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Area under the expiratory flow-volume curve: normative values in the National Health and Nutrition Survey (NHANES) study

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ABSTRACT

The area under the expiratory flow-volume (AEX-FV) loop has been evaluated before as a spirometric tool for assessing respiratory functional impairment. We computed the AEX-FV curves in spirometry tests performed on 20,313 participants in the National Health and Nutrition Examination Survey (NHANES) study.

We analyzed 108,939 spirometry tests performed between 2007 and 2012 (5964 children; 14,349 adults). In these tests, we computed the three areas from existing NHANES raw data on instantaneous expiratory flows measured at 0.01 s intervals.

Mean best-trial measurements for AEX-FV were 3.4 in boys, 2.8 in girls, 11.8 in men and 7.7 L^2/s in women. We characterized indices of central tendency and dispersion of the measurements (eg, means and fifth percentiles—lower limits of normal) by age group (children vs adults), gender, race or ethnicity group and effort grading. Simple regression equations using logarithmic transformations of the above areas and using age, gender and height as inputs provided good predictive ability for the variable AEX-FV.

Regular, digital spirometry could and should make available to clinicians and researchers the area under the curves for flow versus volume graph, providing additional tools in our armamentarium to evaluate ventilatory impairments and patterns, and possibly respiratory disability.

Significance of this study

What is already known about this subject?

- ⇒ Traditional spirometric measurements provide clinically meaningful information: defining normal versus abnormal values, severity stratification of functional defects and the pattern of impairment (eg, obstruction, restriction, mixed defects, small airway disease).
- ⇒ In an era of digital signal processing and significant computational capabilities, alternative spirometric measurements, such as the area under the expiratory flow-volume curve, became available.
- ⇒ Several studies found that area under the expiratory flow-volume loop may become more useful in respiratory functional assessment. So far, no population-based normative data (ie, predicted normal values or lower limits of normal (LLN)) for this measurement have been published.

What are the new findings?

- ⇒ We computed on a large cohort of US population (National Health and Nutrition Examination Survey (NHANES) study) the areas under flow-volume curves. In addition, we characterized their means and LLNs (fifth percentiles), in both adults and children, and we developed simple regression models that predict these functional parameters by age, gender and height.

How might these results change the focus of research or clinical practice?

- ⇒ Current study provides normative data for these alternative spirometric measurements. While the value of area under the expiratory flow-volume curve for diagnosis and severity stratification is currently better understood, further characterization of the other two measurements is warranted in both normal individuals and various disease states.

INTRODUCTION

Normative values or lower limits of normal (LLN) for respiratory function are generally dependent on the subjects' demographic and anthropometric characteristics such as race, gender, age, height and weight.[1–5] In practice, for every measured lung volume or flow, calculated volume or capacity, values below the fifth percentiles (or z scores <-1.645) of gender and race-referenced healthy individuals define the LLN. The most important spirometric parameters that are validated and widely used in respiratory physiology, clinical practice and trial assessments are derived from the expiratory phase of testing: (forced) vital capacity (FVC or VC), forced expiratory volume in 1 s (FEV_1), forced expiratory volume in 6 s (FEV_6), instantaneous isovolumic flows at 25%, 50% or 75% of FVC, or FEF_{25}, FEF_{50} and FEF_{75}, respectively, and occasionally, forced expiratory flow between 25% and 75% of FVC or FEF_{25-75}.

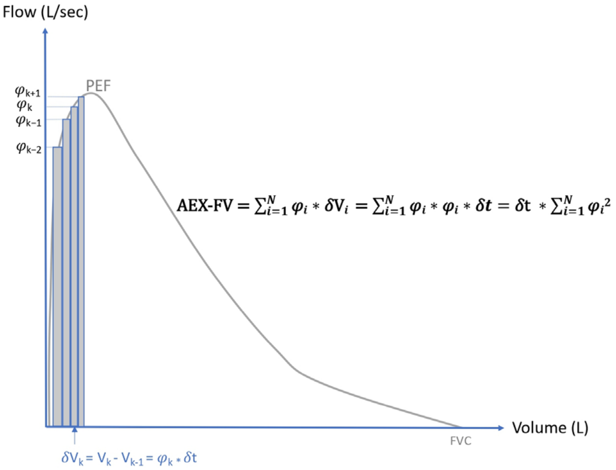

Figure 1 Methodological approach for computing instantaneous exhaled volumes (V_k) from the matrix of instantaneous flows (ϕ_k) collected at $\delta t=10^{-2}$ s. The computations for area under the expiratory flow-volume (AEX-FV) curve are shown. PEF, peak expiratory flow.

Some of these became important functional parameters more than a century and a half ago (eg, Hutchinson's VC[6]), while others have been developed and used more extensively in the 20th century. Their importance in pulmonary function testing (PFT) has been quite significant, yet it may have reached a phase of diminishing returns in providing useful and actionable information on respiratory physiology impairments. Nevertheless, several additional measurements are still available from simple spirometry testing, and their usefulness has not been fully evaluated to date.

We previously evaluated an alternative spirometric measurement, area under the expiratory flow-volume (AEX-FV) loop and its approximations computed from FEF_{25}, FEF_{50} and FEF_{75},[7–13] as global tools for diagnosis of obstructive, restrictive or mixed ventilatory impairments, for identification of small airway disorders or bronchodilator responsiveness and for severity stratification of respiratory functional impairments. The area approximations[10] were found to be good surrogates of the actual area, fact especially relevant when the PFT software did not provide the actual results of the integral function of flow by volume.

