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Chest 2006;129;369-377
DOI: 10.1378/chest.129.2.369

CHEST

Original Research

PULMONARY FUNCTION

Discriminating Measures and Normal Values for Expiratory Obstruction*

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Objectives: **To develop mean and 95% confidence limits for the lower limit of normal (LLN) values for forced expiratory volume in 3 s (FEV_3)/FVC ratio for Latin, black, and white adults; to ascertain comparative variability of the FEV_1/FVC ratio, the FEV_3/FVC ratio, and forced expiratory flow, midexpiratory phase ($FEF_{25–75}$) in never-smoking adults; to evaluate their utility in measuring the effect of smoking on airflow limitation; and to develop and use the fraction of the FVC that had not been expired during the first 3 s of the FVC (1 − FEV_3/FVC) to identify the growing fraction of long-time-constant lung units.**

Design: **Analysis of the Third National Health and Nutrition Examination Survey (NHANES III) database of never-smokers and current smokers.**

Participants: **A total of 5,938 adult never-smokers and 3,570 current smokers from NHANES III with spirometric data meeting American Thoracic Society standards.**

Measurements and results: **After establishing new databases for never-smokers and current smokers, we quantified the mean and LLN values of FEV_3/FVC in never-smokers, and identified spirometric abnormalities in current smokers. When associated with older age, FEV_3/FVC decreases and 1 − FEV_3/FVC increases as FEV_1/FVC decreases. On average, using these measurements, the condition of current smokers worsened about 20 years faster than that of never-smokers by middle age. If < 80% of the mean predicted $FEF_{25–75}$ was used to identify abnormality, over one quarter of all never-smokers would have been falsely identified as being abnormal. Using 95% confidence limits, 42% of 683 smokers with reduced FEV_1/FVC and/or FEV_3/FVC would have been judged as normal by $FEF_{25–75}$.**

Conclusions: **FEV_1/FVC, FEV_3/FVC, and 1 − FEV_3/FVC characterize expiratory obstruction well. In contrast, $FEF_{25–75}$ measurements can be misleading and can cause an unacceptably large number of probable false-negative results and probable false-positive results.**

(CHEST 2006; 129:369–377)

Key words: demographic analysis; FEV_3/FVC; forced expiratory flow rates; obstructive airways disease; reference values; smoking; spirometry

Abbreviations: ATS = American Thoracic Society; $FEF_{25–75}$ = forced expiratory flow, midexpiratory phase; FEF_{75} = instantaneous flow after 75% of the FVC has been exhaled; FEV_3 = forced expiratory volume in 3 s; 1 − FEV_3/FVC = fraction of the FVC that had not been expired during the first 3 s of the FVC; FEV_6 = forced expiratory volume in 6 s; LLN = 95% confidence limits for the lower limit of normal; NHANES III = Third National Health and Nutrition Examination Survey

Since Hutchinson introduced spirometry in 1846,[1] a multitude of measurements, including volumes, flows, time constants, and ratios, have evolved to assess normalcy and disease. Five decades ago Lueallan and Fowler[2] added maximal midexpiratory flow, later labeled as forced expiratory flow, midexpiratory phase ($FEF_{25–75}$), to assess expiratory air-

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This research was supported by the Los Angeles Biomedical Institute at Harbor-UCLA Medical Center.

Manuscript received April 21, 2005; revision accepted June 27, 2005.

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way obstruction. In 1967, Macklem and Mead[3] divided airway resistance between central and peripheral components. Following the morphologic characterization of small airways disease,[4,5] many publications reported reference values not only for FVC, FEV_1, and FEV_1/VC, but also for $FEF_{25–75}$.[6–14]

In 1972, a publication entitled, "A Reduction in Maximum Mid-Expiratory Flow Rate: A Spirometric Manifestation of Small-Airways Disease,"[15] without giving FEV_1/FVC data, described the conditions of 53 symptomatic smokers as abnormal because their $FEF_{25–75}$ values were < 80% of the mean predicted values. The common practice of reporting spirometric values as a percent of predicted values with highlighting of values < 80% of predicted added confusion. Despite evidence of high variability of $FEF_{25–75}$ values and expert opinion recommending the use of statistically derived 95% confidence limits for the lower limit of normal (LLN)[14,16–20] small airways disease continued to be diagnosed if $FEF_{25–75}$ values were < 75 to 80% of mean percentage of predicted values, and FEV_1 or FEV_1/FVC were > 75 to 80% of the mean percentage of predicted values.[21]

In 1981 and 1985, respectively, Crapo et al[22] and Miller et al[23] published reference equations for white adults that included forced expiratory volume in 3 s (FEV_3) and FEV_3/FVC ratio values. Despite this, a recent search of PubMed found 695 citations for "$FEF_{25–75}$," far exceeding the 22 citations found for "FEV_3/FVC."

