Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Original Research

Re-Defining Lower Limit of Normal for FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6 and FEV_3/FVC to Improve Detection of Airway Obstruction

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Abstract

Background: Spirometric values of 5880 never-smoking black, Latin, and white men and women in the Third National Health and Nutrition Examination Survey (NHANES-3) reference population were reviewed. Good published equations for forced expiratory volume in 1 second (FEV_1) over forced expiratory volume in 6 seconds (FEV_6) and FEV_1 over forced vital capacity (FVC) often significantly mis-identified the lower limit of normal (LLN) targets in both younger and older adults. To improve detection of smaller airways disease in adults, we wished to redefine the LLN for these ratios and develop new ones for forced expiratory volume in 3 seconds (FEV_3)/FEV_6 and FEV_3/FVC.

Methods: In each of 6 ethnic/gender, never-smoking NHANES-3 groups, arranged sequentially by age from 20.0 to 79.9 years, the values of FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6, and FEV_3/FVC were placed in groups of 40 so that the actual lowest second (5%) ratios could be identified. The slopes and intercepts of the resulting 24 linear equations through these lowest 5% ratios were then each adjusted by multiple iterations to best identify equations which actually identified the lowest 5% in both younger and older adults.

Results: In all never-smokers, the new equations were closer to the 5% LLN targets than were those of Hankinson for FEV_1/FEV_6 and FEV_1/FVC and Quanjer for FEV_1/FVC. In 3508 NHANES-3 current smokers, the FEV_3/FEV_6 and FEV_3/FVC identified significantly more values below LLN than the FEV_1/FEV_6 and FEV_1/FVC.

Conclusion: New simple linear iterative equations for FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6, and FEV_3/FVC to identify LLN are offered. None require exponents or logarithms. The latter 2 detected more abnormalities in current-smokers and likely better identify small airways disease in adults.

Abbreviations: forced expiratory volume in 1 second, **FEV_1**; forced expiratory volume in 3 seconds, **FEV_3**; forced expiratory volume in 6 seconds, **FEV_6**; forced vital capacity, **FVC**; lower limit of normal, **LLN**; Third National Health and Nutrition Examination Survey, **NHANES-3**; forced expiratory flow at 25%-75% of the forced vital capacity, **$FEF_{25-75\%}$**; forced expiratory flow at 25% of the forced vital capacity, **$FEF_{25\%}$**; forced expiratory flow at 50% of the forced vital capcity, **$FEF_{50\%}$**; forced expiratory flow at 75% of the forced vital capacity, **$FEF_{75\%}$**

Funding Support: No outside funding received.

Date of Acceptance: December 4, 2014

Citation: Hansen JE, Porszasz J, Casaburi R, Stringer WW. Re-Defining lower limit of normal for FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6 and FEV_3/FVC to improve detection of airway obstruction. *J COPD F*. 2015; 2(2): 94-102. doi:http://dx.doi.org/10.15326/jcopdf.2.2.2014.0144

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Keywords:

spirometry; airway obstruction; small airways disease; lower limit of normal

Introduction

After the introduction of spirometry by Hutchinson[1] in 1846 and forced expiratory maneuvers by Tiffeneau[2] in 1947, the ratios of FEV_1/FVC became the standard criterion for establishing the presence of airway obstruction. Because the ranges of absolute forced expiratory timed-volumes found in apparently normal individuals of the same gender, age, height, and ethnicity are so high, less-variable ratios of these same timed-volumes are advantageous.[3] The more recently introduced FEV_1/FEV_6[4-7] has the major advantage of avoiding the variability of the FVC duration inherent in the FEV_1/FVC. The extremely high inherent variability of the forced expiratory flow at 25%-75% ($FEF_{25-75\%}$), (and to a lesser extent the forced expiratory flow at 25% [$FEF_{25\%}$,] forced expiratory flow at 50% [$FEF_{50\%}$] and forced expiratory flow at 75% [$FEF_{75\%}$]) because both time and flow vary, has limited their utility. The FEV_3/FVC[8-13] has been less studied and the FEV_3/FEV_6 apparently not at all. Could the latter ratios be more specific and sensitive than the FEV_1/FEV_6 and FEV_1/FVC in detecting airway obstruction?

