

Spirometric Reference Equations for Elderly Chinese in Jinan Aged 60–84 Years

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Abstract

Background: The interpretation of spirometry varies on different reference values. Older people are usually underrepresented in published predictive values. This study aimed at developing spirometric reference equations for elderly Chinese in Jinan aged 60–84 years and to compare them to previous equations.

Methods: The project covered all of Jinan city, and the recruitment period lasted 9 months from January 1, 2017 to September 30, 2017, 434 healthy people aged 60–84 years who had never smoked (226 females and 208 males) were recruited to undergo spirometry. Vital capacity (VC), forced VC (FVC), forced expiratory volume in 1 s (FEV₁), FEV₁/FVC, FEV₁/VC, FEV₆, peak expiratory flow, and forced expiratory flow at 25%, 50%, 75%, and 25–75% of FVC exhaled (FEF_{25%}, FEF_{50%}, FEF_{75%}, and FEF_{25–75%}) were analyzed. Reference equations for mean and the lower limit of normal (LLN) were derived using the lambda-mu-sigma method. Comparisons between new and previous equations were performed by paired *t*-test.

Results: New reference equations were developed from the sample. The LLN of FEV₁/FVC, FEF_{25–75%} computed using the 2012-Global Lung Function Initiative (GLI) and 2006-Hong Kong equations were both lower than the new equations. The biggest degree of difference for FEV₁/FVC was 19% (70.46% vs. 59.29%, *t* = 33.954, *P* < 0.01) and for maximal midexpiratory flow (MMEF, equals to FEF_{25–75%}) was 22% (0.82 vs. 0.67, *t* = 21.303, *P* < 0.01). The 1990-North China and 2009-North China equations predicted higher mean values of FEV₁/FVC and FEF_{25–75%} than the present model. The biggest degrees of difference were –4% (78.31% vs. 81.27%, *t* = –85.359, *P* < 0.01) and –60% (2.11 vs. 4.68, *t* = –170.287, *P* < 0.01), respectively.

Conclusions: The newly developed spirometric reference equations are applicable to elderly Chinese in Jinan. The 2012-GLI and 2006-Hong Kong equations may lead to missed diagnoses of obstructive ventilatory defects and the small airway dysfunction, while traditional linear equations for all ages may lead to overdiagnosis.

Key words: Aged; Reference Values; Respiratory Function Tests; Spirometry

INTRODUCTION

Lung function tests have been widely used in the diagnosis, evaluation, and screening of respiratory diseases. They play an irreplaceable role in sports medicine and the classification of occupational disease.^[1] As lung function varies with age, sex, and height, the interpretation of the results depends on predicted values that are appropriate for the participant being tested.^[2] At present, there are numerous published spirometric reference equations for Chinese populations, but these frequently include low proportions of elderly people, and few of them focus on the elderly.^[3]

The aging respiratory system has unique physiological characteristics. As a result of the decreasing thorax size,

narrowing intercostal space, and a decline in respiratory muscle function, the vital capacity (VC) and forced expiratory volume in 1 s (FEV₁) decrease gradually.^[4,5] With the decline in small airway diameter and in the amount of the supporting tissue around the airway, the airway resistance

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increases. For this reason, the small airways of the elderly are prone to collapse during forced expiration.^[6]

In 1991, the American Thoracic Society (ATS) pointed out that older people were generally underrepresented in published spirometric reference values.^[1] In 2012, the European Respiratory Society (ERS) and the Global Lung Function Initiative (GLI) analyzed the reference equations from 33 countries and regions including 97,759 reference participants. Results indicated that people older than 80 years merely account for 0.8%.^[2] The reference equations most frequently used in eastern China date to 1988, when they were established by Zhongshan hospital in Shanghai. They apply to participants aged 15–69 years.^[7] Although the equation was updated in 2011 and the age range has been changed to 19–83 years, there were only 120 participants older than 60 years in the sample.^[8]

According to the 1% national population sample survey in China, by November 15, 2015, there may be as many as 222 million people over 60 years old in China, 16.1% of the country's population. Average life expectancy increased to 76.3 years. The elderly account for a larger and larger proportion of individuals undergoing lung function tests. As a consequence, there is a strong need for reference equations that apply to the elderly. This study aimed at developing spirometric reference equations for elderly Chinese in Jinan aged 60–84 years and to compare them to existing equations for Chinese populations.

