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**Lung function after extremely preterm birth – A population-based cohort study
(EXPRESS)**

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Running head: Lung function after extremely preterm birth

ABSTRACT

Background and objectives: Follow-up studies of children and young adults born very-to-moderately preterm show persistent and significant lung function deficits. The aim of the study was to determine lung function and airway mechanics in school-aged children born in 2004 to 2007 and extremely preterm (after 22-26 weeks of gestation). **Methods:** In a population-based cohort of children born extremely preterm and controls born at term (n=350), follow-up at 6½-years-of-age was performed using spirometry and impulse oscillometry. Associations to gestational age, smallness for gestational age (SGA), and bronchopulmonary dysplasia (BPD) were assessed. **Results:** Children born extremely preterm had lower forced vital capacity (FVC, z-score: -0.7, 95% CI: -1.0;-0.4), forced expiratory volume (FEV₁, z-score: -1.1, 95% CI: -1.4; -0.8), higher frequency-dependence of resistance (R₅₋₂₀, 0.09, 95% CI: 0.05; 0.12 kPa·L⁻¹·s⁻¹) and larger area under the reactance curve (AX, 0.78, 95% CI: 0.49; 1.07 kPa·L⁻¹) than controls. In children born at 22-24 weeks of gestation, 24% had FVC and 44% had FEV₁ below the lower limit of normal. SGA and severe BPD only marginally contributed to pulmonary outcomes. Asthma-like disease was reported in 40% of extremely preterm children and 15% of controls. **Conclusion:** Many children born extremely preterm have altered airway mechanics and significant obstructive reduction in lung function. This warrants consideration for treatment and continued follow-up.

INTRODUCTION

In high-income countries, infant survival is nowadays the most probable outcome after extremely preterm birth.¹⁻³ However, improved survival-rates for these patients have not been paralleled by a decrease in neonatal morbidity and long-term disability.^{4,5} The general occurrence of bronchopulmonary dysplasia (BPD)⁶ – a chronic neonatal lung disease characterized by disrupted alveolar development, decreased airway stability and increased airway resistance – still constitutes a significant problem.^{7,8}

Although recent data suggest that the halted alveolarization of the preterm lung has the ability to catch-up throughout childhood, follow-up studies of children and young adults born very-to-moderately preterm show persistent and significant lung function deficits.⁹⁻¹¹ In a population-based study of extremely preterm survivors born below 26 weeks of gestation in 1995, a large proportion suffered from lung function deficits still 11 years after birth: fifty-six percent had abnormal spirometry and 25% had a current diagnosis of asthma.¹² Studies reporting from more contemporary cohorts of children born very preterm suggests that significant impairments in lung structure and lung function still are major concerns.^{13,14}

We hypothesized that extremely preterm birth is associated with an increased risk of clinically important reductions in lung function and altered lung mechanics at early school age. The primary aim of the current study was therefore to determine lung function, before and after pharmacological bronchodilation, in a population-based cohort of 6½-year-old children born extremely preterm. We also investigated three readily available neonatal predictors of later lung function by assessing the associations between gestational age at birth, smallness for gestational age at birth and grades of neonatal bronchopulmonary dysplasia, to childhood lung function. Finally, we aimed to assess the proportions of children born extremely preterm with

lung function below the lower limit of normal and proportions with ongoing respiratory symptoms.

METHODS

Participants

The Swedish national study cohort EXPRESS (Extremely Preterm Infants in Sweden Study) included all infants born before 27 weeks of gestation between April 1 2004 and March 31 2007. Detailed characteristics of this prospectively collected population-based cohort have previously been reported.^{1,4,6}

All EXPRESS-children in three out of the seven Swedish health care regions (n=250, 51% of the total cohort) were invited to a follow-up study on lung function at 6½-years-of-age (± 3 months). Exclusion criteria were congenital cardiovascular or pulmonary malformations. In 27 cases, the date for inclusion was passed, 7 families were lost to follow-up (no address or residing outside Sweden) and 38 declined participation, leaving 178 (71% inclusion rate) children born extremely preterm that participated in the study (Figure 1).

Dropout analyses did not show any significant difference in mean gestational age (participants=25.0 versus non-participants=25.3 weeks, $p=0.13$), mean birth weight (782 versus 769 g, $p=0.15$) or sex distribution (45 versus 50% girls, $p=0.39$) between those participating in the study and those lost to follow-up.

