The applicability of the Global Lung Initiative equations and other regional equations on a sample of healthy Middle Eastern adolescents.

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Abstract:

Background: The Global Lung Initiative 2012 (GLI-2012) spirometry equations are multi-ethnic equations that cover all ages between 3-95. However, there is a need to evaluate the suitability of these equations to a sample of Middle Eastern adolescents prior to being applied in clinical practice. The aim of this study is to evaluate the suitability of GLI-2012 equations and two regional equations to a sample of Jordanian adolescents.

Methods: Spirometric measures were collected from 1036 healthy 14 to 17-year-old Jordanian children. z-scores, predicted values, percent predicted values, and frequency of measures below lower limit of normal (LLN) were calculated for each adolescent using the studied equations.

Results: The means of z-scores produced by GLI-2012 equations for Caucasians in forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC% and mid forced expiratory flow (FEF25-75) for boys were 0.12, -0.06, 0.34 and 0.09 respectively, while for girls they were -0.09,-0.16, 0.19 and -0.05 respectively. The mean of z-scores produced by GLI-2012 Other or Mixed equations in FEV1, FVC, FEV1/FVC% and FEF25-75 for boys were 0.74, 072, 021 and 0.33 respectively, and for girls were 0.53, 0.56,0.02 and 0.2 respectively. The frequency of measures below LLN as produced by GLI 2012 for Caucasians were significantly different from the expected 5% in FEV1 and FEF25-75 in boys only, whereas Other or Mixed produced frequencies significantly different from the expected 5% in most of parameters.

Conclusion: Spirometry reference equations formulated for Jordanian adolescents may improve the diagnosis and treatment of asthma in Jordan.

Keywords: Asthma, Global Lung intuitive, Pulmonary function test, Spirometry reference values, Middle East.

Introduction

Spirometry is a noninvasive procedure used to evaluate lung function for children aged 3 years and above [1]. It is an important test used to diagnose a variety of diseases including asthma, which is the most prevalent chronic disease among children and adolescents [2]. However, the interpretation of the spirometry test results depends mainly on the spirometry reference values applied during the test [3]. Therefore, the adoption of inadequate reference values may lead to inappropriate diagnosis and lung function evaluation [4].

Variation in the normal spirometry reference values has been observed among different groups of healthy subjects [5]. Such variation has been attributed to several factors including age, sex, height, ethnic group and different living settings [5,6].To overcome this limitation, multiethnic spirometry reference equations that covering ages from 3 to 95 years were formulated by the Global Lung Initiative (GLI) [7]. These equations have been endorsed by several societies including the American Thoracic Society (ATS) [8] and European Respiratory Society (ERS) [9]. Nevertheless, several studies have reported that GLI-2012 equations are not a suitable fit for all populations[10,11]. Therefore, prior to adopting the GLI-2012 equations in any population it is necessary to evaluate the suitability of these equations in a healthy representative sample of that population, particularly if this population was not included in the data used to formulate GLI-2012 equations [12]. This is particularly important because a limited number of Arab ethnicity from North Africa region was included in the GLI-2012 final data [7]. The ERS has recommended that more studies should be conducted to evaluate the appropriateness of these equations to Arabs[7].

A recent study that evaluated the application of GLI-2012 equations on 6-13 year old Jordanian children showed that the GLI-2012 for Caucasians equations demonstrated a reasonable fit for this age group [13]. However, prediction bias has been reported when participants move from one age-range to an older one[6]. For example, among the Finish population, the GLI-2012 reference equations showed an age-associated increase in underestimation of FEV1 and FVC and overestimation of FEV1/FVC[14]. Moreover, in two German studies, LUNOKID (N = 1943, 4–19 years) and GINIplus (N = 1042, 15 years), the GLI2012 equations were a suitable fit for children below the age of 10, although larger deviations between GLI-2012 predicted values and actual measured ones were observed among adolescents [15]. Therefore, there is an urgent need to evaluate the suitability of GLI-2012 equations on other age groups including older children and adolescents [13]. Hence, the present study was conducted to evaluate the application of GLI-2012 equations on a sample of adolescents aged from 14-17 years in Jordan.