METHODS

Ethical approval

This study had been approved by the Medical Ethics Committee of Shandong University Qilu Hospital (No. 2017085). All the volunteers signed the informed consent before tests.

Study design

This was a cross-sectional study on elderly Chinese aged 60–84 years. The recruitment of volunteers started in January 1, 2017, and ended in September 30, 2017. All recruitment took place in Jinan, the provincial capital of Shandong Province. Shandong has the second largest population of any province in China and is located in the eastern coastal area.

Study population

By occupation, the volunteers included teachers, managers, accountants, cleaners, workers, drivers, civil servants, technologists, and several other professions. They were invited to participate in the lung function test if they met all of the following criteria:^[1,9,10] no history of smoking whatsoever; no chronic respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, or interstitial lung disease; no history of acute upper respiratory infection during the 4 weeks immediately preceding the tests; no respiratory symptoms such as chronic coughing, dyspnea, chest distress, or shortness of breath at the time of the examination; breathlessness as measured using the Modified British Medical Research Council (mMRC)

questionnaire score ≤ 1 ; no severe cardiovascular disease; no long-term exposure to occupational pollution such as sulfuric acid, sulfur oxide, or photochemical oxidants; and no other diseases capable of affecting lung function such as motor neuron disease or rheumatism.

All the invited volunteers accepted lung function tests and chest X-rays. The exclusion criteria were as follows: the inability to complete the lung function test in a manner consistent with quality control; chest X-ray showing pneumonia, tuberculosis, diaphragm or pleura disease, space-occupying lesion, pleural effusion, or other severe abnormalities. Rejection criteria included the following: people who did not meet the inclusion criteria but had been invited to participate by mistake; participants whose observed FEV_1/FVC (the ratio between FEV_1 and forced VC) were lower than the lower limit of normal (LLN) computed using the 2012-GLI reference equations for Northeast Asians; and height or weight is out of mean ± 3 standard deviation (SD). The results were removed from the final statistical analysis if the volunteer met any of the exclusion or rejection criteria.

Recruitment methods

Promotion stage

We put up and gave out posters to recruit healthy elderly volunteers in communities, universities serving the elderly, and senior centers.

On-site recruitment

All across Jinan, we choose four community hospitals to work with. During the annual-free health examination for elderly, which were funded by the government, our researchers worked registration in the community hospital. After recording the smoking and disease history of the residents, we explained our projects to the healthy prospective volunteers and encouraged them to join our project.

Participants recruited by phone

We screened prospective participants using the health records in the community hospitals and made phone calls to interview them. We scheduled an examination for eligible interviewee.

Data collection

All of the examinations were completed in the same hospital on identical machines. Each participant was given a questionnaire before the tests. The questionnaire involved gender, age, birth date, smoking history, disease, being hospitalized, respiratory symptoms, and mMRC score. Measured and analyzed parameters were VC, FVC, FEV_1 , FEV_1/FVC , FEV_1/VC , FEV_6 , peak expiratory flow (PEF), and forced expiratory flow at 25%, 50%, 75%, and 25–75% of FVC exhaled ($FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, and $FEF_{25-75\%}$).

Quality control

Spirometry was performed in the Jaeger Masterscreen-PFT (Erich Jaeger GmbH, Hoechberg, Germany) in sitting position. Participants' standing height and weight were measured on the same electronic scale with their shoes off and while they were wearing light clothes. Quality control was performed in accordance with the ATS/ERS guidelines

for spirometry.^[11] Researchers who were responsible for quality control included a supervising technician with over 20-year work experience in lung function laboratory and a respiratory specialist.

Statistical analysis

Statistical analyses were performed using the R software (version 3.4.1, download from <https://www.r-project.org>). Reference equations were developed with the lambda-mu-sigma (LMS) method using the generalized additive models for location, scale, and shape package in R. The sample population of 226 women and 208 men satisfied the standard of at least 150 males and 150 females necessary to validate spirometric reference values.^[12] Data were presented as mean \pm SD for continuous variables. When developing the model, we made combinations of various transformations of variables. In addition, we compared the Schwarz Bayesian Criterion (SBC) value when L (Lambda, skewness, the box-cox index) was a fixed number or the function of age. Residual analysis was used to assure the fitness of each model. Through stratified sampling, we randomly chosen 85% of the participants as the training sample to establish equations and 15% as the verification sample to compute the agreement rate of normal values. The agreement rate = number of samples higher than LLN/sample population \times 100%. LLN is defined as the 5th lowest percentile of the parameter value.

