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Spirometric Reference Values in 5 Large Latin American Cities for Subjects Aged 40 Years or Over

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OBJECTIVE: In clinical practice, spirometry is an extremely useful test that requires strict quality control, an appropriate strategy for interpretation, and reliable reference values. The aim of this study was to report spirometric reference values for 5 cities in Latin America.

PATIENTS AND METHODS: From data for 5315 subjects who had undergone spirometry in the PLATINO study in Caracas, Mexico City, Santiago, São Paulo, and Montevideo, we selected information for 906 (17%) individuals aged between 40 years and 90 years to provide reference values. The chosen subjects had never smoked, were asymptomatic, had not been diagnosed with lung disease, and were not obese. Multiple regression models were constructed with the following spirometric parameters: forced expiratory volume in 1 second (FEV_1) and in 6 seconds (FEV_6), peak expiratory flow, forced vital capacity (FVC), FEV_1/FEV_6, FEV_1/FVC, and forced midexpiratory flow rate. Height, sex, and age were also included in the model.

RESULTS: Average values for the subjects studied were similar to those for the white North American population and the Mexican-American population of the third National Health and Nutrition Examination Survey, but exceeded those of the black population of the same survey by 20%.

CONCLUSIONS: The proposed reference values are an improvement on those currently available for Latin America because the participants were chosen by population sampling methods and standardized up-to-date methodology was used.

Key words: *Spirometry. Reference Values. PLATINO. Latin America.*

Valores de referencia espirométrica en 5 grandes ciudades de Latinoamérica para sujetos de 40 o más años de edad

OBJETIVO: La espirometría es una prueba de gran utilidad clínica, que requiere un estricto control de calidad, una estrategia de interpretación y valores de referencia adecuados. El propósito del presente trabajo es comunicar los valores de referencia para la espirometría en 5 ciudades de Latinoamérica.

PACIENTES Y MÉTODOS: El estudio PLATINO se llevó a cabo en Caracas, México, Santiago, São Paulo y Montevideo e incluyó a un total de 5.315 sujetos con espirometría realizada. De ellos, se estudió a 906 (17%) que tenían entre 40 y 90 años de edad para crear valores de referencia, porque nunca habían fumado, estaban asintomáticos y no tenían enfermedad pulmonar diagnosticada ni obesidad. Se efectuaron modelos de regresión múltiple con los valores espirométricos —volumen espiratorio forzado en el primer segundo (FEV_1) y en 6 s (FEV_6), flujo espiratorio máximo, capacidad vital forzada (FVC), FEV_1/FEV_6, FEV_1/FVC y flujo mesoespiratorio forzado—, la talla, el sexo y la edad.

RESULTADOS: Los sujetos estudiados presentaron en promedio valores similares a los de la población norteamericana blanca y americana de origen mexicano del estudio NHANES III, pero superiores a los de la población negra en un 20%.

CONCLUSIONES: Los valores de referencia propuestos representan una ventaja sobre los disponibles en la actualidad en Latinoamérica, ya que se eligió a los participantes por métodos de muestreo poblacional y el método empleado es estandarizado y actualizado.

Palabras clave: *Espirometría. Valores de referencia. PLATINO. Latinoamérica.*

Introduction

Spirometry is the best diagnostic test for assessing the mechanical function of the respiratory system because it is readily accessible, relatively easy to perform, and repeatable, although strict quality control is necessary to take full advantage of the technique.[1,2] A range of applications have been described for spirometry, both in the clinical setting and in research.[3,4]

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The technique is essential for assessing patients with respiratory diseases, in particular those with bronchial asthma and chronic obstructive pulmonary disease (COPD).[5] Correct interpretation of the results requires comparison with reference values,[6] the best of which are peak readings obtained in the same subject during longitudinal follow-up, although this is only possible in a limited number of situations (for example, in groups of workers monitored annually because of work hazards). In general, it is necessary to resort to comparison with previously published reference values. Guidelines have been drawn up for selecting reference values: in general they should be based on large samples of comparable populations, readings should be taken with internationally accepted spirometric devices and methods, and the statistical analysis should be sound.[4]

In Latin American countries, reference values have been generated, and some of these have been published,[7-15] but unfortunately the devices used, the number of subjects studied and where they live, and the statistical methods all vary. The PLATINO project[16] (Spanish abbreviation for Latin American Project for Investigation of Pulmonary Obstruction) was a good opportunity to study a representative sample of the populations of 5 Latin American cities with the same methods, equipment, and quality control. The aim of the present study was to report the spirometric reference values generated by the project for subjects with no history of respiratory disease.

Patients and Methods

The PLATINO project started in 2002 with the aim of determining the prevalence of COPD in 5 large Latin American cities using spirometry as the main diagnostic method. The methods have already been published,[16] as have the main findings.[17] In short, the present study was a cross-sectional study that took a sample of approximately 1000 subjects aged at least 40 years old from the original PLATINO study population. The subjects lived in the following cities: Caracas (mean altitude above sea level, 950 m), Venezuela; Montevideo (35 m), Uruguay; São Paulo (800 m), Brazil; Mexico City (2240 m), Mexico; and Santiago de Chile (543 m), Chile. The sample was representative of the entire metropolitan area of the cities. Sampling was done in a number of stages. First, 68 areas were chosen for each city, and in each one, a census of inhabited homes was generated from which 15 were randomly selected. From these, residents aged 40 years or more were selected.

