruses causing bronchiolitis, and so it was not possible to determine the influence of other viruses as risk factors for late respiratory morbidity and asthma.

Conclusions

- The prevalence of bronchiolitis, recurrent wheezing and asthma at 7–8 years was significantly higher among 32–35-week GA PTIs than among FTIs.
- Prematurity was a risk factor for asthma and an obstructive spirometry pattern and was a protective factor for atopic dermatitis.

In view of our results, 32–35-week GA PTIs with the risk factors detected in this study should be controlled by paediatric pulmonologists, proposing specific interventions to attempt to reduce or prevent the development of asthma or, at least, achieve a better clinical control of these patients.

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Authors' contributions J M-A, MD, and A E-M, MD: conceived and designed the study, drafted the initial manuscript and approved the final manuscript as submitted.

T R-R, MD, and S C-C, MD: carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted.

All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

The period between birth and 3 years of age was already collected in our centre (Infantile Pneumology and Cystic Fibrosis Unit of the Hospital Clínico Universitario Valencia), as part of a national multicentre study (SAREPREM 3235) in which we participated as researchers, and which was approved by the Ethics and Clinical Research Committee of the Donostia Hospital, in San Sebastián, and was carried out under the ethical postulates of the Helsinki Declaration and the guidelines of the Spanish Society of Paediatric Pneumology (SENP).

After its completion, it was proposed to extend it with the follow-up of the children included in our centre until the age of 6–8 years, and was approved by the Ethics Committee of the Hospital Clínico Universitario de Valencia.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All parents signed the written informed consent.

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