Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Lung function between 8 and 15 years of age in very preterm infants with fetal growth restriction

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BACKGROUND: The impact of intrauterine growth restriction (IUGR) on lung function in very preterm children is largely unknown as current evidence is mainly based on studies in children born small for gestational age but not necessarily with IUGR.
METHODS: Spirometry, transfer factor of the lung for carbon monoxide (TLco), and lung clearance index (LCI) were cross-sectionally evaluated at 8.0–15.0 years of age in children born <32 weeks of gestation with IUGR ($n = 28$) and without IUGR ($n = 67$). Controls born at term ($n = 67$) were also included.
RESULTS: Very preterm children with IUGR had lower mean forced expired volume in the first second (FEV_1) *z*-score than those with normal fetal growth (Δ −0.66, 95% confidence interval (CI) −1.12, −0.19), but not significant differences in LCI (Δ +0.24, 95% CI −0.09, 0.56) and TLco *z*-score (Δ −0.11, 95% CI −0.44, 0.23). The frequency of bronchopulmonary dysplasia (BPD) in the two groups was, respectively, 43% and 10% ($P = 0.003$). IUGR was negatively associated with FEV_1 ($B = -0.66$; $P = 0.004$), but the association lost significance ($P = 0.05$) when adjusting for BPD.
CONCLUSIONS: IUGR has an impact on conducting airways function of very preterm children at school age, with part of this effect being mediated by BPD. Ventilation inhomogeneity and diffusing capacity, instead, were not affected.

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IMPACT:

- IUGR does not necessarily imply a low birthweight for gestational age (and vice versa).
- While a low birthweight is associated with worse respiratory outcomes, the impact of IUGR on lung function in premature children is largely unknown.
- IUGR affects conducting airways function in school-age children born <32 weeks with IUGR, but not ventilation inhomogeneity and diffusing capacity.
- The impact of IUGR on FEV_1 seems mainly related to the higher risk of BPD in this group.

INTRODUCTION

Survivors of very preterm birth (<32 weeks gestational age [GA]) may have chronic lung function abnormalities, especially in the presence of bronchopulmonary dysplasia (BPD).[1–4] This is a matter of concern as a reduced forced expired volume in the first second (FEV_1) peak in adulthood is a known risk factor for early onset of chronic obstructive pulmonary disease (COPD)[5] and premature death.[6]

Intrauterine growth restriction (IUGR) refers to a pathological situation (most commonly a placental dysfunction) leading to a poor growth of the fetus.[7] This condition is associated with increased perinatal morbidity and mortality,[8] as well as with long-term metabolic,[9] cardiovascular,[10] and neurodevelopmental complications.[11] Evidence from animal studies shows that IUGR alters lung development,[12] while human birth cohort studies of children born at term or near-term have demonstrated that fetal growth pattern affects subsequent lung function.[13,14] Although a history of IUGR is associated with increased odds of developing BPD in infants born <32 weeks of gestation,[8,15,16] there is very limited evidence regarding the impact of fetal growth restriction on long-term lung function in this group.[17,18] Several studies have shown that infants with low birthweight for GA are at risk of worse respiratory outcomes throughout infancy,[19,20] childhood,[21,22] and in later life.[23] However, children who were born small for gestational age (SGA, birthweight <10th percentile) do not necessarily have a history of IUGR (and vice versa);[24] moreover, perinatal clinical outcomes differ between these two groups.[16,25] In light of this evidence, comparing lung function in very preterm children with and without a history of IUGR could give insight into the effects of restricted fetal growth on lung development and could help to stratify better this population according to the risk of chronic respiratory impairment.

In this cross-sectional study, we tested the hypothesis that IUGR is an independent risk factor for worse lung function at school age

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in children born at <32 weeks GA, as compared with their counterparts with normal fetal growth and with children born at term.

METHODS

Subjects

Subjects aged 8.0–15.0 years, born at 25–31 weeks of gestation between 2004 and 2010, and age-matched controls born at ≥37 weeks GA were included. All preterm children enrolled had been admitted after birth at the Neonatal Intensive Care Unit (NICU) of the University Hospital of Udine, Italy, where data collection was performed between January 2018 and April 2019. Written informed parental/guardian consent and child assent were obtained. The study was approved by the local Ethical Committee (Ceur-2018-Sper-018-ASUIUD).

Diagnosis of IUGR was consensus-based according to fetal biometry and Doppler flowmetry criteria, namely, the presence of a fetal abdominal circumference (AC) or estimated fetal weight (EFW) < 3° centile or an absent end-diastolic flow in the umbilical artery at the most recent obstetric ultrasonography before birth.[7] Alternative criteria were the presence of AC/EFW < 10° centile combined with a uterine-artery pulsatility index >95° centile and/or umbilical artery pulsatility index >95° centile.[7] These measurements are routinely recorded at our center during obstetric ultrasonography.

