



Evaluation of the Global Lung Function Initiative 2012 reference values for spirometry in China: a national cross-sectional study

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To the Editor:

China is facing a high burden of respiratory diseases. There are nearly 100 million people living with COPD and more than 45 million people living with asthma [1–3]. Pulmonary function tests are critical for early diagnosis and management of respiratory disease. An accurate interpretation of pulmonary function measurements requires reliable reference values. Due to complex interactions between genetics, socioeconomic status and other factors/exposures, population-specific reference equations are typically used to facilitate interpretation [4]. Currently, there are no nationally recognised spirometry reference values for the Chinese population. There have been several equations published but these have been limited due to small sample sizes, accounted for limited geographical areas, or lacked standardised quality control [5–8]. In 2012, the European Respiratory Society (ERS) Global Lung Function Initiative (GLI) produced the South East and North East Asia reference values for spirometry and recommended using these separate prediction equations based on the Qinling–Huaihe Line [9]. However, these equations were derived from a limited number of healthy Chinese individuals, and only one centre each was included from South and North mainland China, respectively [9]. Thus, there is limited evidence to support the use of GLI equations in China.

We conducted a national cross-sectional study from January 2018 to October 2020 by recruiting healthy non-smoking subjects aged 20 years and older across 28 provinces in China. The study was approved by the ethics committee of the Shanghai East Hospital and written informed consent from each participant was obtained. All principal investigators were trained with respect to the study aims and protocol, and equipment operation. Convenience sampling methods were used to recruit eligible subjects. Spirometry was typically measured in primary care centres in the communities. Baseline information of each subject, including medical history, was obtained by trained staff prior to spirometry testing. To be eligible for inclusion in this analysis, participants had to meet the following criteria: 1) aged 20 years old and above; 2) never smoker (<100 cigarettes in lifetime) [10]; 3) without known self-reported lung diseases, including COPD, asthma, interstitial lung disease, lung cancer, lung transplantation, pulmonary tuberculosis, *etc.*; 4) no self-reported symptoms of lung diseases (*e.g.* cough, wheeze, shortness of breath, chest pain); 5) without history of long-term exposure to biomaterials (*e.g.* coal dust).

All subjects completed spirometry using identical instruments (BreathHome, China) which met the 2005 American Thoracic Society (ATS)/ERS standards. Lung function testing was performed according to the ATS/ERS recommendations [11]. Spirometry data were initially included if subjects had at least three acceptable forced expiratory manoeuvres and the differences between the highest values of two FEV₁ and FVC measurements were within 5% or 150 mL, based on the ATS/ERS acceptability and repeatability criteria. Data were further screened by AI software for spirometry quality control (ArtiQ.QC) to determine their acceptability using ATS/ERS 2005 guidelines [12]. Only grade A and B data were included in the final analysis [12].

Spirometry z-scores and predicted values were generated for each subject using the GLI 2012 equations under the following scenarios: assigning race/ethnicity-specific equations (*i.e.* South East Asian or North East Asian, depending on the location of the site), South East Asian equations for all participants, and



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GLI South East Asian equations fit well across a contemporary North and South Chinese population. This study suggests a single reference equation for spirometry can be applied to the Chinese population. <https://bit.ly/3zhCc2w>

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North East Asian for all participants. Spirometry data with a z-score <-5.0 or >5.0 were identified as outliers and excluded from further analyses.

