Percentiles of Inspiratory Capacity in Healthy Nonsmokers: A Pilot Study

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Key Words

Inspiratory capacity • Lung function tests • Reference values • General population • Quantile regression

Abstract

Background: Over the past decade inspiratory capacity (IC) has received increasing attention, especially in studies on chronic obstructive pulmonary disease. Though a few recent studies provide reference values for IC, still little is known on the distribution of its values in healthy subjects. **Objective:** To estimate percentiles of IC in a sample of healthy nonsmokers by applying quantile regression. **Methods:** We applied quantile regression to estimate seven percentiles of IC from 5 to 95% for a given age, height and body mass index, separately in males and females, in a sample of 411 healthy nonsmokers, aged 8–73 years, drawn from the general population in Northern Italy. **Results:** The magnitude and statistical significance of the effect of age, height and body mass on IC varied across percentiles and between genders. When the 50th percentile of IC was compared with the predicted values of several studies, including those published by the European Community for Coal and Steel, the differences were as large as 0.86 liters in males and 0.90 liters in females. The

possible advantage of the 5th percentile predicted from quantile regression over the 'traditional 5th percentile' as lower limit of normal was also illustrated. **Conclusions:** Inference on percentiles, rather than just the mean, of IC and other lung function measures may help in the future to better understand the effect of various risk factors, model growth curves and derive more accurate reference values.

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Introduction

The inspiratory capacity (IC) is defined as the maximal amount of air that can be inhaled from the end-expiratory lung volume. The direct measure of IC through spirometry has been demonstrated to be simple and reliable [1].

In recent years IC has received increasing attention, particularly when evaluating chronic obstructive pulmonary disease (COPD) patients. IC has been shown to be a predictor of exercise tolerance, reflecting the presence of dynamic hyperinflation [2, 3]. Increases in IC have been measured to assess the beneficial effects of inhaled anticholinergics and β_2 -agonists, either singly or

combined, on reduction of lung hyperinflation at rest and during exercise [4, 5]. IC has also been used to evaluate reduction of hyperinflation after respiratory rehabilitation programs [6, 7] or long-term home nocturnal noninvasive positive pressure ventilation [8] or best individualized level of continuous positive airways pressure [9]. Importantly, percent predicted values of IC [10] and IC corrected by total lung capacity (TLC) [11] have been shown to be independent predictors of mortality in COPD patients.

Percent predicted values of IC reported in most respiratory pathophysiological and clinical studies are usually computed by using the European Community for Coal and Steel (ECCS) equations published in 1983 [12]. The ECCS equations are based on pooled prediction equations, not on the original lung function data, derived from multiple cohorts of 'normal' subjects collected in the 13 years before their publication. For these summary equations, predicted values of IC are calculated indirectly by taking the difference between the predicted TLC and predicted functional residual capacity (FRC), which were also provided by different methods of measurements (for example, plethysmographic method or dilutional method with helium or nitrogen gas). Only a few more recent studies provide reference values for IC [13–16], and they are mainly based on small samples of subjects within limited age ranges.

Despite the increasing use of IC in respiratory research, however, little is known on the age-dependence relationship of this lung function parameter in healthy subjects from childhood to elderly. The availability of existing data from the Po delta epidemiological study carried out in Italy in the 1980–1990s gave us the opportunity to explore this relationship. A number of papers on several lung function measurements collected in the Po delta study, including flow-volume curve indexes and slow expiratory vital capacity (VC) [17], residual volume (RV) [18], diffusing capacity indexes [19] and single breath nitrogen test indexes [20], have been published previously.

We performed a pilot study aiming to estimate percentiles of IC in a sample of healthy nonsmokers participating in the Po delta study by applying a new statistical approach: quantile regression. Only recently has this statistical method been introduced in biomedical applications [21–24]. We also compared the estimated median values of IC with predicted values from other studies.

Material and Methods

Po River Delta Study

The data were collected in 1988–1991 in Northern Italy on 2,841 subjects who participated in the second survey of the Po river delta study. Previous publications describe in detail study methods and main results, including reference values for lung function tests [17–20, 25, 26].

