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Do the Global Lung Function Initiative reference equations reflect a sample of adult Middle Eastern population?

Abstract

Introduction: The Global Lung Function Initiative (GLI) 2012 introduced new multi-ethnic spirometry reference values for numerous ethnicities. Objectives: The aim of this study was to investigate the suitability of the GLI reference values for the adult Jordanian population. Methods: 1875 (1029 females and 846 males) healthy non-smoking adults were enrolled from several locations in Jordan. Spirometry tests were performed. Z scores and predicted normal values were calculated for each participant using GLI 2012 equations in addition to other local equations from the Middle East. Results: Our results indicated that none of the GLI 2012 or other regional equations studied produced an acceptable fit to our data. Conclusion: A need to formulate a specific equation for the Jordanian population is urgently required to better evaluate their respiratory conditions.

Keywords: Pulmonary function tests; Global Lung intuitive; Spirometry reference values; Middle East; Jordan.

Introduction

Spirometry is a key tool used in screening, diagnosis and monitoring of the therapeutic course of respiratory diseases, including obstructive pulmonary diseases [For review see [1]]. Within- and between-population variation in spirometry measurements have been observed [2]. This has led to numerous studies recording normal pulmonary function test (PFT) results, including spirometry tests, which have shown divergent results according to age, gender, standing height and ethnic group [3]. Between-population variations correlated with sample provenance (urban versus rural) and geographic region[4], which can in part be explained due to variance in altitude and sample mean height as well as the year of the study publication [5]. Population variation has been minimized through the use of relatively small groups with limited age ranges, however this can lead to significant differences in predicted values between the populations [5–8] and to incoherence in results when participants change from one age-range to the next [3]. Furthermore, the explanation of test results differs depending on the predicted values used [5–8] and is also complicated by the fact that coefficient discrepancy for the spirometric results diverges with normal non- smokers subjects.

New multi-ethnic spirometry reference test results were introduced by the Global Lung Function Initiative (GLI) in 2012 within the age-range of 3-95 years [5]. Many respiratory societies recommend the use of the GLI reference values [7,9]. These data were derived from spirometry tests values collected from more than 72,000 healthy lifelong non-smokers from all over the world. However, the European Respiratory Society (ERS) has recommended that more studies should be conducted in Arab populations, as the GLI reference value may not be appropriate for the assessment and the diagnosis of Arab- origin patients [5]. The aim of this study was therefore to evaluate the suitability of the GLI reference values on the adult Caucasian population resident in Jordan.

Materials and Methods

Population

Participants where accessed in AlZaytoonah University of Jordan and in several pharmacies, polyclinics and hospitals from different locations in Jordan, including different areas in the capital city Amman, and other major cities in Jordan. Recruitment was through advertisements and personal approach; others volunteered to participate or after being encouraged by friends/colleagues who had participated in the study. The inclusion criteria included being Jordanian citizen aged at least 18 years old. The exclusion criteria included having chronic respiratory or associated diseases , current respiratory symptoms, being a current or ex-smoker and the inability to perform the spirometry tests successfully.

Participants were given a questionnaire and a consent form. The consent form included a short summary of the study and its objectives. The questionnaire included questions about medication use, smoking habits and health status, including incidence of asthma and other pulmonary diseases. Ethical approval was granted by the Ethical committee of Al-Zaytoonah University of Jordan, Amman, Jordan.

Measurements

Measurement of pulmonary function

Spirometry tests were performed according to the European Respiratory Society (ERS) guidelines [10]. The tests were performed using an MIR-Minispir New computer-based spirometer. During testing, proper measurement posture was ensured by instructing participants to sit upright, have their feet flat on the floor and have their legs uncrossed. A chair with arms was used for the testing. To maintain high levels of hygiene to reduce the potential for any spread of infection, the technician's hands were washed after each participants, a new disposable turbine was used for each participant.