There were 32 subjects who were dropped for having an FEV₁ z-score (according to South East Asian equations) greater than +5, none below -5, and none for FVC or FEV₁/FVC ratio. A total of 11 392 participants (mean±SD age of 55.3±14.0 years; 55.8% male) from 28 (12 in the South, 12 in the North and four lying on the Qinling–Huaihe Line) out of 32 provinces, municipalities and autonomous regions in mainland China met study criteria and were included in this analysis, with 4881 from the South and 6511 from the North (figure 1a). We did not observe significant differences in FEV₁ and FVC between South and North Chinese populations (figure 1b and 1c; FEV₁ mean difference: -0.02, 95% CI -0.05 to 0.01; FVC mean difference: 0.02, 95% CI -0.01 to 0.05). There was a significant, however small, difference in FEV₁/FVC (mean difference: 0.008, 95% CI 0.005 to 0.108. The South East Asian equations for spirometry fit both South and North Chinese populations best (figure 1d). Using the GLI 2012 South East Asia equations, the mean (SD) z-score of the whole study population was -0.192 (1.252) for FEV₁, -0.088 (1.288) for FVC, and -0.245 (1.122) for FEV₁/FVC. North East Asia equations significantly overestimated the spirometry values of both populations (figure 1c), with mean (SD) z-scores of -0.943 (1.550) for FEV₁, -1.098 (1.723) for FVC, and 0.052 (1.235) for FEV₁/FVC.

It was notable that the spirometry values were slightly higher in the elderly population in the North than those in the South (figure 1b and 1c). We investigated the potential for cohort effects by fitting a linear regression model with an interaction term between age (in 10-year categories) and North/South China. Although the effect size was small, there was a statistically significant interaction ($p<0.05$), suggesting possible cohort effects.

We also performed a sensitivity analysis including only ArtiQ.QC grade A data, which showed a marginally improved fit for the South East Asian equations in predicting lung function in both South and North populations, as indicated by smaller standard deviation (change in z-score (SD) of +0.006 (-0.046) for FEV₁, -0.06 (-0.056) for FVC, and +0.129 (-0.1) for FEV₁/FVC).

In addition, reference values were derived based on the collected data using the Lambda-Mu-Sigma method within the GAMLSS (Generalised Additive Models for Location Scale and Shape) package for comparison to the GLI 2012 equations. Reference equations derived from the contemporary Chinese data ($n=11\ 392$) were similar to the GLI South East Asian equations, with differences in the mean z-score for FEV₁, FVC, and FEV₁/FVC all less than 0.5 (figure 1d).

In this large national cross-sectional study across multiple centres in North and South China, we demonstrated spirometry indices are similar between the South and North Chinese populations. A single equation for spirometry, specifically the South East Asian GLI 2012 equations, can be applied to the entire Chinese population. Although South East and North East Asian populations are believed to originate from different ancestries, genetic admixture between these two populations has occurred since the late Neolithic period [13]. Gene analysis revealed that today's East Asians are genetically homogeneous, most of whom are a mixture of northern and southern East Asian ancestries [13]. Furthermore, there have been dramatic changes in socioeconomic status and domestic migration patterns within the Chinese population in the past decades [14, 15]. Hundreds of millions of Chinese people have been lifted out of poverty, which may have improved lung function [14]. Moreover, people now migrate more often between Southern and Northern China than ever before [15]. This domestic migration not only leads to further mixture of the distribution of South and North populations across China but also results in further genetic admixture between two populations, and ultimately reduces the differences in body proportions which is a primary determinant of lung function [16]. Indeed, the average height difference between South and North populations has narrowed dramatically, from 6–7 cm in the 1920s to 2–3 cm in the 1990s [17]. In this study, the height difference is further decreased to about 2 cm (171.03±5.87 cm *versus* 168.84±6.71 cm) in males and 1 cm (160.44±5.14 cm *versus* 159.34±5.35 cm) in females.

We found that GLI South East Asia equations rather than North East Asia equations are appropriate across the Chinese population. There are multiple reasons which may explain this. First, while GLI South East Asia equations were built based on datasets collected from multiple centres in South East Asia, GLI North East Asia equations were derived from only two datasets; one collected from Northern China and one from South Korea [9]. Thus, those subjects from one centre may not be representative of the North Chinese population. Second, there was considerable difference in socioeconomic conditions between South Korea and China; mixing these two datasets could confound the lung function of the North Chinese populations. Third, lung function of the northern populations is probably impaired by air pollution in the past decades,

a)

