

Spirometric and Exhaled Nitric Oxide Reference Values in Preschool Children From the Community of Navarra

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■ Abstract

Background and Objective: Preschool children can perform quality, reproducible spirometric maneuvers, provided appropriate equipment is used and specially trained nursing staff training are available. However, use of spirometry for the diagnosis and follow-up of preschool children with respiratory diseases remains limited in clinical practice, because consensus on test quality and acceptability criteria and reference data are lacking. We initiated the present study with the aim of developing reference equations, since tables of normal values for this age group are not available in our area.

Patients and Methods: The study population comprised healthy preschool children in our community. Normal values for exhaled nitric oxide in this age range were assessed. Regression equations were constructed using univariate and multivariate models.

Results: A total of 114 healthy preschool children aged 3 to 6 years were enrolled. According to the criteria of the American Thoracic Society/European Respiratory Society, 60 children were able to perform acceptable and reproducible spirometric maneuvers. The best correlations were observed for the untransformed linear regression model that included height. The correlation coefficients for forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁), and FEV_{0.5} were 0.89, 0.88, and 0.86, respectively. The regression equations for the calculation of reference values were as follows:

$$FVC = -2.6 + 0.036 \times \text{height, cm}$$

$$FEV_1 = -2.04 + 0.029 \times \text{height, cm}$$

$$FEV_{0.5} = -1.53 + 0.022 \times \text{height, cm}$$

We obtained fraction of inhaled nitric oxide (FeNO) values for 56 children. The mean (SD) value was 11 (4.9) ppb.

Conclusions: Most preschool children in our area were able to perform quality spirometry maneuvers. We obtained regression equations that allowed us to calculate the reference ranges in our population and the distribution of normal FeNO values.

Key words: Spirometry. Preschool children. Reference values. Exhaled nitric oxide.

■ Resumen

Antecedentes: Los niños preescolares pueden realizar maniobras espirométricas de calidad y reproducible, siempre y cuando se utilice un equipamiento adecuado y se disponga de personal de enfermería con entrenamiento específico para ello. Sin embargo su uso clínico en este rango de edad tanto en diagnóstico como en seguimiento de pacientes con enfermedades respiratorias sigue siendo muy escaso, por diversas razones. Entre otras se encuentran la falta de un consenso en los criterios de calidad y aceptabilidad de la prueba la escasez de datos de referencia.

Objetivo y métodos: Debido a que no se disponía de tablas de valores normales para este rango de edad en nuestra área, se inició este estudio con el fin de obtener ecuaciones de referencia provenientes de una población de niños preescolares sanos de nuestra comunidad, aprovechando el esfuerzo para obtener también valores de normalidad de óxido nítrico en aire exhalado en este rango de edad. Para la obtención de las ecuaciones de regresión se utilizaron modelos uni y multivariantes.

Resultados: Se incluyeron un total de 114 niños preescolares sanos con edades comprendidas entre los 3 y los 6 años. De ellos 60 fueron capaces de realizar maniobras espirométricas aceptables y reproducibles, de acuerdo a los criterios ATS/ERS. El modelo de regresión lineal no transformado que incluía la altura, obtuvo las mejores correlaciones. La introducción de otras variables no mejoraba significativamente los resultados. Los coeficientes de correlación para FVC, FEV₁ and FEV_{0.5} fueron 0.89, 0.88 y 0.86 respectivamente. Las ecuaciones de regresión para el cálculo de los valores de referencia fueron:

$$\begin{aligned} FEVC &= -2,6 + 0,036 * \text{altura (cm)} \\ FEV_1 &= -2,04 + 0,029 * \text{altura (cm)} \\ FEV_{0,5} &= -1,53 + 0,022 * \text{altura (cm)} \end{aligned}$$

El cociente FEV_1/FVC disminúa con la edad y la altura, si bien los resultados de los distintos modelos eran pobres y no permitían el uso de las ecuaciones de regresión para el cálculo de valores de referencia.

Obtuvimos valores de FeNO en 56 niños. El valor medio fue 11 ppb (SD 4,9) con un rango entre 5 y 18 ppb.