In the Third National Health and Nutrition Examination Survey (NHANES III),[24] spirometric values for FVC, peak flow, forced expiratory volume in 0.5 s, FEV_1, FEV_3, forced expiratory volume in 6 s (FEV_6), $FEF_{25–75}$, flow after 75% of the FVC has been exhaled (FEF_{75}), and duration of FVC in > 20,000 US residents were collected, using American Thoracic Society (ATS) standards. Using this database, Hankinson et al[25] analyzed and reported the mean and LLN formulas for FEV_1, FVC, FEV_1/FVC, FEV_1/FEV_6, and $FEF_{25–75}$, but not for FEV_3 or FEV_3/FVC in healthy never-smoking white, African-American, and Mexican-American male and female patients from childhood through age 80 years.

Utilizing data from the same NHANES III source,[24–26] we did the following: (1) calculated the mean and LLN values for FEV_3/FVC in these never-smoking and currently smoking groups; (2) compared the variability of FEV_1/FVC, FEV_3/FVC, and $FEF_{25–75}$ values in never-smokers and current smokers; and (3) assessed changes associated with aging and smoking. We hypothesized that the fraction of the FVC that had not been expired during the first 3 s of the FVC ($1 - FEV_3/FVC$) measures the increase in long-time-constant lung units that is associated with aging and smoking, and thus adding value to the spirometric assessment of airflow limitation. We further hypothesized that FEV_3/FVC complements FEV_1/FVC and that both are superior to $FEF_{25–75}$ in identifying and characterizing expiratory airway obstruction.

Materials and Methods

Subjects

Data from NHANES III[24] were extracted for men and women ≥ 20 years of age for the following ethnic-racial groups: white (white); African-American (black); and Mexican-American (Latin or Latina). These data, from unidentified subjects, had been ethically obtained with Institutional Review Board approval. The term *never-smokers* included individuals those who had not smoked pipes, cigars, or > 100 cigarettes in a lifetime, and excluded those with known respiratory, skeletal, or neurologic disorders. The term *current smokers* included all currently smoking adults without known skeletal or neuromuscular disorders. All spirometric tests met ATS standards with at least three reproducible forced expirations and maximal scores for quality and reproducibility. Age was recorded in months, height in 0.1-cm increments, weight in 0.1-kg increments, volumes in milliliters, and flows in milliliters per second.

Calculations

The following calculations were made: (1) the mean, slope, intercept, SE of the estimate, LLN values, and correlation coefficients for FEV_1/FVC and FEV_3/FVC were derived by linear regression for black, Latin, and white men and women 20 to 80 years old who had never smoked; (2) the formulas of Hankinson et al[25] and our formulas for FEV_1/FVC were compared; (3) the LLN as a percentage of the mean predicted values were calculated for FVC, FEV_1, FEV_1/FVC, FEV_3/FVC, and $FEF_{25–75}$ for each never-smoking group; (4) for all subjects, deviations from the mean predicted values were plotted, and individuals with values below those for the LLN were identified; and (5) age coefficients for FEV_1/FVC and $1 - FEV_3/FVC$ were calculated for never-smokers and current smokers.

Pattern Analysis of Current Smokers

We placed each of the currently smoking subjects into 1 of 16 (2^4) potential categories, depending on whether or not their FEV_1, FVC, FEV_1/FVC, and FEV_3/FVC values were below the LLN. This allowed us to decide whether each subject had normal spirometry findins, or had a pattern of obstruction, had probable restriction, or a combination, and whether or not the $FEF_{25–75}$ values confirmed the diagnosis or were probably false-positive or false-negative findings.

Statistical Analysis

Except where noted, values are reported as the mean ± SD and the 95th percentile as the LLN.

Results

Several key spirometric values, with respect to ethnicity, gender, age, and height, are provided for the NHANES III never-smokers and current smokers in Table 1. The number of never-smokers (5,938) differs from that of Hankinson et al[25] because of differences in age ranges and screening procedures. Table 2 gives the factors needed to derive the linear regression equations for FEV_1/FVC and FEV_3/FVC for never-smokers (*eg*, FEV_1/FVC or $FEV_3/FVC = \text{mean constant} - \text{age constant} \times \text{age}$). The mean absolute difference in FEV_1/FVC between the formulas of Hankinson et al[25] and our formula was only 0.28% for the 5,938 adults that we selected. This reflects the similarity between these two never-smoking series extracted from the same NHANES III database.

