

Spirometry and Impulse Oscillometry in Preschool Children: Acceptability and Relationship to Maternal Smoking in Pregnancy



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What is already known about this topic? Measuring pulmonary function in preschool children is challenging. Impulse oscillometry (IOS) does not require active exhalation so it is believed to be easier for children to perform than spirometry.

What does this article add to our knowledge? This direct comparison of performance of spirometry and IOS indicates that more preschool children can perform acceptable spirometry tests than acceptable IOS tests and provides longitudinal data in an African American and Hispanic population.

How does this study impact current management guidelines? This study challenges the assumption that IOS is easier for preschool children to perform than spirometry but the ability of IOS to detect the effects of cigarette smoke exposure on lung function may be better.

BACKGROUND: Comparisons of the technical acceptability of spirometry and impulse oscillometry (IOS) and clinical correlations of the measurements have not been well studied in young children. There are no large studies focused on African American and Hispanic children.

OBJECTIVES: We sought to (1) compare the acceptability of spirometry and IOS in 3- to 5-year-old children and (2) examine the relationship of maternal smoking during pregnancy to later lung function.

METHODS: Spirometry and IOS were attempted at 4 sites from the Urban Environmental and Childhood Asthma Study birth cohort at ages 3, 4, and 5 years (472, 471, and 479 children,

respectively). We measured forced expiratory flow in 0.5 s (forced expiratory volume in 0.5 seconds [FEV_{0.5}]) with spirometry and area of reactance (A_X), resistance and reactance at 5 Hz (R_5 and X_5 , respectively) using IOS.

RESULTS: Children were more likely to achieve acceptable maneuvers with spirometry than with IOS at age 3 (60% vs 46%, $P < .001$) and 5 years (89% vs 84%, $P = .02$).

Performance was consistent among the 4 study sites. In children without recurrent wheeze, there were strong trends for higher FEV_{0.5} and lower R_5 and A_X over time. Maternal smoking during pregnancy was associated with higher A_X at ages 4 and 5 years ($P < .01$ for both years). There was no significant

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Conflicts of interest: M. Kattan reports personal fees from Novartis Pharma. L. B. Bacharier has consultant arrangements with Aerocrine, GlaxoSmithKline,

Genentech/Novartis, Cephalon, Teva, and Boehringer Ingelheim; has received personal fees from Merck, DBV Technologies, AstraZeneca, WebMD/Medscape, Sanofi, and Vectura. G. T. O'Connor has consultant arrangements with AstraZeneca. W. Morgan reports grants from the Cystic Fibrosis Foundation; and personal fees from Genentech, Cystic Fibrosis Foundation, American College of Chest Physicians, and American Thoracic Society. R. A. Wood has consultant arrangements with Stallergenes and Sanofi; and receives royalties from UpToDate. R. Burton has consultancy arrangements with eResearch Technologies (ERT). J. E. Gern has consultancy arrangements with Janssen, Regeneron, GlaxoSmithKline, Genentech, Amgen, and Novartis; and has stock interest in 3V BioSciences. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

ATS- American Thoracic Society
A_x- Area of reactance
ERS- European Respiratory Society
FEV- Forced expiratory volume
FOT- Forced oscillation technique
IOS- Impulse oscillometry
R₅- Resistance at 5 Hz
R₁₀- Resistance at 10 Hz
R_{rs}- Respiratory system resistance
URECA- Urban Environmental and Childhood Asthma Study
X₅- Reactance at 5 Hz
X_{rs}- Respiratory system reactance
Z_{rs}- Impedance of the respiratory system

difference in FEV_{0.5} between children with and without *in utero* exposure to smoking.

CONCLUSION: There is a higher rate of acceptable maneuvers with spirometry compared with IOS, but IOS may be a better indicator of peripheral airway function in preschool children. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1596-603)

Key words: Forced oscillation technique; Pediatric pulmonary function testing; Wheezing; Epidemiology; African American; Hispanic

Assessment of lung function is an essential component for understanding lung development and disease progression in early childhood and can serve as an outcome in clinical trials. Measurement of pulmonary function in preschool children is challenging. Spirometry is used in older children and adults and requires a maximal forced expiratory maneuver. Studies from single sites indicate that more than half of children between the ages of 3 and 5 years can perform spirometry successfully.¹⁻⁶ The forced oscillation technique (FOT) has been used increasingly to assess respiratory mechanics. Impulse oscillometry (IOS) is a widely used application of FOT. IOS superimposes external pressure oscillations on the respiratory system during spontaneous breathing. One potential advantage of this technique is that it requires only tidal breathing and no forced expiratory maneuvers. Being less effort dependent, IOS may be more suitable for measuring lung function in younger children. IOS measures the impedance of the respiratory system (Z_{rs}) that is not directly measured with spirometry. The components of Z_{rs} are respiratory system resistance (R_{rs}) and reactance (X_{rs}). R_{rs} is the part of Z_{rs} associated with frictional losses in the airways and lung parenchyma and X_{rs} is determined jointly by the elastic properties dominant at low oscillation frequencies and the inertive properties at higher oscillation frequencies. The majority of studies with IOS involve older children. There are fewer studies in children between 3 and 5 years of age.⁷⁻¹² Most studies with spirometry and IOS have a limited number of subjects at the lower end of this age range and include predominantly non-Hispanic white children.