In this paper, we expand on prior assessments by computing and determining the LLNs of the area delineated by forced expiratory flow-volume loop (AEX or AEX-FV, figure 1), using an aggregate, large cohort of individuals from the National Health and Nutrition Examination Survey (NHANES), who underwent spirometry between 2007 and 2012 and for whom raw curve data were available.

METHODS

The NHANES is a large population-based study, designed to collect information on health and nutrition of the US population, with two distinct parts: a home interview and a health evaluation in a mobile examination center. The NHANES participants were selected using a random sampling method from the US household population. In this study, we performed computations and analyses on several publicly available NHANES datasets: 2007–2008, 2009–2010 and 2011–2012, which are made accessible to researchers by the Centers for Disease Control and Prevention (CDC, Atlanta, Georgia, USA).[14] Demographic, anthropometric measurements, pre-bronchodilator spirometry/post-bronchodilator spirometry and especially raw curves data from the NHANES sets were extracted and matched using their unique identifiers.

We computed AEX-FV as the sum of all rectangles represented by the instantaneous flows and the (unequal) intervals of volume, the latter being derived from the formula: delta volume=instantaneous flow multiplied by the time interval.

The data for the raw spirometry curves in the variable SPXRAW were recorded at ATPS (ambient temperature and pressure saturated). For the purpose of these analyses, they were converted to BTPS (body temperature ambient pressure saturated) by using the correction factor provided, that is, multiplying by the variable SPAFACT from the NHANES datasets[15] (online supplemental material).

Descriptive statistical analysis of the available variables was performed. Categorical variables were summarized as frequencies or percentages. Continuous variables were characterized by mean, median and 25th–75th IQR (expressed as the difference 75th minus 25th percentile values), as most distributions were non-Gaussian. The Anderson-Darling test[16] was used for goodness of fit of continuous variables. Since usual transformations did not achieve fitting to normality, we used for comparisons mostly non-parametric methods with native or log-transformed variables (eg, Welch's analysis of variance (ANOVA), Mann-Whitney or Wilcoxon rank score test or Kruskal-Wallis test, as appropriate). The Levene test was used as the default test to compare for unequal variances (an F test from an ANOVA where the response is the absolute value of the difference of each observation and the group mean[17]).

Statistical analyses were performed using JMP Pro16 software (SAS Institute). Institutional research oversight approvals were obtained to conduct the study.

RESULTS

A total of 108,939 PFT sets from 20,313 participants (5964 children, ie, of age <18 years) were analyzed: 34,857, 36,421 and 37,661 tests from NHANES 2007–2008, 2009–2010 and 2011–2012 cohorts, respectively (figure 2). Mean age was 11 (range: 6–17, median 11, IQR 6) years in children (49% girls) and 44 (range: 18–79, median 45, IQR 30) years in adults (49% women).

The main anthropometric characteristics and PFT parameters of the combined cohorts are shown in table 1. Among children, race or ethnicity groups were represented as follows: 22%, 29%, 12%, 31% and 6% as non-Hispanic whites, non-Hispanic blacks, non-Hispanic Asians, Hispanics (both Mexican Americans and other Hispanics) and other or multiracial, respectively. Among adults, 36%, 27%, 14%, 21% and 3% were non-Hispanic whites, non-Hispanic blacks, non-Hispanic Asians, Hispanics (both Mexican Hispanics or other Hispanics) and other or multiracial, respectively.

Approximately 37% of the adult participants interviewed about smoking habits reported lifetime smoking of ≥100 cigarettes cumulatively up to the survey date (18% missing

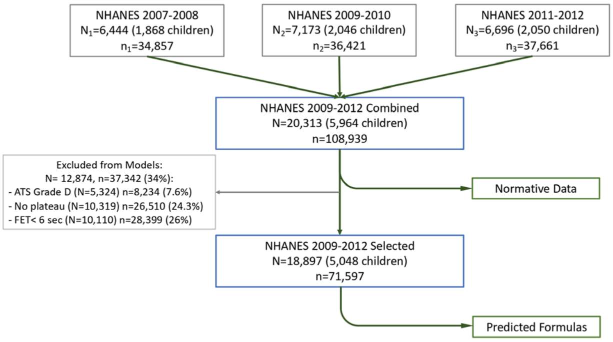

Figure 2 Flow diagram of the study (N: number of participants, n: number of spirometry tests). ATS, American Thoracic Society; FET, forced expiratory time; NHANES, National Health and Nutrition Examination Survey.

response rate); they reported starting to smoke cigarettes at a median age of 17 (25th–75th percentiles: 15–20) years. Smoking history, quantified based on the report of number of cigarettes smoked per day at the time when they quit, was as follows: mean 20, median 10, 25th–75th percentiles: 2–29 pack-years.