The project was approved by the ethics committees of the participating centers and written informed consent was obtained from all subjects. Subjects received a questionnaire to determine respiratory symptoms and exposure to substances potentially harmful to the respiratory system. The questionnaire was based on others used previously, such as that of the American Thoracic Society (ATS),[18] the European Community Respiratory Health Survey II,[19] the Lung Health Study,[20] and the Short Form-12 quality-of-life questionnaire. The height and weight were measured in duplicate and the average value was recorded after standardizing the measurements.[22] The body mass index (BMI) was calculated by dividing weight in kilograms by height, expressed in meters, squared.

Subjects with a history of myocardial infarction, those with heart rate greater than 120 beats/min; pregnant women; those who had undergone thoracic, abdominal, neurological, or ocular surgery in the preceding 3 months; and patients with active tuberculosis were excluded from the study.

Spirometry was done by personnel who had received training in a quality control course for spirometric testing approved by the National Institute for Occupational Safety and Health and who had also participated in the pilot studies in each city. Two spirometric readings were taken, 1 at baseline, and 1 at 15 minutes after aerosol administration of 200 g of salbutamol with a spacer. Subjects were seated and nose clips were used for the readings. The device used was an ultrasound spirometer (Easy One, NDD Technopark, Zurich, Switzerland), which met all the ATS requirements for quality control.[1] Calibration was verified daily with a 3 L syringe. Procedures recommended by the ATS were followed,[1] with the exception that more than 8 maneuvers were allowed (up to a maximum of 15) in order to obtain repeatable readings. The spirometer displayed messages to help the technician improve the quality of subsequent readings and automatically detected the end of expiration when the criteria of the ATS were met. All results were sent to Mexico City for quality control. The investigators in Mexico City wrote a weekly report for each center and technician after approximately 80 to 100 tests.

Generation of Reference Values

To generate reference values, subjects apparently in good respiratory health were selected using the information obtained from the questionnaire and anthropometric data (Table 1). Subjects in good respiratory health were taken to be those who lacked respiratory symptoms (cough, phlegm, wheezing, or dyspnea); had no medical diagnosis of asthma, COPD, chronic bronchitis, or emphysema; and denied ever having suffered tuberculosis or lung cancer or having undergone lung resection. Subjects who were smokers of cigarettes, cigars, or pipes at the interview, and ex-smokers

TABLE 1
Number of Study Subjects Excluded for Generating Spirometric Reference Values[*]

Criterion	No. of Subjects
Current cigarette smoker	1583
Current pipe or cigar smoker	45
Smoked 400 or more cigarettes	3019
Medical diagnosis of asthma	651
Medical diagnosis of pulmonary emphysema, chronic bronchitis, or COPD	237
Their physician told them that they had tuberculosis	132
Their physician told them that they had lung cancer	14
They had undergone pulmonary resection	27
Cough or phlegm without a cold	1595
Wheezing in the past year	1,268
Dyspnea walking on flat ground at normal pace	116
Age >90 years	17
<2 acceptable spirometric maneuvers	67
Body mass index >30 kg/m^2	1596
Remaining subjects (whose data were used to generate the reference values)	906

[*]Figures for the total number of subjects with the characteristic; a given subject might have met several of these exclusion criteria. The sum of subjects with a given exclusion criterion therefore exceeds the number of subjects excluded. COPD indicates chronic obstructive pulmonary disease.

who had smoked more than 400 cigarettes were also excluded. In addition, 23 subjects who performed fewer than 2 acceptable spirometric maneuvers and 8 subjects over 90 years old were excluded, the latter because few subjects in their 90s were available and not all cities contributed to this age group. These criteria are in accordance with those recommended by the ATS.[4] Furthermore, subjects with BMI greater than 30 kg/m^2 were excluded because of the adverse impact on respiratory function. After excluding patients with respiratory disease and symptoms and smokers, the final population was 906 subjects, corresponding to 17% of the sample of 5315 subjects who underwent spirometry. The inclusion and exclusion criteria used here were similar to those of Hankinson et al,[23] except that we did not exclude 61 subjects aged over 80 years because it is becoming increasingly common to assess elderly patients; another exception was that our study excluded obese subjects. Complex sampling with the "survey" command of the STATA statistical package was used to generate regression equations.[24] Each of the spirometric variables analyzed—forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF) rate, FEV_1/FVC, forced expiratory volume in 6 seconds (FEV_6), FEV_1/FEV_6, and forced midexpiratory flow rate ($FEF_{25\%-75\%}$)—was entered into a multiple regression model using age, height in centimeters, and sex as predictors. Nonlinear relationships were also tested by incorporating the square of age and height, but unless the coefficient of determination (R^2) improved and the SE of the differences decreased in the nonlinear analysis, we preferred linear models for simplicity. The models were constructed separately for women and men in order to avoid forcing a fit to the values for one sex and a parallel shift in the other, or greatly complicating the models with interactions. For each spirometric variable, in addition to the mean value, the SE of the estimate (SD of the residuals) was also determined to calculate the lower limit of normal (LLN) (the fifth percentile, which is estimated by subtracting 1.645 times the SD from the mean).