Through a stratified random sampling, a number of children born at <32 weeks with IUGR and twice the number of their counterparts without IUGR (matched for ±1 year of age and ±1 week of GA at birth) was obtained from the whole cohort of survivors of very preterm birth. Controls born at term, matched for age with preterm children without IUGR, were recruited from a local school, on a voluntary basis.

BPD was pragmatically defined as the need for supplemental oxygen at 36 weeks postmenstrual age (PMA),[26] as in other previous studies.[1,27,28] Children with chromosomal anomalies or congenital malformations were excluded, as well as those with respiratory symptoms on test day and those unable to perform the lung function tests (LFTs). A further exclusion criterion for controls was a history of asthma symptoms in the last year.

Assessments

Participants underwent nitrogen (N_2) multiple breath washout (MBW) (Exhalyzer D, Eco Medics AG, Switzerland, running Spiroware Version 3.1.6 software), spirometry, and single-breath transfer factor of the lung for carbon monoxide (TLco) (Jaeger MasterScreen PFT; Viasys Healthcare, Germany) in this sequence, on the same day. LFTs were performed according to European Respiratory Society/American Thoracic Society (ERS/ATS) standards adapted for children.[29–32] For the N_2MBW, a set 2 dead space reducer was used for subjects ≤35 kg and a set 3 for subjects >35 kg, as per the manufacturer's recommendation. The lung clearance index (LCI) was reported as the mean of at least two acceptable washouts (i.e., functional residual capacity variation <10% for two and <25% for three washouts, with stable breathing pattern and no leaks or marked volume drift during the washout).[31] Lung function outcomes were expressed as *z*-scores,[33,34] except for LCI that is not significantly affected by body size.[35] Reference values for N_2MBW in Caucasian children have been recently published,[36] but they could not be applied in this study due to the use of a different MBW device software version in the analysis of the data (3.2.1 vs. 3.1.6 of this study) that could affect results.

Anthropometry parameters were measured and converted to *z*-scores.[37] Neonatal data were extracted from Hospital database and patient medical records. Birthweight was converted to *z*-score according to 2013 *Fenton* growth charts for preterm infants.[38] Maternal placenta, funicle, and membrane specimens of all preterm children enrolled were revised by an experienced pathologist and a diagnosis of chorioamnionitis was established according to international standard criteria.[39]

Prenatal and postnatal smoke exposure, as well as respiratory morbidity following neonatal period (i.e., history of bronchiolitis in the first year of life, preschool wheezing, and recent asthma-like symptoms) were investigated with parents via questionnaire. The International Study of Asthma and Allergies in Childhood core questionnaire on wheezing[40] was used to assess asthma symptoms and the prevalence of recent asthma-like symptoms was based on the answers to the written question "Has your child had wheezing or whistling in the chest in the past 12 months?".[41]

Power of study and statistical analysis

A minimum sample size of 27 preterm-IUGR children and 54 preterm children without IUGR would provide 80% power at the 5% significance level (two tailed) to detect a mean FEV_1 reduced by 0.6 *z*-scores in the IUGR group (SD 0.9 in both groups),[17] with a group ratio IUGR/no-IUGR = 1/2. From a pilot phase of the study, it was estimated that ~40% of the invited preterm-born children would have not completed the assessments for different reasons (i.e., refuse to participate, inability to perform LFTs, etc.).

The normality of distribution was assessed by the *Shapiro–Wilk* test. Group comparisons were performed using unpaired *t* test, *Mann–Whitney* test, χ^2 test, or *Fisher's* exact test as appropriate. The relationship between the most relevant perinatal/postneonatal variables and LFT outcomes in premature children was assessed using simple and multivariable linear regression. The validity of regression assumptions and the models' fit were assessed through the analysis of residuals and the *Cameron and Trivedi's* decomposition of information matrix test. A *P* value <0.05 was considered statistically significant. Analyses were conducted using STATA V.14 software and GraphPad Prism V 8.00.

RESULTS

General and perinatal characteristics of participants

A total of 135 families of children born <32 weeks were invited to take part in the study and 86 families of age- and sex-matched term controls volunteered for being assessed. After exclusions (Fig. 1), data from 28 very preterm children with IUGR, 67 without IUGR, and 67 term controls were analyzed. Characteristics of children born <32 weeks excluded were similar to those of subjects retained in the final analysis in terms of GA at birth and frequency of BPD (data not shown). Failure rates among 118 very preterm children who underwent LFTs were 6% (7/118) for spirometry (2% in controls), 6% (7/118) for TLco (4% in controls) and 12% (14/118) for LCI (12% in controls).