	Sex	Age (years)	N=11392	Height (cm)	Weight (kg)	BMI	FEV ₁ (L)	FVC (L)	FEV ₁ /FVC
South	Male	20-39	468	172.6±6.0	73.3±12.3	24.5±3.8	3.58±0.63	4.34±0.75	0.83±0.06
		40-59	1044	169.7±5.9	72.8±13.4	25.2±4.1	3.11±0.63	3.81±0.73	0.82±0.07
		60-79	1009	166.5±6.7	66.8±12.1	24.0±3.9	2.31±0.70	3.00±0.80	0.76±0.08
		>80	106	165.7±7.4	70.0±10.5	22.5±3.1	1.79±0.66	2.45±0.75	0.72±0.09
	Female	20-39	361	161.4±5.2	57.9±12.6	22.2±4.5	2.83±0.43	3.41±0.55	0.83±0.06
		40-59	1218	160.0±5.0	61.1±10.9	23.9±4.1	2.47±0.43	2.98±0.53	0.83±0.07
		60-79	639	157.3±5.3	60.7±11.7	24.5±4.5	2.03±0.49	2.58±0.58	0.78±0.08
		>80	36	154.7±5.8	55.4±9.6	23.1±3.6	1.30±0.38	1.82±0.45	0.71±0.12
North	Male	20-39	598	173.9±5.6	74.6±15.2	24.6±4.7	3.59±0.54	4.40±0.69	0.82±0.05
		40-59	1563	171.3±5.6	73.8±10.9	25.1±3.5	3.05±0.58	3.79±0.72	0.81±0.06
		60-79	1445	169.7±5.8	71.3±11.8	24.7±3.9	2.46±0.56	3.18±0.68	0.77±0.07
		>80	129	169.4±5.3	66.2±10.8	23.1±3.7	1.92±0.56	2.56±0.68	0.75±0.09
	Female	20-39	286	163.3±4.6	60.3±10.3	22.6±3.4	2.77±0.41	3.41±0.56	0.82±0.06
		40-59	1385	161.1±4.9	61.9±10.0	23.8±3.7	2.37±0.41	2.95±0.55	0.81±0.06
		60-79	1054	159.0±5.1	61.5±9.5	24.3±3.7	2.00±0.42	2.53±0.53	0.79±0.08
		>80	51	156.7±5.0	57.4±9.5	23.4±3.8	1.51±0.39	2.00±0.49	0.76±0.09