Study subjects provided verbal informed consent to voluntarily participate in both surveys. Italian law did not require the approval of Ethics Committee at the time of the field surveys. However, prior to submission, an expert waiver on ethical issues related to the publication of the data analyzed in this study was released by an Internal Review Board of the Institute of Clinical Physiology, National Research Council, Pisa, Italy (where the study was conducted).

Lung Function Measurements

A computerized pneumotachograph (Fleish No. 3, Pulmonary System 47804/S; Hewlett-Packard, Waltham, Mass., USA) was used. The pneumotachograph was heated at 37°C, and volumes reported in liters at BTPS. Volume calibration was performed daily using standard syringe (3 liters). The measurement protocol fulfilled the American Thoracic Society recommendations [27]. IC was recorded during the maneuver to measure VC. Subjects connected to a mouthpiece and wearing a nose clip in the seated position performed at least 4 regular tidal volumes, inhaled up to TLC and then exhaled to RV. End-expiratory lung volume was computed by averaging the baseline signal of at least 4 regular tidal volumes, while TLC was identified as the maximal volume signal. At least two maneuvers were repeated to obtain a satisfactory VC value. The two largest VC values were not allowed to vary by more than 5%. IC was the volume of air inhaled starting from end expiratory lung volume to TLC. The IC measurement from the maneuver yielding the highest VC was used for statistical analyses.

Selection of Subjects

The subjects were selected by excluding from the entire sample (2,841 subjects) those who reported past or current smoking history, including occasional (1,264 remaining subjects), occupational exposure (1,042 remaining subjects), respiratory symptoms, medical diagnosis of emphysema, asthma or chronic bronchitis, self-reported allergic rhinitis, chest injuries, cardiorespiratory and neurological diseases, hypertension, and childhood respiratory diseases (437 remaining subjects). Further, we excluded those who did not meet measurement protocol recommendations (411 remaining subjects). Data were obtained by the interviewer-administered CNR questionnaire, a modified version of the National Heart, Lung and Blood Institute questionnaire [17].

Statistical Methods

Descriptive statistics (mean, median, first and third quartile) were obtained in males and females separately. Quantile regression models [28] were estimated separately in males and females for seven percentiles: 5th, 10th, 20th, 50th, 80th, 90th and 95th. The dependent variable was IC and the independent variables were age (years), height (centimeters) and body mass index (BMI). Departure from linearity was tested for all the covariates as follows: for each covariate a quadratic term, one-knot and two-knot natural cubic splines were introduced, one at a time, in the regres-

Fig. 1. Observed IC values (dots) and predicted values for the 95th (top curve), the 50th (middle) and the 5th (bottom) percentile of IC in healthy male nonsmokers.

Fig. 2. Observed IC values (dots) and predicted values for the 95th (top curve), the 50th (middle), and the 5th (bottom) percentile of IC in healthy female nonsmokers.

Table 1. Descriptive statistics for the five continuous variables included in the quantile regression models among the healthy nonsmoking males and females

	Males (n = 147)					Females (n = 264)				
	mean	SD	percentiles			mean	SD	percentiles		
			25%	50%	75%			25%	50%	75%
Age, years	20.37	12.43	13.00	16.00	24.00	30.96	17.31	17.00	24.50	44.50
Height, cm	164.14	14.44	156.00	166.00	175.00	157.89	7.27	153.00	158.00	163.00
Weight, kg	61.86	18.66	49.00	63.00	74.00	58.42	12.86	52.00	56.50	65.00
BMI, kg/m ²	22.42	4.40	19.29	22.06	24.91	23.40	4.90	20.14	22.63	25.69
IC, liters	2.73	0.82	2.09	2.78	3.39	2.26	0.44	2.00	2.26	2.53

n = Sample size; SD = standard deviation; BMI = body mass index; IC = inspiratory capacity.

sion model. They did not significantly improve the fit and were removed from the final model. *p* values and confidence intervals for the estimates of the regression coefficients were obtained by generating 1,000 bootstrap samples [29].