Direct comparisons of the rate of acceptable tests for spirometry and IOS in young children are lacking. We sought to compare the acceptability of the 2 procedures in a large sample of preschool children of predominantly African American and

Hispanic heritage enrolled in the Urban Environmental and Childhood Asthma Study (URECA).¹³ The second aim of this study was to determine the ability of the 2 tests to detect abnormalities of lung function. The results of studies using IOS and spirometry in preschool children to detect abnormalities or changes in lung function have been inconsistent.¹⁴ Pulmonary function measurements are known to be decreased in infants of mothers who smoked during pregnancy as measured by thoracoabdominal compression techniques, passive respiratory system compliance, and IOS.¹⁵⁻¹⁷ There has been no assessment of the effect of this exposure on pulmonary function in preschool children. Therefore, we examined the relationship of maternal smoking during pregnancy to lung function in the preschool years as assessed by spirometry and IOS.

METHODS

Study design

URECA is a longitudinal multicenter (Baltimore, Boston, New York, St. Louis) birth cohort designed to study the development of asthma and allergies in an inner-city population. Women in their third trimester were recruited between February 2005 and March 2007. Inclusion criteria included a child's gestational age of at least 34 weeks and residence in an area where at least 20% of the population had an annual income below the poverty line. Maternal human immunodeficiency virus, significant congenital anomalies or infections, intubation, or ≥ 4 hours of supplemental oxygen or continuous positive airway pressure for 4 or more days excluded the infant from the study. Overall, 2,090 families were screened, 846 were eligible and consented, and 609 were enrolled; 560 newborns at increased risk for the development of asthma because of the parental history of asthma or allergic disease and a smaller group of 49 babies whose parents had no history of these diseases were enrolled. Written informed consent was obtained from the women enrolled, and, after birth, from the parent or legal guardian of the child. The detailed study design has been published previously.¹³

Study assessments

After a practice session at age 33 months, spirometry and IOS were performed at ages 3, 4, and 5 years using the Jaeger MasterScreen IOS system (CareFusion, Germany; JLab version 4.65) at all 4 centers. Volume and flow calibrations were completed each day of use, and cleaning was done at scheduled intervals. Operators at each site were trained and certified for measurements of spirometry and IOS according to standardized procedures.¹⁸ All measurements were over-read centrally to ensure quality and consistency.

Both spirometry and IOS maneuvers were performed in the sitting position. IOS was done first followed by spirometry. Participants were asked to hold use of bronchodilator medications (including short-acting β agonists [4 hours], and anticholinergics, leukotriene modifiers, and long-acting β agonists [24 hours]) before the spirometry and IOS measurement sessions. For IOS, children were instructed to support their cheeks with their hands, and to breathe normally while maintaining a good lip seal on the mouthpiece with the tongue placed under the mouthpiece and with nose clips in place. The goal for the IOS session was to obtain 3 acceptable tests in a maximum of 8 attempts. An acceptable test had a segment of at least 15 seconds of normal tidal breathing, containing at least 4 breaths, within a 30-second test period. The acceptable tests had a concordance of resistance at 10 Hz (R_{10}) ≥ 0.80 (coherence), and were clustered within 20% of the highest R_{10} . The primary IOS variables used for analyses were

TABLE I. Population characteristics for those who attended a clinic visit and those who attempted a lung function test

	Children who attended ≥ 1 clinic visit N = 503	Children who attempted ≥ 1 pulmonary test N = 485
Study site		
Baltimore	148 (29%)	137 (28%)
Boston	115 (23%)	112 (23%)
New York	96 (19%)	95 (20%)
St. Louis	144 (29%)	141 (29%)
Mother reported smoked during pregnancy	89/502 (18%)	88/484 (18%)
No. of smokers in the home		
0	254/497 (51%)	243/483 (50%)
1-2	218/497 (44%)	211/483 (44%)
3+	29/497 (6%)	29/483 (6%)
Detectable cord blood cotinine	65/372 (18%)	65/372 (18%)
Child's race/ethnicity		
African American	359 (71%)	346 (71%)
Hispanic	102 (20%)	100 (21%)
Other	42 (9%)	39 (8%)
Mother has high school education	300/497 (60%)	288/484 (60%)
Mother is married	71/502 (14%)	69/484 (14%)
Annual household income <\$15,000	344 (68%)	334 (69%)
Child's gender: male	260 (52%)	251 (52%)
Caesarean delivery	153 (30%)	148 (31%)
Child's birth weight (g)	3251 $\pm$ 501	3254 $\pm$ 497
Mother has ever had asthma	228/501 (46%)	220/483 (46%)
Gestational age of child at delivery (wk)	38.8 $\pm$ 1.5	38.8 $\pm$ 1.5
Age of mother at the time of birth (y)	24.4 $\pm$ 6.0	24.4 $\pm$ 6.0

Note: Values are counts (percentages) or means $\pm$ standard deviations.

respiratory system resistance and reactance at 5 Hz (R_5 and X_5 , respectively), and the area of reactance (A_X). Spirometry was conducted in accord with the American Thoracic Society/European Respiratory Society (ATS/ERS) Statement on Pulmonary Function Testing in Preschool Children (a rapid rise, a smooth descent free from artifacts, and a full return to the baseline at no greater than 10% of the peak flow).¹⁹ Because of the age of the subjects, we used forced expiratory volume in 0.5 seconds ($FEV_{0.5}$) in place of forced expiratory volume in 1 second (FEV_1) as the primary spirometric variable for evaluating acceptability and repeatability. The best maneuver was selected by the effort with the largest sum of forced vital capacity and $FEV_{0.5}$ in subjects producing with at least 2 acceptable curves. Values were recorded if there was only a single acceptable maneuver. A maximum of 8 attempts were allowed.

To provide normative longitudinal data in this population, we included children who had acceptable measures for each of the tests at all 3 years without a history of early recurrent wheeze defined *a priori* as at least 2 wheezing episodes with at least 1 episode occurring in the current year.