Using the Swedish Medical Birth Register, each preterm child was matched to a healthy control born at term (controls; gestational age 37-41 weeks). A list of 10 control children matched on the mothers' country of birth, date of delivery, hospital of birth and sex was randomly selected. The first child on the list was invited to the study. If participation was

declined the next control on the list was approached. If participation was declined for all 10 on the list, the control was considered as missing (n=6).

Definitions

Gestational age was determined by ultrasound during gestational weeks 17-18 in more than 95% of the pregnancies.¹

Small for gestational age (SGA) was defined as a birth weight two standard deviations or more below the mean and appropriate for gestational age (AGA) was defined as birth weight within two standard deviations of the mean according to a Swedish sex and gestational age-specific reference for normal fetal growth.¹⁵

Ninety percent of the infants born preterm suffered from bronchopulmonary dysplasia (BPD) in the neonatal period. BPD was categorized as either moderate (breathing >21% but <30% oxygen) or severe (breathing at least 30% oxygen or positive pressure ventilation) at 36 weeks of postmenstrual age.¹⁶

A significant airway response to an inhaled beta-2-agonist (400 micrograms salbutamol) was defined as increase in $FEV_1 \geq 12\%$.

A lung function below the lower limit of normal was defined as a z-score less than -1.64 (corresponding to less than the 5th percentile).

Asthma-like-disease was defined as any episode of respiratory wheeze or use of asthma medication (inhaled corticosteroids, beta-2-agonists, anti-leukotriens) in the last 12 months before follow-up, as reported by the parents at time of clinical examination.

Clinical and lung function assessments

Appointment for follow-up was deferred to at least two weeks following any acute respiratory tract illness.

Information on socioeconomics, current and past parental smoking habits and current respiratory health and respiratory medications was collected using a questionnaire based on the ISAAC-study.¹⁷

Lung function tests consisted of dynamic spirometry and impulse oscillometry (IOS). The tests were performed using the Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA, USA). Spirometry was performed according to ATS/ERS criteria.¹⁸ The test subject performed at least three maximum expiratory flow volume recordings in sitting position, wearing a nose clip. The highest values of forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV₁) were extracted and used for analysis, provided that the subject's effort was coded as being maximal by the test leader, the curve passed visual quality inspection, and that the two highest FVC and FEV₁ readings were reproducible.

The IOS system has previously been described in detail.^{19,20} Briefly, the IOS system generates small pressure oscillations to the airways by a loudspeaker and the software measures respiratory impedance, which includes the respiratory resistance (R_{rs}) and respiratory reactance (X_{rs}). All IOS measurements were performed during tidal breathing with the child sitting in an upright position, with the lips sealed around the mouthpiece and with the cheeks supported by the hands. For each participant, a minimum of two recordings without artefacts for at least 20 seconds were saved for later analysis. A coherence value >0.80 at 10 Hz was used as criteria for an appropriately performed test. The mean value of the resistance at 5 Hertz (R_5), frequency dependence of resistance (R_{5-20}) and area under the curve of negative reactance values (AX) were used for analysis.

The spirometry system was calibrated each day using a 3 L precision syringe and the IOS system verified using a reference resistance of $0.20 \text{ kPa} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$.

Pulmonary function after bronchodilation was measured approximately 20 minutes after an inhaled dose of 400 micrograms of salbutamol through a valved spacer device.

Statistical methods

Data are reported as means and standard deviations, 95% confidence intervals or numbers and proportions. In addition to quantitative data, FVC, FEV₁ and FEV₁/FVC were converted to z-scores using the Global Lung Initiative reference values (GLI).²¹ No significant interaction effect between sex and preterm birth on lung function was found, and results are therefore presented for both sexes combined.

Comparisons between groups of children were performed using the Student's t-test or the Pearson chi-square test. Using multiple linear regression analyses, lung function outcomes were adjusted for age, sex, height and examination site. A p-value <0.05 was considered statistically significant.

Ethical considerations

All parents and children invited to participate received oral and written information, and provided signed informed consent to the study. Study approval was obtained from the Regional Ethical Review Board in Stockholm (no. 2010/520-31/2 and amendment no. 2011/376-32).