The 5th, 50th and 95th percentiles of IC shown in figures 1 and 2 were calculated for age-specific average height and average BMI, which were obtained by smoothing height and BMI values over age using Lowess regression [30] with bandwidth equal to 0.8.

Figure 3 shows Bland-Altman scatter plots [31] to compare the predicted 50th percentile for IC with the predicted mean IC in males and females from the following studies: ECCS [12], Roca et al. [13], Neder et al. [14], Boskabady et al. [15] and Tantucci et al. [16]. The difference in the *y*-axis is calculated by subtracting the predicted mean IC in each study from the predicted 50th percentile from quantile regression. In each comparison predictions are

compared over the age range suggested in the corresponding paper. The comparison with Tantucci et al. [16] is conducted only in females because in males our age range did not overlap with theirs.

We also calculated the cutoff values for IC by applying the more popular 'percentage of predicted' method. These are shown in table 5. They were calculated as follows: for each subject in our sample we estimated the expected IC value from linear regression with age, height and BMI as independent variables separately by males and females. Then, for each subject, we computed the ratio between the observed IC measure and the predicted value from linear regression. The percentage of predicted reported in table 5 is the percentile of the distribution of the observed-to-predicted ratios.

All statistical analyses were performed in Stata version 11 (Stata Corporation, College Station, Tex., USA).

Table 2. Quantile regression models to predict seven percentiles (5th, 10th, 20th, 50th, 80th, 90th, and 95th) of inspiratory capacity in males

Percentile		Estimate	p value	95% CI	
5%	BMI	0.0097	0.8070	-0.0685	0.0878
	Height	0.0340	<0.0001	0.0194	0.0486
	Age	0.0029	0.6910	-0.0115	0.0173
	Constant	-3.7764	<0.0001	5.6844	1.8683
10%	BMI	0.0514	0.0920	-0.0086	0.1114
	Height	0.0346	<0.0001	0.0244	0.0447
	Age	0.0027	0.6670	0.0148	0.0095
	Constant	-4.4922	<0.0001	5.5874	3.3970
20%	BMI	0.0503	0.0140	-0.0104	0.0902
	Height	0.0367	<0.0001	0.0291	0.0444
	Age	0.0005	0.9310	0.0126	0.0116
	Constant	-4.7229	<0.0001	5.6813	3.7644
50%	BMI	0.0552	<0.0001	-0.0366	0.0738
	Height	0.0375	<0.0001	0.0304	0.0446
	Age	0.0019	0.7440	0.0097	0.0135
	Constant	-4.7090	<0.0001	5.7187	3.6992
80%	BMI	0.0355	0.0120	0.0081	0.0629
	Height	0.0419	<0.0001	0.0333	0.0505
	Age	0.0079	0.0670	0.0005	0.0164
	Constant	-4.7791	<0.0001	5.7141	3.8441
90%	BMI	0.0311	0.0050	0.0094	0.0528
	Height	0.0449	<0.0001	0.0386	0.0513
	Age	0.0073	0.0170	0.0013	0.0134
	Constant	-5.0288	<0.0001	5.8169	4.2407
95%	BMI	0.0398	0.0220	0.0058	0.0739
	Height	0.0464	<0.0001	0.0357	0.0570
	Age	0.0026	0.6530	0.0090	0.0142
	Constant	-5.2491	<0.0001	6.4250	4.0733

BMI = Body mass index; 95% CI = 95% confidence interval.

Note: These equations are derived within the following ranges observed in males of our sample: age (8–65 years), height (129–194 cm); and BMI (13–38 kg/m²).

Example to compute the 5 and 95% percentile in a male with age = 20 years, height = 180 cm, and BMI = 21.91 kg/m²: Predicted 5% = 0.0097 × BMI + 0.0340 × Height + 0.0029 × Age – 3.7764 = 2.61 liters. Predicted 95% = 0.0398 × BMI + 0.0464 × Height + 0.0026 × Age – 5.2491 = 4.02 liters.