Traditionally, lower 95% confidence intervals calculated from mean values and their variability have been used to define the lower limits of normal (LLN) of the FEV_1/FVC.[14] Because the distribution of abnormalities has usually been considered *normal*, these LLN have been calculated from age-declining FEV_1/FVC predicted mean values less 1.645 times the standard deviation (SD) of reference populations (apparently healthy and never-smoking) to define the 5% likelihood of airway obstruction in other individuals of the same age, gender, and ethnicity.[3-14] Recently, Quanjer and colleagues,[15] in a major advance, took into account the asymmetry of distribution of several spirometric values plus the differences between ethnicities. Their published equations (each with approximately 20 coefficients) assess many spirometric values, but, unfortunately, do not include any important ratios other than FEV_1/FVC.

Therefore, suspecting that these older ratios might not optimally target borderline individuals across the full adult age span and that FEV_3/FEV_6 and FEV_3/FVC might better define slower emptying airways, we wished to define the LLN for the FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6, and FEV_3/FVC ratios so that those ratios could be better utilized to validly compare the sensitivity and specificity of these spirometric ratios. Finally, we realized that multiple iterative techniques (changing the slope and intercept values) allowed us to best define LLN spirometric ratio equations as close as possible to 5% for each age, ethnicity, and gender.

Initially, using the original values of the best FEV_1, FEV_3, FEV_6, and FVC from the Third National Health and Nutrition Examination Survey (NHANES-3) databases of apparently healthy never-smokers, we were able to calculate, graph, tabulate, and identify the exact number of lowest 5% of values of the ratios of FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6, and FEV_3/FVC for each ethnic/gender group by age.[16] Then, multiple iterations identified new LLN ratio equations to target, by age, ~5% of the never-smoking reference population of each equation as abnormal. We hypothesized that these new equations might better identify airway obstruction in individuals and populations.

Methods

Study population: De-identified digital records of the informed-consent volunteers of NHANES-3 were obtained which included age, ethnicity, gender, height, weight, smoking and other history, measurements relating to their health and diet, and spirometric values of highest peak flow, FEV_1, FEV_3, FEV_6, and FVC.[16] As can be seen in Table 1, the number of individuals in ethnic/gender/age groups differed widely. The spirometric values of the 6 groups, identified as black, white or Latin men or women had been used in 2 Hankinson and co-authors articles[4,7] and our prior publications.[10,11] Because selection criteria for normalcy may have differed minimally, the 5880 apparently healthy, never-smoking reference individuals selected in this study differed slightly from those selected in the Hankinson publications.[4,7] Since the results of the 2 Hankinson publications for LLN values for FEV_1/FEV_6 were nearly identical (see below); the original[4] ratio equations were ultimately used. For comparisons with current-smokers, spirometric measures from 3508 NHANES-3 current-smokers without other identifiable diseases were

Table 1. Number of Adult Reference Never-smokers in Each Group of the Third National Health and Nutrition Examination Survey

Decade of Age	3rd	4th	5th	6th	7th	8th	SUM
Black Men	285	144	90	34	50	24	627
Black Women	370	304	191	97	103	76	1141
White Men	181	178	113	83	119	90	764
White Women	224	272	209	220	201	288	1414
Latin Men	303	165	95	46	70	18	697
Latin Women	426	312	199	85	158	57	1237
SUM	1789	1375	897	565	701	553	5880

utilized.[17]

Processing of data: For each set of ratios (FEV_1/FEV_6, FEV_1/ FVC, FEV_3/FEV_6, or FEV_3/FVC), for each of the never-smoking 6 ethnic/gender groups from ages 20.0 to 79.9 years, we sequentially arranged in groups of 40 each never-smoker by age in EXCEL spreadsheets. Since 5% of 40 is 2, we sorted each group from high to low and selected the second lowest ratio value to represent the LLN for the median age of each group of 40. The 20th lowest ratio was designated the median of the 40. Linear regression equations derived from the intercepts and slopes of the lowest 5% were calculated and plotted. Invariably these initial equations identified less than 5% of all individuals in each ethnic/gender ratio group and were modified by an iterative process.

