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Extrauterine growth restriction and low energy intake during the early neonatal period of very low birth weight infants are associated with decreased lung function in childhood

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Abstract

Premature birth, bronchopulmonary dysplasia or restrictive nutrition in the first weeks of postnatal life may have repercussions on lung development and affect long-term lung function outcomes. This prospective observational study is based on a cohort of 313 very low birth weight (VLBW) neonates, born between 1 January 2008 and 1 December 2016. The daily intake of calories, protein, fat and carbohydrates during the first week of life and evidence of inadequate weight gain (Δwt) until week 36 of gestational age (GA) were recorded. FEV_1, $FEF_{25–75\,\%}$, forced vital capacity (FVC) and the FEV_1/FVC ratio were determined. The relations between these parameters were determined by regression analysis. Spirometric parameters were obtained for 141 children with a mean age of 9 years (95 % CI 7, 11); 69 of them (48·9 %) had presented wheezing episodes on more than three occasions. In addition, 60 (42·5 %) had a history of bronchopulmonary dysplasia. Of these, *n* 40 (66·6 %) had a history of wheezing. Significant association between protein/energy intake in the first week of life and the lung function parameters analysed was observed. Poor Δwt to GA week 36 was significantly associated with decreased mean pulmonary flow. Inadequate protein/energy intake in the first week of life of VLBW newborns and poor Δwt to week 36 of GA is associated with a significant worsening of lung function parameters.

Key words: **Infant: Premature: Extrauterine growth restriction: Bronchopulmonary dysplasia: Lung function: Nutrition**

Preterm neonates constitute approximately 10 % of all human births, totalling approximately 12 million annually worldwide[1]. In recent years, the rate has increased in developed countries; this, together with improvements in perinatal care, has led not only to reduced mortality but also to increased morbidity during childhood and adulthood[2]. Respiratory pathologies derived from preterm birth, such as bronchopulmonary dysplasia (BPD), are frequent in premature newborns and may subsequently affect the lung function of children and adults[3,4]. Various studies have highlighted the importance of nutritional status in the newborn and its relevance to lung development[5,6]. The effects of post-natal undernutrition on lung maturation have been characterised in animal models. For example, rodents are at a saccular stage of lung development when born at term. In very premature infants, deficient nutritional support has been shown to impede the development of the respiratory system and may contribute to the evolution of BPD[7].

Strategies for protecting the lungs of preterm infants are limited and mainly involve reducing the prevalence and intensity of BPD lesions. In this respect, studies have reported that the prevalence of BPD may be reduced by avoiding invasive ventilation and oxygen therapy and/or improving early nutritional intake, observing that BPD has a multifactorial aetiology that alters the normal development of the immature lung[7–9]. Compared with their full-term counterparts, preterm infants have fewer energy reserves. In consequence, the existence of antenatal and/or postnatal malnutrition can aggravate any lung damage resulting from ventilatory therapy during the neonatal period[10]. Infants with BPD have up to 25 % greater energy requirements than full-term infants, in part due to the greater respiratory effort needed[11]. When newborns suffer energy restriction, this is associated with more severe forms of BPD in later infancy[9,12] and these repercussions of early macronutrient intake on lung function in childhood or even adulthood are still

Abbreviations: BPD, bronchopulmonary dysplasia; CRIB, Clinical risk index for babies; EUGR, extrauterine growth restriction; FEF25-75%, mean forced expiratory flow; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; PMA, postmentrual age; VLBW, very low birth weight.