Methods

Study site and population

This present study is part of a project involving three parts. The first and two parts, which were recently published, aimed at testing the applicability of the GLI- 2012 norms on a sample of healthy adults aged ≥ 18 years [16] and school-age children (age: 6-13 years) [13] living in Jordan. The third part is the objective of this study.

The detailed method is described in a previous study [13] , however to summarize, the present study recruited adolescents attending different schools, summer camps and scout groups from different areas in Jordan including the capital city of Amman, Madaba, Fuhais in central Jordan, and Irbid , Ramtha and Mafraq in the north of Jordan. Data were collected from April through September, 2019. In addition to the information sheet describing the study aims and spirometry procedure and questions about adolescent health status and prescribed medications, a questionnaire including the core Arabic translated version of the ISAAC questionnaire [17,18] was given to parents at home through their children under the supervision of the school administrator. After excluding rejected or incomplete consent forms or questionnaires, parents answering ‘Yes’ to any of the following questions were also excluded from the study: “Has your child ever had wheezing or whistling in the chest at any time in the past?”, “Has your child had wheezing or whistling in the chest in the last 12 months?”, “Did your child ever have asthma?”, “In the last 12 months, did your child’s chest sound wheezy during or after exercise?“, “In the last 12 months, did your child have a dry cough at night, apart from a cough associated with a cold or chest infection?”, “Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?”, “In the past 12 months, did your child have a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu”, “Has your child ever had hay fever?” and “Has your child suffered from any respiratory infection (like a common cold) in the past 6 weeks?”. Parents of the study participants were informed that participation is not mandatory, and they had the right to withdraw from the study at any time. The researcher confirmed that the data are confidential and will be kept locked in the office of the principal investigator. The study received ethical approval from the Ethical Committee at Al-Zaytoonah University of Jordan in addition to the Health Ministry and the Ministry of Education. The number of participants from each city/town included in the study was proportional to the total number of inhabitants in that area. Recruits from all the included areas had similar ages.

Spirometry

In a separate room at the institution, participants were divided in groups of five and were asked to remove their heavy clothes and shoes. A researcher recorded ages in two decimals, body weight was measured to the nearest 0.1kg using a standardized electronic scale and height was measured using a stadiometer with the nearest centimeter. Then body mass index (BMI) was calculated using

Quetlet's index [19]. Each group of participants received a detailed explanation followed by a demonstration of spirometry procedure prior to participation.

The spirometry was conducted according to the guidelines of the ATS/ERS [20] using a SPIROBANK II smart with disposable turbines. In order to prevent air leakage, a closed-circuit technique was used in which nasal clips were placed on the nose of the participant who was asked, after sealing lips around the turbine and taking a deep breath to exhale as strongly as possible for at least 6 seconds. The test was not accepted if the participant hesitated or coughed specially during the first second of exhalation. The test was also rejected in case of incomplete exhalation, presence of leakage or obstruction in the turbine and if the extrapolated volume did not reach the cut-off point of 5% of the forced vital capacity (FVC). For the purpose of obtaining the between maneuvers criteria represented as the difference between the two largest forced expiratory volume in the first second (FEV1) and FVC, which must be within .15L, the child was asked to repeat the maneuver up to eight attempts until three acceptable maneuvers are obtained. In order to enhance test accuracy, all the spirometry tests were performed by the same healthcare professional using the same spirometer; this healthcare professional received an intensive training on the proper technique for spirometry use by the principal investigator of the current study who was responsible for data evaluation and interpretation

Statistical analysis

Continuous variables were presented as means and standard deviations while categorical variables were presented as frequency and percentages. Z-scores for BMI-for-age and height-for-age were calculated for each participant using World Health Organization (WHO) reference values [21] that were adopted by Jordan [22]. Chi-square test was performed to compare spirometry success rates between the two sexes. When normality was assumed t-test was performed to compare the differences between the two sexes in anthropometric and spirometry measures, while Mann-Whitney U test was applied if the normality assumption was not met. Predicted normal values, %predicted and z-scores for FEV1, FVC, FEV1/FVC ratio and Mid Forced Expiratory Flow Rates (FEF25-75) were calculated using GLI-2012 Other or Mixed and GLI-2012 for Caucasians. In addition, two other regional equations were evaluated. The first was conducted by Sliman et al. [23] on Jordanian children and adolescents aged between 7-18 years, while the second equation set was conducted on Omani children and adolescents aged between 6-19 years by Al-Riyami et al. [24].