Results

Table 1 shows the descriptive statistics of our sample data for the five continuous variables included in the quantile regression models: IC, age, height, weight and BMI. On average, the 147 healthy nonsmoking males were younger, taller, heavier and with larger IC values

Table 3. Quantile regression models to predict seven percentiles (5th, 10th, 20th, 50th, 80th, 90th, and 95th) of inspiratory capacity in females

Percentile		Estimate	p value	95% CI	
5%	BMI	0.0091	0.3360	-0.0094	0.0275
	Height	0.0346	<0.0001	0.0226	0.0465
	Age	0.0026	0.5080	-0.0051	0.0103
	Constant	-4.0224	<0.0001	5.9492	2.0956
10%	BMI	0.0075	0.4470	-0.0119	0.0269
	Height	0.0369	<0.0001	0.0293	0.0445
	Age	0.0025	0.4180	-0.0035	0.0085
	Constant	-4.3042	<0.0001	5.5421	3.0663
20%	BMI	0.0196	0.1360	-0.0062	0.0454
	Height	0.0345	<0.0001	0.0254	0.0436
	Age	0.0015	0.5790	-0.0039	0.0069
	Constant	-4.0065	<0.0001	5.5704	2.4426
50%	BMI	0.0255	0.0380	0.0014	0.0496
	Height	0.0299	<0.0001	0.0224	0.0374
	Age	0.0038	0.1260	-0.0011	0.0087
	Constant	-3.1524	<0.0001	4.4096	1.8951
80%	BMI	0.0255	0.0190	0.0043	0.0468
	Height	0.0333	<0.0001	0.0256	0.0410
	Age	0.0057	0.0310	0.0005	0.0108
	Constant	-3.4780	<0.0001	4.6467	2.3093
90%	BMI	0.0250	0.0350	0.0018	0.0483
	Height	0.0318	<0.0001	0.0204	0.0432
	Age	0.0070	0.0070	0.0019	0.0120
	Constant	-3.1511	<0.0001	4.8721	1.4300
95%	BMI	0.0274	0.0770	0.0029	0.0577
	Height	0.0444	<0.0001	0.0284	0.0605
	Age	0.0067	0.0120	0.0015	0.0119
	Constant	-5.0584	<0.0001	7.2595	2.8573

BMI = Body mass index; 95% CI = 95% confidence interval.

Note: These equations are derived within the following ranges observed in females of our sample: age (8–73 years), height (130–178 cm), and BMI (13–40 kg/m²).

For an example to compute the 5 and 95% percentile, see table 2.

than the 264 healthy nonsmoking females. BMI values were comparable between males and females.

Figures 1 (males) and 2 (females) show the IC against age in healthy nonsmokers from childhood (8 years of age) to the elderly (65 and 73 years of age in males and females, respectively). The figures show the observed IC values (scattered dots) and the 5th, 50th and 95th percentiles of IC (solid curves), with age-specific average height and BMI as derived from the quantile regression models. The percentiles rapidly increase in the first 20 years and

Fig. 3. Bland-Altman scatter plots to compare the predicted 50th percentile for IC from quantile regression in the present study with the predicted mean IC from various studies: ECCS [12] (first row), Roca et al. [13] (second row), Neder et al. [14] (third row), Boskabady et al. [15] (fourth row) and Tantucci et al. [16] (fifth row). The plots in the left column refer to males and the plots in the right column refer to females. In each comparison predictions

were compared over the age range suggested in the corresponding paper. The comparison with Tantucci et al. [16] is conducted only in females because data did not overlap in the same age range in males. The difference in the y-axis is calculated by subtracting the predicted mean IC in each study from the predicted 50th percentile from quantile regression.

level off or slowly decrease afterward. The spread among percentiles increases along with age in both genders.