The spirometric values for the study population were compared with those of the North American population in the study by Hankinson et al,[23] who reported reference values for 3 ethnic groups (Caucasians, African Americans, and Mexican Americans); with reference values widely used in Latin America, such as those of Knudson et al[25] and Crapo et al[26]; European ones from the European Coal and Steel Community[27] and Roca et al[28,29]; and the reference values of Enright et al[30] for subjects aged over 65 years.

TABLE 2
General Data (Mean [SD]) for the Study Population (n=906)*

Variable	Women (n = 635)	Men (271)
Age, y	57.3 (12.1)	55.7 (12.2)
Height, cm	153.6 (6.9)	167.2 (7.2)
Weight, kg	60.5 (8.3)	71.8 (9.7)
BMI, kg/m^2	25.6 (2.9)	25.6 (2.8)
FEV_1, L	2.26 (0.54)	3.21 (0.73)
FVC, L	2.91 (0.65)	4.21 (0.92)
FEV_6, L	2.81 (0.62)	4.03 (0.88)
FEV_1/FVC, %	77.5 (7.0)	76.3 (6.8)
FEV_1/FEV_6, %	80.2 (5.5)	79.5 (5.4)
FET, s	9.5 (2.7)	11.2 (3.8)
Tests with 1994 ATS criteria†	95.6	95.2

*BMI indicates body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_6, forced expiratory volume in 6 seconds; FET, mean expiratory time; ATS: American Thoracic Society.
†Three acceptable maneuvers and FEV_1 and FVC repeatable to within 200 mL.

Results

Table 2 shows a general description of the sample of healthy subjects used for generating the reference values and Table 3 a breakdown of their age distribution and where they lived.

Of the sample of healthy subjects, 95% of the population met the quality criteria proposed by the ATS (3 acceptable maneuvers and repeatability, defined as readings within 200 mL of each other, for the 2 best FEV_1 and FVC) and 89% achieved a repeatability of within 150 mL for both FEV_1 and FVC, criteria accepted since 2005 by the American and European pulmonology societies.[31] Subjects undertook a mean (SD) of 6 (3) spirometric maneuvers and 18% completed the test correctly in only 3 maneuvers.

The predictive equations for women and men are presented in Tables 4 and 5, respectively. The results are also presented in the form of 2 nomograms to facilitate interpretation (Figures 1 and 2). Either the nomograms or the equations can be used to calculate the predicted value for a given age and height. For example, a 45-year-old woman measuring 160 cm has, according to the equation, a predicted FEV_1 of (0.02699089 160)-(0.02398873 45)-0.51369779=2.72535311 L. The LLN would be 2.72535311-(1.645 0.38)=2.10025311 L. Those results can be rounded to 2.73 L and 2.1 L, respectively.

We tried including weight and BMI in the regression equations. However, their additional contribution to the models with height and age alone was small, although statistically significant for many of the tests. This small or nonexistent impact of weight or BMI on lung

TABLE 3
Distribution of Subjects by Sex, Age, and Place of Residence*

Age, y	Women						Men					
	SP	MX	MN	SAN	CA	Total	SP	MX	MN	SAN	CA	Total
40-45	16	32	6	8	48	110	14	20	13	3	16	66
> 45-55	41	51	28	14	66	200	21	19	11	12	21	84
> 55-65	31	41	24	17	38	151	12	15	9	11	10	57
> 65-75	20	24	24	17	28	113	6	8	10	8	9	41
> 75-90	15	10	27	4	5	61	2	5	4	8	4	23
Total	123	158	109	60	185	635	55	67	47	42	60	271

*SP indicates São Paulo, Brazil; MX, Mexico City, Mexico; MN, Montevideo, Uruguay; SAN, Santiago de Chile, Chile; CA, Caracas, Venezuela.
Total of 906 subjects between 40 and 90 years old in good respiratory health.

TABLE 4
Reference Equations for Women Between 40 and 90 Years Old (n=635)*

Variable	FEV_1 (L)	FVC (L)	FEV_6 (L)	FEV_1/FVC (%)	FEV_1/FVC† (%)	FEV_1/FEV_6 (%)	PEF (L/s)	$FEF_{25\%-75\%}$ (L/s)
Age, y	–0.02398873	–0.02324661	–0.02451519	–0.21964744	–0.20197318	–0.16955436	–0.05360108	–0.03619264
Height, cm	0.02699089	0.03834604	0.03606686	–0.10189407	No	–0.08013511	0.05653161	0.01400578
Intercepto	–0.51369779	–1.6469408	–1.3272314	105.70909	89.042622	102.19303	0.65195532	2.217574
R^2	51.5	46.6	50.4	13.1	12.2	12.8	36.7	25.2
SD of differences	0.3791218	0.47242368	0.43907485	6.5444792	6.5731346	5.1341718	1.123243	0.82395712

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_6, forced expiratory volume in 6 seconds; PEF, peak expiratory flow; $FEF_{25\%-75\%}$, forced midexpiratory flow.
†The equation predicts FEV_1/FVC only with age and sex, and this is the one used in the nomograms.