The following conditions should be met to determine that the reference equation is suitable for the study sample: 1. Normal distribution of. First, the produced spirometry z-scores should be normally distributed 25, 2. Second, the z-scores' mean and standard deviations (SD) should ideally be 0 and 1 respectively [26], however, means up to ± 0.5 are tolerated [15].

The Kolmogorov-Smirnov test was applied to evaluate the normality of the z-scores produced by the studied equations for each sex. Several repeated measures ANOVAs were conducted to detect any significant differences between predicted values produced by the studied equations and the study sample spirometry values, if the equation was suitable for the study data no significant differences should be detected. In addition, several multiple linear regression models were constructed: height, age and sex were included in these models as independent variables while z-scores for each spirometry parameter that were produced by each studied equation were included as a dependent variable.

Finally, lower limit of normal (LLN) was calculated for each child using the different studied equations. A suggested cut-off point for the percentage of children below LLN is 5% [27]. The degree of deviation from the suggested 5% was evaluated by conducting one sample chi-square test. All statistical analysis was conducted using SPSS (Version 20).

Results

The ISAAC questionnaire and consent form were distributed to 1646 Jordanian adolescents aged between 14 to 17 years. Of those, 1498 (91%) returned a completely filled out questionnaires and consent forms signed by the parents, with 1097 meeting the inclusion criteria (69%). The spirometry tests were performed on the healthy 1097 adolescents and 1036 (54% males) completed the spirometry successfully (success rate=94.4%) and their data were included in the final analysis. The chi-square results indicated that there were no significant differences in the spirometry success rates between the sexes. (Figure 1).

<u>FIGURE 1 HERE</u>

The mean age of the total sample of adolescents who were included in the final data was 15.93±1.10 years old. In boys the mean age was 16.1±1.06 years old and 15.71±1.11 years old in girls. As Table 1 shows, there were significant differences in the total sample between the two sexes in height, weight, BMI and all the studied spirometry parameters, however, no significant differences between the two sexes in height-for-age z-scores and BMI-for-age z-scores were found. All the absolute spirometry values were higher in boys except for FEV1/FVC which was higher in girls.

<u>TABLE 1 HERE</u>

All z-scores of both sexes spirometric parameters were normally distributed, except for z-scores produced by GLI-2012 Caucasians and GLI-2012 Other or Mixed in FVC in boys and z-scores produced by Sliman et al. in FEV1/FVC in both sexes. As Table 2 shows GLI-2012 Caucasians produced z-scores with the closest means to zero when compared with the other studied equations in FEV1 and FVC in both sexes and in FEF27-75 in females. GLI-2012 Other or Mixed equations produced the closest mean to zero in FEV1/FVC in both sexes. Finally, Sliman et al. produced the closest mean to zero in FEF25-75 in boys. The z-scores with the closest SDs to 1 were produced by GLI-2012 Caucasians equations in FEV1 in both sexes and FVC and FEV1/FVC in females, GLI-2012 Other or Mixed equations produced the closest standard deviation to 1 in FEF25-75 in both sexes, while Al-Riyami et al. equations produced z-scores with the closest SD to 1 in FVC in boys, however, the z-scores with the closest SD to 1 was produced Sliman et al.in FEV1/FVC in boys.

TABLE 2 HERE

Repeated measures ANOVA results indicated that there were significant differences between the spirometry measures of the studied sample and the predicted values produced by the different studies equations except for FVC produced by GLI-2012 Caucasians in boys, FEF25-75 produced by Sliman et al. in boys, FEF25-75 produced by GLI-2012 Caucasians and Al-Riyami et al. equations in females and FEV1/FVC produced by all studied equations that have equations for FEV1/FVC in females. Repeated measures ANOVA results also showed that there are significant differences between the predicted values produced by all the studied equations except for the predicted values for FEV1 in boys produced by Sliman et al. and Al-Riyami et al. equations.