RESULTS

The success rates were 87% for IOS and 54% for spirometry and did not differ between children born extremely preterm and children born at term. In total, 89% of the children contributed with any lung function assessment data (Figure 1). Parental, perinatal and current characteristics of participants contributing with lung function data are presented in Table 1.

Lung function in children born extremely preterm

Adjusted lung function estimates and mean group differences are presented in Table 2 (for crude values, please see supplemental-on-line Table S1). The adjusted FVC was 9% lower and the adjusted FEV₁ was 13% lower in children born extremely preterm than in children born at term. IOS measurements showed significantly higher peripheral airway resistance (R₅ and R₅₋₂₀) and larger area under reactance curve (AX) in children born extremely preterm than in children born at term.

No child in the term control group had FVC or FEV₁ z-score below the lower limit of normal (5th percentile). In the preterm group, the corresponding proportion for FVC was 14%, and for FEV₁ 23%.

Reported respiratory symptoms

Asthma-like disease was reported to be almost three times more prevalent in children born extremely preterm than in control children born at term (Table 1). Among children born extremely preterm, those with reported asthma-like disease had -0.8 (95% CI -1.3;-0.3) lower FEV₁ z-score and 0.6 kPa.L-1 (95% CI 0.1-1.0) higher AX than those who did not report any symptoms.

Bronchodilator responses

Post-bronchodilator FEV₁ could be assessed in 60 (67%) of children born extremely preterm and in 70 (71%) of term children. A significant airway response to the beta2-agonist was seen in 28% of children born extremely preterm and in 10% of controls (P=0.007). The post bronchodilator FEV₁ z-score was on average 1.0 (95% CI: -1.33; -0.67) lower in children born extremely preterm than in children born at term.

Gestational age and lung function in children born extremely preterm

Adjusted lung function estimates and mean group differences are presented in Table 3 (for crude values, please see supplemental-on-line Table S1). Children born at 22-24 weeks had 10% lower FVC and 15% lower FEV₁ than children born at 25-26 weeks of gestation ($p=0.008$ and <0.001 , respectively). The proportion of children born at 22-24 weeks with lung function below the lower limit of normal was 24% for FVC and 44% for FEV₁, corresponding to 5-10 times higher risk of a lung function below normal than controls born at term. The proportions for children born at 25-26 weeks of gestation were 11% and 15%, respectively. IOS measurements did not differ significantly between the two gestational age groups.

Lung function in children born extremely preterm and SGA

Adjusted lung function estimates and mean group differences are presented in Table 4 (for crude values, please see supplemental-on-line Table S1). Fourteen percent of the children born extremely preterm had a birth weight which was outside the expected range, i.e., small for gestational age, SGA. Spirometry outcomes in children born extremely preterm did not differ significantly between those born SGA and those born AGA. However, children born SGA had higher R₅₋₂₀ assessed with IOS than those born AGA.

Severity of BPD and later lung function

Adjusted lung function estimates and mean group differences are presented in Table 5 (for crude values, please see supplemental-on-line Table S1). In children born extremely preterm, 76% were diagnosed with moderate and 14% with severe BPD in the neonatal period. Significant difference in lung function in relation to severity of BPD was only seen for the FEV₁/FVC ratio, which was lower (-0.73 z-scores, 95% CI -1.36;-0.10, $p 0.02$) in children with severe compared to moderate BPD.

DISCUSSION

In this population-based follow-up study we found that extremely preterm birth was associated with reduced lung function at 6½-years-of-age. Functional deficits included not only reduced maximal expiratory flows and lower lung volumes measured by spirometry, but also altered airway mechanics measured by the IOS technique. Almost half of the children born extremely preterm reported asthma-like disease and one quarter demonstrated reversible airway obstruction. Among those surviving periviable births at 22-24 weeks of gestation, we noted a 5 and 10 times increased risk to have a lung function below the lower limit of normal (<5th percentile) for FVC and FEV₁ respectively. Being born SGA or having severe BPD only marginally contributed to pulmonary outcomes.