For the test, a closed circuit method was used where a nasal clip was used and the participantwas asked to seal their lips around the turbine to prevent any air leakage. Participants were asked to take few normal breaths, then a deep breath after which a quick full inspiration then a quick pause for <1 second before being asked to blow out as hard and fast as possible and to keep on going until there was no air remaining; the blow should last for at least 6 seconds. This technique was repeated for at least three maneuvers. For the maneuver to be acceptable there had to be a strong start with no hesitation and with back-extrapolation volume <150 mL. Furthermore, the maneuver had to be executed with a maximal inspiration and expiration, no coughs especially during the first second, no leakage, no glottis closure and the maneuver had to meet the end-of-test criteria. The differences between the largest two values for FVC and FEV1 should not exceed 5% or 150 mL of each other. If this was not achieved more maneuvers were performed with an upper limit of eight maneuvers. The same spirometer was used by the same researcher for all tests and participants. The was a well-trained nurse with previous experience working in a respiratory clinic. Only data of acceptable trial quality and reproducible PFT results as indicated by the spirometer were included in the final data. The data collection was performed between May 2017 and July 2018.

Measurement of anthropometric parameters:

Weight was measured to the nearest 0.1 kg using a standardized electronic weighing machine, participants were asked to remove heavy outdoor clothes (i.e. jackets) and emptied their pockets before measuring their weight. The height of participantswas measured with a stadiometer without shoes, to the nearest centimeter. Body mass index (BMI) was calculated by using Quetlet's index (body weight in kg/height in m^2)[11].

Statistical analysis

Anthropometric parameters and spirometry parameters were compared between the two genders. T-test was used when the parameter was normally distributed and Mann Whitney U test was conducted for nonparametric variables.

Predicted normal values were calculated for each participantusing different reference equations including the GLI 2012 Caucasian equation, GLI 2012 other or mixed ethnicity equation [5], the Omani equation formulated by Al-Rawas et al [12], the Saudi Arabian equation formulated by Al Ghobain et al. [13], and a Jordanian equation that was published in 1981 by Sliman et al. [14]. Z-scores for FEV1, FVC, and FEV1/ FVC for each participantwere produced using the different reference equations studied, as done in a previous study [15]. Normal distribution assumption of the z scores for each equation was evaluated by examining the Q-Q plots, evaluation of skewness and kurtosis and performing Kolmogorov-Smirnov test. LLN for each participant for each spirometry equation studied was computed including FEV1, FVC and FEV1FVC "obstructive ventilatory defect (OVD)" and in order to be perfectly representative of the data the number of records below LLN should be 5% [16]. A record with FEV1 $<$ LLN, and FVC $<$ LLN and FEV1/FVC $\geq$ LLN was considered as having Tendency to a Restrictive Ventilatory Defect

(TRVD). A record with FEV1/FVC ratio < LLN and a FVC < LLN and a FEV1 < LLN was considered as having a Mixed Ventilatory Defect (MVD) [17].

T-test was used to evaluate the differences in PFT z scores between males and females in each group; for non-parametric data Mann Whitney test was used. Linear regression was conducted to evaluate the relationship between z-scores of the various PFT parameters computed by different equations, as well as height, age, BMI and gender. All data analysis was conducted using SPSS. 23 [18]

Results

Of the 4,945 healthy non-smoking Jordanians who agreed to participate in the study only 1,875 (1,029 females and 846 males), met the inclusion criteria and were able to perform the spirometry successfully (for more details please see Appendix, Figure 1). The wide age range of those recruited is shown in Table 1. As expected, there was a significant difference between the two genders in height and weight. As reported in previous studies [12,19,20] all the PFT parameters studied were significantly higher in males, except for the FEV1/FVC ratio which was significantly higher in females.

<u>Table 1 Here</u>

Q-Q plot and normality tests indicated that normal distributions were found in the z scores of FEV1 and FVC produced by all equations tested, except for FEV1 z scores produced by Sliman et al.'s equation in males. FEV1/FVC z scores were not normally distributed in all the studied equations except for females in GLI 2012 other or mixed and Caucasian equations.