TABLE 5
Reference Equations for Men Between 40 and 90 Years Old (n=271)*

Variable	FEV_1, (L)	FVC (L)	FEV_6, (L)	FEV_1/FVC, (%)	FEV_1/FVC†, (%)	FEV_1/FEV6 (%)	PEF (L/s)	$FEF_{25\%-75\%}$ (L/s)
Age, y	–0.0291673	–0.02488509	–0.02807181	–0.25567933	–0.23404784	–0.18857203	–0.07185995	–0.05188433
Height, cm	0.04116371	0.06450317	0.0593406	–0.17104261	–0.13117006	0.06294803	0.01411121	
Intercept	–2.0483434	–5.1859524	–4.3228	119.14759	89.350282	111.92545	2.4914045	3.573076
R^2	49.5	43.5	47.3	20.8	17.7	18.2	29.3	29.7
SD of differences	0.51760403	0.69569079	0.63939928	6.0762543	6.1843963	4.8908893	1.6716949	1.0234253

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_6, forced expiratory volume in 6 seconds; PEF, peak expiratory flow; $FEF_{25\%-75\%}$, forced midexpiratory flow.
†The equation predicts FEV_1/FVC only with age and sex, and this is the one used in the nomograms.

function can be attributed to the exclusion of subjects with BMI greater than 30 kg/m^2. What is more, the inclusion of these variables would make it impractical to generate simple tables and nomograms. No additional predictive power was obtained with height squared or weight squared, except for prediction of FEV_1/FVC in men (age squared was significant), and simple equations with linear terms were chosen even in this case.

Comparisons with the North American reference values generated in the National Health and Nutrition Evaluation Survey (NHANES) III for each ethnic group are presented in Tables 6 and 7. Values for spirometric variables in healthy subjects in the PLATINO study were approximately 20% above the predicted FEV_1 and FVC for African Americans, 10% above the European values reported by Quanjer,[27] and approximately the same as those of Caucasians and Mexican Americans in the NHANES III[23] and the values published by Crapo et al[26] and Roca et al.[29] These values, however, varied slightly by sex and in different tests performed by the participants. Moreover, when the spirometric values of the PLATINO subjects were expressed as percentage of predicted by several equations, an association with age and height remained, the association being stronger for height (data not shown). This means that the average adjustment for the table, which seems acceptable for several of the reference values, is not uniform for different ages and heights, and breaks down particularly for shorter PLATINO subjects. This variation in the adjustment is reflected in the data in Table 7 showing the subjects of our study below the LLN. It is expected that approximately 5% of the healthy subjects are below the LLN, but this figure changes according to the sex and spirometric variable for each group of reference equations, suggesting an inappropriate adjustment in the equation. This may give rise to either false positives or negatives that would be difficult to predict. Figure 3 shows the mean differences between the spirometric values in our study population and the predicted values from a variety of reference studies (actual value-predicted value), expressed in milliliters. In line with Tables 6 and 7, it can be seen that the mean difference in our population is very small compared to those predicted in the NHANES III for the white and Mexican-American population.

Some variations in lung function were observed among the cities, but rarely did the overall mean values of a variable for a given city vary by more than 4%. For women in Montevideo and Santiago and men in Santiago, FVC was 6% larger, whereas men in Caracas had lower values for FVC and FEV_1 (91.6% and 94.0% of predicted, respectively). Subjects in Santiago had a lower FEV_1/FVC than the rest of the population (96.5% of predicted in women and 96.2% in men). Variables such as city, height above sea level, and race or skin color as defined in the questionnaire (white, brown, black, Asian, and indigenous) were tested for predictive power. Addition of city, race, and height to the models described for the reference equations increased the explained variance by less than 1.5%. Therefore, general equations were retained for the 5 cities. When altitude was added to the model, it did not show a statistically significant association with lung function in the final sample.

Discussion

The present study has the advantage of being based on a representative sample of the populations of 5 large Latin American cities and of having been conducted using standard methods in accordance with international recommendations. It therefore represents a considerable advance with respect to existing reference