Comparable study populations are few, as survival at extremely short gestations has been limited until recently. The 11-year follow-up of the EPICure study including children surviving birth before 26 weeks of gestation in 1995 found slightly larger reductions in lung function than in our study, showing that FEV₁ was -1.7 z-scores below the mean (using the same GLI-standard as used herein).¹² Cazzato et al. included 8½-year-old children born less preterm (gestational age 24-32 weeks) and reported reductions in lung function similar to what we found, z-score -1.13 for FEV₁.²² Also in line with our study, Simpson et al. showed reductions of -1.06 z-score FEV₁ for the BPD group, which is comparable regarding gestational age to our study.¹³ Vergheggen et al. found somewhat less reduced FEV₁ (-0.59 zscore), but the BPD group in that study included less immature children than our study which could explain the difference.¹⁴ Further, our finding of an almost equal drop in spirometric lung function going from 25-26 weeks to 22-24 weeks of gestation as going from term to 25-26 weeks of gestation may indicate non-linear relationship between gestational age and later lung function. Taken together, present and previous observations underline the perception that the degree of preterm birth has a major effect on later lung function.

It has been suggested that other lung function techniques than conventional spirometry – such as forced impulse oscillometry (FOT) – could add to the information concerning both effects and etiology of lung function deficits after preterm birth.²³ The data retrieved from the FOT is thought to represent complex functions of the lung such as small airway obstruction and airway mechanics, including the elastic properties of the lung.^{20,24} Lung resistance was higher and the area under the reactance curve was larger in the current study in children born extremely preterm than in children born at term, without any clear association to degree of prematurity or BPD. Other studies have also reported on altered respiratory mechanics after preterm birth compared to reference values or term controls. Both Malmberg et al.²⁵ and Verheggen et al.¹⁴ showed higher resistance and reduced reactance using FOT-technique among preterm children with BPD compared to preterm children without. Given that almost all childhood survivors of extremely preterm birth in our study had BPD, a comparison of patients with and without BPD was not possible to perform.

Z-scores for healthy subjects have been calculated for the IOS outcome variables AX and R₅₋₂₀ in Finnish and Mexican children.^{26,27} Depending on which reference used in the calculations, we found that the mean z-score for AX (before reversibility test) among healthy 6½-year-old children participating in our study (those with asthma excluded) varied from -0.75 to +1.79, with SDs varying from 1.00 to 1.21. The corresponding mean z-scores for R₅₋₂₀ ranged from -0.50 to 1.15. Possible explanations for this inconsistency include population differences, issues relating to selection bias and possible imprecision of the method. Our reference group was randomly recruited from a list – generated at the Swedish Medical Birth Registry – of 10 controls per index child matched on the mothers' country of birth, date of delivery, hospital of birth and sex. This control group therefore represents a population sample from a large geographical area. Since we assessed healthy controls in our own population, we think group comparisons are more valid than if we had chosen to convert our

lung function data from children born extremely preterm to z-scores using one of the previously published references.

The severity of BPD, here assessed as moderate or severe BPD, was associated with a lower FEV₁/FVC-ratio in children having severe BPD, but not other lung function indices. Brostrom et al. found that lung function in 6 to 8-year-old children with mild BPD was similar to that in children diagnosed with moderate BPD.²⁸ A recent meta-analysis including follow-up studies of subjects born preterm after 24-36 weeks of gestation between 1964 and 2000 reported average FEV₁ reductions of 16% associated with mild BPD and 19% for moderate to severe BPD.²⁹ The modest or non-significant differences in lung function related to degree of BPD found by us and others indicate that childhood respiratory dysfunction can essentially be related to gestational age, and that BPD classification seems to be of limited value for predicting future lung function measured by spirometry.³⁰⁻³²

In extremely preterm children born SGA, the IOS variable R₅₋₂₀ (indicator of airway obstruction) was slightly higher compared to children born AGA, while no differences were found in spirometry measures. Others have – independent of gestational age – found a link between low birth weight and reduced lung function assessed with spirometry in infancy and at school age.^{33,34} Greenough et al. reported higher airway resistance measured with whole body plethysmography (R_{aw}) in children born preterm (gestational age: 23-35 weeks) and SGA compared to children born preterm with a birth weight appropriate for gestational age.³⁵

Strengths and limitations

Major strengths of this study include the population-based, prospective design and the follow-up time. Follow-up rate was 71% and drop-out analysis did not indicate any response bias.