Comparisons between different equations were performed by paired *t*-test. The difference was statistically significant when a two-tailed $P < 0.05$. The difference degree = (the new reference value – the previous reference value)/the previous reference value \times 100%. Equations to be compared include two Shanghai Zhongshan Hospital versions established in 1988 and 2011, respectively;^[7,8] equations for the general population of North China established in 1990 and 2009;^[13,14] reference values for adult Chinese in Hong Kong published in 2006;^[10] and the GLI - 2012 equations.^[2]

RESULTS

Characteristics of the sample

A total of 482 volunteers satisfied the inclusion criteria. Here, 434 participants (226 females and 208 males) were completely qualified. The distribution of exclusion or rejection reasons was presented in Supplementary Table 1. Demographic and clinical characteristics of the study sample were shown in Table 1. The new equations apply to participants aged 60–84 years old, 149.0–179.5 cm in height for men and 140.5–170.5 cm for women.

Spirometric reference equations

For all equations, the addition of spline function was unable to decrease the SBC. Tables 2 and 3 display the final reference equations for mean and LLN. The scatter plot and correlation analysis showed that males' FEV₁/FVC and FEV₁/VC and females' FEV₁/VC and FEF_{50%} to be uncorrelated with height. For males' FEF_{75%} and females' FEF_{75%}, FEF_{25–75%}, although they were found to be statistically significantly related to

Table 1: Demographic and clinical characteristics of the sample for the developing of reference values

Characteristics	Females (n = 226)	Males (n = 208)
Age (years)	69.95 \pm 6.30	69.91 \pm 6.55
60–64, n	53	55
65–69, n	53	51
70–74, n	53	47
75–79, n	51	33
80–84, n	16	22
Height (cm)	155.2 \pm 5.3	166.1 \pm 5.9
Weight (kg)	62.9 \pm 8.7	69.8 \pm 9.6
BMI (kg/m ²)	26.1 \pm 3.3	25.3 \pm 2.8
VC (L)	2.64 \pm 0.44	3.65 \pm 0.56
FVC (L)	2.59 \pm 0.45	3.56 \pm 0.56
FEV ₁ (L)	2.01 \pm 0.37	2.76 \pm 0.47
FEV ₁ /FVC (%)	77.45 \pm 4.26	77.49 \pm 4.22
FEV ₁ /VC (%)	76.04 \pm 4.88	75.62 \pm 5.03
FEV ₆ (L)	2.55 \pm 0.44	3.51 \pm 0.55
FEF _{25%} (L/s)	4.98 \pm 1.20	6.71 \pm 1.64
FEF _{50%} (L/s)	2.40 \pm 0.82	3.06 \pm 0.99
FEF _{75%} (L/s)	0.51 \pm 0.21	0.72 \pm 0.32
FEF _{25–75%} (L/s)	1.59 \pm 0.59	2.15 \pm 0.76
PEF (L/s)	5.75 \pm 1.13	8.27 \pm 1.55

Data are presented as mean \pm standard deviation. BMI: Body mass index; VC: Vital capacity; FVC: Forced vital capacity; FEV₁: Forced expiratory volume in 1 s; FEV₁/FVC: The ratio between FEV₁ and FVC; FEV₁/VC: The ratio between FEV₁ and VC; FEV₆: Forced expiratory volume in 6 s; FEF_{25%}: Forced expiratory flow at 25% of FVC exhaled; FEF_{50%}: Forced expiratory flow at 50% of FVC exhaled; FEF_{75%}: Forced expiratory flow at 75% of FVC exhaled; FEF_{25–75%}: Forced expiratory flow at 25–75% of FVC exhaled; PEF: Peak expiratory flow.

height, the partial regression coefficient of height was not statistically significant ($P > 0.05$). After adjusting for height, the model's SBC decreased. For these reasons, height was not included in the final models of males' FEV₁/FVC, FEV₁/VC, and FEF_{75%} and females' FEV₁/VC, FEF_{50%}, FEF_{75%}, and FEF_{25–75%}. For other spirometric parameters, age and height were both involved in the model.