Therefore, a multiple iterative process (each time changing the slope and/or intercept and reevaluating the fit of the new equation with the actual data) up to 20 times was used to identify a single linear equation that best identified the lowest 5% in both ages ≥45 years and <45 years. These new linear equations (using the best intercept and slope of each ethnic/gender/ratio group) were utilized to identify and visualize the full distribution of values including the exact number and percentage of individual values in the lowest 5% of each group of 40 individuals.

Comparing equations for individuals in the ethnic/ gender groups: The original Hankinson, Odenkrantz, Feder[4] FEV_1/FVC and FEV_1/FEV_6 equations were used, since results from the FEV_1/FEV_6 equations[4] were nearly identical to those of the Hankinson, Crapo, Jensen[7] equations and visually overlaid them graphically. Similarly, the FEV_1/FVC, mean and LLN values from the Quanjer equations[15] were calculated for each individual. Comparisons were then made using: 1) all new iterative equations for LLN values for younger and older individuals in the 6 ethnic/ gender groups; 2) the Hankinson equations[4] for the mean and LLN FEV_1/FEV_6 and FEV_1/FVC; 3) the Quanjer[15] equations for mean and LLN FEV_1/FVC; and 4) the Hansen, Sun, and Wasserman[10] equations for mean FEV_1/FVC, to detect *abnormal* ratios in never-smoking versus current-smoking populations.

Statistical analyses: χ^2 analyses were used to compare the number of abnormal ratios between groups with a $p<0.05$ considered significant.[18]

Results

Population and repeated iterative equations: Table 1 reveals the wide spread in the number of never-smokers in each NHANES-3 ethnic/gender/decade cell and the relative paucity of older individuals in the black and Latin groups. Table 2 shows the 24 equations developed by multiple iterations which best delineated approximately 5.0% of each group as <LLN for that group.

Comparing FEV_1/FEV_6 equations: As an example, Figure 1 shows the FEV_1/FEV_6 data for never-smoked, white women in groups of 40. The regression lines for the LLN as calculated by Hankinson et al[4,7] equations graphically overlap and differ visually from our iterative

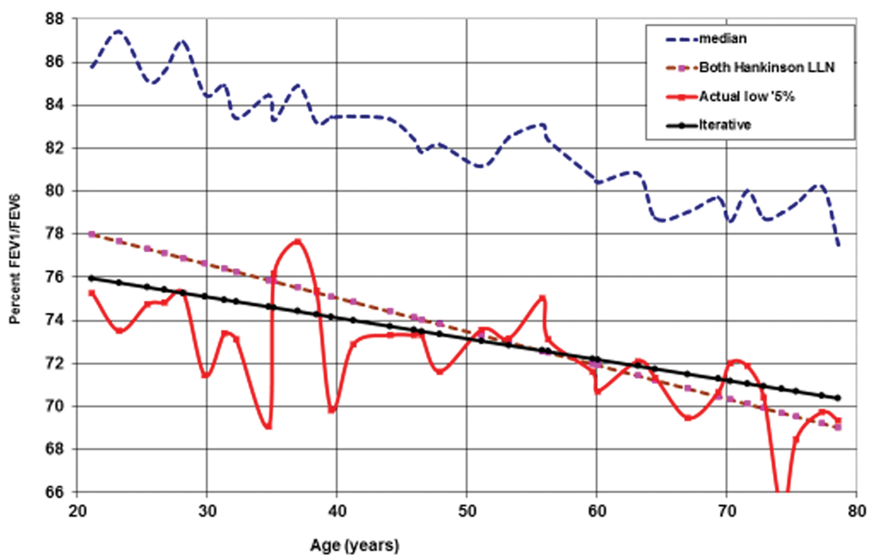
Table 2. Twenty-Four New Adult Iterative Equations Developed Using NHANES-3 Never-Smoking, Apparently Healthy Individuals