The study was controlled by design and the control group was carefully chosen to avoid

selection bias. All results were adjusted for current height, sex and investigation site, and any interaction between sex and extremely preterm birth was excluded. The outcomes, spirometry in particular, were clinically highly relevant.

We note that our control group of children born at term exhibited approximately 0.5 higher z-score for spirometry outcomes than the published reference population (GLI).²¹ If anything, this may suggest an underestimation of the frequency of children born extremely preterm with a lung function below the lower limit of normal, but is not likely to affect differences seen between groups.

Limitations include that those performing the measurements were not blinded. To minimize observer bias, strict predefined criteria for quality control and analysis of recordings were used, and all measurements were controlled for accuracy by a single technician. The success rate for spirometry was low, but anticipated because of the young age at follow-up, but could introduce a selection bias. However, since there was no difference in success rate between children born extremely preterm and controls born at term it is likely to be non-differential.

We did not perform measurements of total lung capacity and could therefore not deduce whether the reduced FVC seen in the preterm group reflected a restrictive lung impairment or hyperinflation as a marker of more severe obstructive lung disease, or both. Our questionnaire on respiratory symptoms was based on questions initially developed for studies on asthma-related outcomes and not for outcomes related to preterm birth.³⁶ Asthma and chronic lung disease after preterm birth have some clinical and physiological features in common, but may differ in other respects such as presence or absence of airway inflammation. We used the term asthma-like disease since the term asthma should be avoided in describing pulmonary problems following preterm birth.³⁷

Clinical aspects of the results

It has been established that preterm birth increases the risk of chronic respiratory morbidity, including asthma-like disease during childhood and later on in life.³⁸⁻⁴⁰ There is however, still a lack of knowledge about the prevalence and magnitude of chronic respiratory morbidity after extremely preterm birth. We find it deeply concerning that asthma-like disease was very prevalent among children born extremely preterm and that up to half of the children born at 22-24 weeks of gestation exhibited a lung function below the lower limits of normal. How these findings translate into quality of life for these children and their families remain to be clarified.

Previous assessments of reversibility of bronchial obstruction in children born preterm have shown varying results.^{12,30,41,42} We found that one quarter of children born extremely preterm responded positively to pharmacological bronchodilation, implying a therapeutic way forward. Nevertheless, the post bronchodilator FEV₁ was still significantly lower in the preterm group than in controls (data not shown), indicating only partially reversible airways. Accordingly, non-reversible airway obstruction remains as significant problem after extremely preterm birth.

Conclusions

In summary, a high prevalence of reported asthma-like symptoms, only partially reversible bronchial obstruction and a large proportion of children with clinically relevant reductions in lung function suggest that children born extremely preterm may benefit from close and continued lung function follow-up and that respiratory medication during childhood could be beneficial in selected cases. Counseling of parents and considerations of long-term lung function outcome among professionals caring for extremely preterm infants are also warranted.

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Legends for figure and tables

Figure 1. Overview of enrollment of participants at 6½ years of age.

Table 1. Characteristics of 6½-year-old children born extremely preterm and of age-matched control children born at term.

Table 2. Lung function in 6½-year-old children born extremely preterm and in age- and sex-matched controls born at term.

Table 3. Lung function in 6½-year-old children born extremely preterm, stratified by gestational age.

Table 4. Lung function in 6½-year-old children born extremely preterm, stratified by small (SGA) or appropriate birth weight for gestational age (AGA).

Table 5. Lung function in 6½-year-old children born extremely preterm stratified on severe or moderate BPD.

Table 1. Characteristics of 6½-year-old children born extremely preterm and of age-matched control children born at term.

	Preterm n=153	Control n=157	P-value (t-test or chi-square test)
Parental data			
University education ^a	53 (34.6)	58 (36.9)	0.67
Current smoking ^b	16 (10)	14 (9)	0.65
Perinatal data			
Maternal smoking during pregnancy	8 (5.3)	2 (1.3)	0.05
Gestational age in weeks, mean (range)	25.0 (22-26)	39.8 (37-41)	n.a
Males	82 (47.7)	90 (53.3)	0.51
Birth weight, g	782 (171)	3583 (467)	n.a
SGA	22 (14)	0	n.a
Surfactant administered	151 (98.7)	0	n.a
Duration of mechanical ventilation (days)	14.2 (15.9)	0	n.a
Moderate or severe BPD	138 (90)	0	n.a
At 6½-years follow-up			
Age, years	6.6 (0.2)	6.6 (0.2)	n.a
Weight, kg	20.7 (3.6)	24.4 (4.0)	<0.001
Height, cm	118 (5.4)	123 (4.9)	<0.001

Asthma-like disease	61 (40)	23 (15)	<0.001

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^a At least one parent with university education. ^b At time of follow-up.