Conclusiones: La mayoría de los preescolares de nuestra área pudieron realizar espirometrías de calidad. Se han obtenido ecuaciones de regresión que nos permiten calcular los rangos de referencia en nuestra población y también la distribución de los valores normales de FeNO.

Palabras clave: Espirometría. Niños preescolares. Valores de referencia. Óxido nítrico exhalado.

Introduction

Respiratory diseases, especially obstructive respiratory diseases, are highly prevalent conditions in pediatric populations [1]. Spirometry is a well-standardized technique that is used routinely in the diagnostic testing and follow-up of obstructive airway diseases in adults and adolescents [2], although it is rarely used in children. Young children can perform forced expiration maneuvers that reveal sufficient dynamic pressures and airflow obstructions [3,4]. However, studies have only recently begun to demonstrate that even preschool children can perform appropriate and reproducible spirometric maneuvers [5-11], with specific incentives in the form of electronic games helping enormously [12]. Standardization regulations and spirometric quality criteria have also been established so that this test can be implemented in standard clinical practice in this age group [13-15]. Ideally, reference values should be obtained from large, prospective, multicenter, multinational studies that follow standardized methods and protocols. When the present study was initiated (2008), no reference equations fulfilling these conditions for preschool children were available. Furthermore, the typical setting for this type of study does not reflect clinical practice in lung function laboratories in terms of equipment and software (for measuring lung function variables), auxiliary equipment (such as antibacterial filters), and quality controls and protocols [16].

The aim of this study was to obtain quality spirometry readings in preschool children (3-6 years of age) from Navarre, Spain using equipment, protocols, and quality assurance methods that meet the current standards of international groups interested in the study of lung function in pediatric patients. Based on these readings, the study also attempted to define regression equations that would enable normal spirometric values to be set for the preschool population of our community.

Given recent interest in the use of fractional exhaled nitric oxide (FeNO) as a useful biomarker for diagnosing asthma [17] and for assessing potential therapeutic needs [18,19], we included the measurement of FeNO in this protocol. We used a simple measuring system based on an electrochemical sensor that is widely used in clinical practice and for which normal values have not been properly defined in preschool children.

Material and Methods

We performed a single-center, cross-sectional study. The protocol was approved by the Research Committee of Hospital

Virgen del Camino, Pamplona, Spain and the Ethics Committee of the Autonomous Community of Navarre. The participants' gave their signed informed consent for their children to participate in the study. Enrollment began in October 2008 and ended in June 2012.

Study Population

We recruited healthy children older than 3 years but younger than 7 years to participate in the study during scheduled physical examinations. The children were recruited from 7 pediatric centers in the Pamplona area. We also included healthy nonatopic children or their siblings who were referred for drug or food allergy workups at the Department of Allergology of the Conde Oliveto Primary Care Center, Pamplona, Spain. To be included in the study, children had to be white, of biological parents, and born in our community or in neighboring communities. Gestational age had to be >36 weeks and birth weight ≥ 2.5 kg. The children's current weight had to lie within the fifth and 95th percentiles for height. The exclusion criteria were as follows: history of neonatal processes other than temporary conditions (less than 24 hours); maternal smoking during pregnancy; history of chronic diseases (cardiovascular, renal, muscle, or skeletal), congenital abnormalities, previous thoracic surgery, or general disorders; chronic respiratory or otorhinolaryngologic diseases; relevant acute respiratory processes (eg, necrotizing pneumonia); hospitalizations due to acute respiratory disease; and 3 or more bouts of documented bronchiolitis.

All enrolled children were in a stable condition, had no signs of acute disease, and had not experienced infectious respiratory processes in the month prior to the examination. None of them had received prior treatment with inhalers or other asthma drugs, and the results of the physical examination were normal.