Ethnic/ Gender	n	$\%FEV_1/FEV_6$	$\%FEV_1/FVC$	$\%FEV_3/FEV_6$	$\%FEV_3/FVC$
Black Men	627	76.15	76.8	96.65	98.0
		-0.085	-0.194	-0.094	-0.24
Black Women	1141	81.5	84.6	97.8	100.7
		-0.15	-0.301	-0.11	-0.28
White Men	764	73.8	74.5	96.45	95.5
		-0.045	-0.12	-0.085	-0.18
White Women	1414	78.0	80.2	98.15	101.5
		-0.097	-0.214	-0.112	-0.287
Latin Men	697	78.9	80.0	97.6	98.7
		-0.104	-0.225	-0.111	-0.24
Latin Women	1237	82.2	85.0	98.4	101.5
		-0.15	-0.29	-0.117	-0.30

Regression equation: Y= mx + b; where x is age (years), m is the slope (lower cells), and b is the Y intercept (upper cells).
NHANES-3 = Third National Health and Nutrition Examination Survey

equation. For those <45 years, 44 of 618 (7.1%) are *abnormal* using the Hankinson[4] equation while 29 of 618 (4.69%) are *abnormal* using our iterative equation. Contrastingly, for those ≥45 years, only 30 of 796 (3.8%) are considered *abnormal* using the Hankinson[4] equation while 41 of 796 (5.15%) are *abnormal* using our new iterative equation. Consequently, the number of *abnormal* younger versus *abnormal* older differs significantly from the iterative equation ($\chi^2 = 4.68$, $p<0.05$). Table 3 also shows the similarity of the 2 Hankinson sets of equations in identifying the percentage of never-smoking individuals <LLN in the 6 ethnic/gender groups, the significant differences in younger versus older men and women and the differences from the iterative equations. Graphically, the 6 paired Hankinson equations visually overlie each other. Thus, logically, the original LLN equations[4] for FEV_1/FEV_6 and FEV_1/FVC were also based on predicted means for any age less 1.645 times the SD as used in the latter publication.[7] In Table 3, both pairs of Hankinson's equations result in more mean and SD variability from the desired LLN mean of 5.0% (6.15±1.06%, 4.04±1.04%, 6.03±1.20%, and 4.34±1.08%) than the iterative equations (4.62±0.56% and 4.95±0.29%). The total numbers of never-smokers < age 45 considered abnormal by either sets of Hankinson equations[4,7] are significantly higher ($\chi^2 = 8.56$, $p<0.01$) than those identified as abnormal by the new iterative equations.

Figure 1. Development of Iterative Equations for Spirometric Ratios



Never-smoking NHANES-3 white women by age versus median and percentage *abnormal* FEV_1/FEV_6 ratios. Dashed blue = median; solid red with solid squares = 5% lowest ratios; dashed with small lavender squares = Hankinson, et al[4] and Hankinson et al[7] lower limit of normal equations which overlie each other; solid black with symbols signifying each group of 40 participants = new LLN iterative equation. The LLN lines for the Hankinson and iterative equations cross at age 55 so that in the reference population there are fewer younger and added older participants considered abnormal using the Hankinson equations. Consequently there are added younger and fewer older patients suspected of having airway obstruction targeted as abnormal using the Hankinson FEV_1/FEV_6 equations.

