



Agreement between spirometry and impulse oscillometry for lung function assessment in 6-year-old children born extremely preterm and at term

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Abstract

Background: Extremely preterm birth is a risk factor for reduced lung function later in life, and clinical follow-up from early childhood is recommended. Dynamic spirometry is the most widely used method to assess airway obstruction, but impulse oscillometry (IOS) may be an alternative method that is easier to perform in young children. The feasibility and agreement between spirometry and IOS outcome variables has not been investigated in children born extremely preterm.

Aim: To determine the feasibility of and correlation between spirometry and IOS in pre-school children born extremely preterm.

Methods: Spirometry and IOS were performed in 6-year-old children born extremely preterm (n = 88) and age-matched term controls (n = 84) in Stockholm, Sweden. Correlations between spirometry and IOS outcome variables were analyzed using Pearson's partial correlation, adjusting for height.

Results: Success rate for spirometry (60%) was lower than for IOS (93%) but did not differ significantly between the preterm and term groups (56% and 64% for spirometry, $P = .25$; and 92% and 94% for IOS, $P = .61$). Correlations between spirometry and IOS outcomes were at best moderate (Spearman's $r = -0.31$ to -0.56). Normal IOS identified 69% to 90% of those with normal spirometry. A negative predictive value of 90% was found for R5-R20 versus $FEV_{0.75}/FVC$, suggesting that IOS may be used to exclude obstructive airway disease as measured by spirometry.

Conclusion: IOS is a more feasible method than spirometry to assess lung function in young children irrespective of gestational age at birth and could be considered an alternative in children who cannot perform spirometry.

KEYWORDS

impulse oscillometry, preterm birth, spirometry

1 | INTRODUCTION

In developed health care settings, survival is now the most probable outcome after extremely preterm birth, defined as birth before 28 weeks of gestation.¹ Nevertheless, it is one of the leading causes of neonatal mortality and morbidity.² The developmental arrest of the respiratory system associated with preterm birth, commonly described as bronchopulmonary dysplasia (BPD) is highly prevalent and a well-known risk factor for long-term respiratory morbidity.³ Therefore, in Sweden and elsewhere, children born extremely preterm are included in national follow-up programs including assessment of lung function.^{4,5} However, performing a technically accurate spirometry, the gold standard method to assess airway obstruction, can be difficult in young children.

An alternative and potentially more feasible method to evaluate lung function is impulse oscillometry (IOS), measuring the resistance and reactance of the respiratory system during tidal breathing.^{6,7} Although in many ways comparable, IOS and spirometry are not directly interchangeable. IOS is perceived to generate better measures of small airway obstruction⁷ whereas spirometry, measuring flow and volume, more reflects airway function in larger airways and overall lung capacity as estimated by forced vital capacity (FVC). Varying degrees of correlation between lung function measured by IOS and spirometry have been demonstrated in children with asthma⁸⁻¹⁰ and cystic fibrosis (CF),¹¹ as well as in adults with asthma¹² and chronic obstructive pulmonary disease.¹³ Further, longitudinal studies of children with asthma or early wheeze have shown that preschool IOS measures predict spirometric outcomes later in childhood or adolescence.¹⁴⁻¹⁶ However, the pathology and lung function deficits associated with asthma and CF are not necessarily directly comparable to those found in children born extremely preterm. Although IOS has been used in several studies to examine outcome after preterm birth,¹⁷⁻²⁰ there are, to our knowledge, no studies on how spirometry and IOS relate to each other in young children born extremely preterm.

Therefore, a significant step in evaluating the usefulness of IOS as an alternative method to assess lung function in the follow up of the growing numbers of children surviving extremely preterm birth would be to investigate how IOS and spirometry parameters correlate, and to assess the accuracy of IOS as an alternative to spirometry. The aim of the current study was to investigate the feasibility and relationship between IOS and spirometry outcome measures in 6-year old children born extremely preterm. We hypothesized that IOS could be a valuable alternative to spirometry.