Mean best-trial AEX-FV values were 3.4 in boys and 2.8 in girls (L^2/s, $p<0.0001$); 11.8 in men and 7.7 in women (L^2/s, $p<0.0001$). Figure 3 shows, in bar graph format, medians and LLNs for AEX-FV by gender and age groups, respectively. Figure 4 illustrates, for better illustration of distribution and dispersion, the same area by gender and age groups as box-and-whisker plots (with means) and side histograms. AEX-FV linear fit versus FEV_1, FVC and $FEF_{25\%-75\%}$ was characterized by R^2 of 0.07, 0.02 and 0.10 in children and 0.01, 0.04 and 0.12 in adults, respectively. Even when analyzed by gender, age group and effort category, R^2 remained below 0.33, which explains the added value of the new physiologic measurement.

For the AEX-FV variable, we found significant differences by gender and race or ethnicity group (table 2). The AEX variables were larger in black girls and boys, while in adults, they were largest in white men and women (bold values in table 2). Adults and children of Asian ancestry had among the lowest AEX values. Perhaps in keeping with the fact that Hispanics and whites shared the same predictive equations in the Global Lung Initiative (GLI) models for normal spirometric values,[18] in our analyses the observed values for FEV_1, FVC and FEV_1/FVC were, indeed, relatively similar. Nevertheless, we found the normative data for these measurements to be both statistically and clinically different between different groups, as defined by race or ethnicity group in the NHANES study. Table 3 includes the AEX ranges, means, medians, IQRs and several quantiles, including the fifth percentiles (LLN, represented as asterisk) in children and adults, by gender, race or ethnicity group and American Thoracic Society (ATS) acceptability grades.

Only 3/17,303 of the acceptable tests (ie, ATS grades A, B or C, plateau present and forced expiratory time (FET) $\geq$6 s) were done in children in the sitting position. Similarly, only 118/54,173 of the acceptable tests were performed on adults in the sitting position; the rest were done while standing. Mean AEX-FV were significantly higher in the sitting versus standing position: 10.7 vs 8.4 (L^2/s, $p<0.0001$), respectively. The statistically significant differences ($p<0.0001$) remained in multivariate analyses, using native or logarithmic transformations of the three Y variables and after adjusting for FET, testing position and their interaction (in all models, R^2 was 0.75 in both the derivation and the validation sets). Overall in these models, testing position contributed slightly less (variable importance main effect 0.46 for AEX-FV) than the main determinant of the Y variables, that is, FET (main effect 0.54 for AEX-FV by dependent resampled method using k nearest neighbors' technique).

In adults and children with spirometry characterized by good effort, reproducible and acceptable curves by visual inspection (NHANES 2009–2012 selected group—figure 2), the calculated AEX-FV measurements were predicted by models that included the following parameters: age, gender and height, as weight and race or ethnicity group were trimmed off due to their minor, yet significant contribution (figure 5). More complex models based on generalized regression or neural network approaches did not provide considerable improvements to warrant their inclusion here (data not shown). Also, cigarette smoking status or intensity, as established from adult participants' interviews, as well the serum concentrations of cotinine (a metabolite of nicotine) or urinary concentrations of NNAL (4-(methylnitrosamino)−1-(3-pyridyl)−1-butanonol, a metabolite of a tobacco-specific nitrosamine) did not influence the AEX-FV measurements (data not shown).

Among all valid tests (ATS grades A, B or C, plateau present and FET >6 s), 18,897 subjects were tested only with 'baseline' spirometry (n=66,307), while 1511 individuals underwent both pre-bronchodilator and post-bronchodilator testing (due to initial FEV_1/FVC ratios <LLN, n=5290). After bronchodilator administration, best AEX-FV increased from 3.0 to 4.6 in children and from 8.7 to 17.0 L^2/s in adults.

DISCUSSION

In this investigation, we computed in a large cohort representative of the US population, the alternative spirometric measurement called AEX-FV curves. Additionally, we characterized indices of central tendency and we identified LLN (as fifth percentiles of the distributions) for various subgroups. Further, we developed a simple regression model for these areas, based on subjects' age, height and gender, which could be used as predictive equations for this population. These new measurements, easily made available by any modern, digital spirometry software, could become new tools in our armamentarium to characterize global respiratory function impairments.

Several years ago, a few PFT vendors made available to clinicians and researchers, together with other spirometric measurements, the AEX for the flow-volume loop, which is, in fact, the integral function of expiratory flow by the variable volume. Either unnoticed, not well understood, or simply unexplored, it took a few years for the flow-volume loop to be studied in more detail and then used to assess various conditions.[7–13] However, the idea is by no means completely new, as other investigators have entertained the

Table 1 Subjects' characteristics of the combined NHANES 2009–2012 (14,349 adults; 5964 children) and pulmonary function testing characteristics