Comparing FEV_1/FVC equations: Overall, Table 4 indicates that younger versus older adults frequently have significant LLN differences using either the Hankinson (4 of 6) or Quanjer (3 of 6) equations. As an example of a group with lesser differences, Figure 2 shows the individual FEV_1/FVC values in never- and current-smoking Latin men plus the predicted means and LLN for the Hankinson[4] and, Quanjer[15] equations and the Hansen, Sun, Wasserman[10] equation for mean and the new iterative equations for LLN. It is noteworthy that, though all equations show a decline in the ratio with age, the Quanjer mean equation (which includes height as a variable) is mildly concave upwards while the Quanjer LLN equation is mildly concave downwards. Thus, in this group, the differences between mean and LLN values are not constant but clearly increase with advancing age. The Hankinson LLN equation values for Latin men are consistently higher than those of the

Table 3. FEV_1/FEV_6: Comparison of Percentage of Abnormal Individuals Detected in the Same NHANES-3 Never-Smoking Population Using Three Sets of Equations[4,7] and New Iterative Equations for Each Ethnic/Gender Group

Ethnic/ Gender Group	Y Intercepts (%) + Slopes (age constants times years)[4]		Y Intercepts (%) + Slopes (age constants times years) - SD times 1.645[7]		New Iterative: Y Intercepts (%) + Slopes (age constants times years)	
	< 45 years	≥45 years	< 45 years	≥45 years	< 45 years	≥45 years
Black Men	7.1	5.3	7.1	5.3	4.5	4.71
Black Women	4.2	3.8	4.1	3.5	5.5	4.71
White Men	6.7	2.4[a]	6.7	2.4[a]	4.03	5.34[d]
White Women	7.1	3.8[b]	7.4	3.8[b]	4.69	5.15
Latin Men	6.1	4.1	5.9	3.9	4.05	4.65
Latin Women	6.0	4.9	5.4	4.3	4.97	5.12
Mean	6.15	4.04[c]	6.03	4.34[b]	4.62[e]	4.95
SD	1.06	1.04	1.20	1.08	0.56	0.29

NHANES-3 = Third National Health and Nutrition Examination Survey
By χ^2:; comparing pairs of <45 years values to ≥45 years values,
[a] $p < 0.05$
[b] $p < 0.01$
[c] $p < 0.001$
comparing new iterative to others
[d] $p < 0.05$
[e] $p < 0.01$

Table 4. FEV_1/FVC: Comparison of Percentage of Abnormal Individuals Detected in the Same NHANES-3 Never- Smoking Population Using Three Sets of Equations[4,15] and New Iterative Equations for Each Ethnic/Gender Group

Ethnic/ Gender Group	Intercepts (%) + Slopes (age constants times years)[4]		Complicated, Using Up to 20 Constants[15]		Intercepts (%) + Slopes (age constants times years)	
	< 45 years	≥45 years	< 45 years	≥45 years	< 45 years	≥45 years
Black Men	6.05	12.21[a]	4.64	9.16[a]	4.23	5.34
Black Women	3.88	7.35[a]	3.00	5.59[a]	4.38	5.29
White Men	6.90	2.91[a]	5.24	2.62	5.24	4.65
White Women	6.47	6.53	3.88	4.52	5.02	4.90
Latin Men	5.88	6.47	3.23	4.12	4.55	4.71
Latin Women	4.85	8.89[b]	2.54	4.85[a]	4.97	4.85
Mean	5.67	7.40[b]	3.75	5.15[a]	4.71	5.03
SD	1.12	3.07	1.03	2.20	0.33	0.29

NHANES-3 = Third National Health and Nutrition Examination Survey
Comparing pairs of <45 years values to ≥45 years values,
[a] $p < 0.05$
[b] $p < 0.001$ by χ^2, other pairs not significantly different