2 | METHODS

2.1 | Participants

The national cohort study EXPRESS included all infants born in Sweden before 27 weeks of gestation between 1st April 2004 and 31st March 2007. The characteristics of this cohort has been reported earlier.²¹⁻²³ The current study included children from the EXPRESS cohort living in the Stockholm region, who participated in a follow-up study assessing

lung function at mean age 6.5 years.¹⁹ For every child born extremely preterm, a healthy control child born at term matched on mother's country of birth, date of delivery, hospital of birth, and sex was randomly recruited using the Swedish Medical Birth Register.

2.2 | Lung function assessment

Lung function was assessed with IOS and dynamic spirometry using the Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA) according to ATS/ERS-criteria.^{24,25} Examination was postponed until at least 2 weeks post any acute respiratory tract illness. IOS is described in detail elsewhere.^{6,26} In summary, the impedance, consisting of the resistance and reactance of the airways is measured by generating pressure oscillations at the mouth of the subject during tidal breathing. IOS was performed with the child seated up-right, lips sealed around the mouthpiece and cheeks supported by hands. A minimum of two recordings meeting the criteria of a coherence value of >0.80 at 10 Hz were saved for later analysis. Mean values of resistance at 5 Hz (R5), 20 Hz (R20), the area under the curve for negative reactance values (AX) and the difference between resistance at 5 and 20 Hz (R5-R20) were saved for later analysis.

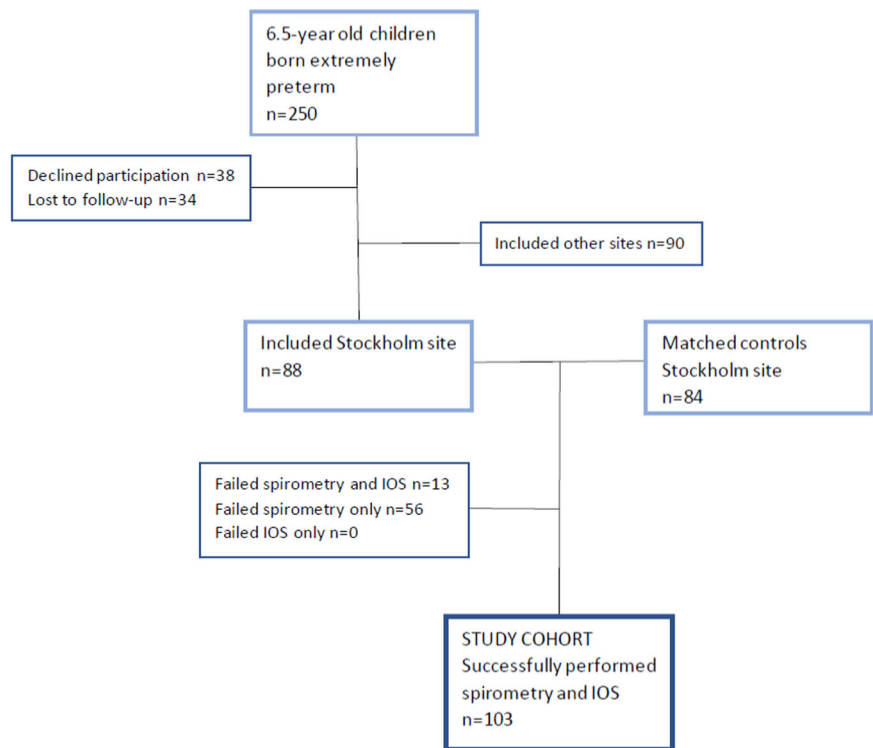
Spirometry was performed with the child seated up-right and wearing a nose clip. A minimum of three maximum expiratory flow recordings were performed. The best forced expiratory volume at 0.75 second (FEV_{0.75}) and FVC values were extracted and saved for analysis given that the trials were assessed as maximal by the test leader, the curve passed visual quality inspection, and the two highest FEV_{0.75} and FVC values were reproducible. FEV_{0.75} was used since it has been suggested to be more accurate than FEV₁ in younger children, due to a constitutionally lower total lung capacity.²⁴ IOS was performed before spirometry to avoid potential interference of forced respiratory maneuvers on IOS outcome variables. The IOS system was verified daily using a reference resistance of 0.20 kPa/L/s. The spirometry system was calibrated using a 3-L precision syringe.