As Table 3 shows, the only equation that produced the suggested cut-off point of 5% below LLN was GLI-2012 Caucasians in FEV1/FVC in boys, some equations produced percentages that were not significantly different from the suggested 5% including GLI-2012 Caucasians in FVC in both sexes and FEV1, FEV1/FVC and FEF25-75 in females, in addition the percentage of females below LLN was not significantly different from 5% in Sliman et al. equation in FEV1/FVC and in Al-Riyami et al. equation in FEF25-75. On the other hand, most of the percentages produced by the different studied equations were significantly lower than 5% in most of the spirometry parameters.

TABLE 3 HERE

The multiple linear regressions results (Table 4) indicated that the z-scores of the different spirometry parameters were significantly associated with at least one independent variables in all the studied equations except for FEV1/FVC and FEF25-75 in GLI-2012 Caucasians and GLI-2012 Other or Mixed.

TABLE 4 HERE

Discussion

This study collected spirometry measures of 1036 adolescent Jordanians and evaluated its suitability for GLI-2012 equations in addition to two other regional equations. The results indicated that although neither of the two GLI-2012 equations nor the regional ones represented a perfect fit for the study data as described in the method section, GLI-2012 Caucasians was a better representation for the study data. As previously reported [28], the absolute values of FEV1, FVC and FEF25-75 were higher in boys when compared with girls, while FEV1/FVC was higher among girls.

Applicability of GLI-2012 equations to the studied sample

The GLI-2012 spirometry equations attempted to formulate multiple equations for different ethnic groups, the main strength of GLI-2012 equations is that it was based on large sample size from different countries and covered a wide age range [7] which encouraged several health society the American Thoracic Society (ATS)[8] and European Respiratory Society (ERS) to endorse applying it in the management of different respiratory diseases [8,29] . However, it was reported previously that different variables including social, economic and environmental factors may result in differences in normal spirometry values among different populations even from the same ethnic group [30].

This is even more evident when applying the GLI-2012 equations on ethnic groups that were not included in the data used to formulate these equations such as the Arabic population from the Middle East [7]. Therefore, the validation of these equations on a sample of Middle Eastern population was necessary.

This study validated the suitability of these equations on a sample of Jordanian adolescents aged between 14-17 years by several methods, First, z-scores generated from the GLI-2012 Caucasians/Other or Mixed were computed, the normality of these z-scores were evaluated by applying Kolmogorov-Smirnov test which indicated that z-scores for FVC in boys were not normally distributed. Moreover, all the z-scores produced when applying GLI-2012 equations for Caucasians or for Other or Mixed did not have a mean of zero and a SD of one leading to either underestimation or overestimation of the predicted values, although none of the z-scores means produced by the GLI-2012 Caucasians exceeded the acceptable level of ±0.5, unlike the z-scores produced by Other or Mixed equations in which many exceeded the acceptable cut-off point including FEV1 and FVC in both sexes. Applying GLI-2012 Caucasians resulted in overestimation of the predicted values of many of the spirometry parameters including FVC in both sexes and FEV1 and FEF25-75 in girls. On the other hand, Other or Mixed equations underestimated the predicted values of all the studied spirometry parameters in both sexes. Furthermore, repeated measures ANOVA showed significant differences between the predicted values produced by GLI-2012 equations and the spirometry values of the studied healthy adolescents in many spirometry parameters. LLN values produced by GLI-2012 Caucasians were significantly different from 5% in fewer spirometry parameters when compared with GLI-2012 Other or Mixed.

Finally, the multiple regression showed that there were significant associations between z-scores produced by GLI-2012 Caucasians and GLI-2012 Other and Mixed and different variables including sex and height, which indicated that the tested predicted equations differ in their suitability between different heights and sexes [10,30,31].

Therefore, this study has indicated that the GLI-2012 Caucasians were more suitable for the studied sample than the Other or Mixed equations. This agrees with previous work that evaluated the suitability of GLI-2012 equations on 6-13 years old Jordanian children [13]. However, the GLI-2012 Caucasian equations showed a better representation in the younger group when compared with the current studied age group [13]. On the other hand, previous work that validated the GLI-2012 equations in Jordanian adults [16] indicated that the GLI-2012 Other or Mixed had a better representation for the Jordanian adults [16]. The results of these three studies indicate that there is a slower pulmonary growth rate and emphasizes the need for long-term studies to evaluate the changes in lung growth rates among the Jordanian population and factors that may influence these.