Age group		Children		Adults	
Gender		Male	Female	Male	Female
N		3042	2922	7182	7167
Age (years)	Mean	11.3	11.5	43.8	44.6
	Median (IQR)	11.0 (6.0)	11.0 (6.0)	45.0 (30.0)	45.0 (29.0)
Height (cm)	Mean	151.4	148.2	176.3	162.5
	Median (IQR)	147.0 (36.0)	148.3 (27.1)	174.7 (10.5)	161.2 (9.9)
Weight (kg)	Mean	50.1	47.9	88.4	75.6
	Median (IQR)	43.9 (31.9)	43.7 (27.8)	83.5 (24.8)	72.0 (25.1)
Body mass index (kg/m^2)	Mean	20.7	21.0	28.4	28.6
	Median (IQR)	19.3 (7.0)	19.7 (6.9)	27.5 (7.2)	27.9 (9.4)
Body surface area (m^2)	Mean	1.4	1.4	2.0	1.8
	Median (IQR)	1.3 (0.6)	1.4 (0.5)	2.0 (0.3)	1.8 (0.3)
FEV_1 (L)	Mean	2.70	2.41	3.71	2.70
	Median (IQR)	2.21 (1.73)	2.18 (1.30)	3.53 (1.18)	2.58 (0.95)
FEV_1 (% predicted NHANES III)	Mean	72	82	94	96
	Median (IQR)	67 (22)	77 (23)	95 (20)	97 (19)
FEV_1 (% predicted GLI)	Mean	100	100	94	95
	Median (IQR)	101 (19)	102 (17)	95 (20)	97 (19)
FVC (L)	Mean	3.20	2.78	4.85	3.41
	Median (IQR)	2.65 (2.03)	2.51 (1.45)	4.56 (1.33)	3.22 (1.06)
FVC (% predicted NHANES III)	Mean	76	88	98	99
	Median (IQR)	72 (20)	85 (19)	98 (18)	99 (18)
FVC (% predicted GLI)	Mean	102	103	99	99
	Median (IQR)	104	104	99	99
	IQR	18	17	18	19
FEV_1/FVC	Mean	0.84	0.87	0.76	0.79
	Median (IQR)	0.86 (0.09)	0.88 (0.08)	0.78 (0.12)	0.81 (0.10)
FEV_1/FVC (% predicted NHANES III)	Mean	98	98	96	96
	Median (IQR)	98 (11)	98 (10)	97 (13)	98 (11)
FEV_1/FVC (% predicted GLI)	Mean	96	96	94	95
	Median (IQR)	98 (11)	98 (9)	97 (13)	97 (11)
$FEF_{25–75}$ (L/s)	Mean	2.88	2.79	3.32	2.64
	Median (IQR)	2.39 (1.83)	2.47 (1.55)	3.13 (2.13)	2.58 (1.60)
$FEF_{25–75}$ (% predicted NHANES III)	Mean	94	97	87	88
	Median (IQR)	89 (38)	92 (41)	83 (45)	87 (42)
$FEF_{25–75}$ (% predicted GLI)	Mean	93	93	87	90
	Median (IQR)	95 (37)	94 (35)	88 (47)	92 (44)
Number of spirometry maneuvers (SPAMANU)	Mean	4	3	3	3
	Median (IQR)	3 (3)	3 (3)	3 (2)	3 (2)
Number of data points in raw curve (SPXPTS)	Mean	622	593	1099	935
	Median (IQR)	648 (450)	605 (475)	1063 (518)	908
AEX-FV (ATPS, L^2/s)	Mean	1.24	1.09	6.31	3.81
	Median (IQR)	0.91 (1.65)	0.74 (1.62)	4.01 (6.26)	2.50 (2.75)
AEX-FV (BTPS, L^2/s)	Mean	1.46	1.27	7.40	4.46
	Median (IQR)	1.06 (1.94)	0.87 (1.90)	4.68 (7.34)	2.93 (3.22)
Best AEX-FV (BTPS, L^2/s)	Mean	2.79	2.29	11.35	7.03
	Median (IQR)	2.26 (2.00)	2.09 (1.69)	8.36 (11.17)	4.93 (5.04)

AEX-FV, area under the expiratory flow-volume; ATPS, ambient temperature and pressure saturated; BTPS, body temperature ambient pressure saturated; FEV, forced expiratory volume; FVC, forced vital capacity; GLI, Global Lung Initiative; NHANES, National Health and Nutrition Examination Survey.

idea of exploring in other ways flow-volume loop concavity, defects beyond the classic obstructive–restrictive–mixed-small airway disease categorization, more global assessment tools, etc.[19–22]

A few comments are warranted here. First, AEX-FV variables were the largest in black children of both genders, while in adults, they were the largest in whites (table 2). While still unclear why, it is our hypothesis that this may