Results from the lung function tests have been reported earlier by Thunqvist et al in the study mentioned above.¹⁹ Lung function variables were converted into z-scores using the reference equations by Quanjer et al²⁷ for spirometry and Gochicoa-Rangel et al²⁸ for IOS since they included all requested variables and included children in fitting age spans. Spirometry-values below the lower limit of normal and IOS-values above the upper limit of normal, defined by the predicted 95th percentiles of the term controls using z-scores based on the equations above, were classified as "outside reference." Accordingly, spirometry values below one-sided -1.64 z-score and IOS-values above one-sided 1.64 z-score were classified as "outside reference." All other values were classified as "within reference."

2.3 | Demographics and definitions

Information on respiratory health and background factors was collected at examination using a questionnaire based on the

FIGURE 1 Overview of enrollment of study participants. IOS, impulse oscillometry [Color figure can be viewed at wileyonlinelibrary.com]



ISAAC-study.²⁹ University education was defined as at least one caregiver with university education. Current smoking in the family was defined as at least one caregiver smoking in the home at time of follow-up. Gestational age was estimated by ultrasound at gestational week 17 to 18.²¹ Small for gestational age was defined as birth weight two standard deviations below the mean according to the Swedish sex- and age specific reference curve for normal fetal growth.³⁰ BPD was defined based on oxygen treatment for at least 28 days and graded as mild, moderate or severe depending on fraction of inspired oxygen or need for positive pressure ventilation at 36 weeks post menstrual age using the definition by Jobe et al.³¹ Respiratory symptoms were defined as symptoms of wheeze and/or having used inhaled bronchodilator/corticosteroid therapy during the last year before examination.

2.4 | Ethics

Ethical approval was granted by the regional ethical review board in Stockholm (no. 2011/376-32). Written informed consent was collected from the caregivers of the child before start of data collection.

2.5 | Statistical analyses

Data was analyzed using Stata 14.2 software pack (StataCorp, College Station, TX). Categorical variables are presented as numbers and proportions. Differences in proportions were tested using the

Pearson χ^2 test. Normally distributed continuous variables are presented as means and standard deviation, and non-normal continuous variables as medians and interquartile ranges. Differences in normally distributed continuous variables were tested using the Student's *t* test. Lung function data was analyzed with Spearman's Rank Order correlation test, as the variables were not normally distributed. Pearson's correlation test was used when performing partial correlation adjusting for height. Sex and age were not adjusted for since they were included in the matching. Variables not meeting the criteria of normal distribution were individually recalculated on a logarithmic or square-rooted scale, whichever was closest to normal distribution.

Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated comparing IOS and spirometry values "within reference" and "outside reference." A *P* value below .05 was considered significant.

3 | RESULTS

Acceptable spirometry or IOS was performed by 160 of 172 examined children. The total success rates were 60% for spirometry and 93% for IOS. There were no significant differences in success rates between children born extremely preterm and controls (92% and 94% for IOS, *P* = .61; 56% and 64% for spirometry, *P* = .25). Additional analysis showed no significant differences regarding sex, age, height, or degree of prematurity among children who failed to perform spirometry and IOS, and those who performed successful

TABLE 1 Characteristics of the study cohort for the methods comparison

	Extremely preterm (n = 49)	Term (n = 54)	P value
Parental data			
University education ^a	33 (67%)	44 (81%)	.14
Current smoking in the family ^b	6 (12%)	6 (11%)	.83
Perinatal data			
Male	27 (55%)	31 (57%)	n.a. ^e
Maternal smoking during pregnancy	3 (6%)	2 (4%)	.55
Gestational age at birth, wk	25.1 (0.89)	39.4 (1.18)	n.a. ^e
Birthweight, g	804.4 (163.2)	3658.5	n.a. ^e
SGA	7 (14%)	0	n.a. ^e
Mild BPD ^c	4 (9%)	...	n.a. ^e
Moderate BPD ^c	36 (78%)	...	n.a. ^e
Severe BPD ^c	6 (13%)	...	n.a. ^e
At examination			
Age, y	6.6 (0.20)	6.6 (0.19)	n.a. ^e
Weight, kg	24.2 (3.47)	20.9 (4.33)	<.001
Height, cm	122.4 (4.54)	118.3 (5.64)	<.001
Respiratory symptoms ^d	31 (63%)	15 (28%)	.22
Spirometry (z-score)			
	Median (IQR)	Median (IQR)	
FVC	-0.61 (-1.38, 0.24)	0.19 (-0.3, 1.16)	<.001
FEV _{0.75}	-1.16 (-2.11, -0.44)	0.37 (-0.27, 0.98)	<.001
FEV _{0.75} /FVC	-0.51 (-1.44, 0.44)	0.38 (-0.60, 0.80)	.017
IOS (z-score)			
R5	0.71 (-0.19, 1.55)	0.03 (-0.70, 0.78)	.009
R5-20	0.75 (-0.17, 2.08)	-0.44 (-1.06, 0.38)	<.001
AX	0.16 (-0.62, 1.48)	-1.07 (-1.48, -0.12)	<.001