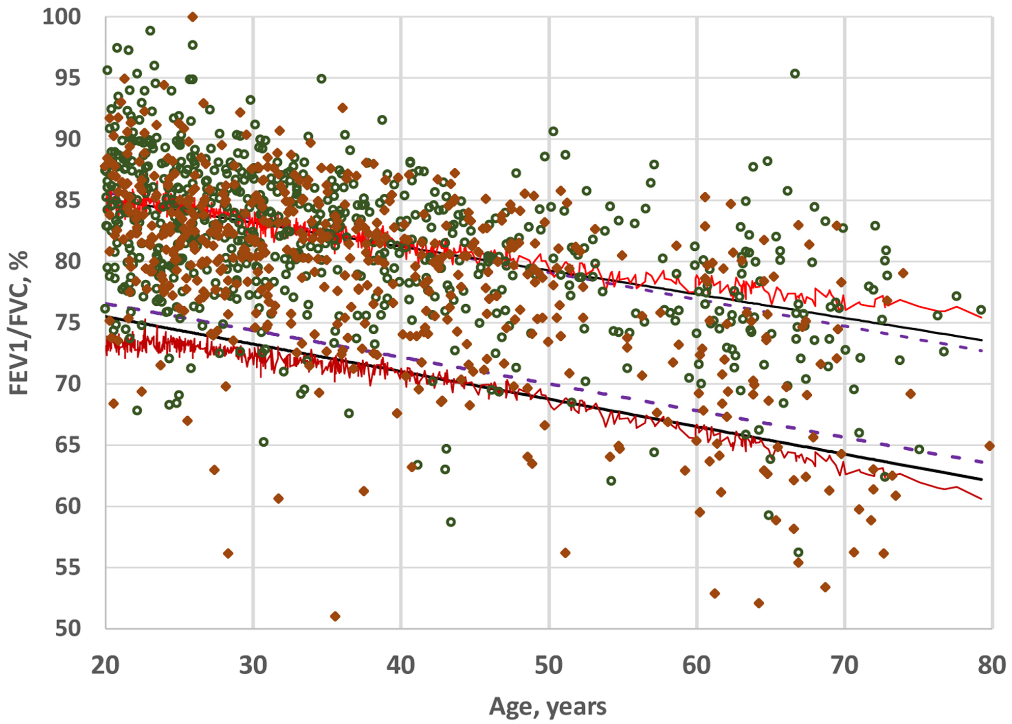
intermediately positioned iterative equation. Further, in all 6 groups, but not shown, at ages 25, 35, 45, 55, 65, and 75 years, the Hankinson equations[4] have the highest LLN values 5/6 of the times, the Quanjer et al equations[15] have the lowest LLN values 5/6 of the times, while the iterative equations give intermediate LLN values 4/6 of the times, suggesting that the iterative equations are the best available to compare spirometric ratios.

Comparing all iterative ratio equations: Table 5. Assessing current-smokers, not surprisingly, the numbers (and percentages) of smoking-individuals below the LLN is much higher in the older (24.5% to 28.5%) than younger (8.5% to 10.5%) age groups ($p<0.001$). Importantly, there are significantly higher numbers and percentages of smokers below the LLN for the FEV_3/FEV_6 and FEV_3/FVC ratios, respectively, than for the FEV_1/FEV_6 (14.4%, $\chi^2=5.53$, $p<0.05$) and FEV_1/FVC (18.6%, $\chi^2 = 9.12$, $p<0.01$).