As expected, the prevalence of maternal pre-eclampsia was higher in preterm infants with IUGR ($P = 0.007$), who also had more frequent neonatal sepsis episodes ($P = 0.03$) (Table 1). The IUGR group needed a more intense and prolonged neonatal respiratory support (Table 1), resulting in a much higher prevalence of BPD compared to preterm children without IUGR (43% vs. 10%, $P = 0.003$). The overall prevalence of BPD in very premature children was 20% (19/95). Of these 19 children, at 36 weeks PMA only one was still intubated, whereas all the others were on nasal cannulae with oxygen requirements <2 L/min. Four (all IUGR) out of 19 children with BPD had a $FiO_2 \geq 30\%$ at 36 weeks PMA and would be considered as "severe BPD" according to the original National Institute of Child Health and Human Development classification.[42]

One child with IUGR and BPD required treatment with inhaled nitric oxide in the perinatal period for a pulmonary hypertension crisis. Other perinatal characteristics are presented in Table 1.

Children born <32 weeks and term controls were comparable as regards sex distribution and current age (Table 2), whereas the former were shorter than the latter at the time of evaluation

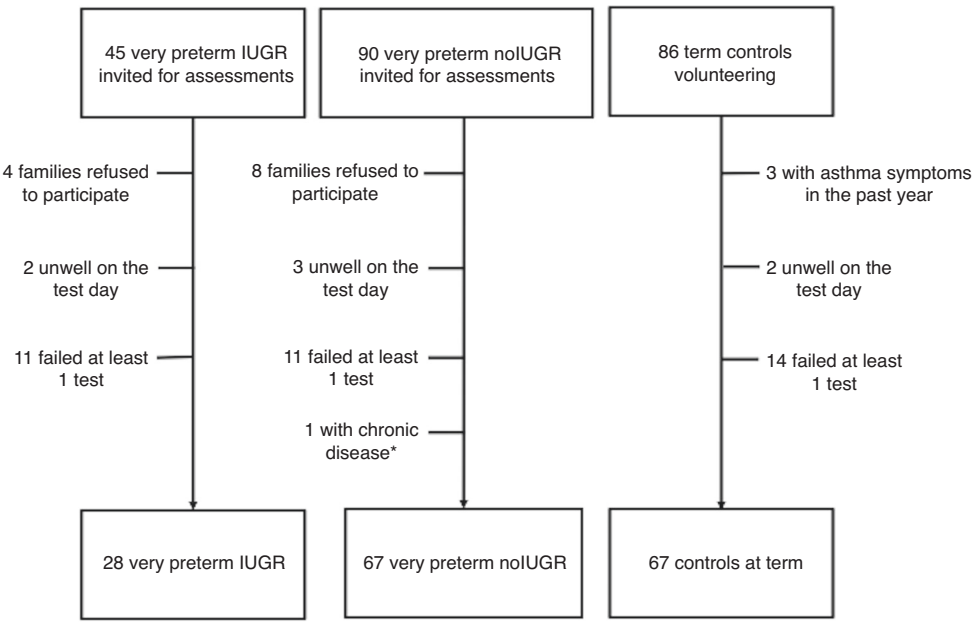

Fig. 1 Study population. Children aged 8.0–15.0 years born very preterm (<32 weeks of gestational age) with and without a prenatal history of intrauterine growth restriction (ratio 1:2) and age-matched controls born at term. *Chronic disease indicating congenital malformation or chromosomal anomalies.

($P = 0.03$) (Table 2). Survivors of very preterm birth did not show differences in anthropometry at school age according to prenatal growth pattern (Table 2). Very preterm children had more frequently a past history of bronchiolitis ($P < 0.001$) and preschool wheezing ($P = 0.002$), whereas the IUGR and no-IUGR preterm groups were comparable as regards postneonatal respiratory comorbidities (Table 2).

Lung function in preterm children and controls

There were significant differences in mean FEV_1 *z*-score, TLco *z*-score, and LCI between children born <32 weeks and controls at term (Table 3). Very premature children with IUGR had reduced FEV_1 by ~0.6 *z*-scores (7% of predicted) compared to their counterparts with normal fetal growth (Table 3), but not significantly different FVC, TLco, and LCI (Table 3).

Among very preterm children with BPD, 4 children with a $FiO_2 \geq 30\%$ at 36 weeks PMA, compared with 15 children with a FiO_2 22–29%, had a lower mean FEV_1 *z*-score (−1.36 vs. −0.58) and a higher mean LCI (8.01 vs. 7.52).