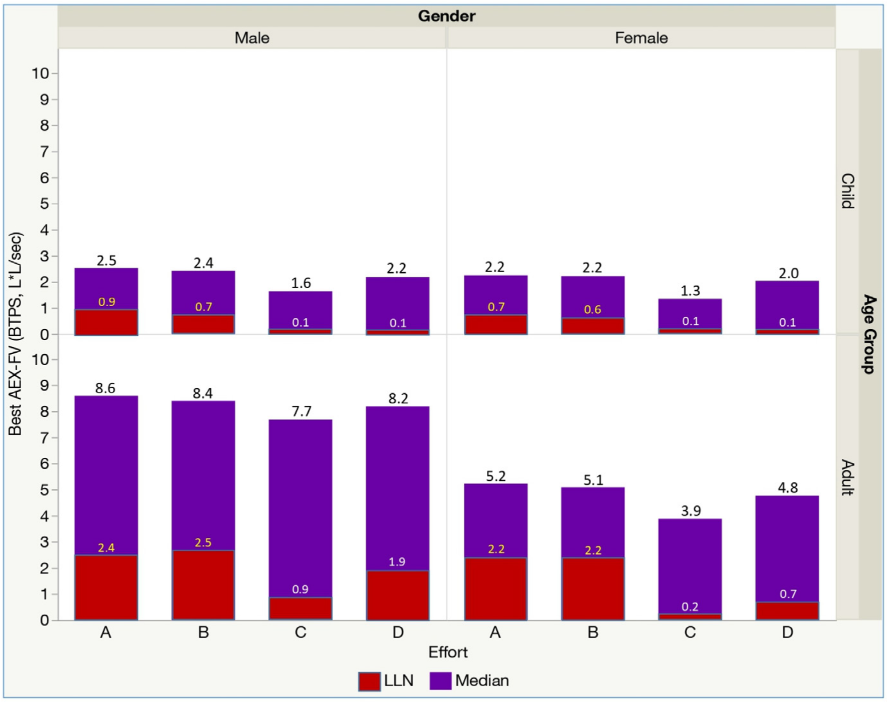

Figure 3 Median values and lower limit of normal ((LLN) fifth percentile) for best area under the expiratory flow-volume (AEX-FV) curves by age group (<18 or >18 years) and gender. BTPS, body temperature ambient pressure saturated.

be due to different rates of truncal growth in various racial or ethnic groups (which directly influences their lung function). Second, both children and adults of Asian heritage had among the lowest AEX-FV values; however, this group

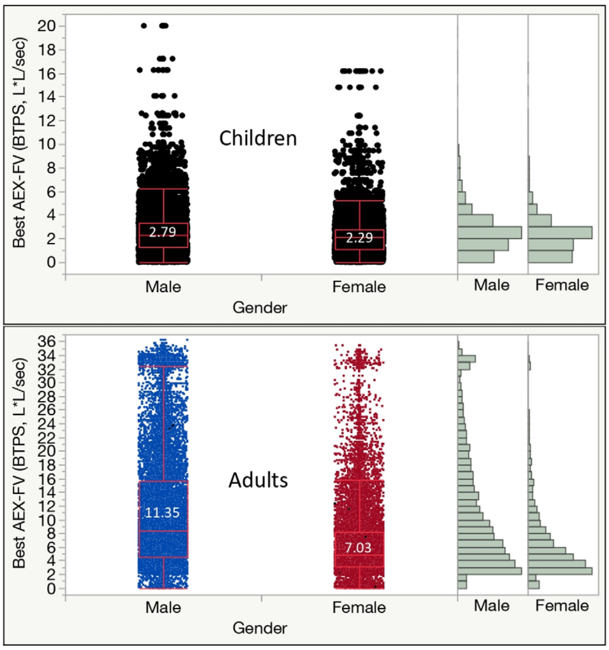

Figure 4 Box-and-whisker plots (means shown) and side histograms of best area under the expiratory flow-volume (AEX-FV) curves by gender and age group (<18 years in upper panel and ≥18 years of age in lower panel). BTPS, body temperature ambient pressure saturated.

Table 2 Mean best value for AEX-FV by gender and race or ethnicity group

Age group	Gender	Race or ethnicity group	n	Mean AEX-FV (BTPS, L^2/s)
Child	Male	Hispanic	1100	3.2
		White	745	3.1
		Black	1032	**3.7**
		Asian	379	2.7
		Other/multiracial	171	2.8
	Female	Hispanic	849	3.1
		White	676	2.6
		Black	853	**3.0**
		Asian	329	2.8
		Other/multiracial	156	2.7
Adult	Male	Hispanic	2087	10.0
		White	3703	**12.4**
		Black	2900	11.1
		Asian	1462	7.7
		Other/multiracial	350	10.0
	Female	Hispanic	1894	5.7
		White	3119	**8.1**
		Black	2690	6.6
		Asian	1253	5.3
		Other/multiracial	244	5.5

RIDRETH1: race or ethnicity group (2007–2008, 2009–2010 surveys).
RIDRETH3: race or ethnicity group (2011–2012 surveys, which separated Asians from other/multiracial).
AEX-FV, area under the expiratory flow-volume; BTPS, body temperature ambient pressure saturated.

Table 3 Best AEX-FV (BTPS, L^2/s)

Age group	Gender	Race or ethnicity group	Effort	n	Mean	Quantile 2.5	Quantile 5*	Quantile 7.5	Quantile 10	Quantile 50 (median)	IQR
Child	Male	Hispanic	A	917	3.16	0.73	**0.81**	0.98	1.03	2.35	1.64
			B	366	2.86	0.44	0.62	0.78	0.98	2.27	1.74
			C	689	2.25	0.06	0.15	0.16	0.25	1.50	1.70
			D	151	2.21	0.04	0.07	0.16	0.26	2.11	1.71
			All	2123	2.76	0.15	0.31	0.48	0.68	2.16	1.84
		White	A	628	2.96	0.64	**0.84**	1.05	1.19	2.52	1.37
			B	198	2.78	0.57	0.80	0.94	1.10	2.41	1.75
			C	456	2.19	0.06	0.15	0.16	0.20	1.73	2.10
			D	112	3.75	0.03	0.15	0.23	0.65	2.55	2.50
			All	1394	2.77	0.16	0.30	0.61	0.70	2.34	1.81
		Black	A	881	3.52	0.69	**1.01**	1.11	1.24	2.70	1.73
			B	301	3.23	0.61	0.94	1.06	1.08	2.57	2.06
			C	629	2.46	0.05	0.15	0.23	0.40	1.69	2.14
			D	132	2.49	0.02	0.17	0.23	0.26	2.24	2.42
			All	1943	3.08	0.19	0.44	0.64	0.79	2.38	2.10
		Asian	A	349	2.47	0.79	**0.92**	0.98	1.08	2.18	1.41
			B	96	2.42	0.07	0.65	0.79	0.85	2.02	1.90
			C	220	1.82	0.08	0.08	0.08	0.10	1.55	1.59
			D	67	2.34	0.07	0.18	0.18	0.18	2.22	1.80
			All	732	2.26	0.08	0.13	0.45	0.79	2.10	1.56
		Other/multiracial	A	135	2.67	0.64	**0.93**	1.17	1.18	2.52	1.81
			B	55	2.31	0.16	0.54	0.71	0.97	2.19	1.68
			C	122	1.42	0.16	0.18	0.31	0.36	1.30	1.72
			D	28	2.33	0.31	0.31	0.35	0.50	3.20	2.26
			All	340	2.12	0.24	0.47	0.52	0.63	2.17	1.87