Spirometric Study

Weight and height (height in the upright position) were measured according to a protocol using the same stadiometer and scale. Spirometry was performed with the same MasterScreen spirometer (Viasys-Jaeger) using a disposable NeumoFilt oval filter/mouthpiece (MRD). The spirometric variables included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), the ratio FEV_1/FVC , and FEV in 0.5 seconds ($FEV_{0,5}$). We selected these values because they had the most robust indices for this age group in the regression equations [20], especially when compared

with those obtained from instantaneous flow values, and to provide more general clinical information. Quality was controlled by measuring the back-extrapolated volume (BEV), forced expiratory time, and the point at which the expiratory flow finished (expressed as a percentage of peak expiratory flow) [14]. We calibrated the spirometer according to the manufacturer's instructions before each spirometry session. The spirometer includes a pneumotachograph; the volume was derived from the digital integration of the flow. As the flow-volume curve is observed in real time, proper effort and training can be ensured. The quality criteria required for the test were those proposed by Aurora et al [15], which were expanded upon in the official statement of the American Thoracic Society/European Respiratory Society (ATS/ERS) [14], whose recommendations are listed in Table 1. The objective was to reach at least 2 or, where possible, 3 quality maneuvers, 2 of which were reproducible. The highest values were selected from the various spirometric variables. If the maneuver was not performed or was not valid, we recorded the reasons. All examinations were reviewed by a single physician (JMO), who analyzed their quality.

All studies were performed by 2 nurses from the lung function laboratory who had considerable experience with lung function testing in children. None of the children included had previously undergone spirometry; they were therefore trained

in a regulated manner and in a friendly environment before undergoing spirometry. The training sessions for learning the maneuver were limited to 30 minutes. Most children achieved a quality examination in a single session, although some children required 2 sessions or a maximum of 3 sessions, which were held on separate days. All examinations were performed while sitting and wearing a nose clip.

To train and encourage the children in the forced maneuver, we used 2 animated games integrated into the equipment: *birthday cake candles* (aimed at flow) to achieve good peaks in the curve and *bowling* (aimed at volume) to achieve extended maneuvers with good endings [12]. All the children were trained using both incentive games. The system was able to store at least 10 spirometric maneuvers and included a brief presentation that facilitated the appropriate selection of maneuvers.

The eNO measurements were performed before spirometry using the Niox Mino system (Aerocrine) equipped with an electrochemical sensor. The equipment essentially follows the ATS/ERS recommendations for measuring FeNO [21] and is able to detect levels >5 ppb, with a precision of <3 ppb and a detection range of 5-300 ppb [22]. To facilitate the correct performance of the expiratory maneuver by the children, expiratory time was limited to 6 seconds. Undetectable values (<5 ppb) were assigned the arbitrary value of 5 ppb.

Table 1. Recommendations of the American Thoracic Society/European Respiratory Society [14] for Measurement, Data Collection, and Interpretation of Spirometry Results in Preschool Children

1. The flow-volume curve should ideally be presented to the operator in real time, with the additional option of viewing the volume-time trace. Alternatively, the operator should be able to view the previous flow-volume curve before the following expiration attempt.
2. The indices from each spirometry attempt that should be available to the operator before the following attempt are forced vital capacity (FVC), forced expiratory volume (FEV) in t seconds (FEV_t), back-extrapolated volume (BEV), and the point at which flow ceases, presented as a proportion of peak expiratory flow (PEF).
3. If it is the child's first attempt at spirometry, a period of training is essential. The child should be familiarized with the equipment and the technician.
4. Interactive computerized incentives may be used to encourage the maneuver, but these are not mandatory. If incentives are to be used, then a volume-driven incentive, or a flow- and volume-driven incentive should be used when maneuvers are to be recorded.
5. Posture and nose clip use should be recorded and reported.
6. The operator should observe the child closely to ensure that there is no leak and that the maneuver is performed optimally.
7. A minimum of 3 maneuvers should be recorded, but no maximum number is stipulated.
8. Both volume-time and flow-volume curves should be visually inspected. The attempt should be excluded if the flow-volume curve does not demonstrate a rapid rise to peak flow and a smooth descending limb, without evidence of cough or closure of the glottis.
9. If the BEV is greater than 80 mL, or 12.5% of FVC, then the curve should be reinspected, but does not necessarily need to be excluded.
10. If cessation of flow occurs at >10% of peak flow, then this maneuver should be classified as showing premature termination. It may be possible to report timed expiratory volumes from such a maneuver, but FVC and forced expiratory flows should not be reported.
11. The highest FEV_t and FVC should be reported after examining data from all of the usable curves, even if they do not come from the same curve.
12. The starting point for FEV_t should be determined by back extrapolation.
13. Posture and nose clip use should be recorded and reported. If flows are to be reported from the "best" maneuver, then this should be identified as that with the highest sum of FEV_{0.5} and FVC.
14. Ideally, the child should produce at least 2 acceptable curves, for which the second highest FVC and FEV_t are within 0.1 L or 10% of the highest value, whichever is greater. If a single satisfactory maneuver is recorded, then these results should not be excluded simply because of poor repeatability. The number of technically satisfactory maneuvers and the repeatability results should always be reported.