Comparing separately the LFT results of very preterm children with IUGR and without IUGR with those of term controls, the IUGR group showed significant differences in average FEV_1 *z*-score (−0.81; 95% confidence interval (CI) −1.18, −0.42; $P < 0.0001$), TLco *z*-score (−0.58; 95% CI −0.88, −0.28; $P = 0.0002$), and LCI (0.39; 95% CI 0.10, 0.68; $P = 0.008$), whereas very premature children with normal fetal growth only had significantly lower TLco *z*-score (−0.47; 95% CI −0.73, −0.22; $P = 0.003$) than controls at term (Fig. 2).

At univariate linear regression, while BPD was significantly associated with FEV_1 *z*-score ($B = -0.90$; 95% CI −1.39, −0.39, $P = 0.001$), TLco ($B = -0.46$; 95% CI −0.83, −0.08, $P = 0.01$), and LCI ($B = 0.46$; 95% CI 0.10, 0.83, $P = 0.01$), IUGR was negatively associated only with FEV_1 *z*-score ($B = -0.66$, 95 CI% −1.10, −0.21, $P = 0.004$) (data not shown).

However, when adjusting for BPD and other perinatal and postnatal variables, the association between IUGR and FEV_1 lost significance ($P = 0.05$). In addition to BPD, also male sex, BMI *z*-score, and a history of preschool wheezing was significantly associated with FEV_1 *z*-score in the multivariable model (Table 4).

DISCUSSION

We showed that very preterm children with a prenatal diagnosis of IUGR had worse conducting airway function (lower FEV_1 *z*-score) than their counterparts with normal fetal growth, when evaluated at school age. However, part of this difference was accounted for by the higher frequency of BPD in the IUGR group. Ventilation inhomogeneity and diffusion capacity, instead, did not significantly differ between very preterm children with or without IUGR.

Children born <32 weeks showed, on average, a pretty normal lung function, although there were statistically significant differences in FEV_1, TLco, and LCI compared with term-born controls.

Strengths and limitations

The main strength of this study is that, to the best of our knowledge, it is the first evaluation of lung function in very premature children with a prenatal diagnosis of IUGR according to recently released international standards.[7] Although there is a large body of evidence indicating worse respiratory outcomes in people who were born SGA,[18,19,21–23] it is estimated that ~40% of children with IUGR have a birthweight >10th percentile,[8,43] whereas 50–70% of SGA children are just constitutionally small, without evidence IUGR.[24] Since perinatal outcomes differ between infants with SGA and IUGR,[16,25] also long-term respiratory outcomes could be different and should be characterized in both groups.

The integration of the results of different LFTs according to the ERS/ATS recommended reference values[33,34] allowed to assess both larger airways and peripheral lung function. Moreover, the availability of detailed information regarding perinatal events, recorded at the time of NICU admission, allowed to evaluate the impact of critical predictors on subsequent lung function.

Among limitations, measurements included only children able to perform correctly LFTs, potentially underestimating the burden of respiratory dysfunction in the whole cohort of survivors of very preterm birth. Ideally, the inclusion of less premature children with IUGR born at >32 weeks of gestation or even born-term children with IUGR would have allowed to disentangle better the real effect of IUGR on later lung function from BPD and the other *sequelae* of

Table 1. Neonatal data of preterm children born at <32 weeks of gestation.

	Preterm		
	IUGR $n = 28$ Median (IQR)	No-IUGR $n = 67$ Median (IQR)	*P* value
Perinatal characteristics			
Gestational age (weeks)	28.5 (27.2, 29.4)	29.0 (27.2, 30.1)	0.3
Birthweight (kg)	0.82 (0.74, 0.92)	1.20 (0.96, 1.40)	**<0.001**
Birthweight *z*-score[a]	−1.29 (−1.67, −0.80)	−0.17 (−0.50, 0.33)	**<0.001**
Oxygen supplementation (days)	34 (0, 89)	5 (1, 39)	0.07
Mechanical ventilation (days)	4 (2, 8)	2 (1, 4)	**<0.001**
CPAP (days)	10 (3, 29)	10 (3, 23)	0.28
Parental nutrition	26 (20, 32)	19 (12, 23)	**0.002**
	n (%)	*n* (%)	
Multiple births	4 (14%)	16 (24%)	0.3
BPD[b]	12 (43%)	7 (10%)	**0.003**
Intubation	27 (96%)	49 (73%)	**0.001**
Surfactant	23 (82%)	42 (63%)	0.06
Postnatal steroids	6 (21%)	3 (5%)	**0.01**
Pneumothorax	1 (4%)	4 (6%)	>0.99
PDA[c]	14 (50%)	19 (28%)	**0.04**
IVH 3–4°	1 (4%)	2 (3%)	>0.99
NEC	1 (4%)	1 (1%)	>0.99
Blood culture-positive sepsis	9 (32%)	9 (13%)	**0.03**
Antenatal steroids	23 (82%)	51 (76%)	0.1
Maternal smoking in pregnancy	1 (4%)	6 (9%)	0.3
Maternal pre-eclampsia	10 (36%)	8 (12%)	**0.007**
PROM (>24 h)	5 (18%)	8 (12%)	0.2
Histological chorioamnionitis[d]	4 (14%)	21 (31%)	0.12