Continued

Table 3 Continued

Age group	Gender	Race or ethnicity group	Effort	n	Mean	Quantile 2.5	Quantile 5*	Quantile 7.5	Quantile 10	Quantile 50 (median)	IQR
	Female	Hispanic	A	750	2.87	0.60	**0.69**	0.89	0.97	2.32	1.53
			B	330	2.72	0.45	0.56	0.64	0.83	2.22	1.74
			C	658	1.63	0.07	0.08	0.13	0.15	1.18	1.89
			D	126	2.28	0.04	0.09	0.16	0.17	1.85	1.90
			All	1864	2.36	0.12	0.17	0.21	0.33	2.03	1.93
		White	A	645	2.50	0.65	**0.77**	0.92	0.99	2.20	1.25
			B	196	2.38	0.54	0.66	0.68	0.72	2.14	1.67
			C	414	1.66	0.09	0.10	0.16	0.17	1.23	1.52
			D	88	2.41	0.08	0.15	0.39	0.59	2.24	1.71
			All	1343	2.25	0.13	0.32	0.54	0.65	2.07	1.67
		Black	A	749	2.43	0.61	**0.72**	0.78	0.86	2.19	1.32
			B	353	2.96	0.48	0.66	0.75	0.79	2.25	1.52
			C	671	1.82	0.06	0.09	0.10	0.17	1.39	1.76
			D	135	2.13	0.02	0.08	0.09	0.20	2.11	1.67
			All	1908	2.30	0.09	0.19	0.30	0.48	2.09	1.58
		Asian	A	327	2.53	0.53	**0.65**	0.79	0.95	2.41	1.68
			B	115	2.45	0.64	0.75	0.87	1.04	2.16	1.83
			C	164	1.68	0.09	0.09	0.14	0.14	1.29	1.78
			D	33	2.18	0.01	0.01	0.35	0.62	2.40	2.10
			All	639	2.28	0.14	0.24	0.53	0.63	2.18	2.01
		Other/multiracial	A	155	2.61	0.55	**0.62**	0.85	0.91	2.13	1.32
			B	45	2.37	0.20	0.60	0.69	0.69	2.08	1.85
			C	102	1.52	0.04	0.04	0.07	0.08	1.05	1.63
			D	16	1.47	0.04	0.04	0.05	0.07	1.49	1.75
			All	318	2.17	0.04	0.08	0.14	0.56	1.92	1.58
	All	All	All	12,604	2.53	0.13	0.22	0.42	0.61	2.14	1.85

Continued

Table 3 Continued

Age group	Gender	Race or ethnicity group	Effort	n	Mean	Quantile 2.5	Quantile 5*	Quantile 7.5	Quantile 10	Quantile 50 (median)	IQR
Adult	Male	Hispanic	A	1464	8.49	2.20	**2.56**	2.80	2.99	7.46	8.34
			B	491	8.68	2.28	2.60	2.91	3.20	7.76	7.38
			C	436	7.47	0.28	0.78	1.23	1.43	5.74	7.25
			D	275	8.76	0.80	2.19	2.45	2.63	8.17	10.88
			All	2666	8.39	2.01	2.21	2.52	2.70	7.30	8.31
		White	A	2788	11.94	2.08	**2.27**	2.46	2.69	9.05	12.44
			B	550	11.07	2.12	2.43	2.56	2.95	8.69	10.69
			C	781	13.21	0.13	0.64	1.93	2.03	10.85	17.12
			D	231	12.14	1.50	2.27	2.58	2.80	10.37	9.86
			All	4350	12.06	2.02	2.16	2.38	2.56	9.39	12.82
		Black	A	1988	9.42	2.21	**2.43**	2.80	2.99	7.69	9.36
			B	620	10.24	2.23	2.43	2.80	3.02	8.33	9.83
			C	833	8.89	0.15	0.24	0.39	1.24	6.20	10.31
			D	306	7.37	0.22	0.24	0.24	0.39	6.23	7.60
			All	3747	9.28	0.39	2.14	2.27	2.65	7.29	9.44
		Asian	A	1072	7.02	2.05	**2.17**	2.31	2.42	5.47	5.27
			B	291	8.06	2.16	2.29	2.58	3.01	6.12	5.61
			C	327	7.45	1.15	1.39	1.73	1.90	4.45	6.56
			D	165	8.27	2.09	2.18	2.23	2.51	6.81	6.55
			All	1855	7.36	1.90	2.10	2.23	2.35	5.51	5.62
		Other/multiracial	A	270	11.76	1.97	**2.10**	2.16	2.19	7.07	7.33
			B	52	11.00	2.04	2.30	2.46	2.51	5.39	5.88
			C	80	13.46	1.25	1.98	1.99	2.11	7.08	19.02
			D	17	9.61	1.24	1.24	1.67	2.22	5.14	7.69
			All	419	11.96	1.97	2.10	2.13	2.18	7.07	7.77