Using LLN levels for FEV_1/FVC, FEV_3/FVC, and FEF_{25-75} in never-smokers, values of 4.4 to 5.1% were "abnormal" (*ie*, similar to the expected value of 5.0%). However, if one had improperly considered 80% of the mean predicted FEF_{25-75} value as the LLN, the conditions of an additional 20.8% of never-smoking NHANES III subjects would be considered to be abnormal.

The relative variabilities of five spirometric measures are shown in Figure 1 for the largest group of never-smokers, white women. The LLN as a percentage of the mean predicted value was approximately 94% for FEV_3/FVC and approximately 88% for FEV_1/FVC with no significant effect with aging. In contrast, the LLN for FEV_1, FVC, and FEF_{25-75} decreased from age 20 to 80 years, ranging from 82 to 72% for FEV_1 and FVC, and 67 to 12% for FEF_{25-75}. Similar patterns of variability (not presented) were seen for spirometric measures for all other never-smoking groups.

Figure 2 shows marked differences in the variability of FEV_1/FVC, FEV_3/FVC, and FEF_{25-75} in never-smokers and current smokers for each fifth percentile of the respective populations when plotted against the percentage of the mean predicted values. The legend emphasizes misclassifications that would result if 80% of mean values was used as the threshold.

Figure 3 shows, for each gender of never-smokers and current smokers, the mean first spirometric fractions of forced expiratory maneuvers (*ie*, FEV_1/FVC) and last spirometric fractions (*ie*, $1 - FEV_3/FVC$). Over this 60-year span for never-smokers, the average FEV_1/FVC percentage decreases from 85.8 to 74.2%, while the average $1 - FEV_3/FVC$ percentage increases from 2.2 to 12.6%. The absolute changes in FEV_1/FVC and $1 - FEV_3/FVC$ are nearly similar, whereas the relative changes are much larger for $1 - FEV_3/FVC$ (Fig 3). There are minimal gender differences and even fewer ethnic differences. Thus, the proportion of flow occurring after the third second, while relatively small at age 20 years, increases markedly in association with older age. The mean fraction of air expelled during the second and third second of forced expiration remains quite stable from ages 20 to 80 years (13 ± 4%). The fact that the correlations of FEV_3/FVC with age are higher than those for FEV_1/FVC is noted in the legend of Figure 3. Importantly, current smokers have further significant decreases in FEV_1/FVC and increases in $1 - FEV_3/FVC$ (the SE for each point averages $< 0.5\%$). By middle age, the fractions of FVC for current smokers are equivalent to those of never-smokers who are 20 years older.

Table 1—*Demographics of Selected Subject Populations**

Variables	Men			Women		
	White	Black	Latin	White	Black	Latina
Never-smokers						
No.	771	623	702	1,413	1,169	1,260
Age, yr	46.6 ± 18.1	36.4 ± 14.6	36.9 ± 14.8	50.2 ± 17.7	40.1 ± 15.9	40.0 ± 15.7
Height, cm	176.4 ± 6.6	176.3 ± 7.0	169.5 ± 6.8	162.9 ± 6.7	162.8 ± 6.4	156.4 ± 6.1
FVC, L	4.96 ± 0.96	4.38 ± 0.79	4.76 ± 0.79	3.35 ± 0.73	3.06 ± 0.66	3.29 ± 0.64
FEV_1, L	3.91 ± 0.85	3.61 ± 0.71	3.89 ± 0.72	2.70 ± 0.66	2.55 ± 0.58	2.76 ± 0.59
FEV_1/FVC, %	78.7 ± 6.7	82.3 ± 6.5	81.7 ± 6.5	80.2 ± 6.9	83.4 ± 7.1	82.9 ± 6.8
FEV_3/FVC, %	92.8 ± 4.6	94.8 ± 3.9	94.4 ± 4.0	93.2 ± 4.5	94.8 ± 4.2	94.7 ± 4.2
$FEF_{25-75\%}$, L/s	3.62 ± 1.36	3.78 ± 1.28	4.04 ± 1.31	2.37 ± 1.10	2.83 ± 1.10	3.04 ± 1.06
Current smokers						
No.	684	705	551	701	612	262
Age, yr	43.7 ± 15.4	41.5 ± 13.5	38.4 ± 14.3	42.1 ± 15.7	39.7 ± 12.8	38.4 ± 13.8
Height, cm	176.5 ± 6.6	176.3 ± 6.9	169.4 ± 6.2	162.9 ± 6.4	163.9 ± 6.4	157.9 ± 6.4
FVC, L	4.89 ± 0.96	4.29 ± 0.80	4.75 ± 0.80	3.44 ± 0.74	3.11 ± 0.62	3.41 ± 0.67
FEV_1, L	3.67 ± 0.89	3.37 ± 0.76	3.76 ± 0.76	2.68 ± 0.72	2.50 ± 0.57	2.79 ± 0.61
FEV_1/FVC, %	74.8 ± 8.8	78.4 ± 8.7	79.0 ± 7.6	77.4 ± 9.3	80.3 ± 8.0	81.5 ± 7.4
FEV_3/FVC, %	90.4 ± 6.2	92.2 ± 5.8	92.9 ± 5.0	92.1 ± 6.3	93.2 ± 5.2	94.3 ± 4.5
$FEF_{25-75\%}$, L/s	3.06 ± 1.46	3.21 ± 1.46	3.64 ± 1.39	2.50 ± 1.24	2.58 ± 1.08	2.94 ± 1.10