Applicability of two regional equations on the studied sample

The suitability of two regional equation sets to the studied sample were evaluated. The first regional study was based on a sample of 6-19 years Omani adolescents and children [24], while the second equation set was based on 7-18 years Jordanian adolescents and children [23]. The Jordanian equations that were formulated by Sliman et al. formulated two sets of equations: the first included height and sex only, while the second set included additionally included BMI [23]. This study evaluated the two sets of equations and found that the first equations' set was more suitable for this sample, therefore, only the results of the first set that included height and sex were used in this study. Neither two study produced z-scores with means of zero and SD of 1. Z-scores produced by Sliman et al. were not normally distributed in FEV1/FVC in either sex. Sliman et al. overestimated the predicted values of our sample in FEV1 in both sexes and FEF25-75 in females and underestimated the rest of the studied spirometry parameters although none of the studied parameters exceeded the physiological relevant cut-off points. Nevertheless, standard deviations of the z-scores produced by Sliman et al.'s equations were low in many of the parameters including FEV1, FVC and FEF25-75 in both sexes, possibly because the variance of age was not included in their equations [23]. Al-Riyami et al.'s equations overestimated the predicted values in most of the studied parameters for both sexes and exceeded the physiologically relevant cut-off point of +0.5 in both sexes for FEV1.

Moreover, when applying the two regional equations the percentages of adolescents under LLN were significantly lower than the 5% in most of the studied parameters. The results of the multiple linear regression indicated that there were significant association between all of the spirometry parameters and age and height; this might be due to the methodology applied in formulating these equations; as these equations were formulated based on linear regression models and as previously reported these models assume constant variance which might not apply in spirometry parameters [6]. A further limitation of the two equations is that they were only based on a sample collected from one city which casts doubt on the representability of the studied samples to the wider population. Finally, Sliman et al.'s paper was published in 1984 while Al-Riyami et al.'s equations were published in 2004: many environmental and cultural changes could have influenced the predicted spirometry values, in addition to technological advances that may have improved spirometer accuracy. The result of this study that indicated that these equations are not currently suitable for the Jordanian population mirrors Al-Qerem et al.'s finings in Jordanian children aged 6-13 years. [13]

Limitations of the study

This study has several limitations. First, we did not measure variables that may have an influence on the spirometry results including exposure to indoor and outdoor air pollution, physical activity, and nutritional status. Second, the sample size - although more than the minimal required sample size for spirometric reference equations studies (150 participants for each sex) as suggested by Quanjer et al. [32] - is relatively small (less than 600 participants of each sex). Therefore, there were few participants below LLN which may cast doubt in the significant p values produced. Lastly, the age range of the study participants was narrow (14-17 years) and did not cover all age groups including preschool children.

Perspectives

New spirometry reference equations formulated using the new gold standard GAMLSS regression methodology s, which uses both means and the shape of the distribution to improve modelling. Using this will improve the accuracy of the derived equations and hence will improve the diagnosis and management of respiratory diseases, not only among Jordanian adolescents, but lung function globally.

Conclusion

The results of this study indicate that GLI-2012 Caucasian equations represented better fit when compared with Other or mixed or the studied regional equations. However, a more specific spirometry equation set for Jordanian adolescents can add benefit to the diagnosis and management of different respiratory diseases in Jordan.

References

1. Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med*. 2007;175(12):1304-1345.

2. Sears. Evolution of asthma through childhood. *Clin Exp Allergy*. 1998;28(s5):82-89. doi:10.1046/j.1365-2222.1998.028s5082.x

3. Richards JA. Office spirometry—indications and limitations. *South African Fam Pract*. 2006;48(2):48-51. doi:10.1080/20786204.2006.10873340

4. Saglani S, Menzie-Gow AN. Approaches to Asthma Diagnosis in Children and Adults. *Front Pediatr*. 2019;7:148. doi:10.3389/fped.2019.00148