Continued

Table 3 Continued

Age group	Gender	Race or ethnicity group	Effort	n	Mean	Quantile 2.5	Quantile 5*	Quantile 7.5	Quantile 10	Quantile 50 (median)	IQR
	Female	Hispanic	A	1260	5.42	2.09	**2.21**	2.33	2.40	4.72	3.91
			B	554	5.55	2.11	2.30	2.46	2.57	4.72	3.72
			C	526	4.39	0.06	0.15	0.18	0.58	3.72	3.85
			D	268	4.68	0.24	0.56	1.03	1.89	4.39	3.90
			All	2608	5.17	0.58	1.99	2.13	2.24	4.44	3.86
		White	A	2438	8.35	2.09	**2.24**	2.42	2.70	6.25	6.63
			B	480	7.63	2.05	2.26	2.38	2.65	5.31	5.65
			C	583	7.16	0.45	0.86	1.16	1.84	4.73	6.63
			D	190	8.34	1.69	2.26	2.41	2.58	5.61	6.54
			All	3691	8.10	2.03	2.14	2.28	2.51	5.80	6.52
		Black	A	1914	6.02	2.14	**2.30**	2.39	2.52	4.92	4.13
			B	629	5.92	2.11	2.25	2.38	2.48	5.00	4.29
			C	879	5.18	0.14	0.25	0.47	0.92	3.75	4.64
			D	269	5.69	0.06	0.11	0.47	1.09	4.20	5.09
			All	3691	5.79	0.47	1.62	2.12	2.25	4.58	4.36
		Asian	A	905	5.17	2.08	**2.14**	2.19	2.25	3.74	3.24
			B	309	5.79	2.04	2.14	2.18	2.27	4.13	4.08
			C	348	4.11	0.18	0.33	0.49	0.97	2.85	2.29
			D	120	5.71	0.23	0.97	1.22	2.18	4.08	4.15
			All	1682	5.10	0.97	1.90	2.08	2.16	3.58	3.34
		Other/multiracial	A	205	6.16	1.85	**2.09**	2.24	2.24	4.16	3.67
			B	25	4.93	1.93	1.99	2.12	2.19	4.65	5.98
			C	96	3.25	0.07	0.07	0.16	0.41	2.13	2.60
			D	22	4.00	0.07	0.13	0.33	0.48	2.82	5.35
			All	348	5.21	0.29	0.43	0.60	1.66	3.25	3.47
	All	All	All	25,057	9.05	1.24	2.08	2.21	2.34	5.82	7.28
All	All	All	All	37,661	7.64	0.25	0.65	0.96	1.18	3.90	5.63

Effort grades: A, exceeds the minimum ATS criteria (three acceptable and two reproducible curves); B, meets ATS criteria (three acceptable and two reproducible curves); C, potentially usable value, but does not meet ATS standards, and estimates are usually based on two curve results with values within 200 mL of each other; D, questionable results, use with caution.

*The fifth percentiles in children and adults.

AEX-FV, area under the expiratory flow-volume; ATS, American Thoracic Society; BTPS, body temperature ambient pressure saturated.

Response Log(AEX-FV)

Term	Estimate	Standard Error	t Ratio	p	Main Effect
Intercept	-1.029	0.0450	-22.85	<0.0001	
Age (years)	0.026	0.0002	159.38	<0.0001	0.39
Height (m)	1.090	0.0230	39.39	<0.0001	0.17
Gender [Male]	0.126	0.0034	37.44	<0.0001	0.44

Source	R^2	RASE
Training Set	0.51	0.55
Validation Set	0.52	0.54
Testing Set	0.52	0.54

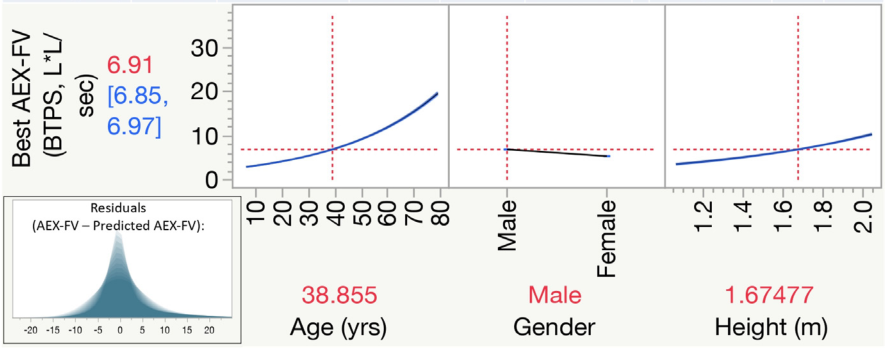

Figure 5 Model for the variable LogAEX-FV (natural logarithm of the area under the expiratory flow-volume curve) based on age (years), height (m) and gender (the coefficient is positive for males and negative for females). The main effects listed represent the variable contribution, as assessed by the dependent resampled inputs method (using k nearest neighbors' technique). BTPS, body temperature ambient pressure saturated; R^2, per cent of variance explained by the model; RASE, square root of the mean squared prediction error.