<u>Table 2 Here</u>

Table 2 shows the means and variances of PFT z-score produced by the studied equations. The closest mean to zero in FEV1 was GLI 2012 other or mixed for both genders. Al Ghobain et al.'s equations produced the closest FVC z scores to zero in males, in females FVC z scores produced by Al Ghobain and Al Rawas were the closest to zero. All the equations over-estimated FVC except for Al-Rawas et al.'s which underestimated FVC z scores in both genders. The closest SD of FEV1 z scores to one was found for the GLI 2012 Caucasian equation, while the closest SD of FVC z scores to one was found in GLI 2012 Caucasian and other or mixed equations, all the other equations' z scores SD were underestimated. The means and variances of z scores of FEV1/FVC produced by different equations were all underestimated.

Table 3 Here

Table 3 shows there were no significant difference in z scores of the studies PFT parameters produced by GLI2012 other or mixed equation between the two genders in all age groups.

Table 4 Here

As Table 4 shows there were differences between the predicted values and predicted % of the different equations.

Table 5 here

As Table 5 shows, almost all the equations in all the studied parameters failed to yield the expected 5% below LLN. However, some equations were closer than others. For example in FEV1, Al-Rawas et al. was the closest to 5% (3.5% in males and 5.2% in females), in FVC the closest to 5% in males was the GLI 2012 other or mixed equation (6.3%) and Al Ghobain et al. was the closest in females (6.4%). In FEV1/FVC (OVD) Al Rawas et al. has the closest percentage to 5% in males and females (7.2% and 10.2% respectively).

Table 6 here

Multiple linear regression was conducted to evaluate the association between height, age, BMI and gender and the different z scores of FEV1 and FVC yielded from the studied equations (Table 6). The results indicated that z scores of FEV1 and FVC produced by all the equations were significantly associated with at least one variable.)

Discussion

This study evaluated the applicability of GLI 2012 equation and other spirometry equations among the Jordanian population. None of the equations evaluated displayed a perfect representation of our data. However, GLI 2012 equation for other or mixed ethnicity was the most suitable particularly in FEV1.

Applicability GLI 2012 equation

The GLI2012 was formulated to be applicable across different ethnicities[5]. Different equations were formulated for different ethnicities including Caucasians, North-Eastern Asian, South-Eastern Asian, African American and other or mixed ethnic groups [5]. However, the final data included in the analysis did not include any Middle East countries, as Oman was excluded from the final data [5]. Therefore the GLI 2012 authors stated that data from the Arab world are urgently required [5].

Z scores were used to evaluate the suitability of GLI 2012 equation to our data. Z scores are superior to predicted% as they are independent of any bias due to age, height, sex or ethnic groups[21]. Our results indicated that the equation for other or mixed ethnicity was a better representation for our data when compared with the Caucasian equation. In addition, the frequencies of records below LLN in FEV1 and FVC were higher in the Caucasian equation when compared with other or mixed equation or the expected 5% in both genders. This was expected as several studies performed worldwide and in the Middle East have reported that Caucasians have higher PFT when compared with Arabs, Asians, Africans and Hispanics [19,20,22,23]

Consequently, GLI2012 other or mixed was investigated thoroughly, and our results indicated that z-scores were normality distributed in FEV1, FVC in males and females, however FEV1/FVC ratio was not normally distributed in males. Although the z scores of FVC and FEV1 were not absolute zero they were lower than the cut-off point of ±0.5 in both genders. This cut-off point was determined by the GLI committee to be the minimum physiologically significant variation in z-scores[5]. However, the z-scores for the FEV1/FVC ratio in both genders were above the cut-off point. In addition, the relationships between the z scores of PFT parameters and age, height and gender were evaluated in linear regression models. As previously reported [6,24,25] results indicated that there was a significant association between age and the z-scores of the studied parameters, which indicates that the equation was not suitable for all the age groups in our studied population. Two possible explanations for this association were mooted [26]; the first was that the all-age reference equations had insufficient data in the older age groups to accurately define the change in the spirometry variable with age, while the second proposed that, as noted previously, variability of spirometry varies with age [27]. Furthermore, there were significant differences between the actual PFT measures and the predicted ones in all the measures except for FEV1 in males. One of the possible limitations of the GLI reference equations is that some of the data used were from 1978 onward, this raises a question about the suitability of using old data today[5]