Abbreviations: SGA, small for gestational age at birth. BPD, bronchopulmonary dysplasia.

Unless otherwise specified, data are presented as means (SD) or numbers (%).

Table 2. Lung function in 6½-year-old children born extremely preterm and in age- and sex-matched controls born at term.

	Extremely preterm	Controls born at term	Adjusted mean difference	95% CI	P-value
Spirometry	n=90	n=98			
FVC (ml) ^a	1446 (211)	1592 (210)	-146	-210; -82	0.001
FVC z-score ^b	-0.44 (1.0)	0.3 (1.0)	-0.7	-1.0; -0.4	<0.001
FEV ₁ (ml) ^a	1251 (184)	1435 (183)	-184	-240; -128	<0.001
FEV ₁ z-score ^b	-0.72 (1.0)	0.41 (1.0)	-1.1	-1.4; -0.8	<0.001
FEV ₁ /FVC (%) ^a	86 (8.3)	90 (7.4)	-3.8	-6.1; -1.6	0.001
FEV ₁ /FVC z-score ^b	-0.43 (1.1)	0.20 (1.14)	-0.6	-0.9; -0.3	0.02
IOS	n=151	n=153			
R ₅ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.90 (0.18)	0.79 (0.18)	0.08	0.04; 0.12	<0.001
R ₅₋₂₀ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.31 (0.14)	0.22 (0.14)	0.09	0.05; 0.12	<0.001

AX (kPa·L ⁻¹) ^a	2.54 (1.2)	1.76 (1.23)	0.78	0.49; 1.07	<0.001

~~Spirometry Lung function~~ data were analyzed by linear regression on the mean ~~and IOS data by linear regression on the median~~. P values were obtained from the regression models. ^a Adjusted for age, height, sex and site. ^b Z-score variables were adjusted for site. Z-scores according to GLI

2012. ¹⁸²¹

Abbreviations: FVC, (forced vital capacity), FEV₁ (forced expiratory volume in 1 sec), IOS (impulse oscillometry), R₅ (Resistance at 5 Hertz).

R₅₋₂₀ (Frequency dependence of resistance), AX (Reactance area)

Table 3. Lung function in 6½-year-old children born extremely preterm, stratified by gestational age.

	22-24 weeks	25-26 weeks	Adjusted mean difference	95% CI	P-value
Spirometry	n=25	n=65			
FVC (ml) ^a	1256 (209)	1392 (207)	-136	-233; -37	0.008
FVC z-score ^b	-0.98 (1.11)	-0.30 (1.10)	-0.7	-1.2; -0.2	0.01
FEV ₁ (ml) ^a	1042 (186)	1225 (184)	-183	-272; -95	<0.001
FEV ₁ z-score ^b	-1.52 (1.10)	-0.46 (1.09)	-1.1	-1.6; -0.5	<0.001
FEV ₁ /FVC (%) ^a	83.7 (7.7)	88.2 (7.6)	-4.5	-8.1; -0.9	0.02
FEV ₁ /FVC z-score ^b	-0.87 (1.16)	-0.23 (1.15)	-0.6	-1.2; -0.1	0.02
IOS	n=37	n=114			
R ₅ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.93 (0.20)	0.89 (0.20)	0.04	-0.03; 0.12	0.29
R ₅₋₂₀ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.34 (0.16)	0.33 (0.16)	0.01	-0.05; 0.07	0.66
AX (kPa·L ⁻¹) ^a	3.02 (1.43)	2.66 (1.40)	0.36	-0.18; 0.89	0.19

~~Spirometry Lung function~~ data were analyzed by linear regression on the mean ~~and IOS data by linear regression on the median~~. P values were obtained from the regression models. ^a Adjusted for age, height, sex and site. ^b Z-score variables were adjusted for site. Z-scores according to GLI 2012. ⁺⁸²¹

Abbreviations: FVC, (forced vital capacity), FEV₁ (forced expiratory volume in 1 sec), IOS (impulse oscillometry), R₅ (Resistance at 5 Hertz). R₅₋₂₀ (Frequency dependence of resistance), AX (Reactance area)

Table 4. Lung function in 6½-year-old children born extremely preterm, stratified by small (SGA) or appropriate birth weight for gestational age (AGA).