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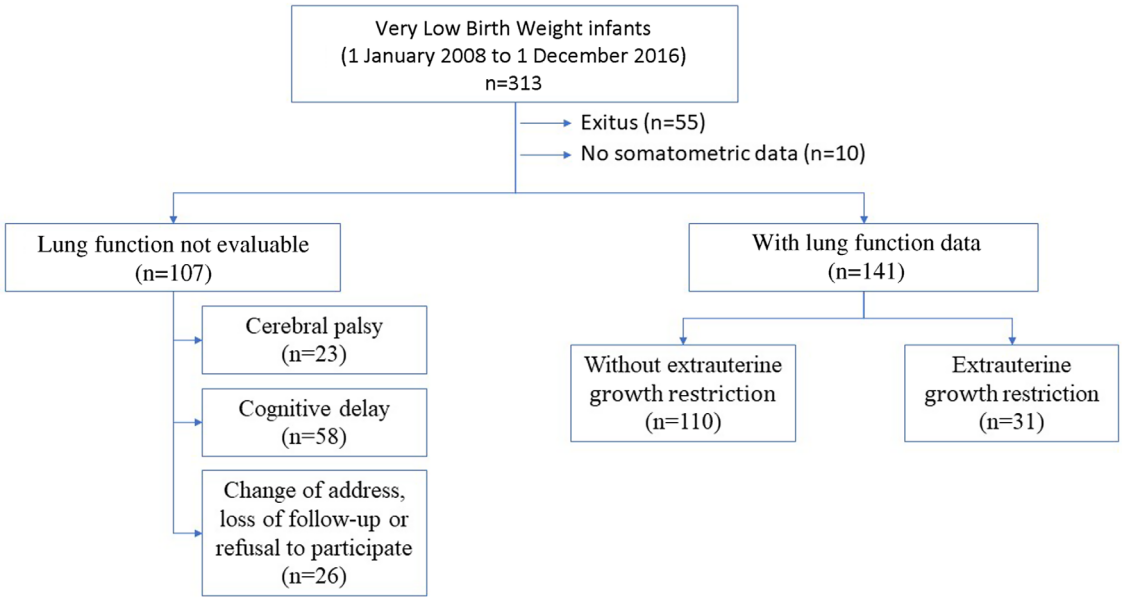

Fig. 1. Flow diagram for the VLBW newborns included in the study. VLBW, very low birth weight.

insufficiently understood. Although the clinical manifestations of neonatal lung disease tend to improve with optimal treatment and with growth, significant deficiencies in lung function may persist among adolescents[4,13]. Furthermore, growth and nutritional status may be associated with changes in FEV_1 during childhood, suggesting that appropriate nutritional intervention at an early stage may enhance lung function both in children and in adults[14].

We consider that nutrition in the early neonatal period has repercussions that go beyond the neonatal period itself. Several authors[15,16] have reported that perinatal malnutrition can cause epigenetic changes with repercussions in adult life.

In the present study, we evaluate the nutritional intake of very low birth weight (VLBW) infants during the early neonatal period, evidence of poor weight gain (Δwt) until week 36 of gestational age (GA) and its association with the parameters considered in spirometric tests of lung function when these same infants are of school age.

Subjects and methods

This longitudinal prospective observational study analysed a cohort of children born at the San Cecilio Clinical Hospital (Granada, Spain) between 1 January 2008 and 1 December 2016. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the CEIM/CEI of Granada (Spain); with number 80ed2fa1b452eca15f1715306d-d309110af92a95 and date January 14, 2020. Written informed consent was obtained from all subjects/patients.

Inclusion and exclusion criteria

All infants weighing < 1500 g or born before week 32 of GA and admitted to the hospital's neonatal intensive care unit during the study period were included in the study group. Subsequently, each child was followed up in pulmonology, neonatology and neurology consultations. Infants who died in the first 28 d of life and those transferred to other hospitals were excluded from the analysis; as in these cases, it was not possible to establish the degree of BPD. Those who presented severe neurological alterations were also excluded from the study, as it was assumed that this would make it impossible to perform the spirometry test. Also excluded were newborns for whom data were not available on total nutritional intake during the first week of life. The flow diagram in Fig. 1 illustrates the process applied for patient recruitment and inclusion.

Anthropometry

Fenton tables were used to calculate the weight z-scores[17]. Intrauterine growth restriction is defined as inadequate weight gain, i.e. weight below the 10th percentile for GA[18]. The main exposure variables were changes in weight (Δwt), z scores from birth to 36 postmentrual age (PMA) weeks, using the closest value recorded between 34^{+0} to 38^{+6} weeks PMA. Δwt was categorised into quartiles. Quartile 4 (Q4) of this difference was used as an indicator of inadequate Δwt or extrauterine growth restriction (EUGR).

Nutritional management

In the Neonatal Unit, the nutritional strategy and the liquid intake supplied are in accordance with the Unit's standard protocol and with the recommendations of the Nutrition and Metabolism Group of the Spanish Neonatology Society[19]. Parenteral nutrition is initiated after birth at 65–80 ml/kg/d and enteral feeding is initiated within 12–48 h. The normal goal is to achieve 376–502 Kj/kg/d and 3·5–4·5 g/kg/d of protein by day 3–5, and full enteral feeding within 2 weeks of life. During the first days of life, enteral nutrition is normally complemented with parenteral

nutrition when complete enteral nutrition cannot be established. The daily requirements of liquids, proteins, carbohydrates and lipids are calculated and recorded daily. At our hospital, breast milk composition is determined according to the Standardised Reporting of Neonatal Nutrition and Growth checklist, and formula composition is assessed according to commercial notifications[20]. In all cases, the aim is that during the first week of life, the minimum nutritional requirements to ensure growth should be met, according to standard recommendations[21,22]. For the purposes of the present study, the enteral and parenteral inputs of liquids, energy, proteins, carbohydrates and lipids during the first week of life were prospectively registered in an Excel database.

