EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

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Please cite this article as: Wang F, Wang K, Bowerman C, *et al*. Evaluation of the Global Lung Initiative 2012 Reference Values for Spirometry in China: A national cross-sectional study. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.00490-2022).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Evaluation of the Global Lung Initiative 2012 Reference Values for Spirometry in China: A national cross-sectional study

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GLI South East Asian equations fit well across a contemporary North and South Chinese population. Our study suggests a single reference equation for spirometry can be applied to the Chinese population.

To the Editor:

China is facing a high burden of respiratory diseases. There are nearly 100 million people living with chronic obstructive pulmonary disease (COPD) and more than 45 million people living with asthma [1, 2, 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 recognized spirometry reference values for the Chinese population. There have been several equations published but these have been limited due to small sample sizes, limited geographical areas, or lacked standardized quality control [5, 6, 7, 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 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 old 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 subject. Spirometry was typically measured in primary care centers at 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 anaylsis, particpants had to meet the following criteria 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 biomaterial (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 maneuvers and the differences between the highest values of two FEV_1s and FVCs were within 5% or 150 mL based on the ATS/ERS acceptability and repeatability criteria. Data were further screened by the AI software for spirometry quality control (ArtiQ.QC) to determine the 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 Global Lung Function Initiative (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 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 FEV_1 z-score (according to SE Asian equations) greater than +5, none below -5, and none for FVC or FEV_1/FVC ratio. A total of 11,392 participants (mean ± SD age of 55.3 ± 14.0 yr, 55.8% male) from 28 (12 in the South, 12 in the North and 4 lie 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 4,881 from the South and 6,511 from the North (Figure 1a). We did not observe significant differences in FEV_1 and FVC between south and north Chinese populations (Figure 1b and 1c; FEV_1 mean difference: -0.02 (95% CI: -0.05-0.01), FVC mean difference: 0.02 (95% CI: -0.01-0.05)). There was a significant, however small, difference in FEV_1/FVC (mean difference: 0.008 (95% CI: 0.005-0.108). The South East (SE) Asian equations for spirometry fit both South and North Chinese populations best (Figure 1d). Using the GLI-2012 SE Asia equations, the mean (SD) z-score of the whole study population was -0.192 (1.252) for FEV_1, -0.088 (1.288) for FVC, and -0.245 (1.122) for FEV_1/FVC. North East (NE) Asia equations significantly overestimated the spirometry values of both populations (Figure 1c), with mean (SD) z-scores of -0.943 (1.550) for FEV_1, -1.098 (1.723) for FVC, and 0.052 (1.235) for FEV_1/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 SE Asian equations in predicting lung function in both South and North population as indicated by smaller standard deviation (change in z-score (SD) of +0.006 (-0.046) for FEV_1, -0.06 (-0.056) for FVC, and +0.129 (-0.1) for FEV_1/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 SE Asian equations, with differences in the mean z-score for FEV_1, FVC, and FEV_1/FVC all less than 0.5 (Figure 1d).

In this large national cross-sectional study across multiple centers 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 SE Asian GLI-2012 equations, can be applied to the entire Chinese population. Although SE and NE Asian populations are believed to originate from different ancestries, genetic admixture between these two populations had occurred since 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]. Further 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 immigrate 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 2-3cm in the 1990s [17]. In this study, the height difference is further decreased to about 2 cm (171.03 ± 5.87 cm vs 168.84 ± 6.71 cm) in males and 1 cm (160.44 ± 5.14 cm vs 159.34 ± 5.35 cm) in females.

We found that GLI SE Asia equations rather than NE Asia equations are appropriate across the Chinese population. There are multiple reasons which may explain this. First, while GLI SE Asia equations were built based on datasets collected from multiple centers in SE Asia, GLI NE Asia equations were derived from only two datasets; one collected from Northern China and one from South Korea [9]. Thus, those subjects from one center 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 North populations is probably impaired by air pollution in the past decades, 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 improved in the past decades. Indeed, a recent study found that GLI-2012 ‘other’ equations rather than SE or NE Asian equations adequately fit spirometry data in Asian Americans [19]. Second, young populations aged less than 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.