Abbreviations: AX, area under the curve for negative reactance value; BPD, bronchopulmonary dysplasia; FEV_{0.75}, forced expiratory volume at 0.75 second; FVC, forced vital capacity; IOS, impulse oscillometry; IQR, interquartile range; SGA, small for gestational age.

^aAt least one parent with university education.

^bAt least one caregiver smoking in the home at time of follow-up.

^cData available for 46 individuals.

^dSymptoms of wheeze and/or inhaled bronchodilator/corticosteroid therapy during the last year.

^eNot applicable.

Unless otherwise noted data presented as means (SD) or numbers (%). Lung function: median and IQR, rank sum test.

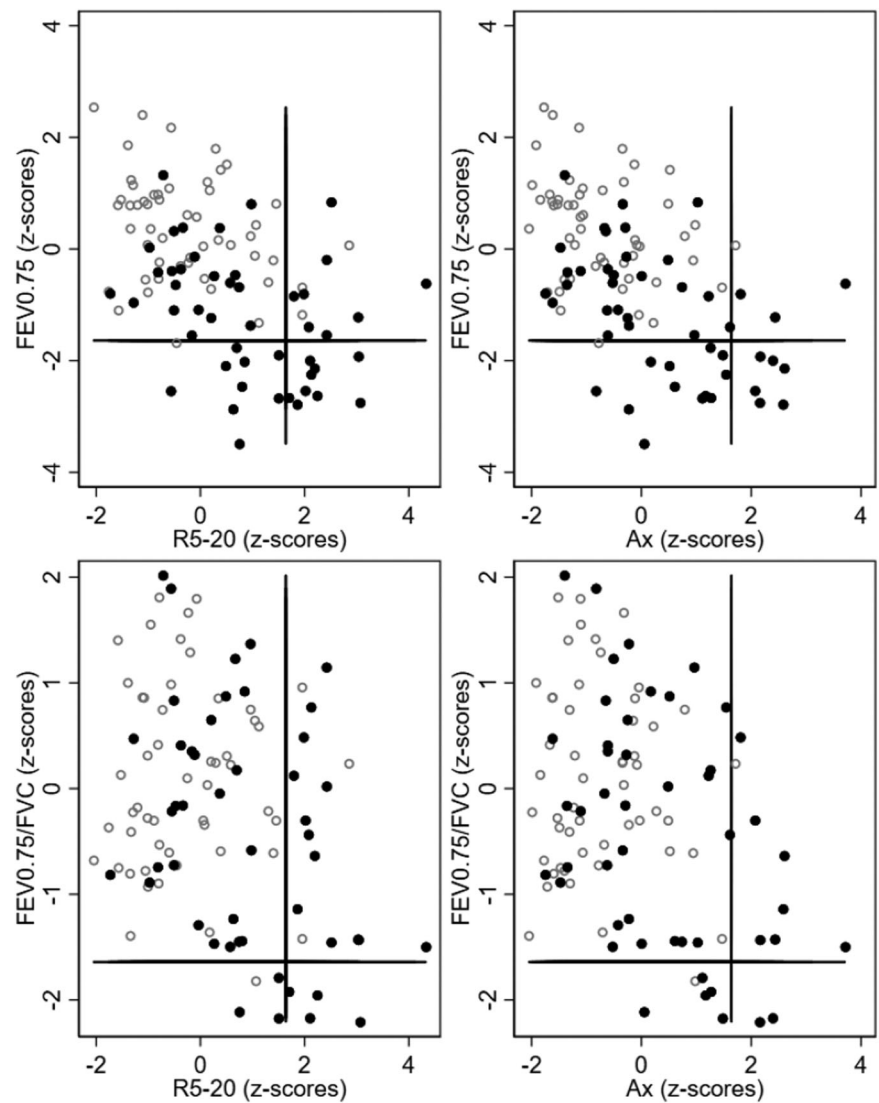
assessments (data not shown). Of the children who managed to perform IOS only (n = 56), 81% (n = 25) of the children born extremely preterm and 92% (n = 23) of the controls had an R5-R20 within the defined reference range. A total of 103 children managed to perform both spirometry and IOS providing the study sample of 49 children born extremely preterm and 54 children born term for the comparison of methods (Figure 1). Baseline characteristics and anthropometry at time of examination are given in Table 1. There were significant differences between children born extremely preterm and term in weight, height, and lung function, but not in regard to parental education, current smoking in the family, maternal smoking during pregnancy, gender or respiratory symptoms.