Comparison with other regional reference equations

The evaluation of the regional equations indicated that Al Ghobain et al's equation, which was formulated based on Saudi Arabian population [13], was the most suitable for our sample in males as compared to other regional equations studied including Sliman et al's equation using Jordanian population[28]. Al Ghobain et al's equation had the closest z-scores to zero in males in FEV1 and FVC. Although z scores of Al Ghobain et al's equation in females were lower than ±0.5 in FEV1 and FVC, the closest to zero was Al-Rawas et al.'s equation. Importantly, Al-Rawas et al.'s equation has the closest percentage of below LLN records to 5% in all PFT measures as compared with other regional equations in both genders. Moreover, both Al Ghobain et al. and Al-Rawas et al. equations showed significant associations between z-scores of PFT parameters and height, age and gender. The variation found between our data and other regional data could be attributed to genetic and environmental factors. In addition, there were several limitations that may have influenced the accuracy of equations produced by those studies; the equations developed by Al Ghobain et al. and Al-Rawas et al. included participants from one city only, which may limit the representability of the population. Moreover, there were few participants from different age groups, for example Al Ghobain et al. only presented data from 3 females and 12 males above the age of 55 while Al-Rawas et al. included only 13 males and 11 females above the age of 55 and had no participants above the age of 65. Finally, Al-Rawas et al. did not use a control group to validate their equation while Al Ghobain et al. used a small control group that only included 154 subjects of which only 51 were females. These limitations were evident in the significant variation between the two equations in the z-scores and predicted values in all PFT parameters in both genders.

The Sliman et al. equation had the worst fit for our data as it had the most divergent means of z-scores form zero in FEV1 and FVC in both genders. In addition, it had the highest percentage of records below LLN in FEV1 and FVC in both genders that reached up to 42.9% in FVC in males. This could be due to the small sample size enrolled by Sliman et al. which included 261 Jordanian adults (117 women and 144 men). This number is lower than 150 males and 150 females set by ERS as the lowest sample size necessary to validate reference values to avoid spurious differences due to sampling errors [29]. In addition, the data used by Sliman et al were collected in 1981, and are now more than 37 years old. Importantly, demographic and environmental differences can result into differences in PFT results between someone of the same age, height and gender maytoday and 37 years ago according to the cohort effect [30]. Indeed, the use of outdated technology can also produce inaccurate results. Finally, Sliman et al. collected data from one center only, which could limit their data's representativeness of the total population.

Strength and limitation of the present study

Sample size and number of centers:

As stated previously, it has been suggested that 150 participants for each gender is sufficient to evaluate applicability of a spirometry reference equation [29], Therefore, our large sample size increases the validity of our results and increases our confidence in the conclusions. In addition, our data were collected from various locations in Amman in addition to other Jordanian cities which makes our sample a better representation of the wider Jordanian population.

Spirometry

The spirometer used in our analysis was a modern computer-based spirometer (Minispir New). The spirometer saves all records of the participants including height, age and weight and allows the automatic production of predicted values from different reference equations, which minimizes human errors including mistakes in recording and coding. It also provides information on the quality and reproducibility of the trials and ensures the selection of successful acceptable PFT results.

One limitation of this study was the positive skewedness of our sample. However, the large sample size provided adequate number of most age groups. In addition, this sample is a good representation of the Jordanian young population, as reported by the Departments of Statistics in Jordan in 2017 which found that 63% of the population is aged 30 or less [31] (for more information see Figure 2 in the appendix). Moreover, our study did not attempt to formulate a new spirometry normal values equation but rather evaluate the present ones in a large sample. Another possible limitation is that some potential factors that may influence spirometry were not measured including biomass exposure.

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Tables

Table 1. Anthropometric and pulmonary function measurements.