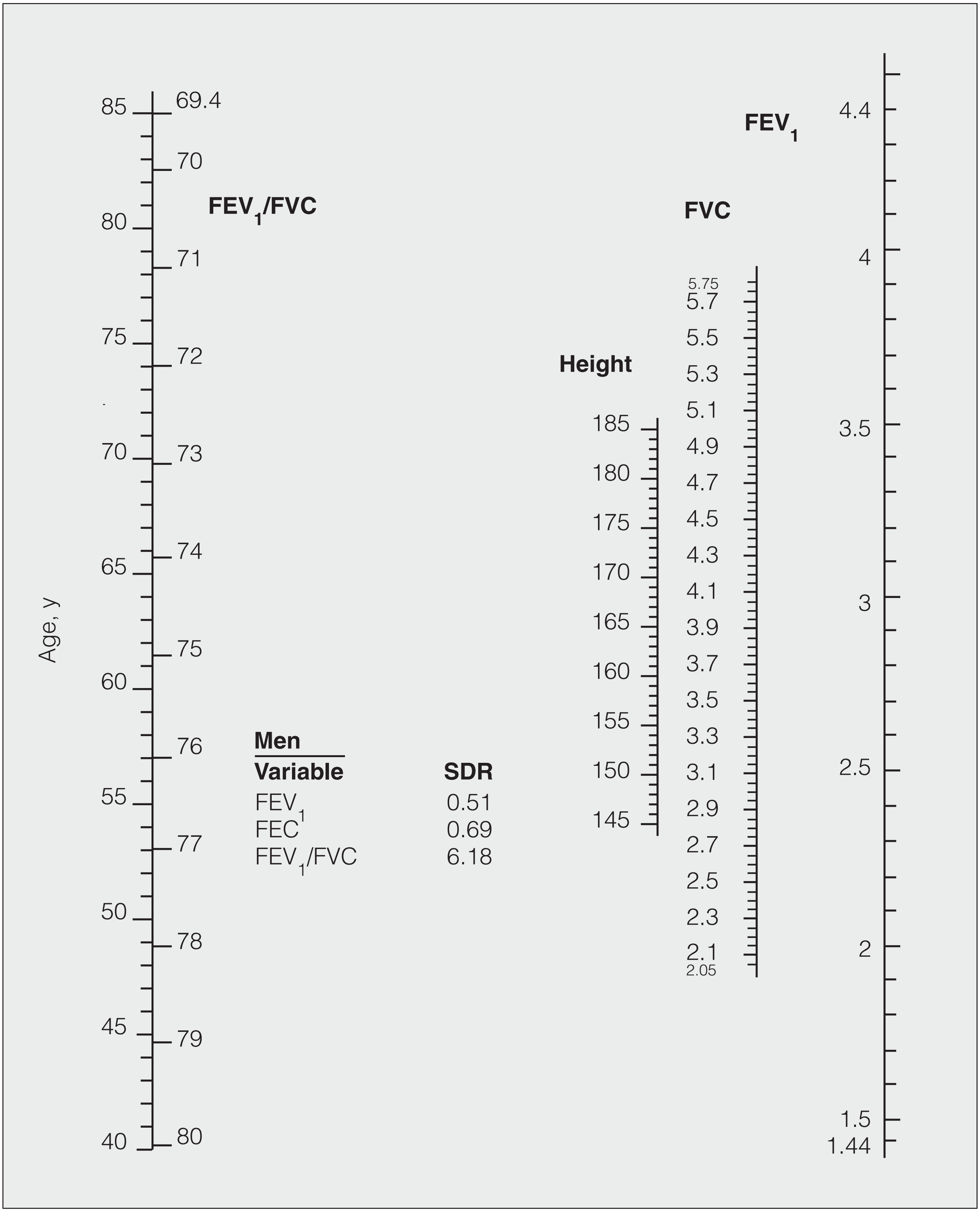

Figure 1. Nomogram to calculate spirometric variables—forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC—from age and height in men. To obtain FEV_1 and FVC, place a ruler passing through the age and height of the subject, and read the corresponding predicted value on the scales on the right of the graph. FEV_1/FVC is read on the scale adjacent to age. The nomogram of FEV_1/FVC was generated using the equation based only on age and not on age and height to simplify the results. Both are described in the text. An approximate value for FEV_1/FVC adjusted for age and height can be obtained by dividing the predicted FEV_1 by the predicted FVC taken from the nomogram. SDR indicates SD of the residuals.