Tables 2 and 3 give the estimates for the quantile regression models in males and females, respectively. Seven percentiles are reported: 5th, 10th, 20th, 50th, 80th, 90th and 95th. In both genders, height is the single most important predictor of the observed IC values in the healthy nonsmoking subjects for all percentiles considered. Height is significant throughout the percentiles and across genders. BMI and age improve prediction accuracy, especially in the higher percentiles. In males and females the estimated magnitude of the effect of height on IC is similar across all percentiles, whereas that of BMI

and age seems to be more conspicuous in the higher percentiles. For example, in females the 10th percentile of IC increases by 37 ml for a 1-cm increase in height, by 8 ml for an increase of 1 kg/m² in BMI and by 3 ml for a 1-year increase in age, whereas the 90th percentile of IC increases by 32 ml for a 1-cm increase in height, by 25 ml for an increase of 1 kg/m² in BMI and by 7 ml for a 1-year increase in age.

Figures 3 shows the Bland-Altman plots to compare the present 50th percentile of IC with the predicted mean values from several studies. The predictions for ECCS are indirectly computed by subtracting predicted FRC from predicted TLC. The predicted 50th percentiles are

Table 4. Observed data and predicted percentiles for inspiratory capacity in three women non-randomly selected from the present sample

Observed data					Predicted percentiles for IC						
ID	age, years	height, cm	BMI, kg/m ²	IC, liters	5%	10%	20%	50%	80%	90%	95%
1	45	159	21.76	1.69	1.79	1.84	1.97	2.33	2.63	2.77	2.91
2	60	153	29.90	2.48	1.69	1.71	1.95	2.41	2.73	2.88	2.96
3	29	158	23.63	2.74	1.73	1.77	1.95	2.28	2.56	2.67	2.81

BMI = Body mass index; IC = inspiratory capacity.

Table 5. Observed proportions of healthy individuals below seven percentiles of normal as predicted by two methods: 'quantile regression' and the 'percentage of predicted'

Age	n	Expected proportion						
		5%	10%	20%	50%	80%	90%	95%
<i>Quantile regression</i>								
0–19	196	4.1	8.2	18.9	51.0	80.1	89.3	94.4
20–39	116	5.2	12.1	20.7	47.4	80.2	90.5	94.8
40–59	75	5.3	8.0	18.7	45.3	78.7	89.3	94.7
60+	24	4.2	12.5	20.8	58.3	75.0	83.3	91.7
Total	411	4.6	9.5	19.5	49.4	79.6	89.3	94.4
<i>Percentage of predicted</i>								
0–19	196	3.1	7.7	17.9	52.0	80.6	87.8	93.9
20–39	116	4.3	11.2	21.6	48.3	83.6	94.0	97.4
40–59	75	8.0	12.0	21.3	44.0	74.7	92.0	97.3
60+	24	12.5	16.7	25.0	58.3	75.0	83.3	87.5
Total	411	4.9	10.0	20.0	49.9	80.0	90.0	95.1

more similar to the mean predictions of Roca et al. [13] both in males and in females, and Tantucci et al. [16] in females (all differences within about 0.5 liters), than to those of the ECCS (largest differences: –0.86 in males, 0.90 in females), Neder et al. [14] (largest differences: –1.23 liters in males, 0.49 in females) and Boskabady et al. [15] (largest differences: 1.12 liters in males, 0.86 in females).

The possible applicability of the quantile regression percentiles when evaluating any given individual IC measure is illustrated in table 4. It shows the values observed in three women nonrandomly selected from our sample, for IC, age, height and BMI, along with the predicted percentiles of IC, computed according to the equations in table 3. For example, IC of the first woman (1.69 liters) falls below the 5th percentile of IC, of the second (2.48

liters) between the 50th and the 80th, and of the third (2.74 liters) between the 90th and the 95th.