Low energy intake

In our sample, energy or protein intake below the 25th percentile was assumed to represent energy restriction. This value is equivalent to about 60 % of the recommended energy or protein intake during the first week of life.

Morbidity

In accordance with the thresholds proposed by NIHCD[23] and by Jobe and Bancalari[24], BPD is defined as a need for supplemental oxygen > 21 % at 28 d of life and/or a need for supplemental oxygen > 21 % or for positive airway pressure at 36 weeks' corrected GA.

The clinical risk index for babies (CRIB II score) for each newborn was performed using the following variables: sex, GA (in weeks), birth weight (in grams) and excess base. The total CRIB II score (range 0–27) was calculated[25]. The diagnosis of intraventricular haemorrhage is based on Papile's classification[26]. All neonates in this study received a transfontanellar ultrasound examination on the third day of life and every week thereafter. Psychomotor and sensory development were monitored during neuropaediatric consultation. The degree of motor or cognitive impairment and the impossibility of completing the spirometric study were considered a key element in the exclusion of patients from the study.

Lung function

Spirometry is a non-invasive test that evaluates lung function by measuring the amount of air mobilised in the lungs during maximum inspiration and expiration, in both normal and forced expiration. In our tests, forced spirometry was performed with a Jaeger Type MSC Power-Unit Flow Pneumotachograph of approximately 230 V, 50/60 Hz, 0·1 A, IP 20.

In the spirometry tests performed, disposable mouthpieces were used, with forceps to cover the nostrils and thus prevent the exhaled flow from escaping. Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and mean expiratory flow ($FEF_{25–75\,\%}$) were measured, and the FEV_1/FVC ratio was determined. FEV_1 is the volume of air expelled during the first second of forced expiration. Although it is expressed as volume (L), since it is related to time, in practice FEV_1 is a measure of flow. The FEV_1 result is considered normal if it is > 80 % of the theoretical value. This is the most important parameter considered to assess whether there is obstructive airway pathology, and in normal conditions, it must be > 75 %. FVC is the maximum volume of expired air, with the maximum possible effort, starting from maximum inspiration. It is expressed as a volume (L) and is considered normal when it is > 80 % of the theoretical value. The maximum mid-expiratory flow velocity ($FEF_{25–75\,\%}$) is the airflow velocity during the middle half of the FVC test (i.e. 25–75 % of the FVC) and should be ≥ 65 % of the theoretical value.

The parameters of the lung function tests present great interindividual variability and depend on the patients' anthropometric characteristics (sex, age, height, weight and race). Interpretation of the spirometry results is based on comparing the values produced by the patient with those that would theoretically correspond to a healthy individual with the same anthropometric characteristics. This theoretical value or reference value is obtained from a school-age prediction equation (3). The spirometry results are expressed as the z-score ($z = (x - \mu)/\sigma$), where x is the value obtained, μ is the population mean for the anthropometric characteristics of the subject and σ is the standard deviation)[4].

Statistical analysis

The descriptive data were summarised using the median (p50) and the interquartile range (p25–p75) for the continuous values and the frequency distribution for the categorical ones. Quartiles were calculated for the z-score of the difference between weight at birth and at week 36 PMA. Univariate comparisons were made of the continuous variables, using a Mann–Whitney analysis for 2 × 2 comparisons. Categorical variables were compared using the X^2 test. In addition, a simple and multivariate linear regression analysis was performed. Collinearity was assessed by the variance inflation factor > 5. An adjustment was made to account for the variables that did not present multicollinearity with the other predictor variables when variance inflation factor < 5 was obtained[27]. All statistical analyses were performed using IBM SPSS 28.0 for Windows (IBM).

Results

During the study period, 313 neonates with a birthweight < 1500 g were admitted to our Neonatal Intensive Care Unit. Of these, fifty-five died. In another ten clinical histories, the somatometric data for the neonatal period could not be located. Of the remaining 248 infants, 107 either presented pathologies incompatible with the study criteria (such as cerebral palsy or moderate-severe cognitive delay) and were excluded, or permission for their participation in the study was refused (Fig. 1).