The relationships between IOS and spirometry variables for children born term and extremely preterm are illustrated in Figure 2. Correlations between IOS and spirometry outcome variables for the

extremely preterm group are presented in Table 2. Overall, all IOS variables except for R20 were significantly correlated to all spirometry variables except for FVC, with correlation coefficients ranging from -0.31 to -0.56.

The sensitivity, specificity, PPV and NPV of the IOS variables R5-20 and Ax to predict FEV_{0.75} and FEV_{0.75}/FVC classified as being within or outside the reference interval are presented in Table 3 for the infants born extremely preterm and in Table 4 (online only) for the healthy controls. For the extremely preterm group IOS outcome variables showed a low sensitivity compared with specificity in relation to both FEV_{0.75} and FEV_{0.75}/FVC. The PPVs were low; 22% to 67% of individuals with IOS outside the reference had spirometry outside the reference, whereas the NPVs were higher; 69% to 90% of those identified with IOS within reference had a spirometry result within reference.

FIGURE 2 Relationships between IOS and spirometry outcome variables for children born term ($n = 54$) and extremely preterm ($n = 49$) Black/white dots represent children born extremely preterm/at term, respectively. Vertical and horizontal lines represent cut off for defined “within reference” (below/above the lower/upper limit of normal, defined by the predicted 95th percentiles of the term controls for spirometry/IOS, respectively). IOS, impulse oscillometry



4 | DISCUSSION

The current study found that the success rate for IOS (93%) was higher than for spirometry (60%) measures, but no significant differences between children born extremely preterm and controls were found. A NPV of 90% was found for R5-R20 versus FEV_{0.75}/FVC, suggesting that IOS may be used to exclude obstructive airway disease as measured by spirometry.

Spirometry, perceived as gold standard among lung function tests, may be difficult to perform adequately in younger children. IOS, on the other hand, demands less cooperation and has been shown to be easier to perform at a young age.^{6,7,20} Our results that showed no significant differences in success rates suggests that young children born extremely preterm eligible for lung function testing have the same difficulties in performing an adequate spirometry test as children born at term.

The strongest correlation between spirometry and IOS variables among children in the extremely preterm group was found between FEV_{0.75} and the reactance measure AX. FEV_{0.75} is highly correlated to

forced exhaled volume in 1 second, FEV₁, but the former may be more accurate than FEV₁ in younger children, due to a constitutionally lower total lung capacity and hence FVC.²⁴ Similarly, Batmaz et al⁸ reported significant correlations between FEV₁ and AX ($r = -0.53$) in 6 to 17-year-old children with asthma and healthy controls. In two studies of children and teenagers with mild to moderate asthma, Vink et al³² reported a significant correlation between FEV₁ and reactance at 5 Hz (X5) ($r_p = 0.52$) in 5 to 17-year old children, whereas no significant correlations between spirometry variables and X5 were found by Song et al¹⁰ in 7 to 15-year-old. In a group of children 4 to 19-year-old with CF Moreau et al¹¹ reported a significant correlation between FEV₁ and X5 ($r_p = 0.59$). Notably, none of the studies above adjusted for height, which is related to both IOS and spirometry outcomes, albeit not necessarily in an equivalent manner.