IUGR intrauterine growth restriction, *CPAP* continuous positive airway pressure, *BPD* bronchopulmonary dysplasia, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *PDA* patent ductus arteriosus, *PROM* prolonged rupture of membranes (>24 h).
IUGR definition based on Gordijn et al.[7]
[a]Birthweight *z*-scores were based on Fenton and Kim.[38]
[b]BPD defined as FiO_2 >21% at 36 weeks postmenstrual age.[26]
[c]PDA that required pharmacological or surgical treatment
[d]Histological chorioamnionitis defined according to Redline et al.[39]
Bold entries indicate *P* values < 0.05.

prematurity. However, this was beyond the scope of the study that specifically focused on very premature children as they are at higher risk of a low lung function trajectory until adult age,[4] which is associated with increased risk of early-onset COPD in later adulthood.[5] The final study group included only four children with "severe" BPD"[42] and one with grade 3 BPD according to the more recent classification proposed by Jensen et al.[44] These small numbers prevented us from stratifying for the severity of BPD when evaluating the long-term impact of IUGR on lung function. The study was adequately powered to detect differences in mean FEV_1 *z*-score (main outcome) between IUGR and no-IUGR preterm children, but it was underpowered in relation to the other outcomes (differences in LCI and TLco), given the small difference that we found between groups for these outcomes. Finally, although at our center very premature children routinely undergo echocardiogram screening before discharge, data on the prevalence of pulmonary hypertension in this cohort were not collected and could not be taken into account when performing the analysis.

Comparison with previous studies

Only one previous study evaluated lung function in very preterm children with IUGR,[17] comparing school-age children born at <30 weeks with and without a prenatal history of umbilical artery absent/reversed end-diastolic blood flow (criteria of early IUGR). Differences of FEV_1 between groups were almost the same as in our cohort (~0.6 *z*-scores), although they resulted not significant in that study.[17] Compared to Morsing et al.,[17] we used a more comprehensive and updated definition of IUGR that takes into account also fetal biometry,[7] allowing a better identification of children with early IUGR and a more precise characterization of long-term lung function outcomes in this group.

Several studies showed a lower lung function in preterm or term-born infants,[19,20] children,[21,22] and adults[23,45] who were SGA at birth (thus, not necessarily IUGR) compared to their counterparts with a normal birthweight.

In very preterm children, Ronkainen et al.[18] reported that a birthweight *z*-score <−2 (likely to be IUGR) was associated with a 6% of predicted FEV_1 reduction at school age, consistently with our finding (7% reduction) in the IUGR group. They also found a negative association between SGA and TLco,[18] similarly to what was reported by Narang et al.[46] in a cohort of ex-preterm children evaluated at 21 years of age. In that study, the SGA group had an abnormal diffusing capacity at rest that tended to normalize on

Table 2. Anthropometry and respiratory morbidity in preterm children born at <32 weeks of gestational age and term controls.

	Preterm, $n = 95$	Controls, $n = 67$	Mean diff. (95% CI), *P* value	Preterm		
				IUGR, $n = 28$	No-IUGR, $n = 67$	Mean diff. (95% CI), *P* value
Boys	53 (55%)	32 (48%)		14 (50%)	38 (56%)	
Age (year)	10.9 (1.9)	11.3 (2.0)	−0.4 (−1.0, 0.2), $P = 0.18$	11.0 (2.0)	10.9 (1.8)	0.1 (−0.7, 1.0), $P = 0.7$
zHeight	0.01 (0.93)	0.33 (0.88)	**−0.32 (−0.60, −0.02), $P = 0.03$**	−0.01 (0.95)	0.07 (0.91)	−0.08 (−0.51, 0.33), $P = 0.4$
zBMI	0.63 (1.24)	0.31 (1.09)	0.32 (−0.05, 0.69), $P = 0.4$	0.57 (1.22)	0.65 (1.26)	−0.08 (−0.65, 0.50), $P = 0.6$
Respiratory morbidity	*n* (%)	*n* (%)	*P* value	*n* (%)	*n* (%)	*P* value
Bronchiolitis	28 (29%)	7 (15%)	**<0.001**	6 (21%)	22 (33%)	0.3
Preschool wheezing	28 (29%)	6 (9%)	**0.002**	7 (25%)	21 (31%)	0.5
Recent asthma-like symptoms[a]	11 (12%)	–		3 (11%)	8 (12%)	>0.9
Secondhand smoke	22 (23%)	12 (18%)	0.4	7 (25%)	15 (22%)	0.7

IUGR intrauterine growth restriction, *zBMI* *z*-score body mass index, *zHeight* *z*-score height.
Values are presented as mean (SD), unless otherwise specified.
IUGR definition was based on Gordijn et al.[7]
Anthropometry *z*-scores were based on WHO growth reference.[37]
[a]Based on the answer to the written question "Has your child had wheezing or whistling in the chest in the past 12 months?".[41]
Bold entries indicate 95% CI not overlapping and *P* values < 0.05.