Table 1 details the characteristics of all infants considered, both those included in the study and those excluded for the above reasons. 41·1 % of those included presented BPD, compared to 28 % of those excluded. The neonates included had received slightly longer periods of oxygen therapy and mechanical ventilation, which a priori suggests this group may present greater prematurity and respiratory morbidity. On the other hand, the sample group consists of infants who had been

Table 1. Comparison of the obstetric and neonatal characteristics of the patients who participated in the lung function study and those who refused or were unable to do so

Characteristics	Not included *n* 107		Included *n* 141		
	n	%	*n*	%	*P*
Maternal					
IVF	16	14·9	25	17·7	0·52
PIH	6	5·6	10	7·1	0·63
Chorioamnionitis	14	13·0	16	11·3	0·67
Antibiotics	43	40·1	50	35·4	0·44
Glucocorticoids	89	83·1	120	85·1	0·40
PPROM	24	22·4	31	21·9	0·93
Gestation (w)*					
Median	30		30		0·12
IQR	29, 31		28, 31		
Gestation ≤ 27 w	13	12·1	33	23·4	0·02
Twin birth	40	37·3	56	39·7	0·70
Caesarean section	83	77·5	122	86·5	0·04
Neonatal period					
Birth weight (z-score)*					
Median	−0·48		−0·61		0·22
IQR	−1·15, 0·16		−1·30, −0·15		
Weight 36 w PMA (z-score)*					
Median	−1·38		−1·53		0·39
IQR	−2·11, −1·01		−2·21, −1·05		
△ Weight at 36 w. PMA (z-score)*					
Median	1·07		0·92		0·18
IQR	0·66, 1·53		0·50, 1·38		
Parenteral nutrition (days)*					
Median	10		13		0·01
IQR	5, 15		7, 20		
CRIB score	2	1, 5	2	1, 4	0·47
Male gender	51	47·6	65	46·0	0·80
Apgar < 5 at 5 min	9	8·4	9	6·3	0·69
IUGR	20	18·6	33	23·4	0·37
Human milk feeding†	60	56·0	80	56·7	0·41
Mechanical ventilation (days)*					
Median	0		1		0·02
IQR	0, 2		0, 7		
CPAP (days)*					
Median	3		3		0·74
IQR	2, 6		0, 10		
Oxygen (days)*					
Median	14		21		0·01
IQR	4, 32		6, 50		
BPD	30	28·0	58	41·1	0·03
NEC ≥ Stage II	10	9·3	15	10·6	0·19
Late-onset sepsis	31	28·9	39	27·6	0·13

IVF, *in vitro* fertilisation; PIH, pregnancy-induced hypertension; PPROM, preterm pre-labour rupture of membranes; PMA, postmenstrual age; CRIB, clinical risk index for babies; IUGR, intrauterine growth restriction; CPAP, continuous positive airway pressure; BPD, bronchopulmonary dysplasia; NEC, necrotising enterocolitis.
Counts and percentages.
* Median (IQR).
†Supplemented by less than 25 % of the weekly volume with premature formula milk.

more premature and therefore needed greater respiratory assistance.

Table 2 presents a comparative analysis of the variables recorded for neonates with or without EUGR. In summary, 51·6 % of those with EUGR had a GA < 27 weeks and a significantly lower birth weight than those without EUGR. The former, therefore, needed longer in the NICU and more extended PN. Among the neonates with EUGR, the prevalence of IUGR was significantly lower than among those without EUGR (3·2 % *v.* 29 %). The need for ventilatory support and oxygen therapy and the presence of comorbidities such as BPD, enteral nutrition or late sepsis were also more prevalent in the neonates with EUGR.

Lung function variables in school-age children with very low birth weight

The mean age of the 141 premature infants who underwent a subsequent lung function study was 9 years (95 % CI 7, 11); of these, 69 (48·9 %) had presented wheezing episodes on more than three occasions. Sixty (42·5 %) had a history of BPD, and of these, 40 (66·6 %) had a history of wheezing. In our cohort, a history of wheezing was significantly correlated with a decrease in $FEF_{25–75\,\%}$ ($r = -0{\cdot}20$; $P = 0{\cdot}03$).

The evaluation of lung function parameters at school age correlated positively and significantly with gestational age. FVC ($r = 0{\cdot}19$; $P < 0{\cdot}01$), FEV1 ($r = 0{\cdot}19$; $P < 0{\cdot}01$), $FEF_{25–75\,\%}$ ($r = 0{\cdot}23$; $P < 0{\cdot}004$) and FEV_1/FVC ($r = 0{\cdot}23$; $P < 0{\cdot}005$) (Fig. 2).