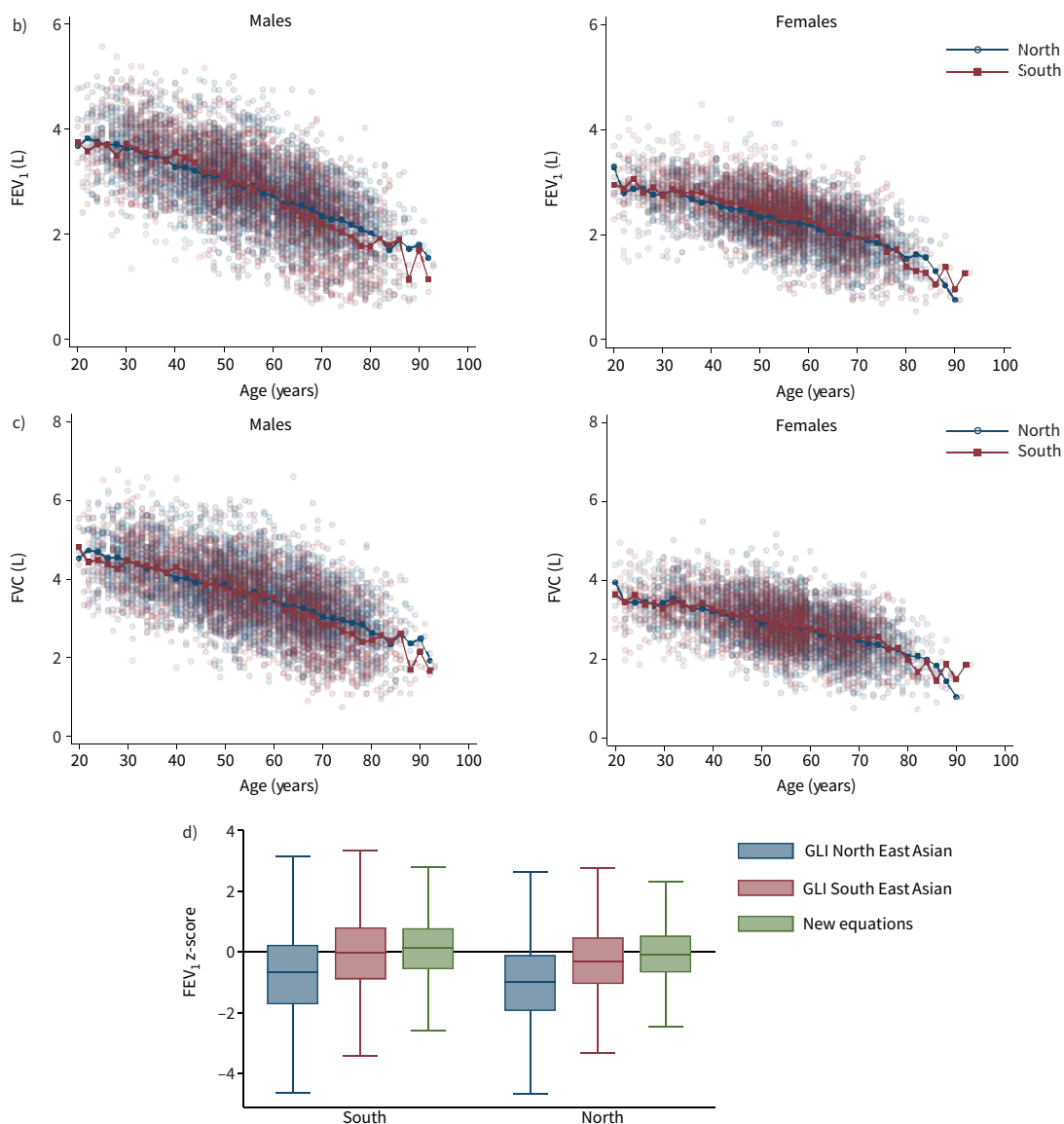


FIGURE 1 a) Characteristics of North and South Chinese participants in different age ranges. b) Comparison of raw forced expiratory volume (FEV₁) (L) (data points) and mean values (connected plots; calculated in 2-year age intervals) between North and South Chinese participants by age. c) Comparison of raw forced vital capacity (FVC) (L) (data points) and mean values (connected plots; calculated in 2-year age intervals) between North and South Chinese participants by age. d) Overall fit of the Global Lung Function Initiative (GLI) 2012 equations to the dataset in terms of calculated FEV₁ z-score separated by North East and South East Asian race/ethnicity (excludes values outside whiskers). BMI: body mass index.

which was more severe in the North than the South and has been shown to be related with a shortened life expectancy of people living in North China [18].

There are some limitations of this study. First, we did not recruit populations from Hong Kong and Taiwan. We believe these two populations may require different lung function prediction equations from the mainland Chinese population, as socioeconomic levels of people in Hong Kong and Taiwan were much better than people in the mainland, despite significant improvements in the past decades. Indeed, a recent study found that GLI 2012 “other” equations rather than South East or North East Asian equations adequately fit spirometry data in Asian Americans [19]. Second, young populations aged <20 years of age were not included in this study. Further studies are needed to evaluate whether South East Asia equations are also appropriate for children. Third, there were limited participants aged above 80 years old, therefore, results should be interpreted with caution for this population.

In conclusion, lung function indices are similar between South and North Chinese populations. Our study suggests that GLI South East Asian equations are appropriate across the whole Chinese population.

Feilong Wang¹, Kun Wang¹, Cole Bowerman^{2,3}, Hogne Ulla⁴, Jiaxing Sun¹, Marko Topalovic⁴, Sanja Stanojevic³ and Qiang Li¹

¹Department of Pulmonary and Critical Care Medicine, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China. ²Michael G. DeGroot School of Medicine, McMaster University, Hamilton, ON, Canada. ³Department of Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada. ⁴ArtiQ NV, Leuven, Belgium.