Using percentiles derived by quantile regression also offers the opportunity to overcome potential limits of using the 'traditional 5th percentile' as lower limit of normality. For illustration, table 5 reports the observed proportions of healthy individuals below seven percentiles of normal as predicted by two methods: quantile regression and percentage of predicted. The former is based on the predictive equations in tables 2 and 3, and the latter is based on the percentile of the observed distribution of the individuals' observed-to-predicted ratios for IC. For quantile regression the observed proportions within the table are fairly close to the nominal expected proportion listed in the second row of the header (that is, 5, 10, 20, 50, 80, 90 and 95%). On the contrary, the percentage of predicted method shows a correct overall proportion (bottom total row), but it is incorrect in nearly all age groups. For example, for the 5%, the percentage of predicted method underestimates the proportion of healthy subjects by a factor of 0.62 (3.1/5.0) in the age group 0–19 years and overestimates it by a factor of 2.5 (12.5/5.0) in the group above 60 years.

Discussion

Over the past decade IC has been used increasingly in numerous settings, especially in clinical and pathophysiological studies on COPD [2, 4–6, 8–11]. Yet, little is known on the growth and decline of IC over time on healthy nonsmokers. The scarcity of reference values of normality for this parameter of lung function has been acknowledged [10, 32]. In this study we applied quantile regression to model IC over age and obtain percentiles of IC from a sample of healthy nonsmokers aged 8–73 years, selected from a general population sample living in Northern Italy.

Quantile Regression Percentiles of IC

While the statistical theory of quantile regression has long been known, its medical applications have appeared only recently [21–24]. Quantile regression has many advantages over ordinary linear regression [23, 33]. Among them, its inference is unaffected by the presence of outlying values in the sample data, it is more robust to measurement errors and it makes no distributional assumptions (for example, normality) about the residuals of regression [28].

Quantile regression has proved particularly useful when estimating percentiles of some variable of interest given some observed characteristics [21]. It is related to the lambda-mu-sigma method [34, 35]. Unlike lambda-mu-sigma, quantile regression can be estimated on widely available statistical software (such as SAS quantreg procedure, Stata qreg command, R quantreg library) [21, 23]. We used quantile regression to model IC throughout the entire age span of a general population sample and calculate percentiles of IC for any given individual's age, height and BMI. Any observed IC value can also be placed within a range of percentiles, as exemplified in table 4. This may provide added value when evaluating individual lung function measurements. Typically, values that fall below the 5th percentile may be considered abnormal. We believe that using percentiles of normality also for all other lung function measures might contribute to improve accuracy and insight in clinical practice [21].

In a simulation study [36] it was found that predicting the 5th percentile of normality for any given index of lung function by applying quantile regression consistently provided better estimates of the proportions of normal subjects than traditional methods, such as the 95th percentile of normality [17] and the methods based on estimates of the mean and the standard deviation from linear regression [12]. The results shown in table 5, commented on in the Results section above, illustrate this.

In addition to abnormally low IC values (that is, values below the 5th percentile), the present set of reference percentiles allows for the detection of abnormally high IC values (that is, values above the 95th percentile) for a further characterization of an individual lung function measurement.

Percentiles of IC could be monitored from childhood to elderly. Percentile crossing with ageing, either upward or downward, may be suggestive of abnormal growth. In this respect, percentiles of IC are similar to the popular growth charts for height and weight. When applied to

children, they may help assess the growth of IC at early stages of development.

Like our previous reference equations [17], the percentiles of IC are continuous over the entire age range. Unlike these previous equations and other important published material on this topic [37, 38], however, splines for modeling the nonlinear growth of IC over time did not improve the fit of the regression models, after height and BMI were adjusted for. Lack of statistical power may in part explain this difference.

Predictors and Existing Predictive Values of IC

Our data confirm that height is the best predictor of lung volume, to which IC is strongly related. In combination with height, BMI significantly improved prediction of IC. The effect of BMI was more evident among the higher percentiles of IC. Our sample was chiefly comprised of nonobese individuals, only 7% had BMI greater than 30 for whom BMI could represent a proxy measure for body type (e.g. slim vs. stout) rather than a measure of obesity. Including BMI in the regression models could help differentiate the predicted percentiles of IC of healthy individuals with different body type. It is well known that lung volumes decrease as body weight increases. Lung volumes, particularly FRC and expiratory reserve volume, have been shown to decrease exponentially with increasing BMI, an effect occurring even at BMI values lower than 30 [39]. BMI has also been shown to affect longitudinal decline of VC and indexes from the flow-volume curve, including forced VC as well as forced expiratory volume in 1 s [40].