Umbilical cord blood was collected as described previously, and cotinine was measured by gas chromatography as a marker for *in utero* smoke exposure.^{13,20}

Statistical methods

There were 281, 368, and 427 spirometry and 216, 352, and 402 IOS tests considered for analysis of performance at ages 3, 4, and 5, respectively. Only those maneuvers considered acceptable by the central over-readers were included in further analyses. Cochran-Mantel-Haenszel tests were performed to compare potential

differences in the proportions of participants who attempted and completed acceptable lung function tests with respect to IOS and spirometry. Cochran-Armitage trend tests were examined to determine if trends of increasing proportion of successful maneuvers across time were present, for both spirometry and IOS. Linear trends from a mixed model, adjusted for child's race/ethnicity, gender, height, and recurrent wheezing, were tested to determine whether the mean values of $FEV_{0.5}$ and IOS measures increased or decreased across time. Only participants with acceptable data at all 3 years were included in this model.

Linear regression was used to examine relationships between height, maternal smoking during pregnancy as measured by cord blood cotinine, and both spirometry ($FEV_{0.5}$) and IOS (R_5 , X_5 , A_X) lung function tests at ages 3, 4, and 5 years of age. Cord blood cotinine was considered as a binary exposure because of a high proportion of data below the limit of detection: above (>2 ng/mL) versus at or below the limit of detection (≤ 2 ng/mL). All cotinine models were adjusted for child's race/ethnicity, gender, and height at the time of test. Detectable cotinine was considered the independent predictor, and lung function measurement was modeled as the outcome. Models examining an association with height among nonrecurrent wheezers are unadjusted.

RESULTS

Study population

Of the 609 participants enrolled initially in the birth cohort study, 503 attended at least one of the 3 clinic visits of interest. Seventy-one percent were African American, 52% were male, and 68% had an annual household income of less than \$15,000

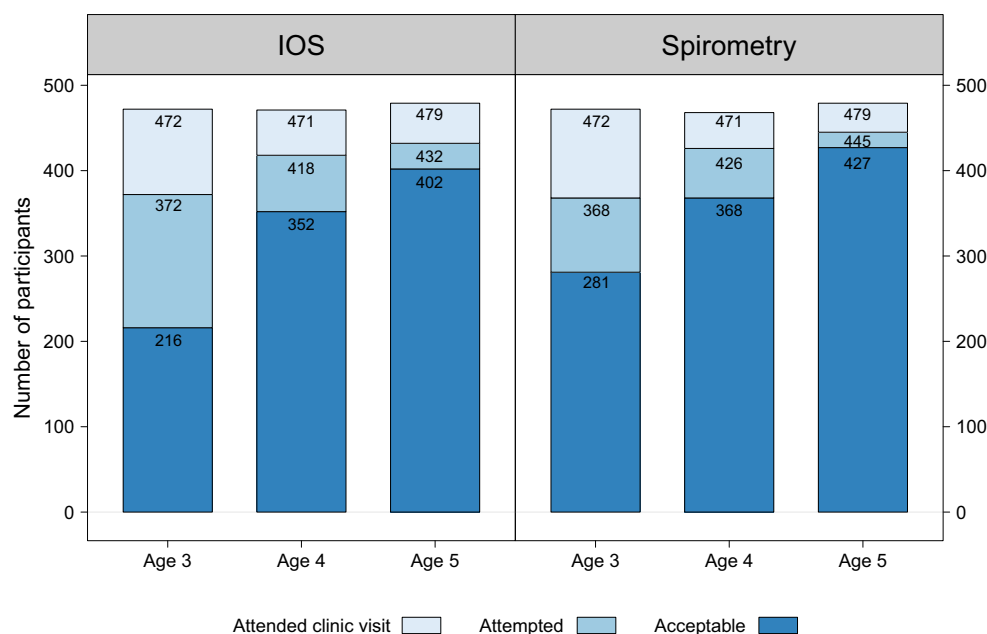


FIGURE 1. The number of children who attended a clinic visit (darkest shade of blue) attempted to perform a pulmonary function test (middle shade of blue) and had an acceptable pulmonary function test (lightest shade of blue) at ages 3, 4, and 5 years. The number of participants attending, attempting, and completing an acceptable test are shown on top of each stacked bar. Percentages of acceptable spirometry maneuvers were higher than percentages of acceptable IOS measurements at ages 3 and 5 ($P < .001$ and $P = .02$, respectively). Acceptable test percentages for both IOS and spirometry showed significant improvement over time in a test for trend ($P < .001$). IOS, Impulse oscillometry.

TABLE II. Reasons for unacceptable IOS tests

	Age 3 N = 151	Age 4 N = 66	Age 5 N = 30	Total N = 247
Did not have minimum of 4 breaths per 15 s of data	71% (107)	68% (45)	50% (15)	68% (167)
Tidal breathing was unsatisfactory*	74% (111)	82% (54)	80% (24)	77% (189)
X_5 values were positive	52% (79)	55% (36)	30% (9)	50% (124)
Failed to meet coherence criteria	84% (128)	88% (58)	87% (26)	85% (212)
Fewer than 3 acceptable maneuvers	96% (146)	95% (63)	97% (29)	96% (238)
R_{10} not reproducible	81% (123)	89% (59)	93% (28)	85% (210)

IOS, Impulse oscillometry; R_{10} , resistance at 10 Hz; X_5 , reactance at 5 Hz.

Note: Over-readers were able to select all applicable reasons for a session to be considered “unacceptable.” Reasons were provided for 247 of the 252 total unacceptable IOS sessions; 248 answered questions regarding coherence, acceptable number of maneuvers, and reproducibility.