	SGA	AGA	Adjusted mean difference	95% CI	P-value
Spirometry	n=14	n=76			
FVC (ml) ^a	1345 (218)	1356 (215)	-11	-137.0; 115.4	0.87
FVC z-score ^b	-0.57 (1.15)	-0.48 (1.14)	-0.09	-0.75; 0.58	0.79
FEV ₁ (ml) ^a	1184 (203)	1173 (201)	11	-107.0; 128.9	0.85
FEV ₁ z-score ^b	-0.73 (1.20)	-0.76 (1.19)	0.03	-0.7; 0.7	0.93
FEV ₁ /FVC (%) ^a	88.8 (7.9)	86.7 (7.8)	2.1	-2.5; 6.7	0.37
FEV ₁ /FVC z-score ^b	-0.13 (1.18)	-0.46 (1.18)	0.33	-0.36; 1.02	0.39
IOS	n=22	n=129			
R ₅ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.94 (0.20)	0.89 (0.20)	0.05	-0.04; 0.14	0.29
R ₅₋₂₀ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.39 (0.16)	0.32 (0.16)	0.07	0.001; 0.148	0.046

AX (kPa·L ⁻¹) ^a	3.11 (1.43)	2.68 (1.41)	0.43	-0.22; 1.08	0.19

Spirometry-Lung function data were analyzed by linear regression on the mean ~~and IOS data by linear regression on the median~~. P values were obtained from the regression models. ^a Adjusted for age, height, sex and site. ^b Z-score variables were adjusted for site. Z-scores according to GLI 2012. ⁺⁸²¹

Abbreviations: FVC, (forced vital capacity), FEV₁ (forced expiratory volume in 1 sec), IOS (impulse oscillometry), R₅ (Resistance at 5 Hertz). R₅₋₂₀ (Frequency dependence of resistance), AX (Reactance area)

Table 5. Lung function in 6½-year-old children born extremely preterm stratified on severe or moderate BPD.

	Severe BPD	Moderate BPD	Adjusted mean difference	95% CI	P-value
Spirometry	n=17	n=65			
FVC (ml) ^a	1328 (232)	1366 (215)	-38	-166.0; 90.6	0.50
FVC z-score ^b	-0.65 (1.17)	-0.42 (1.15)	-0.24	-0.75; 0.58	0.46
FEV ₁ (ml) ^a	1100 (218)	1192 (207)	-92	-212.1; 28.1	0.13
FEV ₁ z-score ^b	-1.24 (1.21)	-0.62 (1.20)	-0.61	-1.27; 0.04	0.07
FEV ₁ /FVC (%) ^a	82.6 (8.2)	87.8 (7.8)	5.1	-9.7; -0.6	0.03
FEV ₁ /FVC z-score ^b	-1.03 (1.15)	-0.30 (1.14)	-0.73	-1.36; -0.10	0.02
IOS	n=20	n=116			
R ₅ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.91 (0.22)	0.90 (0.21)	0.004	-0.10; 0.11	0.95
R ₅₋₂₀ (kPa·L ⁻¹ ·s ⁻¹) ^a	0.35 (0.17)	0.33 (0.16)	0.02	-0.06; 0.10	0.68
AX (kPa·L ⁻¹) ^a	2.9 (1.55)	2.77 (1.46)	0.13	-0.61; 0.87	0.73

~~Spirometry Lung function~~ data were analyzed by linear regression on the mean ~~and IOS data by linear regression on the median~~. P values were obtained from the regression models. ^a Adjusted for age, height, sex and site. ^b Z-score variables were adjusted for site. Z-scores according to GLI 2012. ⁺⁸²¹

Abbreviations: FVC, (forced vital capacity), FEV₁ (forced expiratory volume in 1 sec), IOS (impulse oscillometry), R₅ (Resistance at 5 Hertz). R₅₋₂₀ (Frequency dependence of resistance), AX (Reactance area)