Table 2. Obstetric and neonatal characteristics of preterm infants with or without EUGR. We observed that newborns with EUGR have a lower gestational age, lower birth weight and higher oxygen and mechanical ventilation needs with more BPD. Except in the cases of detection of multicollinearity, these variables are considered adjustment variables in the regression models

Characteristics	No EUGR (*n* 110)		EUGR (*n* 31)		
	n	%	*n*	%	*P*
Maternal					
IVF	17	15·4	8	25·8	0·19
PIH	8	7·2	2	6·4	0·87
Chorioamnionitis	10	9·1	6	19·3	0·11
Antibiotics	35	31·8	15	48·3	0·08
Glucocorticoids	95	86·3	25	80·6	0·50
PPROM	23	20·9	8	25·8	0·56
Gestation (w)*					
Median	30		27		0·001
IQR	28·5, 32·0		26·0, 29·0		
Gestation ≤ 27 w	17	15·4	16	51·6	0·001
Twin birth	45	40·9	11	35·4	0·58
Caesarean section	99	90·0	23	74·1	0·013
Neonatal period					
Birth weight (g)*					
Median	1195		1100		0·001
IQR	991, 1430		950, 1339		
Birth weight (z-score)*					
Median	−0·89		−0·05		0·001
IQR	−1·47, −0·19		−0·35, 0·53		
Weight 36 w PMA (g)*					
Median	2108		1910		0·080
IQR	1787, 2305		1760, 2210		
Weight 36 w PMA (z-score)*					
Median	−1·45		−1·93		0·040
IQR	−2·13, −0·98		−2·75, −1·24		
Days stay at NICU*					
Median	28		39		0·009
IQR	17·5, 38·0		25·0, 53·0		
Parenteral nutrition (days)*					
Median	11		15·5		0·018
IQR	6·5, 18·0		9·75, 25·0		
CRIB score*					
Median	2		2		0·20
IQR	1, 3		1, 5·5		
Male gender	52	47·2	13	41·9	0·59
Apgar < 5 at 5 min	8	7·2	4	12·9	0·27
IUGR	32	29·0	1	3·2	0·03
Human milk feeding†	63	57·2	17	54·8	0·59
Mechanic ventilation (days)*					
Median	1		3		0·008
IQR	0, 5		1, 12		
CPAP (days)*					
Median	3		8		0·005
IQR	0, 7·75		2, 15		
Oxygen (days)*					
Median	15		37		0·002
IQR	5, 44		26, 58		
BPD	38	34·5	20	64·5	0·004
NEC ≥ Stage II	8	7·2	6	19·3	0·041
Late-onset sepsis	20	18·1	15	48·3	0·001

BPD, bronchopulmonary dysplasia; EUGR, extrauterine growth restriction; IVF, *in vitro* fertilisation; PIH, pregnancy-induced hypertension; PPROM, preterm pre-labour rupture of membranes; PMA, postmenstrual age; CRIB, clinical risk index for babies; IUGR, intrauterine growth restriction; CPAP, continuous positive airway pressure; NEC, necrotising enterocolitis; NICU, Neonatal Intensive Care Unit.
Counts and percentages.
* Median (IQR).
† Supplemented with < 25 % of weekly volume with premature formula milk.

As can be seen in Table 3, both the BMI and the lung function of the preterm infants in our cohort, at school age, were below average (negative Z-score). There were statistically significant differences in $FEF_{25–75\,\%}$, with lower values in the premature infants who had a history of EUGR. Moreover, BPD was much more prevalent among those with EUGR (Table 2). Table 4