Statistical Analysis

We performed a descriptive analysis of all the variables. Continuous variables were expressed as mean (SD); categorical variables (in this case, only gender) were reported as number of cases and percentages. We calculated the Spearman correlation coefficient and used univariate and multivariate linear regression models to determine the linear association between the lung function measurements and the independent variables. The variables included were height, weight, gender, and age. We used IBM SPSS Statistics, version 20 (IBM Corp) for the statistical analysis.

Results

We recruited a total of 114 healthy preschool children, 12 of whom did not attend the examination. Of the 102 children who did attend, 93 agreed to undergo the tests; the 9 children who did not accept were younger than 4 years. Of the 93 children who agreed to the test, we were able to obtain at least 2 acceptable maneuvers in 76 children, and in 60 we obtained acceptable and reproducible maneuvers. Our success rate in obtaining a quality examination was therefore 59%, taking into account the 102 children who attended the lung function laboratory, or 64% considering only the children who actually performed the test. In 4 of the 60 children (all younger than 4 years), the duration of the expiration was less than 1 second; an FEV₁ was therefore not recorded, although the forced expiration maneuver was technically acceptable and the FVC value was reproducible. The 16 children for whom the result of the examination was not of sufficient quality were comparatively younger than the group in whom a quality examination was obtained. All 16 children, except for 2, were younger than 5 years.

The regression equations for defining normal values were based only on the group of 60 children with quality maneuvers. The main characteristics of this group are presented in Table 2. The children had a mean (SD) age of 4.8 (1.1) years, with a mean weight and height of 112.2 (10.3) cm and 20 (3.9) kg. Moreover, 53% of the 60 preschool children were girls. We also observed a strong linear association between age, weight, and height on the one hand and lung function parameters on the other, especially in the case of height, for which it had

Table 2. Anthropometric Data of the 60 Children With Quality Function Examinations

Parameters	Mean (SD) or %	FVC	Correlations		
			FEV ₁	FEV _{0.5}	FEV ₁ /FVC
Gender, girls	53%				
Age, years	4.8 (1.1)	0.84	0.792	0.776	-0.554
Height, cm	112.2 (10.3)	0.891	0.883	0.858	-0.374
Weight, kg	20.0 (3.9)	0.827	0.784	0.718	-0.5
NO	10.9 (4.9)	0.052	0.058	0.08	0.061

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NO, nitric oxide.

a correlation >0.8 in all cases, except with FEV₁/FVC, for which it had an inverse correlation. Table 3 shows the group characteristics and the main functional variables grouped by age. As we can see, the distribution among the ages was relatively homogeneous, although the most numerous group was the one with age ≥6 years. The distribution by gender was also fairly homogeneous in all groups.

Table 3. Anthropometric and Lung Function Data (Means) Grouped by Age Range

Age, y	3	4	5	≥6
No.	10	14	12	24
Boy/Girl, No.	6/4	8/6	4/8	12/12
Height, cm	98	105	113	121
FVC, L	0.94	1.15	1.57	1.80
FEV ₁ , L	0.83	1.02	1.38	1.54

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 4. Univariate Models (Height) of Lung Function Measurement

Spirometric Variable	Univariate Model			
	β ₀	Height (SE)	SD	R ²
FEV ₁	-2.04	0.029 (0.002) ^a	0.16	0.78
FVC	-2.6	0.036 (0.002) ^a	0.19	0.79
FEV _{0.5}	-1.53	0.022 (0.002) ^a	0.14	0.73
FEV ₁ /FVC	1.12	-0.002 (0.001)	0.06	0.13