This study found stronger correlations between FEV_{0.75} and R5 compared with resistance measured at higher frequencies, a result that is consistent with previous studies. Batmaz et al⁸ and Olaguibel et al⁹ reported the strongest correlation between FEV₁ and R5

TABLE 2 Correlation between spirometry and IOS indices in children born extremely preterm

	R5			R20			AX			R5-20		
	Spearman	z-score ^a	Adjusted ^b	Spearman	z-score ^a	Adjusted ^b	Spearman	z-score ^a	Adjusted ^b	Spearman	z-score ^a	Adjusted ^b
FEV _{0.75}	<i>r</i>	-0.43	-0.37	-0.43	-0.26	-0.15	-0.56	-0.52	-0.53	-0.45	-0.39	-0.48
	<i>P</i>	.002	.010	.002	.21	.30	<.001	<.001	<.001	.001	.007	<.001
FVC	<i>r</i>	-0.15	-0.085	-0.18	-0.14	-0.02	-0.31	-0.22	-0.25	-0.21	-0.13	-0.24
	<i>P</i>	.30	.56	.21	.50	.88	.030	.13	.08	.14	.38	.10
FEV _{0.75} /FVC	<i>r</i>	-0.37	-0.41	-0.39	-0.18	-0.21	-0.39	-0.39	-0.41	-0.34	-0.36	-0.36
	<i>P</i>	.008	.004	.006	.37	.15	.005	.006	.004	.016	.012	.010

Abbreviations: AX, area under the curve for negative reactance value; FEV_{0.75}, forced expiratory volume at 0.75 second; FVC, forced vital capacity; IOS, impulse oscillometry.

^aBased on reference equations by Quanjer et al²⁷ for spirometry and Gochicoa-Rangel et al²⁸ for IOS.

^bPearson's correlation test was used when performing partial correlation adjusting for height.

($r = -0.71$ and $r_p = -0.51$ respectively), Vink et al³² and Song et al¹⁰ between FEV₁ and R10 ($r_p = -0.73$ and -0.62 respectively) all in pediatric populations with asthma. In children with CF, Moreau et al,¹¹ also reported the strongest correlation for FEV₁ to resistance at low frequencies (FEV₁-R5 $r_p = -0.59$).

In the current study, IOS was evaluated as a potential alternative method to spirometry. The NPVs of R5-R20 and AX in relation to FEV_{0.75}/FVC were high, suggesting that these IOS outcome variables may be used to exclude a low FEV_{0.75}/FVC-ratio, the primary indicator of obstructive airway disease as measured by spirometry. Similar results were reported in a study by Knithilä et al¹⁴ They reported a 90% NPV of R5 to FEV₁ (presented post bronchodilator) in children with asthma, even though IOS was performed approximately 9 years before spirometry. Our results suggest that a normal IOS can exclude obstructive airway disease as measured by spirometry, a finding that can be useful to clinicians, patients and parents involved in follow-up programs of children born extremely preterm. Under this assumption, the 25 children born extremely preterm in our study who could only perform IOS and performed a R5-R20 value within reference would be predicted to have a normal FEV_{0.75}/FVC-ratio.

The significance of the relatively poor PPV of IOS versus spirometry needs further attention. A possible explanation could be that compared with spirometry, IOS is more sensitive in measuring airway dysfunction, especially in peripheral airways. Studies in adults have suggested that IOS is more accurate in measuring small airway dysfunction,^{33,34} although evidence of this in pediatric populations is sparse. In children with asthma, IOS has been shown to differentiate children at risk of more severe morbidity. Marotta et al³⁵ reported that bronchodilator response in IOS, in contrast to spirometry, could differentiate 4-year-old children with asthma. Shi et al³⁶ reported that IOS could discriminate uncontrolled versus controlled asthma in 6 to 17-year-old children whereas Smith et al³⁷ reported greater sensitivity but lower specificity for IOS compared with spirometry in predicting poor control in 7 to 15-year-old children with asthma.