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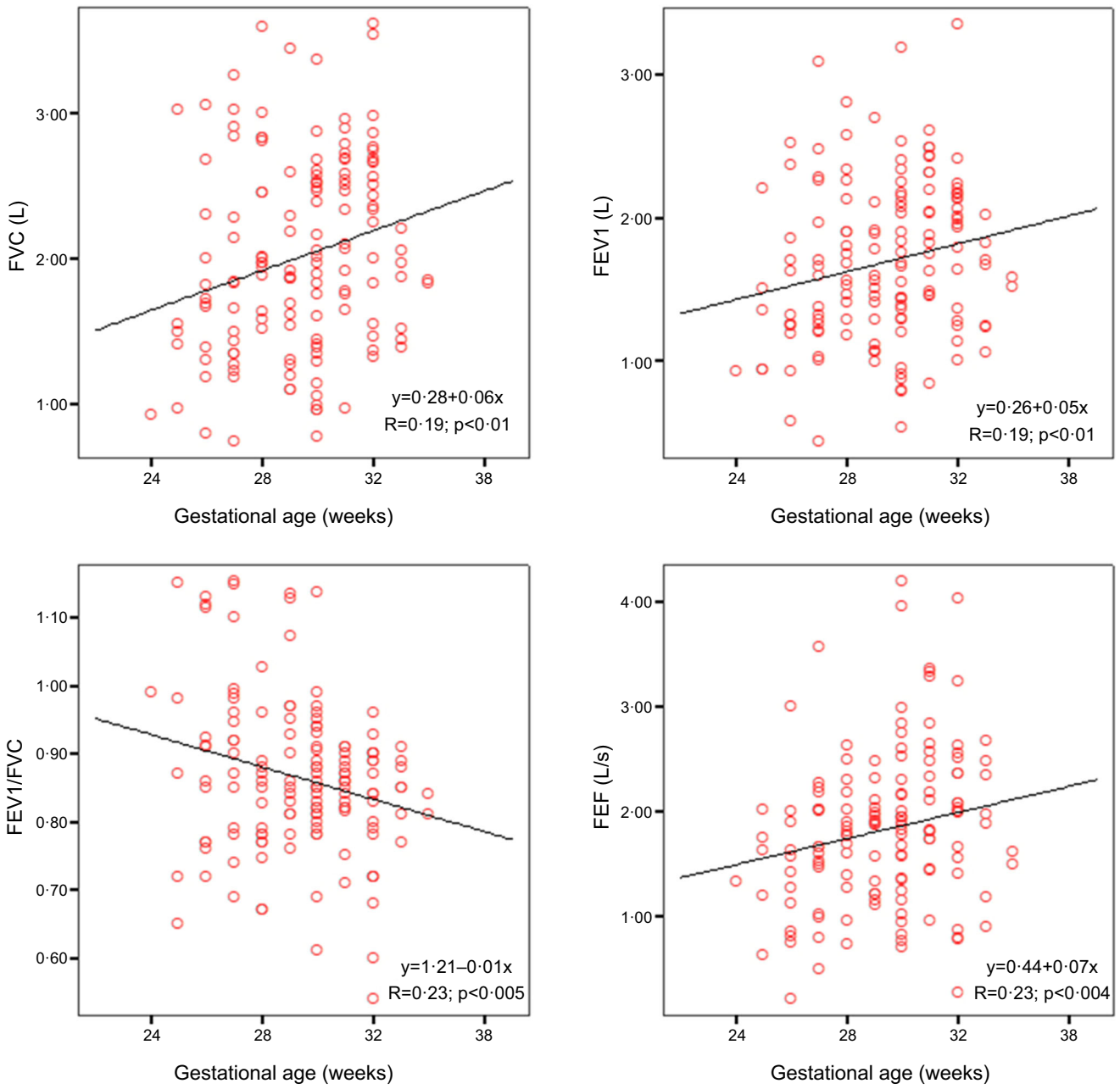

Fig. 2. Scatterplot for FVC, FEV1, FEV1/FVC and $FEF_{25–75\,\%}$ in school age with gestational age at birth. FVC, forced vital capacity.

shows the results of the regression analysis for each of the lung function parameters considered, after adjusting for GA. A history of EUGR is significantly associated with decreased $FEF_{25–75\,\%}$ and FEV1/FVC. Furthermore, a history of BPD is negatively associated with FVC, FEF25–75 % and FEV1/FVC.

Energy intakes in neonatal period and lung function in childhood

In the study cohort, IUGR was more prevalent among the neonates who did not develop EUGR (Table 2). VLBW infants may suffer malnutrition for several reasons, including the interruption of transplacental nutrition following delivery. In these situations, early nutritional restitution usually causes rapid weight gain; we observed BPD in 33 % of the VLBW infants with IUGR.

Nutritional intake in the first week of life of VLBW newborns is significantly associated with the lung function parameters analysed (Table 5). After adjusting for GA, BPD and EUGR, we observed a significant association of nutritional parameters with FEV_1, FVC and $FEF_{25–75\,\%}$. Of the 141 children included in the study (with lung function data), thirty-one received a caloric intake of less than 391 kcal/week during the early neonatal period, corresponding in both cases to the 25th percentile. In the

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Table 3. Somatometric and lung function descriptors of preterm children aged 5–13 years, with or without EUGR. We observed that the children who presented EUGR showed significantly lower $FEF_{25–75}$, z-score, we did not observe differences for the other indices of lung function