5. Mayeux R. Biomarkers: potential uses and limitations. *NeuroRx*. 2004;1(2):182-188. doi:10.1602/neurorx.1.2.182

6. Quanjer PH, Hall GL, Stanojevic S, Cole TJ, Stocks J, Global Lungs Initiative. Age- and height-based prediction bias in spirometry reference equations. *Eur Respir J*. 2012;40(1):190-197. doi:10.1183/09031936.00161011

7. Quanjer PH, Cole TJ, Hall GL, Culver BH. Muti-ethnic reference values for spirometry for thee 3-95 years age range: the global lung function 2012 equations. *Eur Respir J*. 2013;40(6):1324-1343. doi:10.1183/09031936.00080312.MULTI-ETHNIC

8. Culver BH, Graham BL, Coates AL, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical statement. *Am J Respir Crit Care Med*. 2017;196(11):1463-1472. doi:10.1164/rccm.201710-1981ST

9. Cooper BG, Stocks J, Hall GL, et al. The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. *Breathe*. 2017;13(3):e56 LP-e64. doi:10.1183/20734735.012717

10. Ben Saad H, El Attar MN, Hadj Mabrouk K, et al. The recent multi-ethnic global lung initiative 2012 (GLI2012) reference values don't reflect contemporary adult's North African spirometry. *Respir Med*. 2013;107(12):2000-2008. doi:10.1016/j.rmed.2013.10.015

11. Peradzyńska J, Krenke K, Szylling A, Krenke R, Kulus M. The influence of the reference values on the interpretation of lung function in children: Comparison of global lung initiative 2012 and polish 1998 reference values. *Adv Exp Med Biol*. 2015;858:31-38. doi:10.1007/5584_2014_102

12. Quanjer PH, Stanojevic S. Do the global lung function initiative 2012 equations fit my population? *Eur Respir J*. 2016;48(6):1782-1785. doi:10.1183/13993003.01757-2016

13. Al-Qerem WA. How applicable are GLI 2012 equations to a sample of Middle Eastern school-age children? *Pediatr Pulmonol*. 2020;55(4):986-993. doi:10.1002/ppul.24685

14. Kainu A, Timonen KL, Toikka J, et al. Reference values of spirometry for Finnish adults. *Clin Physiol Funct Imaging*. 2016;36(5):346-358. doi:10.1111/cpf.12237

15. Hüls A, Krämer U, Gappa M, et al. Age dependency of GLI reference values compared with paediatric lung function data in two German studies (GINIplus and LUNOKID). *PLoS One*. 2016;11(7). doi:10.1371/journal.pone.0159678

16. Al-Qerem WA, Hammad AM, AlQirem RA, Ling J. Do the global lung function initiative

reference equations reflect a sample of adult Middle Eastern population? *Clin Respir J*. 2019;13(7):429-437. doi:10.1111/crj.13027

17. Behbehani NA, Abal A, Syabbalo NC, Abd Azeem A, Shareef E, Al-Momen J. Prevalence of asthma, allergic rhinitis, and eczema in 13- to 14-year-old children in Kuwait: an ISAAC study. International Study of Asthma and Allergies in Childhood. *Ann Allergy Asthma Immunol*. 2000;85(1):58-63. Accessed August 27, 2019. http://www.ncbi.nlm.nih.gov/pubmed/10923606

18. Al-Qerem WAWA, Ling J, Pullen R, McGarry K. Reported prevalence of allergy and asthma in children from urban and rural Egypt. *Air Qual Atmos Heal*. 2015;9(6):1-8. doi:10.1007/s11869-015-0372-1

19. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. *Int J Obes*. 1985;9(2):147-153. Accessed August 27, 2019. http://www.ncbi.nlm.nih.gov/pubmed/4030199

20. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805

21. De Onis M. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Int J Paediatr*. 2006;95(SUPPL. 450):76-85. doi:10.1080/08035320500495548

22. de Onis M, Onyango A, Borghi E, et al. Worldwide implementation of the WHO Child Growth Standards. *Public Health Nutr*. 2012;15(9):1603-1610. doi:10.1017/S136898001200105X

23. Sliman NA, Dajani BM, Shubair KS. Pulmonary function in normal Jordanian children.

Thorax. 1982;37(11):854-857. Accessed January 6, 2019. http://www.ncbi.nlm.nih.gov/pubmed/7164005