Applicability of new equations

Final equations were determined by the smallest SBC value and the tendency in the independent variable-dependent variable scatter plot. All models' residuals conform to standard normal distribution. In the verification sample, the agreement rate of normal values was over 90%; except for females' VC and FEV₆ and males' FEV₁/VC, the agreement rate for these three parameters was all 88%. For females' FEV₁/VC, FEF_{75%}, FEF_{25–75%}, and PEF, the agreement rate can reach 100% (not shown). The results of residual analysis and agreement rate in the verification sample further confirm the fitness of the reference equations.

Comparisons of new and previous equations

Table 4 shows the degree of difference between the newly predicted LLN and the previous LLN. The LLN of FEV₁/FVC and maximal midexpiratory flow (MMEF, equals to FEF_{25–75%}) computed using the 2012-GLI equations and 2006-Hong Kong equations was both lower than the present

Table 2: Spirometric reference equations for males*

Parameters	Equations			SBC
	M	S	L	
VC (L)	$-25.240+6.119\ln H-0.035A$	$\exp(-2.057-0.001A)$	$12.337-0.185A$	243.93
FVC (L)	$-25.014+6.089\ln H-0.037A$	$\exp(-2.272+0.003A)$	$13.034-0.193A$	245.61
FEV ₁ (L)	$-18.387+4.525\ln H-0.028A$	$\exp(-3.185+0.016A)$	1	166.72
FEV ₁ /FVC (%)	$\exp(4.861-0.120\ln A)$	$\exp(-4.283+0.320\ln A)$	1	1028.27
FEV ₁ /VC (%)	$\exp(4.829-0.118\ln A)$	$\exp(-2.051-0.191\ln A)$	$-84.320+20.160\ln A$	1042.47
FEV ₆ (L)	$-25.045+6.038\ln H-0.037A$	$\exp(-2.221+0.002A)$	$13.052-0.193A$	237.36
FEF _{25%} (L/s)	$-35.315+9.039\ln H-0.060A$	$\exp(-2.365+0.012A)$	1	665.69
FEF _{50%} (L/s)	$-0.020+0.037H-0.045A$	$\exp(-2.310+0.014A)$	1	455.34
FEF _{75%} (L/s)	$6.030-1.253\ln A$	$\exp(-7.779+1.613\ln A)$	1	55.41
FEF _{25-75%} (L/s)	$-14.874+3.870\ln H-0.040A$	$\exp(-2.853+0.023A)$	1	346.60
PEF (L/s)	$21.566+0.078H-6.192\ln A$	$\exp(-7.917+1.430\ln A)$	1	619.46

*The lower limit of normal (LLN) is defined as the 5th lowest percentile of the parameter value. $LLN (5^{th} \text{ percentile}) = \exp(\ln M + \ln[1-1.645 \times L \times S]/L)$. L: Lambda, the Box-Cox index, it can change the primary skewness; M: Predicted mean value; S: Coefficient of variation; H: Height in centimeter; A: Age in year; SBC: Schwarz Bayesian Criterion; VC: Vital capacity; FVC: Forced vital capacity; FEV₁: Forced expiratory volume in 1 s; FEV₁/FVC: The ratio between FEV₁ and FVC; FEV₁/VC: The ratio between FEV₁ and VC; FEV₆: Forced expiratory volume in 6 s; FEF_{25%}: Forced expiratory flow at 25% of FVC exhaled; FEF_{50%}: Forced expiratory flow at 50% of FVC exhaled; FEF_{75%}: Forced expiratory flow at 75% of FVC exhaled; FEF_{25-75%}: Forced expiratory flow at 25-75% of FVC exhaled; PEF: Peak expiratory flow.