*Uninterrupted and regular breathing without leak or hyperventilation was required to be considered satisfactory.

(Table I). There were only differences for site ($P = .04$) and race ($P = .04$) when comparing the 485 children who attempted one or more lung function tests and those who attended a clinic visit but did not attempt a maneuver ($n = 18$, data not shown). A total of 472, 471, and 479 children attended a clinic visit at ages 3, 4, and 5 years, respectively.

Thirty-four percent of the evaluable children had recurrent wheeze at 3 years according to the study *a priori* definition. Clinical characteristics of the children at ages 3 and 5 are included in Table E1 (available in this article’s Online Repository at www.jaci-inpractice.org).

Successful completion of lung function testing

Overall rates of successfully completed lung function tests increased over time for both spirometry and IOS (trend test

$P < .001$ for both). At ages 3, 4, and 5 years, 78%, 90%, and 93%, respectively, were willing to perform spirometry and 79%, 89%, and 90%, respectively, were willing to perform IOS (Figure 1). A higher proportion of children attending clinic visits had acceptable spirometry sessions compared with IOS sessions (Figure 1). At 3 years, 60% of children who attended a clinic visit had an acceptable test with spirometry compared with 46% with IOS maneuver ($P < .001$); at 4 years, 78% had acceptable spirometry versus 75% with IOS ($P = .22$), and at 5 years, 89% had acceptable spirometry versus 84% with IOS ($P = .02$). Of those children who attempted the tests, 76% had acceptable spirometry and 58% had acceptable IOS at 3 years ($P < .001$); 86% had acceptable spirometry and 84% had acceptable IOS at 4 years ($P = .37$); and 96% had acceptable spirometry and 93% had acceptable IOS at 5 years ($P = .06$). There were no

TABLE III. Reasons for unacceptable spirometry tests

	Age 3 N = 81	Age 4 N = 49	Age 5 N = 17	Total N = 147
Effort was submaximal	37% (30)	57% (28)	71% (12)	48% (70)
Glottic closure	14% (11)	8% (4)	12% (2)	12% (17)
Exhale <0.5 s	17% (14)	12% (6)	6% (1)	14% (21)
Equipment malfunction	2% (2)	2% (1)	0% (0)	2% (3)
Other reasons*	22% (18)	14% (7)	0% (0)	17% (25)
2+ reasons	7% (6)	6% (3)	12% (2)	7% (11)

Note: Over-readers answered in free text and most often provided the primary reason that the session was unacceptable; occasionally, 2 or more reasons were provided. Reasons were provided for 147 of the 163 total unacceptable spirometry sessions. *Other reasons include the following: participant not cooperating, technician error, inspiratory volumes greater than expiratory, inconsistent expiratory flow, etc.

differences in rates of acceptable tests between males and females (data not shown).

For spirometry at ages 3, 4, and 5 years, 65%, 78%, and 92%, respectively, had 3 acceptable and 2 reproducible efforts. Each of the 4 sites had a high proportion of children who were able to complete at least 1 acceptable spirometry or IOS test during the 3 years (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Reasons for unacceptable spirometry results were provided for 90% (147/163) of unacceptable spirometry sessions and for 98% (247/252) of unacceptable IOS sessions. Specific reasons for unacceptability are shown in Tables II and III.

There were significant correlations between FEV_{0.5} and the IOS measures at every year ($P < .001$ for all). These correlations ranged from -0.39 to -0.53 for FEV_{0.5} versus R_5 , 0.35 to 0.43 for X_5 , and -0.38 to -0.46 for A_X (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Lung function at 3, 4, and 5 years

We performed a descriptive analysis of lung function at 3, 4, and 5 years to provide reference data in primarily African American and Hispanic children by examining the relationships between height and FEV_{0.5}, R_5 , X_5 , and A_X (Figure 2) in children without recurrent wheeze. This analysis excluded children by each year of age who had recurrent wheeze defined as at least 2 wheezing episodes with at least 1 episode occurring in the current year. The relationship between height and lung function values did not differ by sex, but there were small differences by race/ethnicity (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org).

Of the nonwheezing children, there were 131 children who performed successful spirometry at all 3 years and 97 children who had acceptable IOS at all 3 years. A_X and R_5 decreased significantly across time in a linear fashion, whereas FEV_{0.5} and X_5 significantly increased over time ($P < .001$ for all comparisons, Table E3 and Figure E3, available in this article's Online Repository at www.jaci-inpractice.org).

Prenatal exposure to environmental tobacco smoke and lung function

Table IV shows the lung function at ages 3 to 5 years as measured by spirometry and IOS in subjects with *in utero* exposure to smoking compared with those who were not exposed. The median and interquartile range for the cord blood cotinine level for the cohort were at the level of detection:

2 ng/mL (2 ng/mL, 2 ng/mL). Cord blood cotinine above the level of detection was found in only 18% of the analysis population, and was associated with significantly higher A_X at ages 4 and 5 years (age 4: 5.44 kPa/L vs 4.63 kPa/L, $P = .006$; age 5: 4.46 kPa/L vs 3.82 kPa/L, $P = .009$). There was no association of the cotinine level with FEV_{0.5} at any age.

DISCUSSION

This study compared the performance of 3-5-year-old predominantly African American and Hispanic children in spirometry and IOS. IOS is generally believed to be easier than spirometry for young children in that it requires less active effort. The results of this study do not support this assumption. The data show that more than half of 3-year-old children can perform acceptable spirometry and slightly less than half can perform acceptable IOS maneuvers. The data confirm that pulmonary function testing can be performed with a high degree of success in 4- and 5-year-old children, although the success rate remained higher with spirometry. This is in line with our clinical observation that it is easier to get young children to blow hard than it is to have them sit still and breathe quietly on a mouthpiece for 30 seconds.