Discussion

Summary of the challenge:
Admittedly, if the LLN of a population is set at exactly 5.0%, it is impossible to

Figure 2. FEV_1/FVC Values of Never-smoking and Current-smoking Latin Men by Age



The green open circles are never-smokers, the solid red diamonds are current-smokers. Shown in upper part of figure are the means of predicted FEV_1/FVC by Quanjer[15] (wavy red), Hansen[10] (solid black), and Hankinson[4] (dashed lavender), and, lower in figure, with the same colors, the LLNs predicted by Hankinson, iterative process, and Quanjer. As years of age increase, the Quanjer mean equation is concave upward while Quanjer LLN equation is concave downward. The Hankinson equations are parallel. The iterative mean and LLN equations are located between the Quanjer and Hankinson equations.

find exactly 5.0% below that level in a group or subgroup of a reference population if the number of individuals is not divisible by 20 into a whole number. Advantageously, Quanjer and his colleagues[15] recognized that the distributions of values about the means of reference population were not exactly normal and that their mean and LLN equations were not necessarily parallel (Figures 1 and 2). Excellent as they are, their published equations do not define important spirometric ratios other than the FEV_1/FVC; they are also more subject to calculation error since each equation requires approximately 20 coefficients and natural logarithms. Hankinson's equations and our iterative equations for FEV_1/FEV_6 and FEV_1/FVC LLN are simpler but omit using height as a predictor. Hankinson's LLN FEV_1/FEV_6 and FEV_1/FVC equations[4,7] are all parallel to the mean ratio equations because they are based on mean values –1.645 times the SD. Although they may at times approximate 5% *abnormal* values across the full age range in a reference population, their range of percentage abnormalities of 3% to 10% or more in younger or older ages of the reference populations (Tables 3 and 4) results in lowered reliability in defining and judging abnormalities in other populations and in comparing other ratio formulas. Therefore, new simple LLN linear equations for FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6, and FEV_3/FVC are likely to be advantageous in comparing the relative value of several spirometric ratio equations in detecting airway obstruction.

Significance of the findings: In order to compare the validity of different ratios to identify *abnormalities* or differences in a targeted population from the normal distribution of these same ratios in a reference population, the reference population variables should select as close as possible to 5% of individuals below the LLN of their formulas along the entire age span. As noted, this is not an easy task. Using standard methods of calculating the LLN (mean –1.645 times the SD) is likely invalid since in multiple ethnic/gender groups Quanjer's[15] FEV_1/FVC mean and LLN equations uncommonly are parallel. Thus the lowest 5% of any ratio is unlikely to be distributed in a line parallel to that of the mean [Figure 2]. The multiple iterative but simple LLN spirometric ratios developed in this study are linear, and do not require squares or logarithms of age or height or the addition of weight variables in order to define the lower 5% of the never-smoking population reasonably well.

The variability of absolute values of FEV_1, FEV_3, FEV_6, and FVC in individuals of a specific height, gender, ethnicity, and age is high, higher than the variability of the ratios of these values.[3] Thus ratios became important in identifying obstructive airways disease.

Table 5. Numbers of NHANES-3 Younger and Older Current-Smokers Below LLN Using New Iterative FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6 and FEV_3/FVC Equations and Quanjer Equations for FEV_1/FVC

n	Group	Iterative FEV_1/FEV_6	Iterative FEV_3/FEV_6	Iterative FEV_1/FVC	Iterative FEV_3/FVC	Quanjer[15] FEV_1/FVC
	Under Age 45 years					
472	Black Men	23	37	35	36	21
441	Black Women	43	46	35	46	49
387	White Men	34	42	46	35	40
438	White Women	55	67	55	70	57
397	Latin Men	25	33	18	34*	25
187	Latin Women	19	18	8	14	18
2322	All < 45 years	199 (8.6%)	243 (10.5%)[a]	197 (8.5%)	235 (10.1%)	210 (9.0%)
	Age 45 years and Older					
233	Black Men	43	65[a]	55	62	47
171	Black Women	33	38	31	31	34
294	White Men	84	101	95	119[a]	108
259	White Women	76	92	78	82	79
154	Latin Men	40	32	32	33	36
75	Latin Women	15	10	14	11	16
1186	All ≥ 45 years	291 (24.5%)[c]	338 (28.5%)[a,c]	305 (25.7%)[c]	338 (28.5%)[c]	320 (27.0%)[c]
	Ages 20.0 to 79.9 Years					
3508	All	490	581 (18.6% more)[b]	502	573 (14.4% more)[a]	530