*Values are given as the mean ± SD, unless otherwise indicated.

Table 2—*FEV_1/FVC and FEV_3/FVC Formulas for Never-Smoking Adults**

Group	Age Factor	Mean Constant	LLN Constant	SEE	r^2 Value
FEV_1/FVC					
White men	−0.1600	86.03	76.13	6.00	0.198
Black men	−0.2016	89.87	80.27	5.84	0.204
Latin men	−0.1947	89.09	80.25	5.38	0.222
All men	−0.1952	88.38	78.36	6.09	0.220
White women	−0.2116	90.84	81.29	5.81	0.295
Black women	−0.1936	91.21	80.72	6.38	0.333
Latina women	−0.2029	91.24	81.94	5.65	0.240
All women	−0.2030	91.11	80.98	6.16	0.288
FEV_3/FVC					
White men	−0.1692	100.63	95.00	3.42	0.445
Black men	−0.1699	100.99	96.03	3.02	0.405
Latin men	−0.1773	101.02	96.58	2.70	0.485
All men	−0.1756	100.86	95.56	3.22	0.449
White women	−0.1826	102.41	96.56	3.57	0.453
Black women	−0.1568	100.86	95.16	3.46	0.323
Latina women	−0.1740	101.74	96.78	3.01	0.449
All women	−0.1782	101.83	96.02	3.53	0.436

*SEE = SE of the estimate. Formulas: mean FEV_1/FVC (%) = age factor × years + mean constant; LLN FEV_1/FVC (%) = age factor × years + LLN constant; mean FEV_3/FVC (%) = age factor × years + mean constant; LLN FEV_3/FVC (%) = age factor × years + LLN constant.

Physiologic Defects in Current Smokers

Table 3 shows the spirometric patterns (normal, expiratory obstruction, possible restriction, combinations, and uncertain) found in individual current smokers and indicates in what groups FEF_{25-75} values might be either confirmatory or suggest inappropriate interpretations. Fewer than 15 smokers (21 of 2,403 smokers) had exclusively abnormal and probably false-positive FEF_{25-75} (line a, Table 3). These 12 men and 9 women had average ages of 29 and 35 years, respectively.

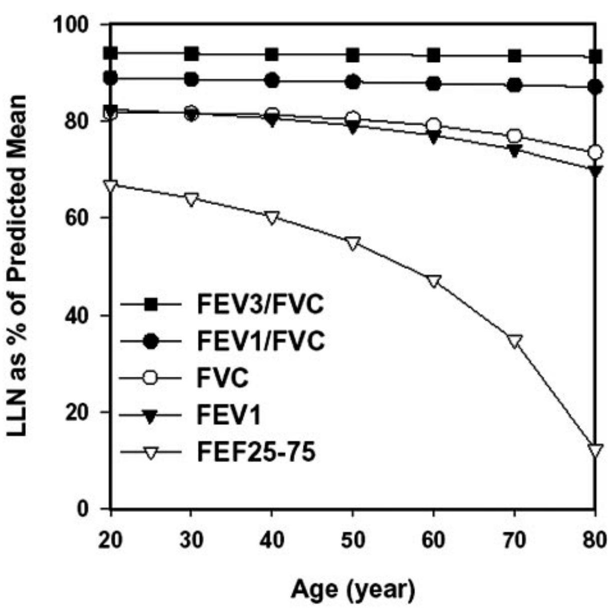

FIGURE 1. LLN as a percentage of the mean predicted spirometric values. Values are derived for ages 20 to 80 years from 1,413 never-smoking white women, assuming that height remains constant. The pattern for men and other ethnic groups is similar. With changes in height, there are additional small increases in the variability of the LLN of FEV_1 and FVC, and larger increases in the variability of the LLN of FEF_{25-75}.