Corresponding author: Qiang Li (liqressh@hotmail.com)

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Conflict of interest: C. Bowerman and S. Stanojevic have an intellectual interest through their role as executive members of the Global Lung Function Initiative. S. Stanojevic also reports consulting fees from Chiesi, outside the submitted work, and acts on the Pulmonary Function Testing Proficiency committee for the American Thoracic Society. H. Ulla is an employee of ArtiQ. M. Topalovic is CEO and co-founder of ArtiQ, including ownership of stock or stock options. Q. Li is Chair of Shanghai Respiratory Society. There are no disclosures for other authors related to this work.

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References

- 1 Wang C, Xu J, Yang L, *et al.* Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. *Lancet* 2018; 391: 1706–1717.
- 2 Fang L, Gao P, Bao H, *et al.* Chronic obstructive pulmonary disease in China: a nationwide prevalence study. *Lancet Respir Med* 2018; 6: 421–430.
- 3 Huang K, Yang T, Xu J, *et al.* Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. *Lancet* 2019; 394: 407–418.
- 4 Stanojevic S, Kaminsky DA, Miller M, *et al.* ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J* 2021; 60: 2101499.
- 5 Ip MS, Karlberg EM, Karlberg JP, *et al.* Lung function reference values in Chinese children and adolescents in Hong Kong. I. Spirometric values and comparison with other populations. *Am J Respir Crit Care Med* 2000; 162: 424–429.

- 6 Wu Y, Zhang Z, Gang B, *et al.* Predictive equations for lung function based on a large occupational population in North China. *J Occup Health* 2009; 51: 471–477.
- 7 Ma YN, Wang J, Dong GH, *et al.* Predictive equations using regression analysis of pulmonary function for healthy children in Northeast China. *PLoS One* 2013; 8: e63875.
- 8 Jian W, Gao Y, Hao C, *et al.* Reference values for spirometry in Chinese aged 4–80 years. *J Thorac Dis* 2017; 9: 4538–4549.
- 9 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
- 10 Centers for Disease Control and Prevention (CDC). National Health Interview Survey. Date last accessed: 1 April 2022. www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm
- 11 Graham BL, Steenbruggen I, Miller MR, *et al.* Standardization of Spirometry 2019 Update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019; 200: e70–e88.
- 12 Das N, Verstraete K, Stanojevic S, *et al.* Deep-learning algorithm helps to standardise ATS/ERS spirometric acceptability and usability criteria. *Eur Respir J* 2020; 56: 2000603.
- 13 Yang MA, Fan X, Sun B, *et al.* Ancient DNA indicates human population shifts and admixture in northern and southern China. *Science* 2020; 369: 282–288.
- 14 Popkin BM, Du S, Zhai F, *et al.* Cohort Profile: The China Health and Nutrition Survey—monitoring and understanding socio-economic and health change in China, 1989–2011. *Int J Epidemiol* 2010; 39: 1435–1440.
- 15 Shen J. Increasing internal migration in China from 1985 to 2005: institutional *versus* economic drivers. *Habitat Int* 2013; 39: 1–7.
- 16 Rossiter CE, Weill H. Ethnic differences in lung function: evidence for proportional differences. *Int J Epidemiol* 1974; 3: 55–61.
- 17 Morgan SL. Richer and taller: stature and living standards in China, 1979–1995. *China J* 2000; 44: 1–39.
- 18 Chen Y, Ebenstein A, Greenstone M, *et al.* Evidence on the impact of sustained exposure to air pollution on life expectancy from China’s Huai River policy. *Proc Natl Acad Sci USA* 2013; 110: 12936–12941.
- 19 Zhang J, Hu X, Tian X, *et al.* Global lung function initiative 2012 reference values for spirometry in Asian Americans. *BMC Pulm Med* 2018; 18: 95.