Table 3. Lung function in children born at <32 weeks of gestation and controls at term.

	Preterm $n = 95$	Controls $n = 67$	Mean diff. (95% CI), P value	Preterm		
				IUGR, $n = 28$	No-IUGR, $n = 67$	Mean diff. (95% CI), P value
$zFEV_1$	−0.03 (1.04)	0.31 (0.81)	**−0.34 (−0.64, −0.03), $P = 0.03$**	−0.51 (0.94)	0.15 (1.08)	**−0.66 (−1.12, −0.19), $P = 0.006$**
zFVC	−0.04 (1.12)	0.18 (0.78)	−0.22 (−0–52, 0.09), $P = 0.2$	−0.35 (0.93)	0.10 (1.16)	−0.45 (−0.95, 0.03), $P = 0.07$
$zFEV_1$/FVC	−0.02 (0.91)	0.11 (0.73)	− 0.13 (−0.39, 0.12), $P = 0.3$	−0.20 (1.01)	0.05 (0.88)	−0.25 (−0.65, 0.15), $P = 0.2$
zTLco	−0.24 (0.76)	0.27 (0.68)	**−0.51 (−0.74, −0.28), $P = <0.0001$**	−0.31 (0.63)	−0.20 (0.80)	−0.11 (−0.44, 0.23), $P = 0.5$
zVa	0.36 (0.85)	0.43 (0.76)	−0.07 (−0.35, 0.21), $P = 0.4$	0.39 (0.75)	0.35 (0.92)	0.04 (−0.37, 0.44), $P = 0.3$
zKco	−0.52 (0.63)	−0.01 (0.65)	**−0.51 (−0.72, −0.28), $P < 0.001$**	−0.60 (0.60)	−0.48 (0.64)	−0.12 (−0.42, 0.17), $P = 0.7$
LCI	7.25 (0.73)	7.02 (0.43)	**0.23 (0.02, 0.42), $P = 0.03$**	7.42 (0.99)	7.18 (0.59)	0.24 (−0.09, 0.56), $P = 0.14$

IUGR intrauterine growth restriction, *zFEV$_1$* *z*-score forced expired volume in the first second, zFVC *z*-score forced vital capacity, *zTLco* *z*-score transfer factor of the lung for carbon monoxide, *zVa* *z*-score alveolar volume, *zKco* *z*-score carbon monoxide transfer coefficient, LCI, lung clearance index.
Values are expressed as mean (SD) and unadjusted mean difference (95% CI), unless otherwise specified.
IUGR definition was based on Gordijn et al.[7]
Spirometry and TLco *z*-scores were according to Global Lung Function Initiative reference values.[33,34]
Bold entries indicate 95% CI not overlapping and P values < 0.05.

exercise, possibly due to a low pulmonary blood flow at rest.[46] Our study, instead, which evaluated very preterm children with IUGR but not necessarily SGA at birth, did not show significant differences in diffusing capacity according to fetal growth pattern (Table 3).

In school children born extremely preterm (<28 weeks), Thunqvist et al.[47] found similar spirometry values between those with and without birthweight *z*-score <−2. It is possible that in such premature infants the consequences of IUGR on lung function are overcome by those related to the great immaturity of the lungs at birth; however, given the small number of individuals in the study group ($n = 14$),[47] further verification in larger cohorts is warranted.

In children born at term or near term, Turner et al.[13] found that a persistent low growth from the first trimester of pregnancy was associated with a reduced FEV_1 at 10 years of age,[13] while the "Generation R" study showed that, at the same age, a history of restricted fetal growth (change of weight growth percentile < −0.67 *z*-scores in the second and third trimester of pregnancy) predicted a FEV_1 lower by −0.25 *z*-scores (95% CI −0.51, −0.00) compared with children with normal fetal growth.[14] Overall, these data support a negative impact of IUGR on conducting airway development as also suggested by our findings, although in our study this effect was not independent of other perinatal and postneonatal factors, in particular from BPD (Table 4).