Characteristics	No EUGR (*n* 110)		EUGR (*n* 31)		
	Median	IQR	Median	IQR	*P*
Age (years)*	10	7·5, 11·0	9	6·0, 11·0	0·22
BMI (g/cm^2)*	16·2	15·1, 18·8	15·5	14·3, 17·8	0·12
BMI, z-score*	–0·26	–0·90, 0·72	–0·44	–1·34, 0·41	0·35
Lung function					
FVC, z-score	–0·38	–1·22, 0·19	–0·31	–1·28, 0·17	0·98
FEV_1, z-score	–0·71	–1·57, 0·09	–0·65	–1·79, –0·24	0·26
FEV_1/FVC	0·86	0·81, 0·93	0·85	0·77, 0·91	0·343
$FEF_{25–75}$, z-score	–1·13	–1·78, –0·11	–1·57	–2·30, –0·95	0·007

EUGR: extrauterine growth retardation; $FEF_{25–75\,\%}$: mean expiratory flow; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.
* Median (IQR).

Table 4. Gestational age-adjusted regression analysis of lung function variables (dependent variables) for currently school-age preterm infants with EUGR and BPD (independent variables). We observe how the EUGR is associated with lower $FEF_{25–75}$ z-score and FEV_1/FVC, associations obtained after adjusting for gestational age

	Cte.	b	SE	t	*P*
Independent variable: EUGR*					
FEV_1 (L)	0·22	–0·02	0·12	–0·21	0·829
FEV_1, z-score	–6·42	–0·13	0·32	–0·42	0·669
FVC (L)	–0·08	0·06	0·14	0·45	0·651
FVC, z-score	–7·63	0·37	0·28	1·33	0·184
$FEF_{25–75}$ (L/s)	0·20	–0·24	0·15	–1·60	0·110
$FEF_{25–75}$, z-score	–2·16	–0·56	0·28	–2·00	0·047
FEV_1/FVC	1·38	–0·04	0·02	–2·05	0·042
Independent variable: BPD*					
FEV_1 (L)	1·52	–0·24	0·12	–2·01	0·046
FEV_1, z-score	–4·12	–0·65	0·33	–1·96	0·056
FVC (L)	1·48	–0·23	0·14	–1·58	0·114
FVC, z-score	–4·15	–0·62	0·29	–2·11	0·036
$FEF_{25–75}$ (L/s)	1·56	–0·38	0·15	–2·45	0·015
$FEF_{25–75}$, z-score	–1·16	–0·55	0·29	–1·90	0·059
FEV_1/FVC	1·22	0·001	0·02	0·02	0·983

EUGR, extrauterine growth restriction; $FEF_{25–75\,\%}$: mean expiratory flow; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.
* Adjusted for gestational age.

sample, low caloric intake during the early neonatal period was associated with BPD (R = 0·18; *P* = 0·03).

Discussion

Achieving an adequate energy intake and protein/energy ratio in the first week of life improves the FEV_1, FVC and $FEF_{25–75\,\%}$ results of children who were VLBW infants. A history of EUGR and BPD is negatively associated with $FEF_{25–75\,\%}$ at school age.

Lung function variables in school-age children with very low birth weight

A large multicentre study reported that VLBW infants whose growth was in the lowest quartile in the first 3 weeks of life were at higher risk for BPD and neurodevelopmental problems[28].

The question arises as to whether respiratory dysfunction after preterm delivery is (1) due to the disruption of normal lung development after premature exposure of an immature lung to unfavourable extrauterine conditions; (2) related to factors that contribute to or foster preterm birth; (3) subsequent to lung injury caused during resuscitation, subsequent ventilatory support or the deficient intake of nutrients at critical moments of development. Research has provided clear evidence of altered lung development after preterm delivery, in which respiratory morbidity and reduced lung function are both much more severe in preterm infants with prior BPD[29].

Therefore, extreme preterm birth and BPD may be risk factors for the future development of chronic obstructive pulmonary disease. In this respect, Halvorsen *et al.*[13] observed a substantial decrease in FEV_1, an increase in bronchial hyperresponsiveness and a more pronounced decrease in lung function among adolescents who had been preterm, in comparison with controls. In our cohort, a history of wheezing was commonly observed and was significantly associated with a history of BPD and a decrease in mesoflows in spirometry. Similarly, Anand *et al.*[30] found evidence of obstruction in the flow of the small and medium airways, which paralleled our own findings of reductions of nearly 20 % in $FEF_{25–75\,\%}$. Fawke *et al.*[31] warned of an increased risk of respiratory morbidity, airway obstruction and bronchial hyperresponsiveness among premature infants, and for such cases, proposed strategies to prevent or reduce the severity of BPD, such as reducing the duration of invasive ventilation, favouring non-invasive ventilation strategies or applying postnatal surfactant therapy or antenatal steroids. In contrast, Doyle *et al.*[32] found that decreased invasive ventilation in a cohort of VLBW infants was not associated with an improvement in lung function at school age.