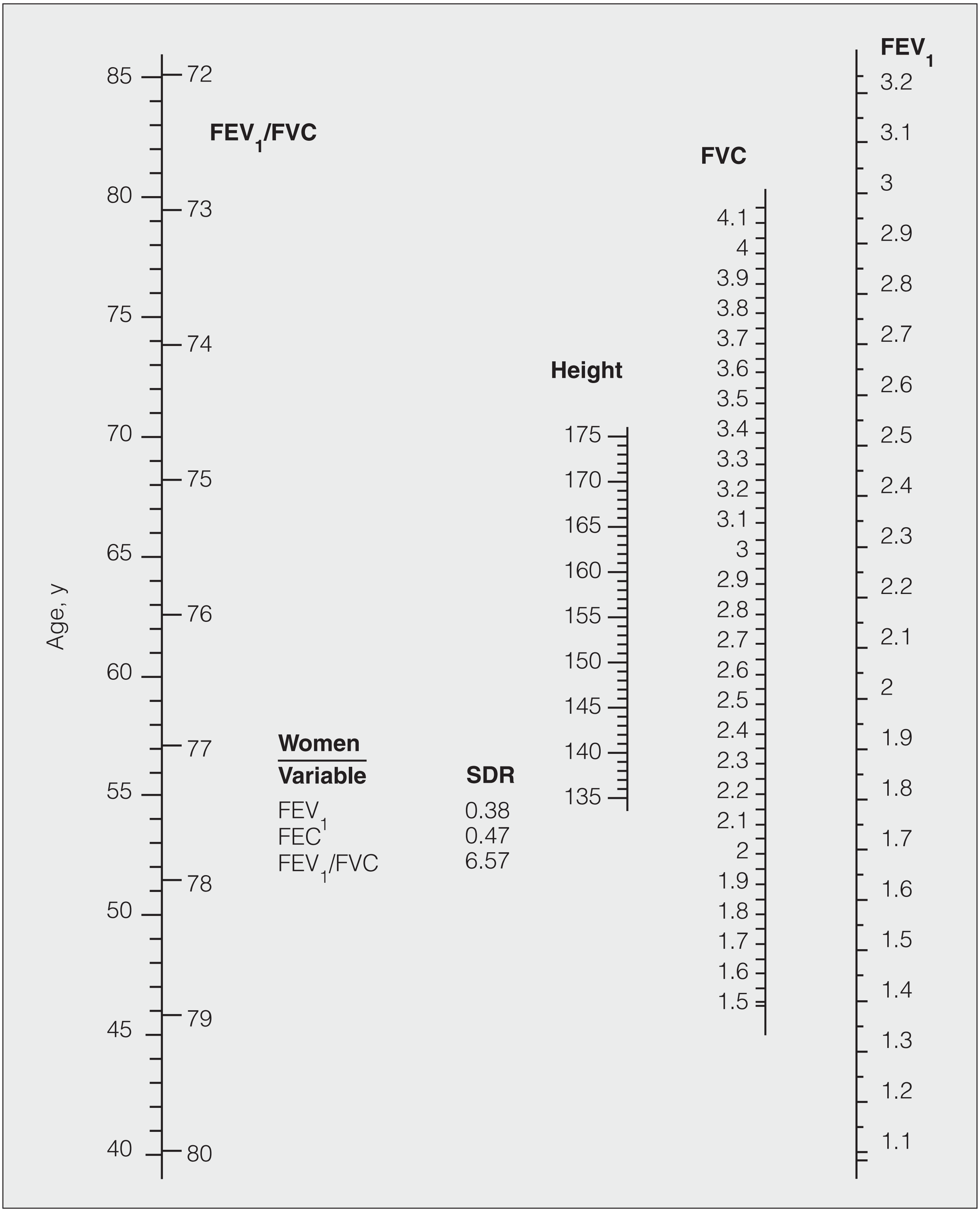

Figure 2. Nomogram to calculate spirometric variables—forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC—from age and height in women. To obtain FEV_1 and FVC, place a ruler passing through the age and height of the subject, and read the corresponding predicted value on the scales on the right of the graph. FEV_1/FVC is read on the scale adjacent to age. The nomogram of FEV_1/FVC was generated using the equation based only on age and not on age and height to simplify the results. Both are described in the text. An approximate value for FEV_1/FVC adjusted for age and height can be obtained by dividing the predicted FEV_1 by the predicted FVC taken from the nomogram. SDR indicates SD of the residuals.

TABLE 6
Spirometry Values (Mean [SD]) for the Study Population, Expressed as Percentage of Predicted According to the Equations of Hankinson et al[23] for Different North American and European Racial Groups*

Variable	Women	Men
FEV_1% predicted for Mexican Americans[23]	100.6 (19.2)	99.6 (16.4)
FVC% predicted for Mexican Americans[23]	102.6 (18.1)	101.9 (17.0)
FEV_1% predicted for African Americans[23]	124.8 (25.6)	116.9 (19.2)
FVC% predicted for African Americans[23]	128.2 (25.6)	120.5 (20.0)
FEV_1% predicted for European Americans[23]	99.9 (18.9)	100.2 (16.5)
FVC% predicted for European Americans[23]	100.8 (18.0)	100.7 (16.8)
FEV_1% predicted according to Knudson et al[25]	104.7 (17.6)	107.9 (17.7)
FVC% predicted according to Knudson et al[25]	109.8 (17.7)	111.6 (18.3)
FEV_1% predicted by Crapo et al[26]	102.4 (17.9)	95.0 (15.4)
FVC% predicted by Crapo et al[26]	107.8 (18.0)	100.4 (16.6)
FEV_1% predicted for Europeans, Quanjer[27]	112.0 (20.6)	104.2 (16.8)
FVC% predicted for Europeans, Quanjer[27]	120.9 (21.1)	109.9 (17.8)
FEV_1% predicted for Europeans, Roca et al[29]	99.1 (18.9)	95.2 (14.7)
FVC% predicted for Europeans, Roca et al[29]	99.2 (15.6)	96.2 (14.9)
FEV_1% predicted for subjects aged over 65 years, Enright et al[30]	103.6 (23.8)	97.6 (17.0)
FVC% predicted for subjects aged over 65 years, Enright et al[30]	107.6 (22.0)	97.6 (18.7)

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity.
The sample (n=906) comprised 635 women and 271 men. However, the means and SD were estimated for subjects within the age ranges used to generate the reference values. These age ranges were 85 years or younger for NHANES III[23]; 80 years or younger for Knudson et al[25] and Quanjer[27]; 70 years or younger for Roca et al[29]; 65 years to 85 years for Enright et al[30]; and 84 years or younger for Crapo et al.[26]

values, which were generally calculated for convenience samples and with different devices and techniques. The quality of the tests was excellent. On the other hand, the study population was aged over 40 years—a drawback in that there is no information on peak lung function, which would have been attained when the subjects were in their 20s. However, this drawback is not really relevant to many applications, such as assessment of pulmonary obstruction and COPD, which almost always present in subjects aged over 40 years. In fact, the study population included subjects as old as 90 years, which represents a considerable advantage with respect to previous studies.