Interpretation of results

Fetal growth restriction seemed to affect mainly larger conductive airways function rather than the distal lung, considering that significant differences in lung function outcomes according to fetal growth pattern were found at spirometry but not at MBW and TLco. This finding is not surprising, considering that our study group suffered from early-onset fetal growth restriction that might have affected the conductive airway development, which occurs at a earlier stage of fetal life, compared to the alveolarization process.[48] Differences of FEV_1 *z*-scores between the IUGR and no-IUGR group were >0.4 *z*-scores, a cut-off under which differences in spirometry results within the same population could just depend on sampling variability.[49] However, it is encouraging that average lung function outcomes in the IUGR group, although worse than in control at term, were well within the limit of normal (Fig. 2).

When adjusting for other perinatal and postnatal predictors, the negative association between IUGR and FEV_1 in very preterm children lost statistical significance, although it showed a borderline P value (0.05). It is likely that BPD contributed to this result as its prevalence was dramatically higher in the IUGR group (43% vs. 10%) and it had the strongest association with FEV_1. Besides, as expected, within the BPD group higher oxygen requirement at 36 weeks PMA was associated with worse outcomes at spirometry and MBW. BPD is likely to act as a mediator in the causal pathway between IUGR and FEV_1 in very preterm children. Animal models showed that fetal growth restriction triggers epigenetic changes that affect signaling pathways involved in airway maturation[50–53] and we hypothesize that this could contribute to the pathogenesis of BPD in IUGR very preterm children. Other associations found at multivariable regression in children born <32 weeks were already known from the literature, such as the one between FEV_1 and male sex[54] or wheezing,[27] whereas the positive effect of BMI *z*-score on FEV_1 was previously demonstrated in the general pediatric population.[12]

In animal studies, undernutrition occurring during the saccular stage of lung development mainly affects alveolarization, pulmonary vascular growth, and the efficiency of alveolar–capillary barrier, resulting in postnatal reduced diffusing capacity.[12,55] All preterm children enrolled in this study experienced similar conditions during most of the saccular stage that occurred outside the uterus. Probably, for this reason, there were no significant differences in TLco *z*-scores according to a fetal growth pattern in premature children, although they showed lower diffusing capacity than term controls (Fig. 2).

Although the mean LCI was significantly higher in very preterm children with IUGR than in controls at term, this difference was mainly due to the presence in the IUGR group of a few outliers with BPD and elevated LCI (Fig. 2), whereas the great majority of very preterm children had no evidence of increased ventilation inhomogeneity, irrespectively of their fetal growth pattern. Previous studies had reported a mild increase of LCI in extremely premature children,[27,56] but no differences between very premature children and term controls.[57] Our study confirms that LCI has a marginal role in the respiratory follow-up of children born before 32 weeks of gestation.

In conclusion, we showed that fetal growth restriction had an impact on FEV_1 in survivors of very preterm birth. We did not find evidence of a detrimental effect of IUGR on ventilation inhomogeneity and diffusion capacity, although, as regards TLco, confounding factors such as prematurity and BPD might have hidden a possible association with IUGR. The association between