From a research perspective, the combination of multiple lung function testing techniques describing different aspects of lung physiology can be useful in mapping the different phenotypes of the chronic lung disease associated with extremely preterm birth.³⁸ BPD is, given the definition based on oxygenation criteria or need of positive pressure ventilation at 36 weeks of postmenstrual age, a heterogeneous condition that will include varying phenotypes in a spectrum from normal lung function to obstructive and restrictive lung disease with impaired diffusion capacity.^{3,31,39} Further studies utilizing and comparing different lung function techniques are needed in populations of children born extremely preterm of sufficient size to provide more information.

The main strength of the current study is the relatively large population sample of children born extremely preterm providing lung function data with multiple techniques and the combination with a matched control group born at term as a reference. Another strength, given the technical comparisons on the current study, is the confinement to one test site, one test apparatus and few test leaders reducing the risk of measuring error and misclassification of the outcome.

TABLE 3 IOS versus spirometry in children born extremely preterm

	FEV _{0.75}		Statistical analysis			
	Outside reference ^a	Within reference ^a	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
R5-R20						
Outside reference	9	8	50	73.3	52.9	71
Within reference	9	22				
AX						
Outside reference	6	3	33.3	90	66.7	69.2
Within reference	12	27				
	FEV _{0.75} /FVC		Statistical analysis			
	Outside reference ^a	Within reference ^a	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
R5-R20						
Outside reference	4	13	57.1	68.3	23.5	90.3
Within reference	3	28				
AX						
Outside reference	2	7	28.6	82.9	22.2	87.2
Within reference	5	34				

Note: Test characteristics for IOS versus spirometry.

Abbreviations: AX, area under the curve for negative reactance value; FEV_{0.75}, forced expiratory volume at 0.75 second; FVC, forced vital capacity; IOS, impulse oscillometry; NPV, negative predictive value; PPV, positive predictive values.

^aSpirometry-values below the lower limit of normal and IOS-values above the upper limit of normal, defined by the predicted 95th percentiles of the term controls, were classified as "outside reference." All other values were classified as "within reference." Data available for 48 individuals.

An observed weakness is the cross-sectional design of the study. Repeated tests at alternate time points could have provided information on how feasibility, correlation and predictions developed over time. However, the investigated time point was well timed with

the research question at hand. At 6 years of age, spirometry remains a challenge although valid data is relatively feasible. Hence, the time window for additional information from- and comparison with IOS is optimal.

TABLE 4 IOS versus spirometry in term controls

	FEV _{0.75}		Statistical analysis			
	Outside reference ^a	Within reference ^a	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
R5-R20						
Outside reference	0	3	0	94.1	0	98.0
Within reference	1	48				
AX						
Outside reference	0	3	0	94.1	0	98.0
Within reference	1	48				
	FEV _{0.75} /FVC		Statistical analysis			
	Outside reference ^a	Within reference ^a	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
R5-R20						
Outside reference	0	3	0	94.1	0	98.0
Within reference	1	48				
AX						
Outside reference	0	1	0	98.0	0	98.0
Within reference	1	50				

Note: Test characteristics for IOS versus spirometry.

Abbreviations: AX, area under the curve for negative reactance value; FEV_{0.75}, forced expiratory volume at 0.75 second; FVC, forced vital capacity; IOS, impulse oscillometry; NPV, negative predictive value; PPV, positive predictive values.

^aSpirometry-values below the lower limit of normal and IOS-values above the upper limit of normal, defined by the predicted 95th percentiles of the term controls, were classified as "outside reference." All other values were classified as "within reference." Data available for 52 individuals.

The lack of global reference equations for IOS is regrettable, and we acknowledge the drawback that the reference values (Gochicoa-Rangel et al.²⁸) are not fitting our study population perfectly. However, this was the reference data that was available and that had equations for all the included variables. Another potential limitation is confinement to one geographically localized test site, which may raise issues on external validity.

In conclusion, results from the current study suggest that young children born extremely preterm have the same difficulties in performing spirometry as children born at term. Overall, spirometry and IOS outcomes correlate at best moderately in this group. However, given that IOS was found to be more feasible and potentially could exclude obstructive airway disease as measured by spirometry, IOS may still be considered as an alternative in follow-up programs of children born extremely preterm especially at young age.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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