A longitudinal study by Guilbert et al²¹ compared spirometry and IOS in 4- and 5-year-old children. They found no differences between the 2 tests in the percentage of acceptable tests. However, the percentage of acceptable tests for both spirometry and IOS was much lower than that in our study. At 4 years of age, 84% of children who attempted IOS had acceptable tests compared with 21% in the Guilbert study and 86% who attempted spirometry had acceptable tests compared with 24%. At 5 years of age, 93% of children who attempted IOS had acceptable tests compared with 58% in that study and 96% who attempted spirometry had acceptable tests compared with 57%.²¹

We used FEV_{0.5} as our primary spirometric measure because children in this age group typically have short forced expiratory time, and empty their lungs in less than 1 second. Using FEV_{0.5} in studies of young children helped achieve a greater frequency of acceptable maneuvers as similarly reported in other studies.^{2,22,23} Our success rates with spirometry for each age group between the ages of 3 and 5 years are consistent with other studies reporting FEV_{0.5} with smaller numbers of children.^{2,5,22}

The study demonstrated that both spirometry and IOS can be performed reliably and consistently in a multicenter study. This was achieved by having centralized training and over-reading with feedback to those performing the tests. The longitudinal study design of URECA is a factor that may have contributed to the high success rates in performing the tests. A practice session to familiarize the children with the equipment and procedures was held at 33 months, and the first attempt at performing the tests was at 3 years. By ages 4 and 5, the children were experienced. Prior experience can improve performance on pulmonary function testing.^{24,25}

Strict quality control procedures were in place for this study. Research assistants were trained to accept studies without physical artifacts and all the studies were over-read centrally. We required at least 3 acceptable maneuvers with reproducibility within 20% at R_{10} for IOS. One criterion used for acceptability of an IOS maneuver was a coherence value of ≥ 0.80 at 10 Hz similar to one used in the Childhood Asthma and Research

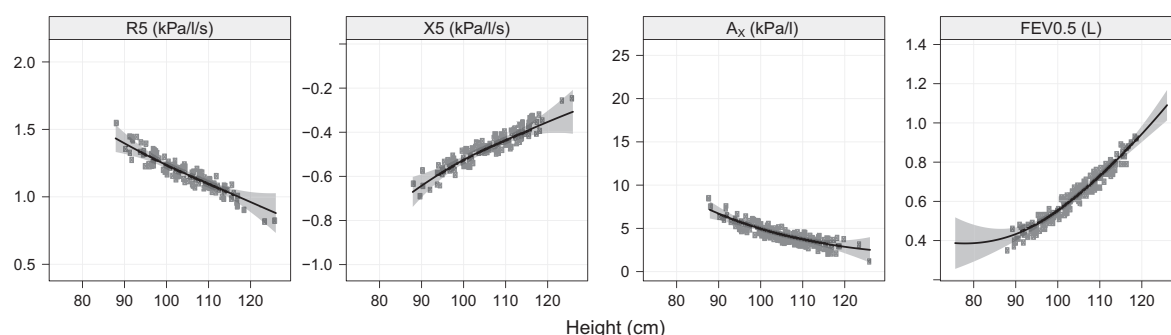


FIGURE 2. R_5 (kPa/L/s), X_5 (kPa/L/s), and A_X (kPa/L), and $FEV_{0.5}$ (L) plotted by height (cm) in URECA children without recurrent wheeze. Each point indicates a raw pulmonary measurement for an associated height. The thick lines are a smoothed regression line plotted from an unadjusted linear model. A_X , Area of reactance; $FEV_{0.5}$, forced expiratory volume in 0.5 s; R_5 , resistance at 5 Hz; URECA, Urban Environmental and Childhood Asthma Study; X_5 , reactance at 5 Hz.

TABLE IV. Adjusted means and 95% confidence intervals for IOS and spirometry values at ages 3, 4, and 5 by detectable cotinine level at birth

	Detectable cotinine		<i>P</i> value
	No (≤2 ng/mL)	Yes (>2 ng/mL)	
	N = 307	N = 65	
Age 3			
FEV _{0.5} (L/s)	0.50 (0.49, 0.51)	0.47 (0.44, 0.50)	.09
<i>R</i> ₅ (kPa/L/s)	1.31 (1.27, 1.34)	1.30 (1.23, 1.37)	.83
<i>X</i> ₅ (kPa/L/s)	−0.56 (−0.58, −0.53)	−0.51 (−0.56, −0.45)	.10
<i>A_X</i> (kPa/L)	5.49 (5.17, 5.81)	5.46 (4.80, 6.12)	.91
Age 4			
FEV _{0.5} (L/s)	0.62 (0.61, 0.63)	0.59 (0.56, 0.62)	.19
<i>R</i> ₅ (kPa/L/s)	1.19 (1.17, 1.22)	1.25 (1.19, 1.30)	.12
<i>X</i> ₅ (kPa/L/s)	−0.51 (−0.53, −0.49)	−0.54 (−0.59, −0.50)	.30
<i>A_X</i> (kPa/L)	4.63 (4.40, 4.85)	5.44 (4.97, 5.92)	.006
Age 5			
FEV _{0.5} (L/s)	0.77 (0.75, 0.78)	0.76 (0.73, 0.79)	.89
<i>R</i> ₅ (kPa/L/s)	1.10 (1.07, 1.12)	1.14 (1.09, 1.18)	.15
<i>X</i> ₅ (kPa/L/s)	−0.44 (−0.45, −0.42)	−0.47 (−0.51, −0.44)	.08
<i>A_X</i> (kPa/L)	3.82 (3.62, 4.01)	4.46 (4.04, 4.87)	.009

A_X , Area of reactance; $FEV_{0.5}$, forced expiratory volume in 0.5 s; IOS, impulse oscillometry; R_5 , resistance at 5 Hz; X_5 , reactance at 5 Hz.