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Acknowledgements: We would like to thank all physicians, nurses and medical assistants who participated in recruiting subjects at each center.

Author contributions: All authors have made substantial contribution to the study and approved the final version to be submitted. F. Wang and Q. Li designed the study; F. Wang drafted the article; C. Bowerman and S. Stanojevic performed the statistical analysis, revised and edited the manuscript; K. Wang and J. Sun participated in the data collection; H. Ulla and M. Topalovic performed the data screen for quality control;

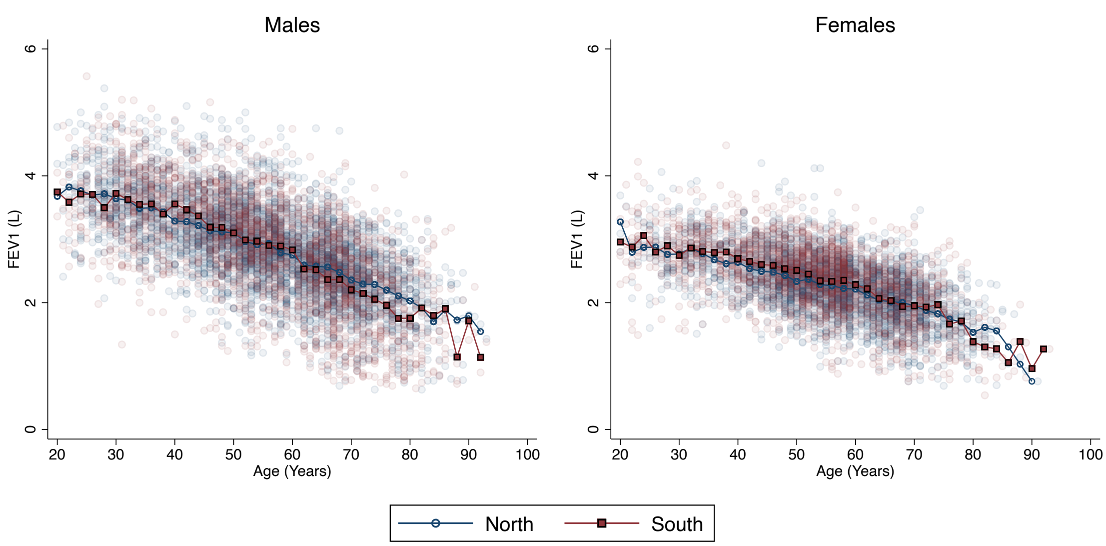
Conflict of interest: C. Bowerman and S. Stanojevic have an intellectual interest through their role as Executive members of the Global Lung Function Initiative. There are no disclosures for other authors related to this work.

Support statement: This study was supported by the National Key & Development Project (2018YFC1313700), the Shanghai Pujiang Program (2020PJD051), the Top-level Clinical Discipline Project of Shanghai Pudong (PWYgf2021-05) and the Academic Leaders Training Program of Pudong Health and Family Planning Commission of Shanghai (PWRd2019-02).

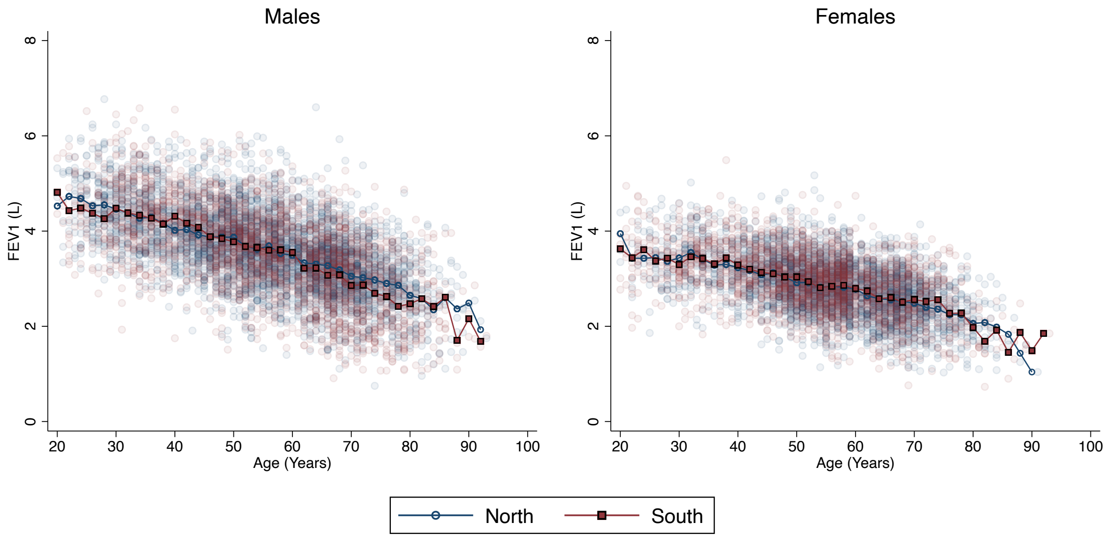
a)