Table 3: Spirometric reference equations for females*

Parameters	Equations			SBC
	M	S	L	
VC (L)	$\exp(-7.847+1.923\ln H-0.013A)$	$\exp(-2.037-0.001A)$	1	126.96
FVC (L)	$\exp(-7.751+1.912\ln H-0.014A)$	$\exp(-2.157+0.001A)$	1	136.57
FEV ₁ (L)	$7.820+0.021H-2.157\ln A$	$\exp(-3.436+0.337\ln A)$	1	63.67
FEV ₁ /FVC (%)	$\exp(5.333-0.002H-0.156\ln A)$	$\exp(-7.651+1.104\ln A)$	1	1101.84
FEV ₁ /VC (%)	$89.684-0.200A$	$\exp(-3.129+0.005A)$	1	1160.95
FEV ₆ (L)	$\exp(-7.441+1.855\ln H-0.014A)$	$\exp(-2.218+0.002A)$	1	133.43
FEF _{25%} (L/s)	$-13.023+4.728\ln H-0.083A$	$\exp(-1.565+0.0005A)$	1	598.48
FEF _{50%} (L/s)	$16.294-3.307\ln A$	$\exp(-3.907+0.651\ln A)$	$-4.977+1.196\ln A$	444.93
FEF _{75%} (L/s)	$5.272-1.130\ln A$	$\exp(-4.211+0.767\ln A)$	$12.232-2.760\ln A$	-89.84
FEF _{25-75%} (L/s)	$15.458-3.287\ln A$	$\exp(-4.978+0.910\ln A)$	$17.245-3.969\ln A$	296.40
PEF (L/s)	$-22.741+6.901\ln H-0.090A$	$\exp(-1.739-0.0005A)$	1	560.35

*The lower limit of normal (LLN) is defined as the 5th lowest percentile of the parameter value. $LLN (5^{th} \text{ percentile}) = \exp(\ln M + \ln[1-1.645 \times L \times S]/L)$. L: Lambda, the Box-Cox index, it can change the primary skewness; M: Predicted mean value; S: Coefficient of variation; H: Height in centimeter; A: Age in year; SBC: Schwarz Bayesian Criterion; VC: Vital capacity; FVC: Forced vital capacity; FEV₁: Forced expiratory volume in 1 s; FEV₁/FVC: The ratio between FEV₁ and FVC; FEV₁/VC: The ratio between FEV₁ and VC; FEV₆: Forced expiratory volume in 6 s; FEF_{25%}: Forced expiratory flow at 25% of FVC exhaled; FEF_{50%}: Forced expiratory flow at 50% of FVC exhaled; FEF_{75%}: Forced expiratory flow at 75% of FVC exhaled; FEF_{25-75%}: Forced expiratory flow at 25-75% of FVC exhaled; PEF: Peak expiratory flow.

version. The biggest degree of difference for FEV₁/FVC was 19% (70.46% vs. 59.29%, $t = 33.954$, $P < 0.01$) and for MMEF was 22% (0.82 vs. 0.67, $t = 21.303$, $P < 0.01$). However, the predicted LLN of FEV₁/FVC and small airway-related parameters FEF_{50%} and FEF_{75%} computed using the 2011-Zhongshan system was higher than the present model. The biggest degree of difference for FEV₁/FVC was -3% (71.65% vs. 73.53%, $t = -38.009$, $P < 0.01$) and for FEF_{75%}, it was great as -71% (0.26 vs. 0.90, $t = -52.580$, $P < 0.01$).

Table 5 shows the degree of difference of the predicted mean between the new and previous equations. After extrapolating the 1988-Zhongshan equations (applicable age 15-69 years), the predicted FEF_{75%} showed a large number of negative values. That was why the degree of difference of predicted

FEF_{75%} between the new and 1988-Zhongshan values was not computed. The 1990-North China and 2009-North China equations predicted higher mean values of FEV₁/FVC and MMEF than the present model. The biggest degree of difference was -4% for FEV₁/FVC (78.31% vs. 81.27%, $t = -85.359$, $P < 0.01$) and -60% for MMEF (2.11 vs. 4.68, $t = -170.287$, $P < 0.01$). The 1990-North China equations overestimated the mean of FEF_{50%} and FEF_{75%} also. The biggest degrees of difference were -15% (2.98 vs. 3.50, $t = -24.351$, $P < 0.01$) and -49% (0.71 vs. 1.42, $t = -49.976$, $P < 0.01$).