A total of 1,167 (*ie*, the sum of values from lines b to n, Table 3) of 3,570 smokers had abnormal patterns. Eight hundred one smokers had expiratory obstruction; 66% of smokers (530 of 801 smokers) [lines d to f, Table 3] had both early and late expiratory obstruction with or without possible restriction; 16% of smokers (130 of 801 smokers) [lines g to i, Table 3] had late expiratory obstruction with or without possible restriction; and 18% of smokers (141 of 801 smokers) [lines j to l, Table 3] had early expiratory obstruction with or without possible restriction.

Many smokers with expiratory obstruction had probable false-negative FEF_{25-75} test results. A total of 683 smokers (lines d, e, g, h, j, and k, Table 3) had expiratory obstruction but without restriction, 42% of whom (287 of 683 smokers) had normal and probable false-negative FEF_{25-75} test results. These results included 40% of smokers (114 of 268 smokers) with both abnormal FEV_1/FVC and FEV_3/FVC values (line d, Table 3) and 84% of smokers (90 of 107 smokers) with abnormal FEV_3/FVC values (line g), with both groups being older (mean ages, 59 and 54 years, respectively). But, 64% of smokers (67 of 104 smokers) [line j, Table 3] with abnormal FEV_1/FVC values with normal and probable false-negative

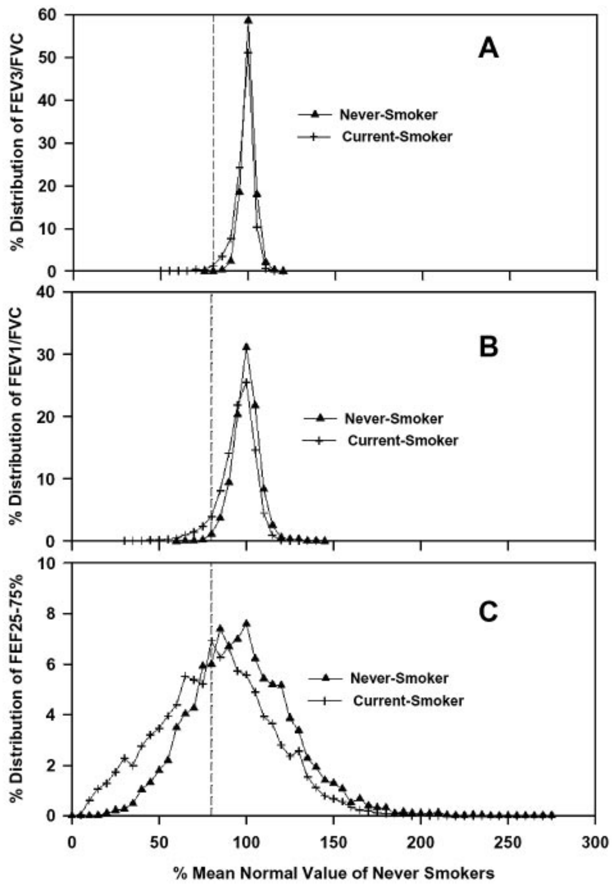

FIGURE 2. The distribution of spirometric values as percentage of mean normal values. *Top*, *A*: FEV_3/FVC. *Middle*, *B*: FEV_1/FVC. *Bottom*, *C*: FEF_{25-75}. Individuals are grouped by fifth percentiles above, at, and below mean normal values (using gender, age, height, and ethnicity) of 5,938 individual adult never-smokers from NHANES III data. Values for 3,570 adult current smokers are similarly grouped. In each graph, symbols extend laterally until the incidence is zero. The breadth of the distributions differs markedly, with least for FEV_3/FVC and the most for FEF_{25-75}. Vertical dashed lines separate those < 80% of predicted and > 80% of predicted means, and demonstrate the irrationality of using < 80% of predicted spirometric parameters to identify abnormal values. Using the 80% criterion, 0.0% of never-smokers and 1.5% of current smokers would have abnormal FEV_3/FVC values; 0.6% of never-smokers and 7.9% of current smokers would have abnormal FEV_1/FVC values; and 25.3% of never-smokers and 46.1% of current smokers would have abnormal FEF_{25-75} values.

FEF_{25-75} test results tended to be younger. Thus, measurements of FEF_{25-75}, especially in older individuals, often disagree with other spirometric measurements with less inherent variability.