	Sex	Age (years)	N=11392	Height (cm)	Weight (kg)	BMI	FEV1 (L)	FVC (L)	FEV1/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

b)

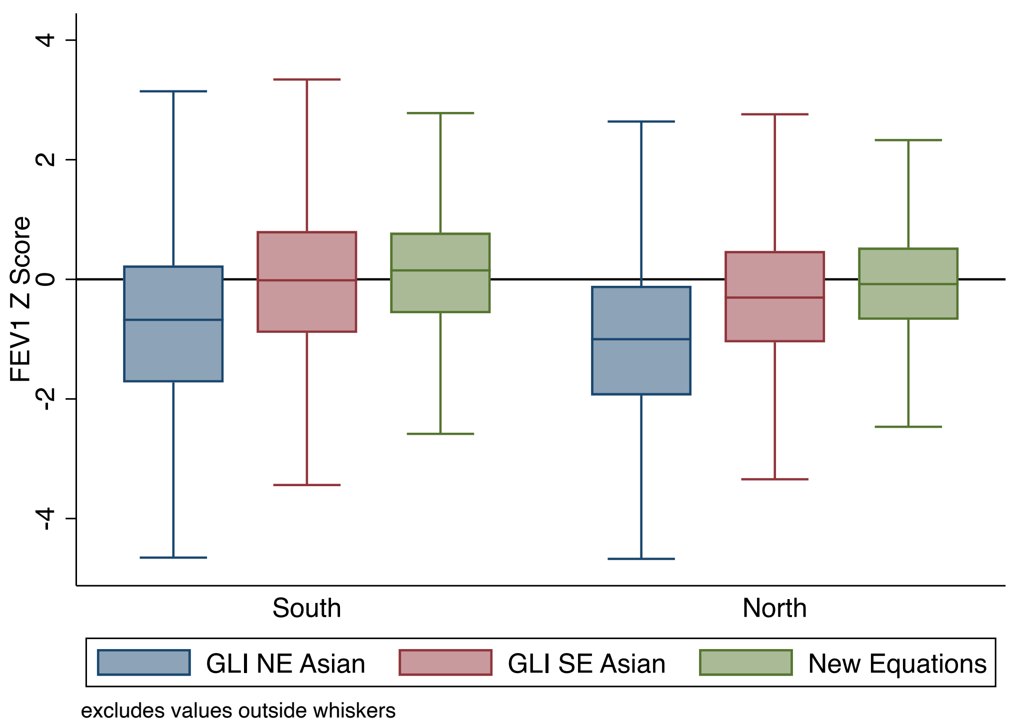


c)



Males
Females
FEV1 (L)
0
2
4
6
8
20
30
40
50
60
70
80
90
100
Age (Years)
North
South

d)



FEV1 Z Score
4
2
0
-2
-4
South
North
GLI NE Asian
GLI SE Asian
New Equations
excludes values outside whiskers

Figure 1
a) Characteristics of North and South Chinese participants in different age ranges.
b) Comparison of raw 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 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 GLI 2012 equations to the dataset in terms of calculated FEV1 z-score separated by North East and South East Asian race/ethnicity.