DISCUSSION

Specialization in elderly and comprehensive parameters

Studies on spirometric reference values for the elderly have been reported since 1996,^[15-19] and most of them were for

Table 4: Degree of difference* in LLN between new and previous reference equations

Parameters	New equation [†]	2012-GLI-Quanjer <i>et al.</i> ^{[12]‡}	<i>t</i>	<i>P</i> [§]	2011-Zhongshan-Ren <i>et al.</i> ^{[8]‡}	<i>t</i>	<i>P</i> [§]	2006-Hongkong-Ip <i>et al.</i> ^{[10]‡}	<i>t</i>	<i>P</i> [§]
Male (<i>n</i> = 208)										
VC (L)	2.92	–	–	–	3.03 (–4)	–56.349	<0.01	–	–	–
FVC (L)	2.90	2.92 (0)	–1.742	0.08	2.90 (0)	1.907	0.06	2.47 (17)	43.475	<0.01
FEV ₁ (L)	2.17	2.20 (–1)	–6.028	<0.01	2.28 (–5)	–10.844	<0.01	1.78 (22)	43.718	<0.01
FEV ₁ /FVC (%)	70.46	66.59 (6)	62.241	<0.01	72.26 (–2)	–37.028	<0.01	59.29 (19)	33.954	<0.01
FEF _{50%} (L/s)	1.69	–	–	–	2.04 (–17)	–33.726	<0.01	–	–	–
FEF _{75%} (L/s)	0.26	0.30 (–13)	–14.288	<0.01	0.90 (–71)	–52.580	<0.01	–	–	–
MMEF (L/s)	1.12	1.07 (5)	8.257	<0.01	–	–	–	1.02 (10)	11.223	<0.01
Female (<i>n</i> = 226)										
VC (L)	2.07	–	–	–	1.96 (6)	23.252	<0.01	–	–	–
FVC (L)	2.00	1.95 (3)	41.416	<0.01	1.86 (8)	28.069	<0.01	1.74 (15)	42.841	<0.01
FEV ₁ (L)	1.50	1.45 (3)	30.513	<0.01	1.53 (–2)	–3.369	<0.01	1.24 (21)	60.442	<0.01
FEV ₁ /FVC (%)	71.65	67.98 (5)	90.262	<0.01	73.53 (–3)	–38.009	<0.01	65.7 (9)	84.169	<0.01
FEF _{50%} (L/s)	1.33	–	–	–	1.45 (–8)	–9.470	<0.01	–	–	–
FEF _{75%} (L/s)	0.22	0.19 (16)	26.602	<0.01	0.59 (–63)	–28.546	<0.01	–	–	–
MMEF (L/s)	0.82	0.77 (5)	16.861	<0.01	–	–	–	0.67 (22)	21.303	<0.01

*Degree of difference = (The new LLN – the previous LLN)/the previous LLN × 100%; [†]Data are presented as mean, the degree of difference is presented in the previous equations; [‡]Data are presented as mean (degree of difference %); [§]Compared with new equation. –: Not applicable; VC: Vital capacity; FVC: Forced vital capacity; FEV₁: Forced expiratory volume in 1 s; FEV₁/FVC: The ratio between FEV₁ and FVC; FEF_{50%}: Forced expiratory flow at 50% of FVC exhaled; FEF_{75%}: Forced expiratory flow at 75% of FVC exhaled; MMEF: Maximal midexpiratory flow, equals to FEF_{25–75%}; LLN: The lower limit of normal; GLI: Global Lung Function Initiative.

Table 5: Degree of difference* in predicted mean between new and previous reference equations

Parameters	New equation [†]	1988-Zhongshan-Zhu <i>et al.</i> ^{[7]‡}	<i>t</i>	<i>P</i> [§]	1990-North China ^{[12]‡}	<i>t</i>	<i>P</i> [§]	2009-North China-Wu <i>et al.</i> ^{[14]‡}	<i>t</i>	<i>P</i> [§]
Male (<i>n</i> = 208)										
VC (L)	3.53	3.74 (–6)	–13.269	<0.01	3.21 (10)	30.953	<0.01	–	–	–
FVC (L)	3.53	3.67 (–4)	–8.972	<0.01	3.53 (0)	–0.429	0.67	3.47 (2)	5.197	<0.01
FEV ₁ (L)	2.78	2.21 (25)	53.688	<0.01	2.11 (31)	60.533	<0.01	2.73 (2)	5.610	<0.01
FEV ₁ /FVC (%)	77.31	75.84 (2)	17.726	<0.01	79.11 (–2)	–600.294	<0.01	78.31 (–1)	–22.980	<0.01
FEF _{50%} (L/s)	2.98	3.28 (–9)	–24.674	<0.01	3.50 (–15)	–24.351	<0.01	–	–	–
FEF _{75%} (L/s)	0.71				1.42 (–49)	–49.976	<0.01	–	–	–
MMEF (L/s)	2.11	2.34 (–10)	–14.758	<0.01	2.53 (–16)	–53.035	<0.01	4.68 (–60)	–170.287	<0.01
Female (<i>n</i> = 226)										
VC (L)	2.59	2.61 (–1)	–1.857	0.06	2.07 (25)	67.580	<0.01	–	–	–
FVC (L)	2.51	2.60 (–3)	–6.200	<0.01	1.90 (32)	93.746	<0.01	1.90 (32)	93.746	<0.01
FEV ₁ (L)	1.93	1.33 (45)	58.090	<0.01	1.95 (–1)	–4.351	<0.01	2.22 (–13)	–39.729	<0.01
FEV ₁ /FVC (%)	78.31	76.59 (2)	24.858	<0.01	79.32 (–1)	–13.205	<0.01	81.27 (–4)	–85.359	<0.01
FEF _{50%} (L/s)	2.26	2.32 (–3)	–3.272	<0.01	2.33 (–3)	–23.104	<0.01	–	–	–
FEF _{75%} (L/s)	0.48				0.93 (–48)	–78.122	<0.01	–	–	–
MMEF (L/s)	1.51	1.69 (–11)	–8.368	<0.01	2.40 (–37)	–125.343	<0.01	2.49 (–39)	–93.347	<0.01