The population that met the criteria for good respiratory health amounted to approximately one fifth of the total sample. This population was too small to attempt to break down the equations further by city. Given the extensive resources required to generate representative samples of the population, the current values could be used until a region or country has sufficient resources available to obtain a larger sample.

Latin America contains a large population of several ethnic origins, and a substantial proportion of this population lives at high altitude.[32] Race is known to influence lung function, the clearest example being blacks, whose mean spirometric values are 12% lower than those of white subjects of a similar height. The differences between Mexican Americans and Caucasians in the United States are much smaller than those between African Americans and Caucasians. The differences between Mexican Americans and Caucasians were nonetheless large enough warrant different spirometric equations in the NHANES III.[23] It might be expected that lung function would vary in Latin America according to the contribution from different ethnic groups to the population mix in an area, the height above sea level, and other possible differentiating environmental factors. For example, São Paulo and Caracas have a higher proportion of blacks whereas Caucasians are more strongly represented in Santiago and Montevideo, and Mexico has a greater indigenous component and is also situated at 2.2 km above sea level. Unfortunately, the size of the population in good respiratory health was too small as defined to carry out a more detailed analysis of the variations in lung function by city, height, and race. Certain differences were identified, however, that would be worth studying in more detail in the future. For example, it was not clear why FVC in Santiago and Montevideo tended to be higher than in other cities, or

TABLE 7
Percentage of Healthy Subjects in the Present Study Who Were Below the Lower Limit of Normal (LLN) According to a Selection of Spirometric Reference Studies*

Studies	Women (%)		Men(%)	
	FEV_1 Below LLN	FVC Below LLN	FEV_1 Below LLN	FVC Below LLN
Knudson et al[25]	1.9	0.1	2.2	0
Quanjer[27]	2.4	0.2	4.4	0
Crapo et al[26]	5.8	0.3	11.4	0.3
Roca et al[29]	7.7	0.3	15.5	1.1
NHANES III[23]				
Whites	7.6	6.6	11.4	10.7
Mexicans	8.2	8.7	9.6	10.7
Blacks	0.6	0.6	1.5	1.8
Enright et al[30]				
(>65 years)	8.0	0.5	9.4	0
Current study	4.6	3.9	5.2	5.5

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity.
In total, 635 women and 271 men were included in our study. However, the estimates come from healthy subjects within the age ranges used to generate the reference values. These age ranges were 80 years or younger for Knudson et al,[25] Quanjer,[27] and NHANES III[23]; 70 years or younger for Roca et al[29]; 65 to 85 years for Enright et al[30]; and 84 years or younger for Crapo et al.[26]