	Women (n=1029)	**Men (n=846)**	**p value**
Mean age ± SD (range) in years	37.8 ± 13.4 (18-78)	38.5 ± 14.4 (18-82)	0.587
Mean height ± SD (range) in cm	158.4 ± 6.4 (136-182)	173.1 ± 7 (150-198)	**<0.001**
Mean weight ± SD (range) in kg	70.57 ± 13.0 (40-106)	82.8 ± 14.6 (46-130)	**<0.001**
Mean BMI ± SD (range)	28.2 ± 5.3 (17.19-39)	27.6 ± 4.6 (17.08-39)	0.036
Mean FEV_1 ± SD	2.6 ± 0.5	3.7 ± 0.8	**<0.001**
Mean FVC ± SD	3.0 ± 0.6	4.3 ± 0.9	**<0.001**
Mean PEF ± SD	5.2 ± 1.3	8.0 ± 2.0	**<0.001**
Mean FEF75 ± SD	1.8 ± 0.7	2.14 ± 0.9	**<0.001**
Mean FEF2575 ± SD	3.3 ± 1.0	4.3 ± 1.3	**<0.001**
Mean FEV_1/FVC ± SD	88.0 ± 7.1	85.9 ± 7.5	**<0.001**

n = Number of participants, SD = Standard Deviation, BMI = Body Mass Index, FEV_1 = Forced Expiratory Volume in one second, FVC = Forced Expiratory Vital Capacity, PEF = Peak Expiratory Flow, FEF75 = Forced Expiratory Flow at 75%, FEF2575= Forced Expiratory Flow at 25-75%. All variables except for age differed significantly between men and women.

Table 2. Z score data presented mean (SD)

	FEV1		**FVC**		**FEV1/FVC**	
	M	**F**	**M**	**F**	**M**	**F**
GLI Caucasian	-0.57 (0.92)	-0.63 (0.95)	-0.93 (1.00)	-0.98 (0.99)	0.76(1.33)	0. 80 (1.23)
GLI Other	-0.03 (1.00)	-0.09 (1.02)	-0.33 (1.15)	-0.41 (1.11)	0.66 (1.41)	0.69 (1.31)
Al-Ghobain et al.	0.26 (1.36)	0.36 (1.26)	0.00 (1.39)	-0.13(1.24)	0.93 (2.34)	1.45 (2.47)
Al-Rawas et al	0.84 (1.34)	0.20 (1.10)	0.66(1.5)	0.12 (1.18)	0.53 (1.50)	0.63 (1.71)
Silman et al.	-1.20 (1.02)	-0.73 (0.92)	-1.42 (1.11)	-1.22(0.94)	-	-

Table 3. Mean GLI Other Z-scores for FEV 1, FVC and the FEV 1 /FVC ratio by age group and gender.

			FV1			FVC			FEV_1/FVC		
Age group	**Gender**	**N**	**Mean**	**SD**	**p-value**	**Mean**	**SD**	**p-value**	**Mean**	**SD**	**p-value**
18-29	Male	278	0.15	1.00	0.149	0.09	1.15	0.055	0.14	1.20	0.091
	Female	350	0.04	1.00		-0.09	1.08		0.31	1.21	
30-39	Male	209	-0.09	1.06	0.758	-0.42	1.21	0.965	0.74	1.56	0.489
	Female	233	-0.12	1.10		-0.42	1.15		0.64	1.30	
40-49	Male	162	-0.08	0.92	0.579	-0.56	1.04	0.569	1.06	1.40	0.796
	Female	231	-0.13	1.06		-0.65	1.10		1.10	1.35	
50-59	Male	103	-0.12	1.00	0.283	-0.57	1.00	0.493	0.96	1.36	0.570
	Female	141	-0.26	0.99		-0.66	1.06		0.86	1.25	
60-69	Male	73	-0.34	0.81	0.125	-0.81	0.95	0.259	0.98	1.23	0.518
	Female	60	-0.10	0.97		-0.62	1.0		1.12	1.18	
≥70	Male	21	0.05	1.07	0.205	-0.5	1.16	0.476	1,01	1.37	0.630
	Female	14	-0.40	0.87		-0.78	1.02		0.80	1.18	
All ages	Male	846	-0.29	1.00	0.187	-0.33	1.15	0.161	0.66	1.41	0.416
	Female	1029	-0.91	1.02		-0.41	1.12		0.69	1.31	

SD = standard deviation.

P-values for difference between sexes (independent samples *t*-test).

GLI = Global Lung Function Initiative.

FEV_1 = Forced Expiratory Volume in one second.

FVC = Forced Expiratory Vital Capacity

Table 4. Predicted and predicted percent values. Data presented as mean (SD).