*Degree of difference = (the new predicted mean – the previous predicted mean)/the previous predicted mean × 100%; [†]Data are presented as mean, the degree of difference is presented in the previous equations. [‡]Data are presented as mean (degree of difference %); [§]Compared with new equation; ||: After extrapolating the 1988-Zhongshan equation (applicable age 15–69 years), the predicted mean of FEF_{75%} shows lots of negative values, so we didn't perform the comparison; –: Not applicable; VC: Vital capacity; FVC: Forced vital capacity; FEV₁: Forced expiratory volume in 1 s; FEV₁/FVC: The ratio between FEV₁ and FVC; FEF_{50%}: Forced expiratory flow at 50% of FVC exhaled; FEF_{75%}: Forced expiratory flow at 75% of FVC exhaled; MMEF: Maximal midexpiratory flow, equals to FEF_{25–75%}.

Americans or Europeans. Few involved the Chinese. This study focused on the spirometric reference values for healthy elderly Chinese who had never smoked. Results were strictly screened according to rigorous quality control standards to ensure reliability. All equations provided both predicted mean values and the LLN. The analysis covered relatively comprehensive parameters, especially for parameters seldom

involved, such as VC, FEV₆, FEV₁/VC, FEF_{25%}, FEF_{50%}, FEF_{75%} and FEF_{25–75%}.

Rejection of asymptomatic obstructive ventilatory defective participants

We rejected some asymptomatic obstructive ventilatory defective subjects through the LLN of FEV₁/FVC. We

preferred LLN rather than the fixed ratio 70% mainly because the emphasis on primary functional diagnosis instead of disease such as COPD. In terms of the Chinese Epidemiological Survey of COPD, the overall prevalence of COPD among nonsmokers was 5.2%.^[20] Even in participants diagnosed COPD through spirometry, 35.3% were asymptomatic.^[21] In addition to smoking, indoor and outdoor air pollution also contributes to the increased incidence of lung diseases.^[22-24] However, these risk factors are extremely difficult to evaluate. For this reason, using the LLN rejects asymptomatic obstructive ventilatory defective participants could to some degree guarantee the health, as defined by the needs of this study, of reference population.

Using the lambda-mu-sigma method without splines

The LMS method can be used to convert the distribution of the variable to standard normal distribution.^[25] It was first applied in exploring the reference ranges for spirometry in 2008.^[26] Instead of copying similar studies using the LMS method,^[27-29] we did not add spline function into the reference equations according to the participants' narrow age range and small sample size.^[30] Age has complex effects on lung function. For instance, between the ages of 3 and 95 years old, male humans' FEV₁ values first rise, then fall. The speed with which they rise and falling varies across different age stages.^[2] That is why spline function is included in all age prediction equations. However, the present study focused on participants aged 60–84 years. The narrow age range resulted in the single variation tendency of spirometric parameters. Statistical analysis showed that incorporating spline function into the model cannot decrease the SBC value. Consequently, considering the scatter plot tendency and SBC value, splines were not included in our final models.