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^aP<.05

In the linear regression models, height was significantly associated with lung function (Table 4). Height by itself largely explains the variance in the response variables (expiratory volumes), both in the models where we considered all cases and in the models differentiated by gender. If we introduce more covariates into the model, the variance increases by scarcely 1% or 2% in most cases (Table 5). In light of these data and to facilitate the calculation of normal values, we are inclined to choose the model with the simple linear regression with height as the only covariate. We can say that the linear regression satisfactorily represents the relationship between height and lung function. Therefore, the equations for the calculation of normal values would be as follows:

$$FVC = -2.6 + 0.036 \times \text{height}$$

$$FEV_1 = -2.04 + 0.029 \times \text{height}$$

$$FEV_{0.5} = -1.53 + 0.022 \times \text{height}$$

We were not able to establish a good correlation for FEV₁/FVC, even in multivariate models, although a clear inverse relationship with age was detected (Tables 4 and 5).

The Figure shows this relationship for the spirometric variables FVC, FEV₁, and FEV_{0.5}. Our findings are similar to those of the main previously published models, including those by Eigen et al [23], Nystad et al [24], and Perez-Yarza et al [25].

Table 5. Comparison of Lung Function Measurement Models

Covariates Introduced	FEV ₁		FVC		FEV _{0.5}		FEV ₁ /FVC	
	R ²	RSD	R ²	RSD	R ²	RSD	R ²	RSD
Height	0.78	0.16	0.79	0.19	0.73	0.14	0.13	0.06
Height, gender	0.78	0.16	0.8	0.18	0.74	0.14	0.16	0.06
Height, gender, weight	0.78	0.16	0.8	0.18	0.75	0.13	0.25	0.05
Height, gender, weight, age	0.79	0.16	0.81	0.18	0.75	0.13	0.44	0.04
Height, gender, age	0.78	0.16	0.81	0.18	0.73	0.14	0.36	0.05
Height, weight, age	0.77	0.16	0.8	0.18	0.74	0.13	0.45	0.04
Height, weight	0.77	0.16	0.79	0.19	0.74	0.14	0.25	0.05
Height, age	0.77	0.16	0.8	0.18	0.73	0.14	0.35	0.05

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; RSD, residual standard deviation.

We obtained a suitable recording of FeNO measurements in exhaled air for 56 of the 93 children who agreed to perform the tests. The total success rate for FeNO readings was 60%. The mean measurement was 11 (4.9) ppb, ranging from <5 ppb to 18 ppb. The values had no relationship with the anthropometric characteristics, age, or gender of the preschool children.

Discussion

Our results confirmed that it is possible to obtain quality forced spirometry measurements in preschool children. Our 64% success rate is in line with that achieved by other authors such as Eigen et al [23], Nystad et al [24], and Pesant et al [20], despite the fact that these authors used less demanding quality criteria for the maneuvers. Conversely, our success rate was significantly below the 82% achieved by Perez-Yarza et al [25], who used quality criteria similar to those of our study. Obtaining a high success rate in this population is linked to the availability of proper equipment and laboratory staff with experience in this age group [15,23,26]. Another crucial factor is the use of animated game software. Achieving quality maneuvers is greatly facilitated by the use of these incentivizing techniques, provided that they cover the various test phases [12]. It is advisable to use at least 2 types of games: those that encourage maximum flows (such as the birthday cake candles), which are aimed at the first phase of the maneuver; and subsequently those that encourage maximum expiratory times and volumes (such as bowling games), which are aimed at obtaining quality final phases.

The main strength of our study is the careful selection of healthy children, with well-defined and physician-certified inclusion criteria that were verified by physical examination. Most studies aimed at obtaining data on normal values were performed in daycare centers [20,24] or with very large samples in which individualized health examinations could not be performed [16,23]. Another strength is that the study was conducted in a single center using the same spirometry equipment for all tests with only 2 technicians involved in obtaining the maneuvers and only 1 physician in the implementation of acceptability criteria. Using

different equipment and technicians leads to significant variability, which detracts from the value of the results, as does interpretation of the acceptability of the maneuvers by several doctors [15,27]. These sources of variability appear in studies such as the multicenter study performed in Spain by Perez-Yarza et al [25] and in other studies performed in a single center but with different equipment [24,28].