24. Al-Riyami BM, Al-Rawas OA, Hassan MO. Normal spirometric reference values for Omani children and adolescents. *Respirology*. 2004;9(3):387-391. doi:10.1111/j.1440-1843.2004.00608.x

25. Madanhire T, Ferrand RA, Attia EF, Sibanda EN, Rusakaniko S, Rehman AM. Validation of the global lung initiative 2012 multi-ethnic spirometric reference equations in healthy urban Zimbabwean 7-13 year-old school children: A cross-sectional observational study. *BMC Pulm Med*. 2020;20(1):1-11. doi:10.1186/s12890-020-1091-4

26. Cole TJ, Stanojevic S, Stocks J, Coates AL, Hankinson JL, Wade AM. Age- and size-related reference ranges: a case study of spirometry through childhood and adulthood. *Stat Med*. 2009;28(5):880-898. doi:10.1002/sim.3504

27. Coates AL. Using Reference Values to Interpret Pulmonary Function Tests. *Paediatr Respir Rev*. 2011;12(3):206-207. Accessed September 3, 2018. https://www.sciencedirect.com/science/article/pii/S1526054211000133

28. Quanjer PH, Stanojevic S, Stocks J, et al. Changes in the FEV1/FVC ratio during childhood and adolescence: An intercontinental study. *Eur Respir J*. 2010;36(6):1391-1399. doi:10.1183/09031936.00164109

29. Quanjer PH, Brazzale DJ, Boros PW, Pretto JJ. Implications of adopting the Global Lungs Initiative 2012 all-age reference equations for spirometry. *Eur Respir J*. 2013;42(4):1046-1054. doi:10.1183/09031936.00195512

30. Backman H, Lindberg A, Sovijärvi A, Larsson K, Lundbäck B, Rönmark E. Evaluation of the global lung function initiative 2012 reference values for spirometry in a Swedish population sample. *BMC Pulm Med*. 2015;15(1):1-8. doi:10.1186/s12890-015-0022-2

31. Hall GL, Thompson BR, Stanojevic S, et al. The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. *Respirology*. 2012;17(7):1150-1151. doi:10.1111/j.1440-1843.2012.02232.x

32. Quanjer PH, Stocks J, Cole TJ, Hall GL, Stanojevic S, Global Lungs Initiative. Influence of secular trends and sample size on reference equations for lung function tests. *Eur Respir J*. 2011;37(3):658-664. doi:10.1183/09031936.00110010

Table 1. Sample anthropometric and spirometry measures. Data presented as mean (SD)*

Variable	Boys					Girls					p-value
	14 y N=112 (20%)	15 y N=114 (20.4%)	16 y N=209 (37.4)	17 y N=124 (22.2%)	Total N=559	14 y N=131 (27.5%)	15 y N=162 (34%)	16 y N=105 (22%)	17 y N=79 (16.6%)	Total N=477	
Height (cm)	163.81 (11.26)	170.04 (8.59)	173.89 (6.76)	171.59 (5.84)	170.57 (8.85)	157.52 (5.78)	158.21 (5.62)	159.2 (6.13)	158.89 (6.56)	158.35 (5.96)	<0.01
Weight (Kg)	60.86 (15.38)	64.99 (13.62)	69.80 (13.70)	72.75 (14.39)	67.68 (14.78)	59.13 (11.34)	60.14 (12.93)	60.28 (14.93)	61.05 (11.21)	60.04 (12.70)	<0.01
BMI	22.53 (4.56)	22.41 (4.21)	23.02 (3.96)	24.65 (4.38)	23.16 (4.30)	23.80 (4.21)	23.94 (4.52)	23.64 (5.0)	24.21 (4.35)	23.88 (4.51)	0.02
Height-for-age z-scores	-0.15 (0.94)	-0.40 (0.93)	-0.40 (0.86)	-0.40 (0.90)	-0.35 (0.90)	-0.32 (1.06)	-0.33 (0.99)	-0.49 (1.15)	-0.55 (1.0)	-0.40 (1.05)	N/S
BMI-for-age z-score	0.65 (1.16)	0.63 (1.10)	0.69 (1.25)	0.97 (1.09)	0.73 (1.17)	0.70 (1.148)	0.66 (1.25)	0.74 (1.18)	0.69 (1.23)	0.69 (1.20)	N/S
FEV_1 (L)	3.49 (0.73)	3.90 (0.63)	4.20 (0.59)	4.22 (0.48)	4.0 (0.67)	2.96 (0.46)	3.0 (0.35)	3.06 (0.43)	3.14 (0.30)	3.02 (0.40)	<0.01
FVC (L)	4.07 (0.91)	4.45 (0.79)	4.82 (0.77)	4.65 (0.62)	4.56 (0.82)	3.25 (0.54)	3.32 (0.43)	3.44 (0.55)	3.58 (0.41)	3.37 (0.50)	<0.01
FEV_1/ FVC%	86.50 (6.84)	88.04 (6.70)	87.80 (7.27)	91.08 (7.26)	88.32 (7.22)	91.33 (6.35)	90.67 (6.62)	89.55 (6.28)	88.27 (5.84)	90.21 (6.42)	<0.01
FEF2575 (L/s)	3.90 (0.96)	4.37 (0.94)	4.74 (1.02)	5.05 (1.00)	4.5 (1.06)	3.67 (0.81)	3.73 (0.79)	3.72 (0.81)	3.71 (0.65)	3.71 (0.78)	<0.01