was under-represented in the NHANES cohorts. Third, the differences between whites and Hispanics were both statistically and clinically relevant, while the FEV_1, FVC and FEV_1/FVC were very similar, perhaps in line with the fact that they share same GLI predictive equations. This points toward the fact that these new spirometric measurements may be able to better separate normal lung function in non-Hispanic whites versus Hispanics of either Mexican or non-Mexican origin.

Several authors have also derived and published the past linear regression-based predictive equations for normal AEX-FV, based on subjects' age, gender and/or height.[20 23] We also found in a PFT laboratory/clinic cohort, which combined normal participants from the Madrid area of Spain and individuals with normal spirometry from Cleveland, Ohio, USA, that a neural network approach (machine learning or artificial intelligence methods) may be superior to other modeling techniques in defining predicted values and LLNs.[12] In the current study, performed using NHANES cohorts (which are more closely representative of the general US population), we aimed to accomplish acceptable model performance by using simple regression models. The overall R^2 of our current regression models was approximately 0.52, suggesting that the models can be further refined or that factors other than those considered may be of importance. If a testing parameter, that is, the duration of the exhalation (FET), was added to the models, the R^2 increased to ~0.79. While the NHANES cohorts did not exclude those with a history of past or present cigarette smoking, neither smoking status nor smoking intensity significantly influenced the normative data, nor the LLNs in the 2007–2012 surveys. In a previous analysis on acceptable flow-volume curves with the integral function flow by volume variable using best tests for comparison (data not published), we have found that the intraindividual coefficient of variation for best AEX-FV was comparable with that of FVC or FEV_1, that is, $<10\%$ both before and after bronchodilator administration. Here, the mean interindividual coefficient of variation of the best AEX-FV was 2% in children and 9% in adults, respectively, also comparable with the interindividual coefficients of variation for FEV_1 and FVC. These analyses confirm that the reproducibility of these tests is excellent and could be used confidently for functional assessments.

The present study has several strengths. First, this is a computation of these global measurements of respiratory physiology derived from simple spirometry signals. Second, the present derivation of LLN values was done on a very large cohort, representative of the US household population. Third, we derived predictive models for the AEX-FV by using the simplest regression models (ie, not resorting to optimized regression techniques or artificial neural networks), which makes it widely accessible. Fourth, our study found significant differences between various demographic groups, thereby offering to become a useful tool in defining normal respiratory function in various populations. Lastly, the evaluation of the effects of bronchodilator administration on these measurements, while limited to 'only' 1565 individuals (6531 tests), warrants further exploration, as it may become a useful global tool to assess bronchodilator responsiveness.

Several limitations of this investigation also warrant comment. First, to assure the generalizability of our observations, the computed AEX-FV measurements require further investigation in patients with different pathologies or disease pheno/endotypes, that is, in chronic obstructive pulmonary disease, asthma, small airway disease, restrictive disorders. Second, the 2007–2012 NHANES cohorts included relatively few individuals of Asian origin, hence their normative values may lack the precision of the other ethnic or racial groups. This limitation could be overcome in the future by extending the geographic coverage and the diversity of the pooled tests. Third, the NHANES study did not exclude those with a history of past or present cigarette smoking (an older criticism of the NHANES cohorts being representative of the 'normal' US population). While in our analyses on the 2007–2012 surveys, smoking status and its intensity did not significantly influence neither the normative data nor the LLNs, the effects of recall bias and/or secondary smoking exposure could not be completely eliminated. Fourth, standard spirometry is done today in the sitting position, which was not the default position in the NHANES examinations. Once made available on standard commercial PFT platforms, these assessments need to be reproduced in future cohorts and testing conditions. Fifth, the AEX measurements may not be easily available on most spirometry testing equipment at this time. However, digital PFT platforms could very easily resolve the calculation of the AEX for flow-volume curves by computing the integral function of the Y variables versus the X inputs and include them in the standard reporting systems. Lastly, the utility of different AEX measurements needs to be further explored over a broad spectrum of respiratory impairments and disease severities.

CONCLUSION

While traditional spirometry measurements inform clinical management in important ways, it is conceivable that newer measurements may add materially to the diagnostic value of spirometry. Specific questions include: how much actionable information can these new parameters provide about respiratory physiology impairments or levels of disability, and what is the separation between normal and abnormal by using 'hard' LLN? In an era of advanced digital signal processing, now is the time to explore new technologies and other innovative ways of assessing respiratory function. Fortunately, several new metrics are still available in spirometry, and their contribution to clinical assessment has yet to be fully evaluated. To address this gap, the current analysis computed actual and predicted values of AEX-FV curves, prompting consideration of how these new parameters can inform clinically meaningful distinctions in patients.

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