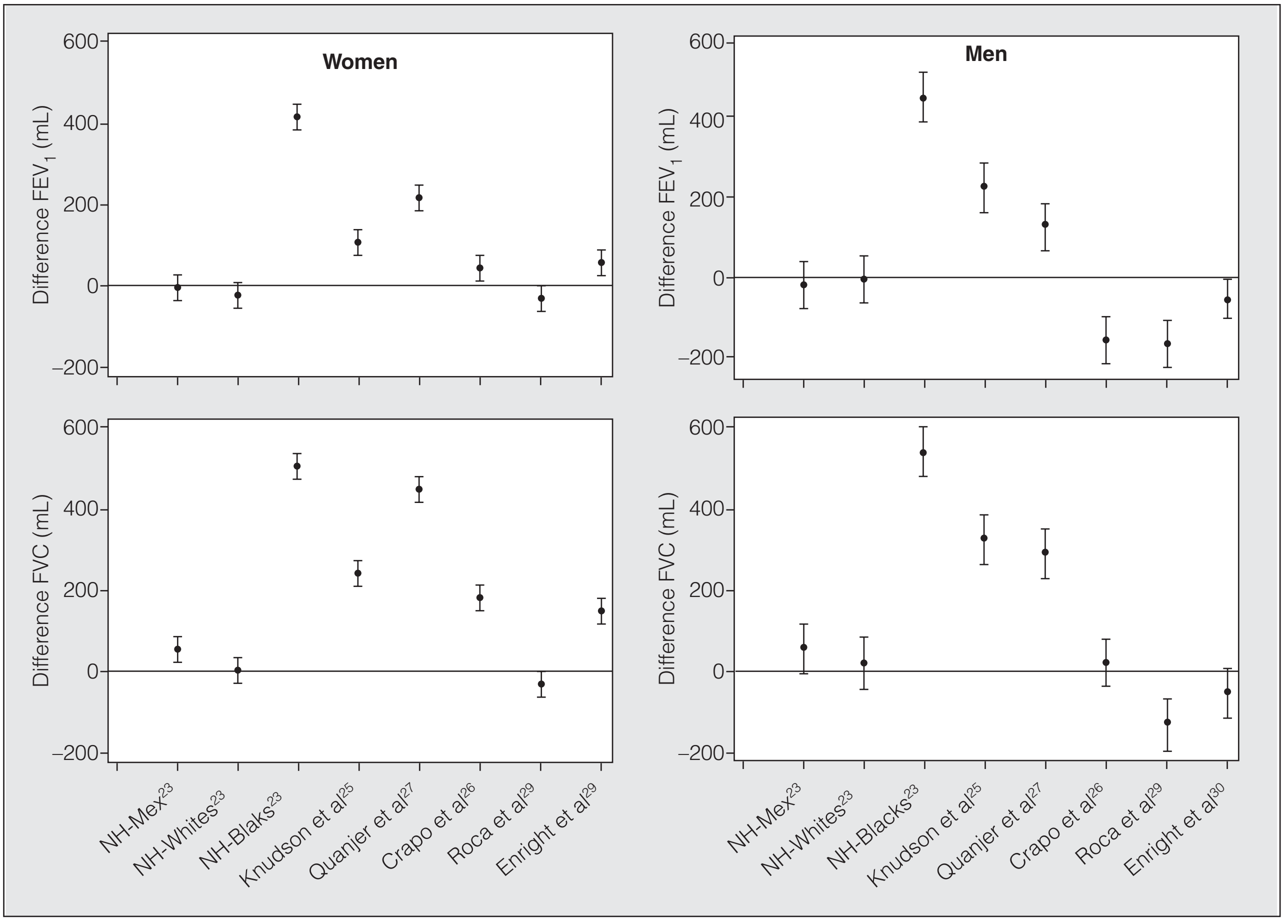

Figure 3. Mean differences (mL) between spirometric values in our study population and predicted values according to different reference studies (actual spirometric value-value predicted by reference equation), with 95% confidence intervals for women and men. The differences in forced expiratory volume in 1 second (FEV_1) are shown in the upper panels and differences in forced vital capacity (FVC) in the lower panels. Reference values are specified on the horizontal axis. NH indicates National Health and Nutrition Evaluation Survey III published by Hankinson et al[23] for Mexican Americans (Mex), Whites, and Blacks.

why FEV_1/FVC tended to be higher in Mexico. PEF rate increases with altitude because of the lower air density,[33,34] and a nonsignificant trend to that effect was reflected in our study. White et al[35] found that lung function increased with altitude (greater FEV_1 and FVC). More recently, subjects of the same ethnic origin were observed to have higher values of FEV_1 and FVC at high altitude compared to sea level.[36,37] In the study by Wood et al,[36] an increase in FEV_1/FVC implied better airway function. These associations were not significant in the population chosen for reference values in the present study, although this is not surprising given that this population represented only 17% of the overall sample. A more permissive definition of respiratory health, for example, one that did not exclude obese subjects, would have resulted in a larger sample (1330 subjects), and the association with altitude seen in other studies would have been obtained. This association would, however, still only explain a small part of the variation in lung function once age, height, and sex had been accounted for. The same applies to the contribution of the variables city and race in our study. Both smoking and obesity are important problems in Latin America and both negatively affect lung function. It is therefore desirable that reference values be sensitive to changes in lung function in smokers and obese subjects. Exclusion of these subjects from the calculation of the reference values helps ensure that such sensitivity is attained.

The LLN is often defined as a fixed percentage of the mean value or the predicted value. Often, 80% is used as the lower limit for FEV_1 and FVC, and 90% for FEV_1/FVC. Such an approach assumes that the data dispersion (SD) decreases in subjects with lower spirometric values, that is, in older and shorter subjects, whereas it actually remains constant. Thus, LLN expressed as a percentage of the mean also varies. Moreover, in the present study, which included adults 40 years old or more and many elderly subjects, LLN was considerably less than 80%. For example, in our study, the mean LLN was 72% for FEV_1, 72% for FVC, 73% for FEV_6, 86% for FEV_1/FVC, 89.6% for FEV_1/FEV_6, 70% for PEF, and 39% for $FEF_{25\%-75\%}$ but with sex-, age-, and height-dependent variations. Therefore, it is more appropriate to use the fifth percentile as the LLN. This value can be approximated by subtracting 1.645 times the SD from the predicted mean value (Tables 4 and 5 and Figures 1, 2, and 3).

Spirometry will become more widespread if the methods are simplified. To this end, a single set of reference equations would be of help. The main problem with spirometry at present is that it is underused in medical practice. Therefore, rational use of this technique should be encouraged, something that should include comparison with appropriate reference values. For example, the values of Knudson et al[25] are still widely used even though they reported a value for FEV_1 that was 6% higher than our reference value and a value for FVC that was 10% higher than our reference value. Likewise, the European equations of Quanjer[27] are inappropriate, particularly for women. We think that, despite the limitations described, the values proposed represent an advance that will no doubt contribute to better use of spirometry in Latin America. For interested readers, the tables generated with the reference equations are available in electronic form and as a program for palmtop devices.[38]

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