We compared the present percentiles of IC with several other equations. The predicted 50th percentiles are similar to the mean predictions of Roca et al. [13] in both sexes and Tantucci et al. [16] in females, but they differ from those of the other equations (ECCS [12], Neder et al. [14], Boskabady et al. [15]). Differences may be due to several factors, which include different populations, different sets of predictors (for example, most do not include BMI), different age range considered and possible lack of power. For the ECCS summary equations, differences can also be partly accounted for by the methodology used for computing IC predicted values. While we estimated IC predicted values from direct measures of IC, ECCS predicted values were computed indirectly as the difference between predicted values of TLC and FRC. The resulting ECCS prediction for IC cumulated the error inherent in the predictions for both TLC and FRC. Note that all other studies predict the mean IC, not the median as quantile regression does, and that the mean is equal to

the median only if the conditional distribution of IC was perfectly symmetrical, which is hardly to be expected in general. The Bland-Altman plots are therefore to be interpreted with caution.

IC values may be measured during an inspiratory or an expiratory slow VC maneuver, though there are not clear recommendations on which method is preferable and no discriminating studies have specifically addressed this issue. We observed predicted IC 50th percentiles similar to the mean predictions of Roca et al. [13] in both sexes and Tantucci et al. [16] in females, who used IC measurements obtained from an expiratory slow VC maneuver as we did (fig. 3).

Limits and Strengths

In the present work we opted for strict inclusion criteria when selecting the sample of healthy subjects. Although this reduced the number of subjects available to the analysis, particularly for males over 50 years of age, it ensured high quality of our inference. The number of selected healthy nonsmoking males ($n = 147$) was just below the limit ($n = 150$) recently indicated by Quanjer et al. [38] as necessary to validate reference values to avoid spurious differences due to sampling error. Despite the relatively small sample size, however, the confidence intervals for the quantile regression coefficients, which reflect the sampling variability, were quite narrow. The confidence intervals were obtained by the bootstrap method. The validity of these confidence intervals was discussed by Buchinsky [41], who showed that they perform well even with sample sizes as small as 100 observations. Under the assumption that the decline of IC with age in the elderly is approximately linear, as for related indexes as forced VC, the estimate for the 5th percentile might still be satisfactorily accurate.

As the percentiles from the present pilot study are based on a relatively limited dataset collected in a specific geographical area about 20 years ago, they are not immediately applicable in clinical practice. Applying the proposed percentiles as reference for current measurements of IC observed in subjects from other geographical areas should be preceded by an evaluation of its applicability to the new study subjects. When assessing lung function in clinical practice, percentiles of IC from the present pilot study or other future studies should be interpreted in conjunction with other pulmonary functions. The reference equations for other lung function indexes derived from healthy nonsmokers from the same epidemiological study have been published previously and included flow-volume curve indexes and VC [17], RV

[18], diffusing capacity indexes [19] as well as single breath nitrogen test indexes [20].

The present study has several strengths. First, it provides a description of growth and decline of IC in healthy nonsmokers from a general population sample over a wide age range starting from childhood, which is lacking in respiratory literature. Second, it illustrates the use and interpretation of quantile regression to analyze lung function data and derive reference values. Finally, the present study may provide some insight on the potential limits of using the traditional 5th percentile as lower limit of normality.

Conclusions

We applied quantile regression to describe percentiles of IC in a sample of healthy nonsmokers as they vary with age, height, BMI and sex. Inference on percentiles, rather than just the mean, of IC and other lung function measures may in the future help to better understand the effect of various risk factors, model growth curves or derive more accurate reference values.

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