Hirata *et al.*[14] evaluated the spirometry variables of lung function in preterm infants now of school age and observed that lung function did not improve after the age of 8–12 years; in comparison with the general population, lung function tends to be poorer among those with a history of preterm birth. Furthermore, a history of severe BPD is associated with greater deterioration in lung function at school age. In an earlier study[9], our research group observed that energy restriction during the early postnatal period is directly associated with the severity of BPD.

Energy intakes in neonatal period and lung function in childhood

Research findings have confirmed the existence of an association between higher energy intake in the first week of life and the

Table 5. Regression analysis week 1 nutritional intake and infanthood spirometric variables. We observed a significant association of the protein/energy ratio with all the lung function indices

Lung functionInfanthood period	Week 1 postnatal	R	Cte.	b Adjusted*	SE	*P*
FEV_1 (L)						
	Energy	0·424	1·478	0·002	0·001	0·001
	Protein	0·546	2·300	0·055	0·008	0·001
	Carbohydrates	0·251	1·405	–0·005	0·003	0·125
	Lipids	0·314	0·957	0·029	0·010	0·005
	Protein/energy	0·418	3·110	0·219	0·049	0·001
FVC (L)						
	Energy	0·433	1·244	0·003	0·001	0·001
	Protein	0·545	2·202	0·064	0·010	0·001
	Carbohydrates	0·262	1·243	–0·006	0·003	0·072
	Lipids	0·308	0·638	0·033	0·012	0·007
	Protein/energy	0·391	2·986	0·236	0·059	0·001
$FEF_{25–75\,\%}$ (L/s)						
	Energy	0·387	1·944	0·002	0·001	0·004
	Protein	0·486	2·756	0·054	0·011	0·001
	Carbohydrates	0·308	1·790	–0·003	0·004	0·379
	Lipids	0·334	1·514	–0·024	0·013	0·073
	Protein/energy	0·448	3·916	0·258	0·063	0·001
FEV_1/FVC						
	Energy	0·324	1·391	–0·001	0·001	0·369
	Protein	0·349	1·444	–0·003	0·002	0·081
	Carbohydrates	0·296	1·375	0·001	0·001	0·637
	Lipids	0·328	1·354	–0·002	0·002	0·286
	Protein/energy	0·364	1·569	–0·023	0·011	0·034

$FEF_{25–75\,\%}$, mean expiratory flow; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity. Energy (kcal/kg/week); protein (g/kg/week); carbohydrates (g/kg/week); lipids (g/kg/w); protein/energy (g/100 kcal).
* Adjusted for gestational age, bronchopulmonary dysplasia and extrauterine growth restriction.

proportion of FVC that is expelled during the first second of forced expiration. After birth, nutrition plays a critical role in the respiratory development of preterm infants, especially those who are VLBW, whose saccular–alveolar stage of lung maturation occurs mostly or entirely in post-natal life. Pulmonary alveolation continues until at least the age of two, and therefore malnutrition at very early stages of postnatal life could plausibly have repercussions on future lung function[7].

VLBW infants may suffer malnutrition for several reasons, including the interruption of transplacental nutrition following delivery, or a delay in the start of EN, due to poor clinical status and/or haemodynamic and respiratory instability, generally related to the infant's lower GA[11,33]. Finally, it has been reported that preterm infants with BPD tend to grow more slowly than their peers, and that this delay persists beyond the period of hospital stay[11,34].

The main limitation of our study is the relatively high proportion of eligible participants who did not perform the spirometry test, an absence that signals a potential selection bias; however, as shown in Table 1, the two groups of patients (included or not in subsequent analysis) did not differ significantly as concerns most of the study variables analysed. Most of those who were recruited were BPD patients who were already under follow-up in paediatric pulmonology clinics, while many of the children who were healthy and had been discharged from the paediatric pneumology clinic several years previously did not accept the invitation to participate.

In conclusion, we find that EUGR, early postnatal nutrition and subsequent lung function of the child are related. Active nutritional management in the early neonatal period can improve lung function in the child and possibly in the adult.

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The authors affirm that the work is original and is not currently being evaluated in any other journal. The authors have no relevant conflicts of interest to declare.

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