Note: Values are adjusted mean estimates (95% confidence intervals) and P values from a linear regression model adjusted for race/ethnicity, gender, and height of participant at time the pulmonary measurement was taken.

Education network studies.²⁶ As noted in the ATS/ERS statement on pulmonary function testing, there is no systematic study of cutoff values for coherence in preschool children.¹⁹ There were no instances where coherence was the only criterion for exclusion in our study.

Several factors must be taken into consideration in making comparisons of our values for spirometry and IOS in preschool children without recurrent wheeze to those published in other studies of healthy children. The study population was representative of black and predominantly Puerto Rican and Dominican Hispanic preschool children in whom there are limited published data. In addition, prior studies were cross-sectional and had smaller sample sizes particularly at the lower

end of the age range.²⁷⁻³⁰ The $FEV_{0.5}$ in our study is comparable with the healthy children in this age group reported by Nystad et al.² Our data are also in the range of those reported by Kampschmidt et al,⁴ whose subjects included Hispanics. However, 26% of children in that study had a previous diagnosis of asthma. Comparisons with other spirometry studies are limited by small sample sizes in the 3-year-old age group and inclusion of children with a history of wheezing or asthma. Our values for R_5 are in the range of the comparative data of several studies reported by Malmberg et al³⁰ and for A_X published by Calogero et al.⁸ The measures of R_5 and X_5 at 4 years are similar to a study of 45 predominantly Hispanic and African American 4-year-old children without asthma.¹¹

Maternal smoking during pregnancy is associated with deficits in lung function at birth and infancy.^{15,16,31} Most studies in offspring of mothers who smoked during pregnancy assessed pulmonary function in infancy or after age 5, but there is limited data between 3 and 5 years of age. Using IOS, Gray et al¹⁷ demonstrated that 6- to 10-week-old healthy African infants whose mothers smoked during pregnancy had lower compliance than infants not exposed to tobacco smoke during pregnancy. In a longitudinal study, Turner et al¹⁵ reported that lung function was diminished between 1 month and 12 months with the thoracoabdominal compression technique and again at 6 years with spirometry, but no measurements were made between 12 months and 6 years. Our study found that cotinine was associated with a greater area of reactance but not lower $FEV_{0.5}$. This suggests that IOS may be better than spirometry in detecting the deficits in lung function in this age group associated with *in utero* exposure to maternal smoking. Experimental studies in animal models indicate that *in utero* nicotine exposure increases collagen and decreases elastin in the lung. Our findings are in line with the fact that IOS measures the mechanical properties of the respiratory system that include resistive and elastic properties.³² In addition to the effects of smoking on mechanical properties, central airway shunting or peripheral inhomogeneities may affect the A_X results. Although one cannot extrapolate our findings regarding the ability of IOS to distinguish physiologic differences in other diseases better than spirometry, our results are consistent with a study in 4-year-old children demonstrating that IOS was better than spirometry at discriminating asthma on the basis of their bronchodilator response.¹¹ In contrast, spirometry was

better able to detect lung disease in preschoolers with cystic fibrosis.²⁸

Interestingly, cord blood cotinine was more closely associated with reduced lung function at ages 4 and 5 years than at 3 years. This could be due to ascertainment bias (older children were more likely to successfully complete the test) or progressive changes in lung function. Additional follow-up of these children may help resolve this question.

There are unique aspects to this study. This is one of the largest studies to compare IOS and spirometry in preschool children followed prospectively, and unlike other studies, has a large number of children at 3 years. Results from URECA children without a history of recurrent wheeze provide reference data because there are limited data on spirometry and IOS in African American and Hispanic children in this age group. Of note is that the Hispanic children in this cohort were predominantly Caribbean. Furthermore, similar rates of success with lung function testing were obtained at multiple medical centers, providing evidence that these results are generalizable. It is important to consider that the high rates of success at ages 4 and 5 years might be partially due to experience gained by the children during the visits at age 3 years and practice is also likely to be helpful in the clinical setting. Finally, we present longitudinal data that allowed us to examine the ability of the 2 methods to detect deficits in lung function between 3 and 5 years associated with exposure to smoking during pregnancy.

There are limitations to this study that should be noted. The number of children who did not attempt a pulmonary function test may have been affected by fatigue because testing was part of a visit that included questionnaires. The results may not be generalizable to different racial/ethnic or higher socioeconomic populations. One limitation of using cord blood cotinine as a marker of transplacental passage of nicotine and its metabolites is that it reflects exposure in late gestation but not chronic exposure.

In summary, both spirometry and IOS can be used successfully in studies of lung function in preschool children in a low-socioeconomic population. Despite the theoretical advantages of IOS over spirometry on performance of pulmonary function, there was a higher rate of acceptable spirometry in younger children. Although the 2 tests are correlated, IOS may be able to detect changes in respiratory system properties and reflect peripheral airway obstruction not seen with usual spirometric measures.