Discussion

This study introduces the concept of the $1 - FEV_3/FVC$ fraction and gives data confirming the utility of the FEV_3/FVC ratio in assessing expiratory airway obstruction We took advantage of the NHANES III-verified spirometric and demographic data that were available from a large and diverse US population, and expand on the prior excellent analyses of Hankinson et al[25] by adding normal reference values for FEV_3/FVC in white, black, and Latin men and women, 20 to 80 years of age (Table 2). We confirm the use of polynomial formula for FVC and FEV_1 by Hankinson et al,[25] and offer our linear regressions for FEV_1/FVC and FEV_3/FVC values over a broad age and height range for each gender and ethnic group. Variability in group and individual values for FEV_1/FVC, FEV_3/FVC, and FEF_{25-75}, and our findings in current smokers confirm our hypothesis that FEF_{25-75} poorly discriminates normal values and those for expiratory obstruction (Fig 1, 2, Table 3). In contrast, FEV_3/FVC correlates even better with age than FEV_1/FVC and is an excellent measure of late expiratory obstruction (Fig 3, Table 3).

Two prior studies[22,23,27] have given reference values for FEV_3/FVC. Each study used 200 to 300 nonsmoking white adults of northern European ethnicity. Over a broad age and height range, our mean FEV_3/FVC values for white never-smokers are, on average, approximately 1.7% and 1.0% lower than those for men and women reported in the study by Crapo et al[22] and < 1% lower than those reported in the study by Miller et al.[23,27] These small differences may relate to resident altitudes, socioeconomic factors, or other unknown factors.[28] Although Miller et al[27] did not emphasize the following information, their data from 359 current smokers showed that FEV_3/FVC abnormalities exceeded those of FEV_1/FVC, FEF_{50}, FEF_{25-75}, FEV_1, FEV_3, FEF_{75}, and flow between 75% and 85% of the FVC (FEF_{75-85}).

In a consensus statement from the National Lung Health Education Program, Ferguson et al[34] reported that 9.6% of the adult (*ie*, 18 to 89 years of age) NHANES III smokers had an obstructive pattern, which they defined as FEV_1/FEV_6 and FEV_1 values below the LLN. In our series of 3,570 current smokers, aged 20 to 80 years, a considerably larger percentage (Table 3) showed airflow limitation as manifested by significant decreases in FEV_1/FVC and FEV_3/FVC.

In the past, comparatively little attention has been paid to the FEV_3/FVC or to the fraction of the FVC that had not been expired during the first 3 s of the FVC (*ie*, $1 - FEV_3/FVC$). Lower flow rates with aging or disease may be due to both intrinsic airway changes and the loss of lung elastic recoil, promoting increased compression of the airways with forced expiration.[30–34] In contrast to FEV_1/FVC, which reflects the reduction in short-time-constant lung units, an increase in $1 - FEV_3/FVC$ assesses the increase in long-time-constant lung units and there-