Applicability of previous equations

Previous reference equations were found to be less appropriate than the present equations. Different study populations led to the difference. None of the previous equations included any participants from Jinan city or even Shandong Province and they generally included the low proportion of the elderly. What cannot be overlooked was that the prediction equations of 2011-Zhongshan, 1990-North China, and 2009-North China may lead to the overdiagnosis of obstruction and small airway dysfunction. The situation revealed the disadvantage of traditional linear regression equations: such equations perform less well at the edges of the data distribution and in areas where there are few participants.^[1]

Forced expiratory volume in six seconds and forced expiratory volume in one second/vital capacity

The FEV₆ and FEV₁/VC are important for the explanation of lung function reports. For participants who cannot achieve complete forced expiration or for those whose small airway collapses in the early stage of forced expiration, FEV₁/FVC can be normal or nearly normal. In this case, FEV₁/VC could judge the airway limitations more accurately than FEV₁/FVC.^[31] For the elderly, FEV₆ had the better

repeatability and was easier to accomplish than FVC.^[32] In addition, FEV₁/FEV₆ could also ensure the presence of airway limitations.^[33]

Strengths and limitations

The study had limitations with respect to its regional participants and relatively modest sample size. However, we hoped that the study design such as the recruitment methods, rejection criteria, and the statistical analysis could be enlightening for similar studies. The conclusions are identical to those drawn when using retrospective samples or former 235 prospective volunteers in preparing experiments. Results indicated that regional disparity still requires emphasis even within the same ethnicity.

In summary, the newly developed spirometric reference equations are suitable for elderly Chinese in Jinan. The 2012-GLI equations for Northeast Asians may lead to missed diagnoses of obstructive ventilatory defects or of small airway dysfunction, while traditional linear equations for all ages may lead to overdiagnosis of both.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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济南地区老年人肺通气功能正常预计值方程的初步探讨

摘要

背景: 肺通气功能正常预计值对检查结果的判读至关重要。目前用于老年人的预计值大多是基于代表性较差的样本建立的。本研究旨在建立济南地区老年人专用的肺通气功能正常预计值方程，并与已发表的预计值进行比较。

方法: 在济南地区招募无吸烟史，60–84周岁的健康老年人434例（男208例，女226例），进行肺通气功能检查。记录肺活量（VC），用力肺活量（FVC），第1秒用力呼气容积（FEV₁），FEV₁/FVC，FEV₁/VC，第6秒用力呼气容积，呼气峰流量，用力呼出25%、50%、75%、25–75%肺活量的呼气流量（FEF_{25%}，FEF_{50%}，FEF_{75%}，FEF_{25%–75%}）。预计值方程的建立采用LMS法，不同预计值的比较采用配对*t*检验。

结果: 本研究建立了均值和正常值下限（LLN）的预计值方程。2012全球肺功能倡议（GLI）和2006香港版FEV₁/FVC，FEF_{25%–75%}的LLN预计值均低于新版，FEV₁/FVC的最大差异度为19%（70.46% vs. 59.29%，*t* = 33.954，*P* < 0.01），FEF_{25%–75%}为22%（0.82 vs. 0.67，*t* = 21.303，*P* < 0.01）。1990华北，2009华北版FEV₁/FVC和FEF_{25%–75%}的均值预计值均高于新版，两个参数的最大差异度分别为-4%（78.31% vs. 81.27%，*t* = -85.359，*P* < 0.01），-60%（2.11 vs. 4.68，*t* = -170.287，*P* < 0.01）。

结论: 新建立的肺通气功能预计值适用于济南地区老年人。2012GLI和2006香港版预计值可能导致老年人阻塞性通气功能障碍和小气道功能障碍诊断不足，传统的线性全年龄段通用版预计值则可能会导致过度诊断。

Supplementary Table 1: The distribution of excluded or rejected reasons for the study subjects

Reasons being excluded or rejected	Number of subjects excluded or rejected
Ever smokers	7
Respiratory symptoms	7
Age younger than 60	1
Coalminer	1
Abnormal chest X-ray	6
Unqualified quality control	19
Observed FEV ₁ /FVC < LLN	4
Height is out of (mean \pm 3SD)	3
Total	48

SD: Standard deviation; FVC: Forced vital capacity; FEV₁: Forced expiratory volume in 1 s; FEV₁/FVC: The ratio between FEV₁ and FVC; LLN: The lower limit of normal.