NHANES-3 = Third National Health and Nutrition Examination Survey
Comparing pairs of FEV_1/FEV_6 with FEV_3/FEV_6 and comparing pairs of FEV_1/FVC with FEV_3/FVC within age groups.
[a] $p < 0.05$
[b] $p < 0.01$ by χ^2; other pairs not significantly different.
Comparing <age 45 years versus ≥ 45 years, [c] $p < 0.001$

For decades, the FEV_1/FVC has been the favored ratio to evaluate obstruction. The more recently introduced FEV_1/FEV_6, though still infrequently used, has high sensitivity and specificity by meta-analysis,[19] has advantages over the FEV_1/FVC in that the latter has a shifting denominator from test to test and laboratory to laboratory - because breath duration times vary - while the FEV_1/FEV_6 has a fixed denominator, is less stressful for patients, and appears to evaluate airway obstruction as well as or better than the FEV_1/FVC when *normality* and *abnormality* are defined according to the bottom 5% as detailed in this paper.

Ratios derived later in forced exhalations have rarely been used, although FEV_3/FVC has been asserted to be of value.[12,13] Many authorities have accepted the assumption that the exponential-like curves seen when expiratory volumes are plotted against time are adequately defined by the FEV_1/FEV_6 or FEV_1/FVC ratios. The possible additional value of FEV_3/FEV_6 and/or FEV_3/FVC has largely been ignored. Because data from large reference or diseased populations for other time points in the exhalation were not available, our decision was to evaluate FEV_3/FEV_6 and FEV_3/FVC ratios. In the NHANES-3 population, it appears that in the detection of abnormal airway obstruction in current-smokers, the FEV_3/FEV_6 is superior to the FEV_1/FEV_6 (18.6% more, $p<0.01$) and the FEV_3/FVC is superior to the FEV_1/FVC (14.4%, $p<0.05$) (Table 5). With further evaluations, we suspect the FVC ratios may be less discriminating than the FEV_6 ratios because of the uniform denominators of the latter.

Limitations: Testing the new equations in other populations would be advantageous. It would be helpful to have larger numbers of healthy older individuals in a reference population. Perhaps an age other than 45 years would be preferable for separating *younger* from *older* smokers. That age was selected since a) age 45, rather than later ages, helps equalize the group sizes and b) the severity of airway obstruction in surviving current-smokers increases significantly in the 5th decade of life.[17] Although the effect of changing the LLN value of ratios a few percentage points away from 5% remains uncertain, it seems likely that in comparing the sensitivity of different spirometric ratios, it is best to use ratios with approximately the same percentage (presumably ~5%) of LLN in the reference population. The evaluation of specificity should be more relevant when the available ratios are compared with non-spirometric evidence of airways disease, such as inspiratory and expiratory chest imaging.

Conclusion: To compare the value of different spirometric ratios in detecting airway disease, the ratios should identify approximately 5% of apparently normal reference individuals as below the LLN throughout the age span being considered. New simple linear iterative equations which do that for FEV_1/FEV_6, FEV_1/FVC, FEV_3/FEV_6, and FEV_3/FVC are offered. The latter 2 likely better identify small airways disease in adults. We suggest that these equations be further tested in routine spirometric evaluation of airway obstruction in adults and that consideration should be given to using FEV_3 ratios as well as FEV_1 ratios.

Acknowledgments

We appreciate the high quality participation of the many volunteer participants, health professionals, and others who assembled and organized these data and the U.S. Department of Health and Human Services which made these data available for us to use. ***Author comments regarding prior publications:*** Some of the NHANES-3 data used in this manuscript have been used for other purposes (i.e. LLN = mean –1.645 times SD) in the following publications:

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Declaration of Interest

JP has received consulting fees from Boehringer Ingelheim.

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