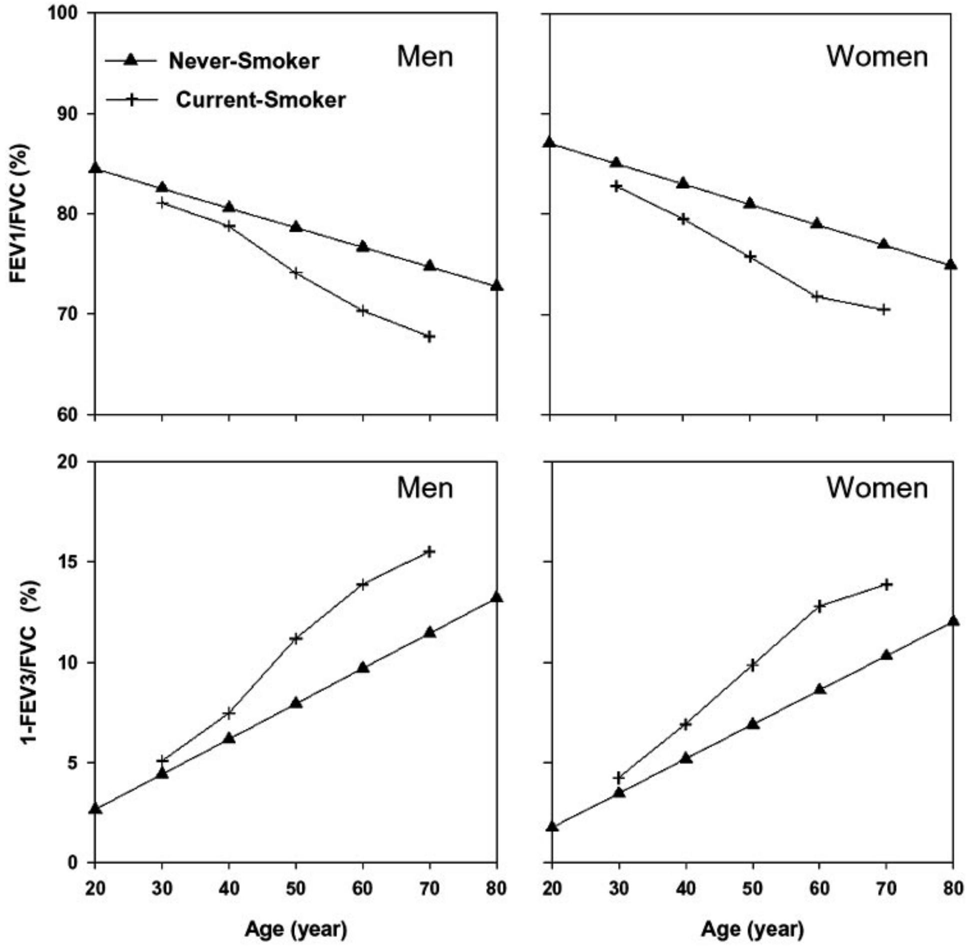

FIGURE 3. Association of spirometric fractions with age and smoking. The values depicted were derived from NHANES III data for FEV_1/FVC (*top left* and *top right*) and $1 - FEV_3$/FVC (*bottom left* and *bottom right*), for men (*top left* and *bottom left*) and women (*top right* and *bottom right*) from ages 20 to 80 years, and for 5,938 never-smokers and 3,570 current smokers. For never-smokers, the absolute changes in FEV_1/FVC and $1 - FEV_3$/FVC are approximately equivalent but in opposite directions. FEV_3/FVC correlations with age (never-smokers: men, $r^2 = 0.449$; women, $r^2 = 0.437$) are much higher than those of FEV_1/FVC (never-smokers: men, $r^2 = 0.220$; women, $r^2 = 0.290$). Relatively, $1 - FEV_3$/FVC changes more than FEV_1/FVC with aging and cigarette smoking. The average SEM for current smokers is $< 0.5\%$. By middle age, the spirometric values for average current smokers are similar to those of never-smokers who are approximately 20 years older.

fore should be sensitive in detecting developing expiratory flow limitation. With aging and injury, lung units with low elastic recoil and increased airway resistance may proportionally increase. These changes will affect expiratory flow after 3 s (*eg*, the $1 - FEV_3$/FVC measurement, which increases proportionately more than the decrease in FEV_1/FVC (Fig 3). The very low variability in FEV_3/FVC in healthy subjects makes for small deviations from the mean predicted values (Fig 1–3).

In evaluating the cigarette-smoking effect in the NHANES III population, both the decreases in FEV_1/FVC and increases in $1 - FEV_3$/FVC for a given age group are striking (Fig 3). Using either measurement, fractions progressively deteriorate with age relative to the never-smoking subjects. Consequently, by middle age current smokers have similar values to those of never-smokers who are about 20 years older (Fig 3). In both our study (Table 3) and that of Miller et al,[27] abnormal FEV_3/FVC values were as common as abnormal FEV_1/FVC values. This suggests that attention similar to that accorded to FEV_1/FVC should be paid to FEV_3/FVC and $1 - FEV_3$/FVC in evaluating airway obstruction. Because values for both FEV_1/FVC and FEV_3/FVC normally decline at a relatively constant rate with aging, using fixed ratios such as 70% or 73% for FEV_1/FVC[29] or any other value for FEV_3/FVC as the mean or LLN values should be avoided.

Measurements (in liters per second) of either

Table 3—*Spirometric Patterns for Normal, Expiratory Obstruction, Possible Restriction, or Combinations in 3,570 Current Smokers**

	Test Result				No.		
						$FEF_{25–75}$	
Line and Spirometric Pattern	FVC	FEV_1/FVC	FEV_1/ FVC	FEV_3/FVC	Total	N	A
(a) Normal	N	N	N	N	2403	2382	21†‡
(b) Possible restriction	A	A	N	N	167	105	62
(c) Possible restriction	A	N	N	N	156	155	1
(d) Expiratory obstruction	N	N	A	A	268	114§‖	154
(e) Expiratory obstruction	N	A	A	A	170	10§	160
(f) Obstruction ± possible restriction	A	A	A	A	92	4§	88
(g) Late expiratory obstruction	N	N	N	A	107	90§¶	17
(h) Late expiratory obstruction	N	A	N	A	12	2§	10
(i) Late expiratory obstruction ± possible restriction	A	A	N	A	11	2	9
(j) Early expiratory obstruction	N	N	A	N	104	67§#	37
(k) Early expiratory obstruction	N	A	A	N	22	4§	18
(l) Early expiratory obstruction ± possible restriction	A	A	A	N	15	1	14
(m) Uncertain	N	A	N	N	39	21	18
(n) All other				4	2	2	
(o) Total				3,570	2,959	611	

*A = abnormal; N = normal; ± = with or without.
†Probable false positive result.
‡Mean age 32 years.
§Probable false-negative result.
‖Mean age 59 years.
¶Mean age 54 years.
#Mean age 38 years.

instantaneous flow (*ie*, forced expiratory flows of 25%, 50%, 75%, or 85% of FVC) or average flow ($FEF_{25–75}$ or $FEF_{75–85}$) over any given volume are necessarily dependent on both flow and volume measurements. As Miller et al[23,27] point out, such flow measurements at differing volumes are inherently and necessarily variable.