We chose highly demanding quality criteria for the spirometric maneuvers; these were initially proposed by Aurora et al [15] and reinforced and standardized by the ATS/ERS working group [14]. We also followed the recommendations of the ATS/ERS for the statistical analysis. In pediatric patients, lung function parameters are closely linked to height. In our study, no other variable was able to provide significantly more information on the variability of these parameters than height. In this respect, our results agree with those of most studies on preschool children, such as those from a review by Stanojevic et al [26]. Age and gender are more relevant in older patients, especially preadolescents [29]. In our case, the untransformed linear regression model achieved optimal results, which means that the resulting calculation for normal values is highly simplified for daily clinical practice. Given their particular lung physiology, children can generate completely adequate forced expirations in less than 1 second [15,24]. In our series, we recorded FEV₁ values in 93% of the children, which is consistent with results obtained elsewhere [20]. Other functional parameters such as FEV_{0.5} and FEV_{0.75} and indices such as the area of the expiratory curve may be of interest, although there are insufficient studies to determine which would be clinically more useful [20]. The values we recorded helped us to obtain a regression equation for the calculation of normal values for FEV_{0.5}, with a reliability similar to that obtained for FEV₁ and FVC.

As we can see in the Figure, our model provides results that are similar to those obtained by Eigen et al [23] (both genders) and do not differ much from those obtained by Nystad et al [24] (boys only). We can observe a certain difference in girls, but we have to consider that, in our case, R² is greater than that obtained by Nystad et al (both genders). Similar results were generated in the model obtained by Perez-Yarza et al [25] in Spain.