Gender	GLI Caucasian			GLI Other			Al-Ghobain et al.			Al-Rawas et al.			Silman et al.		
	FVC	**FEV1**	**FEV1/ FVC**	**FVC**	**FEV1**	**FEV1/ FVC**	**FVC**	**FEV1**	**FEV1/ FVC**	**FVC**	**FEV1**	**FEV1/ FVC**	**FVC**	**FEV1**	**FEV1/ FVC**
Predicted values															
M	4.90 (0.65)	4.00 (0.59)	81.74 (2.75)	4.51 (0.60)	3.73 (0.55)	82.66 (2.79)	4.34 (0.46)	3.61 (0.42)	82.97 (1.33)	4.07 (0.53)	3.40 (0.43)	83.26 (0.84)	5.12 (0.60)	4.26 (0.60)	-
F	3.43 (0.43)	2.87 (0.41)	83.74 (3.00)	3.15 (0.38)	2.67 (0.38)	84.67 (3.04)	3.05 (040)	2.54 (0.38)	83.89 (1.84)	2.97 (0.39)	2.58 (0.36)	85.45 (0.99)	3.56 (0.42)	2.92 (0.41)	-
Percent Predicted Values															
M	88.18 (12.74)	92.53 (11.89)	105.20 (9.54)	95.76 (13.83)	99.32 (12.77)	104.03 (9.44)	99.44 (14.87)	102.06 (13.88)	103.56 (9.00)	106.19 (15.06)	108.69 (14.36)	103.20 (8.95)	84.32 (12.28)	86.83 (11.26)	-
F	87.42 (12.61)	91.89 (12.11)	105.20 (8.72)	95.01 (13.70)	98.63 (13.00)	104.04 (8.63)	98.37 (14.11)	103.86 (13.80)	104.94 (8.41)	101.25 (14.49)	102.29 (13.73)	103.00 (8.24)	84.30 (12.16)	90.33 (11.98)	-

Table 5. Frequency of lowest 5%. Data presented Count (Percentage%).

	GLI Caucasian		GLI Other		Al-Ghobain et al.		Al-Rawas et al		Silman et al.	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
FEV1	196 (23.2)	253 (24.6)	53 (6.3)	78 (7.6)	72 (8.5)	66 (6.4)	57 (6.7)	68 (6.6)	271 (32.0)	160 (15.5)
FVC	103 (12.2)	154 (15.0)	92 (10.9)	120 (11.7)	102 (12.1)	117 (11.4)	30 (3.5)	53 (5.2)	363 (42.9)	348 (33.8)
FEV1/ FVC (OVD)	0 (0)	0 (0)	0 (0)	0 (0)	109 (12.9)	119 (11.6)	61 (7.2)	105 (10.2)	-	-
TRVD	79 (9.3)	123 (12.0)	40 (4.7)	58 (7.6)	49 (5.8)	61 (5.9)	16 (1.9)	31 (3.0)	-	-
MVD	0 (0)	0 (0)	0 (0)	0 (0)	10 (1.2)	4 (0.4)	2 (0.2)	1 (0.1)	-	-

Table 6. Linear regression of z scores produced by studied equations.

Variables	FEV1 Unstandardized coefficient (p value)					FVC Unstandardized coefficient (p value)				
	GLI Caucasian	GLI Other	Al-Ghobain et al.	Al-Rawas et al.	Silman et al.	GLI Caucasian	GLI Other	Al-Ghobain et al.	Al-Rawas et al	Silman et al.
Height	N/S	N/S	0.012 (0.01)	0.013 (0.02)	N/S	N/S	N/S	0.014 (<0.01)	0.019 (<0.001)	N/S
Gender	N/S	-0.007 (<0.001)	0.26 (<0.01)	-0.467 (<0.001)	0.44 (<0.001)	N/S	N/S	N/S	-0.274 (<0.01)	.230 (<0.01)
Age	N/S	N/S	-0.018 (<0.001)	-0.017 (<0.001)	N/S	-0.012 (<0.001)	-0.001 (<0.001)	-.021 (<0.001)	-0.015 (<0.001)	-0.008 (<0.001)
BMI	N/S	N/S	N/S	N/S	N/S		N/S	N/S	N/S	N/S