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TABLE E1. Clinical characteristics of the URECA population at ages 3 and 5

Age 3	
Skin test positive*	37% N = 161/438
No. of positive skin tests	0.9 ± 1.6 N = 438
Any aeroallergen-specific IgE ≥ 0.35 kU _A /L	27% N = 115/423
Total IgE (kU _A /L)	47 (17, 125) N = 423
Recurrent wheeze	34% N = 174/511
Age 5	
Skin test positive*	44% N = 190/430
No. of positive skin tests	1.2 ± 1.9 N = 430
Any aeroallergen-specific IgE ≥ 0.35 kU _A /L	36% N = 157/440
Total IgE (kU _A /L)	63 (24, 190) N = 439

URECA, Urban Environmental and Childhood Asthma Study.

Note: Values in the table are frequencies, mean ± standard deviation, or mediation (interquartile range).

*Wheal 3 mm larger than negative control.

TABLE E2. Frequency of participants attending, attempting, and completing acceptable lung function tests by site between 3 and 5 years of age

	Active participants at 36 mo	Participants who attended ≥1 clinic visit	Participants who attempted ≥1 pulmonary test*	Participants who completed ≥1 acceptable pulmonary test*
Site	N = 522	N = 503	N = 485	N = 479
A	153	148 (97%)	137 (93%)	132 (89%)
B	117	115 (98%)	112 (97%)	112 (97%)
C	103	96 (93%)	95 (99%)	95 (99%)
D	149	144 (97%)	141 (98%)	140 (97%)

*Percentages represent those who attempted or completed an acceptable pulmonary function test of those who attended a clinic visit.

TABLE E3. FEV_{0.5}, respiratory resistance, and reactance at ages 3, 4, and 5 years in children without a history of recurrent wheeze

Age (y)	Height (cm), mean ± SD	FEV _{0.5} (L)*	R ₅ (kPa/L/s)*	X ₅ (kPa/L/s)*	A _X (kPa/L)*
		N = 131†	N = 97†		
3	97.1 ± 4.1	0.51 (0.48, 0.54)	1.29 (1.22, 1.36)	−0.53 (−0.59, −0.47)	5.31 (4.62, 6.00)
4	104.7 ± 3.9	0.66 (0.62, 0.69)	1.15 (1.08, 1.22)	−0.46 (−0.53, −0.39)	4.17 (3.57, 4.77)
5	111.7 ± 4.1	0.83 (0.79, 0.86)	1.02 (0.96, 1.08)	−0.37 (−0.41, −0.33)	2.91 (2.40, 3.43)

A_X, Area of reactance; FEV_{0.5}, forced expiratory volume in 0.5 s; R₅, resistance at 5 Hz; X₅, reactance at 5 Hz.

*Values are mean estimates and 95% confidence limits from a general linear model controlled for race, height, gender, and recurrent wheeze; only the estimates from non-wheezing participants are shown.

†Sample sizes listed (N = 131 for FEV_{0.5} and N = 97 for resistance and reactance) include only those participants who had acceptable maneuvers at every year.