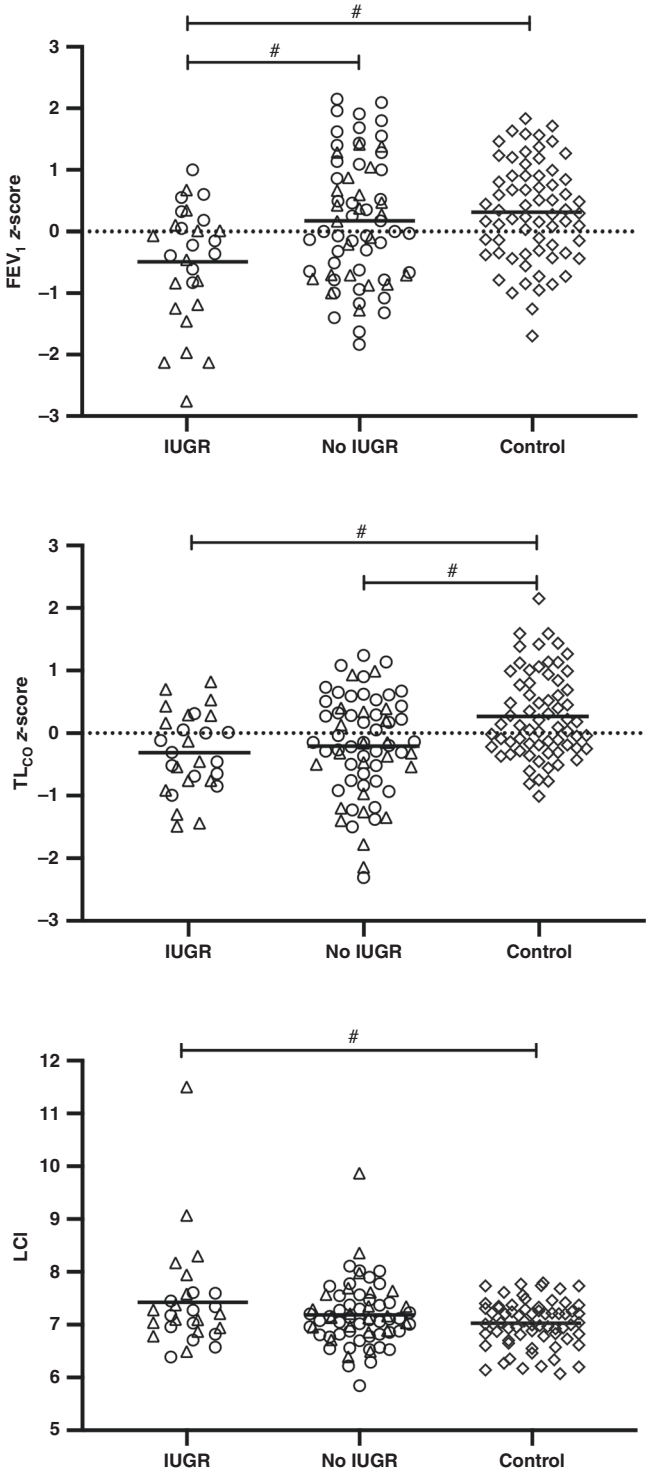

Fig. 2 Comparison of lung function in very preterm children with IUGR, no IUGR and controls at term. Comparison of FEV_1 *z*-scores (**a**), TLco *z*-scores (**b**), and lung clearance index (LCI) (**c**) in 95 school-age preterm children (<32 weeks) with or without intrauterine growth restriction (IUGR) and 67 term-born controls. The straight bars indicate the mean values in each group. In premature children, open triangles represent subjects with bronchopulmonary dysplasia (BPD) and open circles for those without BPD. Spirometry and TLco *z*-scores based on Global Lung Function Initiative reference values.[33,34] #$P < 0.05$ between two groups (unpaired *t* tests).

Table 4. Multivariable linear regression model for FEV_1 *z*-score in 95 children aged 8.0–15.0 years born <32 weeks of gestation.

Covariate[c]	FEV_1 *z*-score		
	Adjusted *B* (95% CI; *P* value)	95% CI	*P* value
Male	**−0.46**	**−0.87, −0.04**	**0.03**
Multiple birth	−0.11	−0.64, 0.40	0.6
Current age	−0.03	−0.11, 0.11	0.9
BMI *z*-score	**0.19**	**0.02, 0.35**	**0.03**
Gestational age[a]	0.006	−0.00, 0.13	0.08
IUGR	−0.46	−0.93, 0.004	0.05
Prenatal smoke exposure	−0.20	−1.01, 0.60	0.6
Maternal pre-eclampsia	−0.13	−0.65, 0.39	0.6
Histological chorioamnionitis[b]	0.04	−0.49. 0.58	0.8
BPD	**−0.72**	**−1.29, −0.16**	**0.01**
Sepsis	−0.04	−0.58, 0.48	0.9
Postnatal smoke exposure	−0.33	−0.78, 0.18	0.2
Bronchiolitis	−0.15	−0.67, 0.37	0.5
Preschool wheezing	**−0.65**	**−1.18, −0.13**	**0.02**
Recent asthma-like symptoms[c]	0.68	−0.03, 1.39	0.06

BMI body mass index, *IUGR* intrauterine growth restriction, *FEV_1* forced expired volume in the first second.
Adjusted R^2 of the models: 0.24
BMI *z*-scores based on WHO growth reference.[37]
Birthweight *z*-scores based on Fenton et al.[38]
Spirometry and TLco *z*-scores according to Global Lung Function Initiative reference values.[33,34]
[a]Unitary increase of week of gestational age at birth.
[b]Histological chorioamnionitis defined according to Redline et al.[39]
[c]Based on the answer to the written question "Has your child had wheezing or whistling in the chest in the past 12 months?".[41]
Bold entries indicate 95% CI not overlapping and *P* values < 0.05.

IUGR and a lower FEV_1 appeared to be, at least in part, related to the higher risk of BPD in very premature children with IUGR.

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AUTHOR CONTRIBUTIONS

M.A. and C.S. conceived the study, performed data collection, performed the analyses, interpreted data, and wrote the manuscript. C.D.P., E.V., C.C., M.E.F., L.D., M.O., Lu Cat performed data collection, interpreted data. and revised to the manuscript. Lu Cas performed the statistical analysis, interpreted data. and contributed to the manuscript. P.C. conceived the study, interpreted data. and contributed to the manuscript. All authors approved the final draft of the manuscript.

ADDITIONAL INFORMATION

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