The inherently high variability of $FEF_{25–75}$, in both never-smoker and current smoker groups, is confirmed in Figure 2. The error of using 80% of the mean predicted value has been confirmed and emphasized by many authorities,[16–20] and has been reconfirmed by our finding that approximately 25% of healthy never-smoking NHANES III adults have $FEF_{25–75}$ values < 80% of the mean predicted value.

Even when 95% confidence limits for $FEF_{25–75}$ are used, there are an inordinate number of individuals with probable false-negative results (42%) who clearly have obstructive airways disease, especially among those who are > 60 years of age (Table 3). Probable false-negative results for $FEF_{25–75}$ measurements are also frequent in subjects with abnormally low FEV_3/FVC values (*ie*, those with later expiratory obstruction or obstruction of long-time-constant airways). On the other hand, apparent false-positive $FEF_{25–75}$ values (Table 3) are found almost exclusively in younger adults. The fact that the LLN for $FEF_{25–75}$ is an absolute rather than a relative value in all predicting equations is a factor in the high incidence of probable false-negative results.

There are several possible limitations in this study. Although the spirometric measurements followed ATS guidelines,[25] it is possible that some subjects gave incomplete historical details. While we do not have data for Asian individuals or other ethnic groups, the similarity of FEV_1/FVC and FEV_3/FVC values among thousands of white, black, and Latin adults in the United States, who differed considerably in height and nutritional status, suggests that the values given in Table 4 are likely to be universally valid. In clinical practice, we would express uncertainty when spirometric findings are equivocal, but purposely did not do so in this study. Rather, we distinguished normalcy from abnormality on purely statistical grounds, as have other authors.[27,29] The use of a single-tailed LLN at the 95% confidence level in a healthy population causes approximately 5% of each measurement to be "abnormal," although the subject may not really be abnormal. Therefore, testing four parameters in 3,570 healthy subjects at the 5% level should result in approximately 714 abnormal values ($3,570 \times 0.05 \times 4 = 714$). Lung restriction cannot be diagnosed definitively in this series in the absence of measurements that were not available on the NHANES III database, although Dykstra et al,[35] assessing patients with FEV_1/FVC

Table 4—*Approximate FEV_1/FVC and FEV_3/FVC for All Adults*

Age, yr	FEV_1/FVC, %		FEV_3/FVC, %	
	Mean	LLN	Mean	LLN
Men				
20	84.5	74.5	97.4	92.0
30	82.5	72.5	95.6	90.3
40	80.6	70.6	93.8	88.5
50	78.6	68.6	92.1	86.8
60	76.7	66.7	90.3	85.0
70	74.7	64.7	88.6	83.3
80	72.8	62.7	86.8	81.5
Women				
20	87.1	76.9	98.3	92.5
30	84.8	74.7	96.5	90.7
40	82.6	72.4	94.7	88.9
50	80.3	70.2	92.9	87.1
60	78.1	67.9	91.1	85.3
70	75.8	65.7	89.4	83.6
80	73.6	63.5	87.6	81.8

values of < 70%, found a relatively low incidence of reduced total lung capacity. Left ventricular failure with cardiomegaly can result in abnormal spirometry with combined restrictive and obstructive pattern. Thus, significant heart or other diseases, unknown to surveyors, might have been present. Although the FEV_6 has been suggested as a substitute for the FVC,[36] the FVC often exceeds the FEV_6, especially with older age and smoking. Therefore, our analysis does not include FEV_1/FEV_6 or FEV_3/FEV_6 values. We did not investigate the role of the duration or intensity of cigarette smoking on spirometric values.

We recommend that manufacturers replace the reporting of spirometric values as "a percent of predicted" with "mean predicted, and lower limit of normal." In addition, thoracic societies should consider the elimination of $FEF_{25–75}$ and other forced expiratory flow values from reports, and their replacement with simpler, more valid, and easier to interpret FEV_3/FVC values.

ACKNOWLEDGMENT: We thank the planners, surveyors, technicians, and subjects who participated in the NHANES III, and the manuscript reviewers for their suggestions.

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