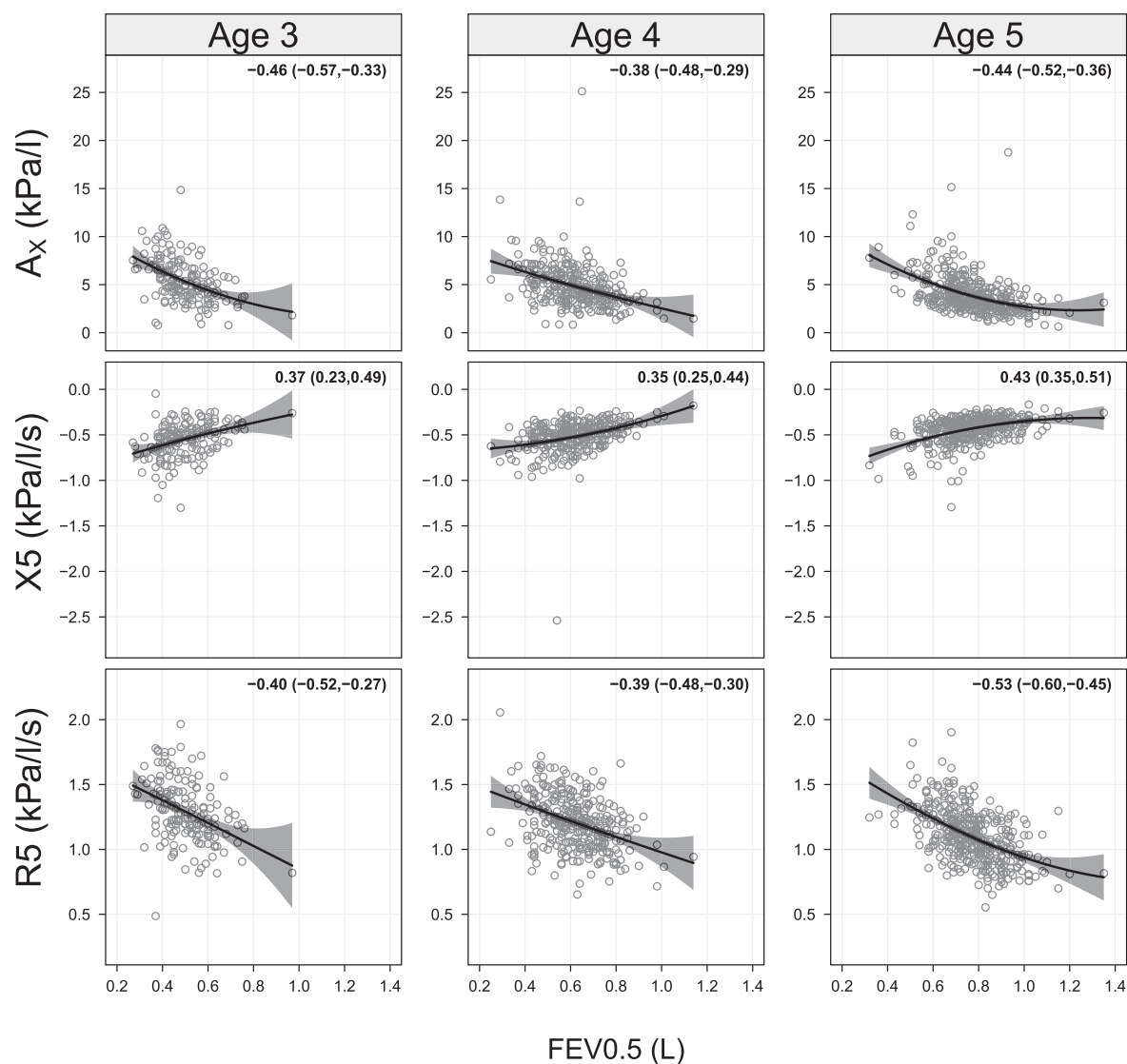


FIGURE E1. Scatterplot and correlations of association between FEV_{0.5} and R_5 , X_5 , and A_x values at each year. The values in the upper-right corner of panels indicate the Pearson correlation coefficient (95% confidence interval) and the thick lines are a smoothed regression line. A_x , Area of reactance; FEV_{0.5}, forced expiratory volume in 0.5 seconds; R_5 , resistance at 5 Hz; X_5 , reactance at 5 Hz.

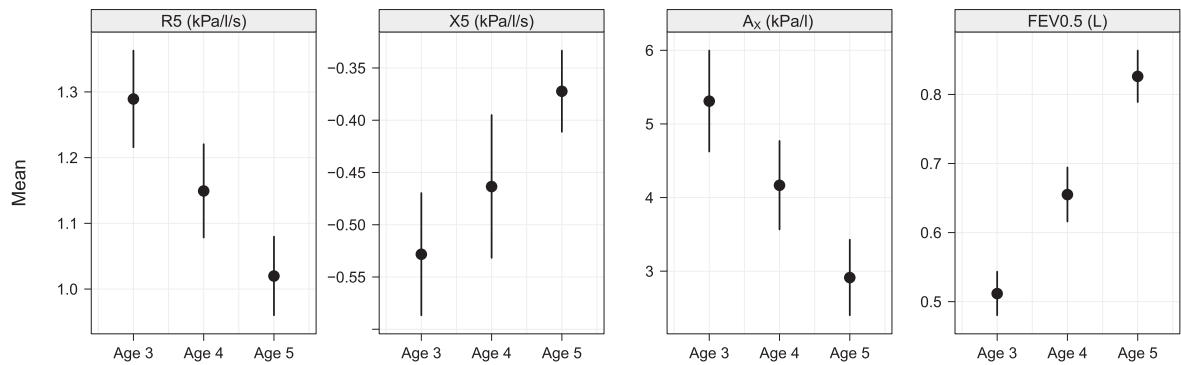


FIGURE E2. Mean estimates (95% confidence intervals) for each pulmonary function measurement at ages 3, 4, and 5 for nonrecurrent wheezers. Estimates of the means and 95% confidence intervals are from linear regression models adjusted for race, gender, height, and recurrent wheezing, and only results for nonrecurrent wheezers with measurements at all 3 time points are plotted. A_X , Area of reactance; $FEV_{0.5}$, forced expiratory volume in 0.5 seconds; R_5 , resistance at 5 Hz; X_5 , reactance at 5 Hz.

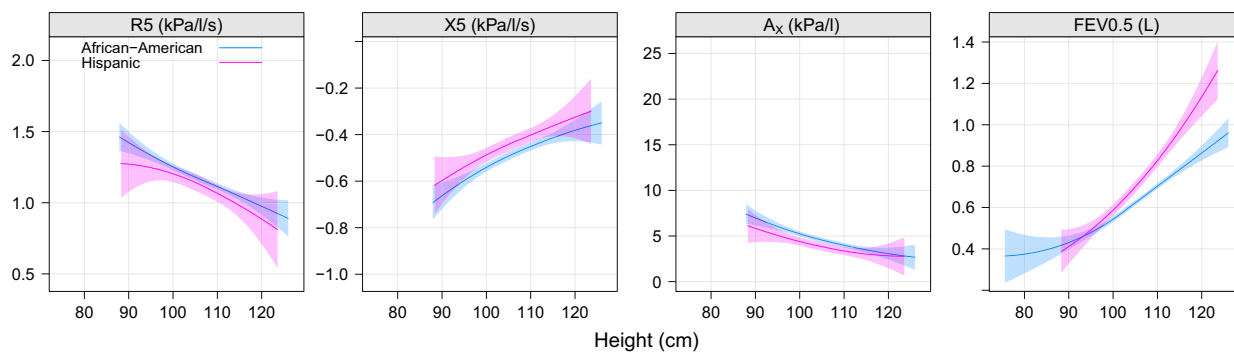


FIGURE E3. R_5 (kPa/L/s), X_5 (kPa/L/s), A_X (kPa/L), and $FEV_{0.5}$ (L) plotted by height (cm) and race/ethnicity in URECA children without recurrent wheeze. Each point indicates a raw pulmonary measurement for an associated height. Regression line is plotted from unadjusted linear models. A_X , Area of reactance; $FEV_{0.5}$, forced expiratory volume in 0.5 seconds; R_5 , resistance at 5 Hz; URECA, Urban Environmental and Childhood Asthma Study; X_5 , reactance at 5 Hz.