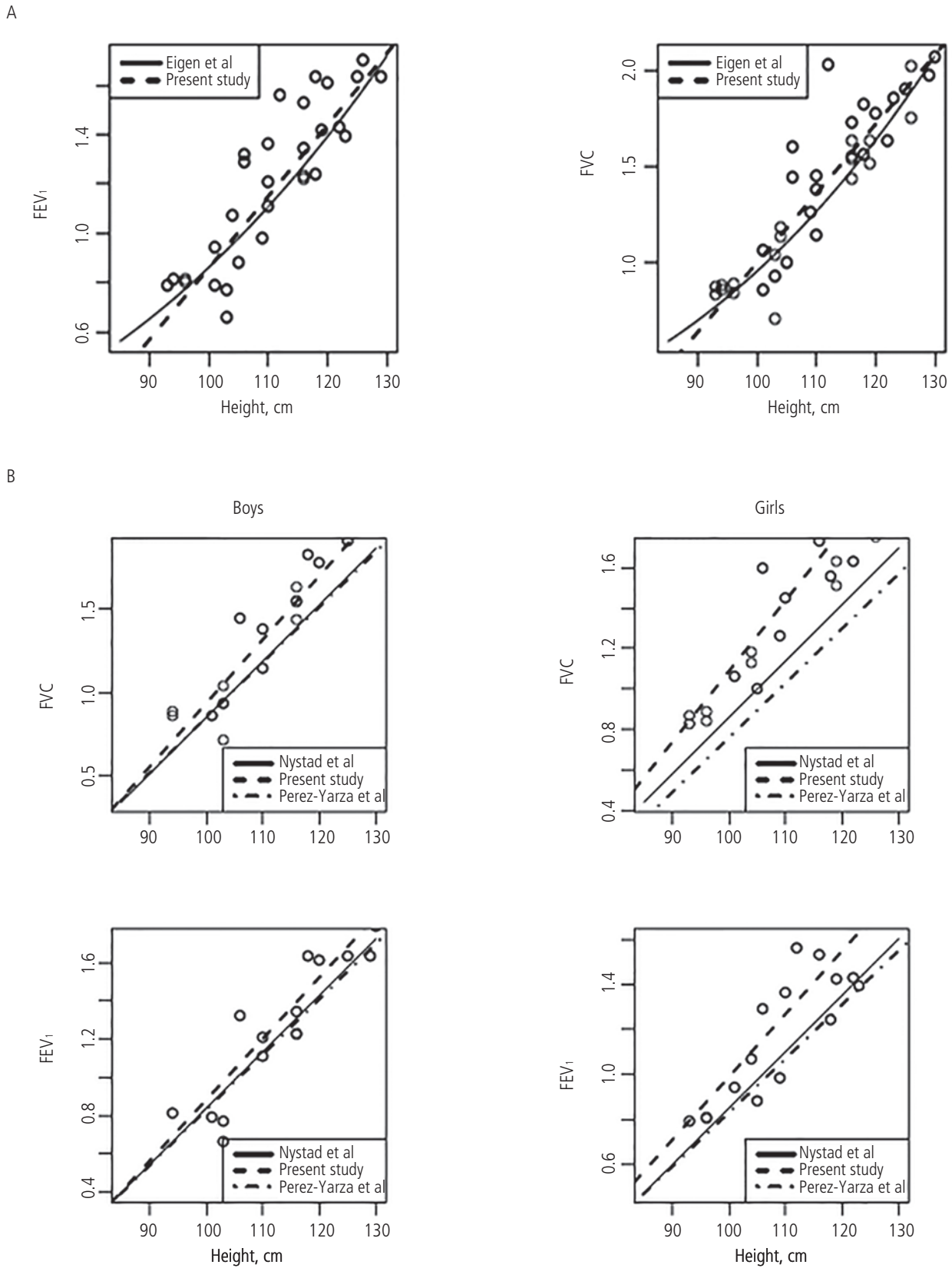


Figure. A, Predicted values for lung function vs height measurements. B, Predicted values for lung function vs. height measurements by gender. FEV₁ indicates forced expiratory volume in the first second; FVC, forced vital capacity.

Nitric oxide is produced in the lung by the enzyme endothelial nitric oxide synthase, and its high levels in exhaled air have been associated with the presence of eosinophilic inflammation in the airways. Since it can be measured quickly, easily, and cheaply using a noninvasive procedure, it is an ideal candidate for clinical practice. In addition to applications in asthma and allergic diseases, FeNO has been proposed in several emerging areas of clinical interest, such as assessment of the response to inhaled corticosteroids in chronic obstructive pulmonary disease, therapy for patients with pulmonary hypertension, and the diagnosis—in children—of diseases such as primary ciliary dyskinesia and cystic fibrosis [30].

The ATS recently presented a number of recommendations indicating that measurement of FeNO could play a role in the diagnosis of active eosinophilic inflammation, determination of the response to inhaled corticosteroids, assessment of the need for inhaled corticosteroids, and identification of poor adherence to treatment [31]. The ATS guideline suggests that, when interpreting FeNO levels, decision-making cutoff points may have more clinical value than using reference values and that these cutoff points are different for children and adults. In particular, the guideline states that FeNO values below 20 ppb in children younger than 12 years indicate a low likelihood of eosinophilic inflammation and response to corticosteroids, whereas values greater than 35 ppb indicate the opposite [31].

To our knowledge, this is the first study to report FeNO values in a healthy Spanish preschool population using an exhaled nitric oxide monitoring device with an electrochemical sensor, which is the system that is most frequently used in clinical practice. We calculated a mean of 11 (4.9) ppb as a normal value with an upper limit of normal of 20 ppb. We conducted a rigorous selection of healthy individuals, ensuring that participants had normal lung function. Our results are similar to those obtained by Buchvald et al [32] in a European population and significantly higher than those recently reported by See et al [33] and Linn et al [34] in the USA. The population values of FeNO are highly variable, and numerous intrinsic factors influence this variability [35]. Preliminary studies reflect a certain relationship between FeNO on one hand and age and anthropometric variables such as height on the other. Our results do not confirm this relationship and, in this respect, are consistent with those obtained in recent large series [33,36]. It is possible that the significant variability in population FeNO values is due more to other factors such as ethnicity, the presence of atopy, or genetic factors that modulate the expression of the enzyme nitric oxide synthase, which governs the production of nitric oxide in the bronchial epithelium [37].

In conclusion, forced spirometry is a feasible examination in preschool children, even while adhering to strict quality criteria such as those recommended by the ATS/ERS. We obtained regression equations that provide us with reference values for normality for our preschool aged population. In addition, we have defined the values of normality in this age group for FeNO, a biomarker of airway inflammation, which is frequently used in clinical practice.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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