*SD: Standard deviation, N/S: Not significant, BMI: Body mass index, FEV1: forced expiratory volume in the 1st second, FVC: forced vital capacity, FEF2575: mid forced expiratory flow rates.

Table 2. Predicted, predicted percent values and z-scores of spirometry measures as produced by different studied equations. Data presented as mean (SD)*.

Variables	**Boys**			**Girls**		
	Predicted values	**Percent predicted values**	**z-scores**	**Predicted values**	**Percent predicted values**	**z-scores**
GLI Caucasian						
FEV1 (L)	3.96 (0.51)	101.29 (11.91)	**0.12** (1.01)	3.07 (0.26)	98.81 (11.70)	**-0.09** (1.00)
FVC (L)	4.60 (0.63)	99.38 (13.70)	**-0.06** (1.19)	3.44 (0.31)	98.19 (13.03)	**-0.16** (1.07)
FEV1/FVC%	86.63 (0.66)	101.95 (8.27)	0.34 (1.15)	89.76 (0.38)	100.50 (7.12)	0.19 (1.01)
FEF 25-75(L/s)	4.42 (0.48)	103.08 (20.62)	0.09 (0.89)	3.73 (0.21)	99.53 (20.48)	**-0.05** (0.96)
GLI other						
FEV1(L)	3.68 (0.48)	108.72 (12.79)	0.74 (1.08)	2.86 (0.24)	106.06 (12.56)	0.53 (1.08)
FVC(L)	4.23 (0.58)	107.92 (14.88)	0.72 (1.35)	3.16 (0.28)	106.72 (14.16)	0.56 (1.21)
FEV1/FVC%	87.55 (0.66)	100.87 (8.19)	**0.21** (1.22)	90.71 (0.39)	99.44 (7.05)	**0.02** (1.15)
FEF25-75 (L/s)	4.20 (0.46)	108.71 (21.75)	0.33 (1.0)	3.54 (0.20)	104.96 (21.59)	0.20 (0.99)
Al-Riyami et al.						
FEV1(L)	3.63 (0.56)	110.81 (13.98)	0.76 (0.99)	2.71 (0.32)	112.29 (14.57)	0.86 (1.04)
FVC(L)	4.35 (0.71)	105.46 (15.06)	0.35 (1.10)	3.02 (0.36)	112.25 (16.20)	0.82 (1.10)
FEF25-75(L/s)	4.17 (0.53)	109.90 (22.91)	0.31 (0.88)	3.70 (0.36)	100.83 (21.27)	-0.06 (0.93)
Sliman et al.						
FEV1(L)	3.69 (0.52)	108.89 (13.26)	0.34 (0.52)	2.94 (0.31)	103.07 (12.96)	0.09 (0.54)
FVC(L)	4.93 (0.69)	92.69 (12.58)	-0.36 (0.56)	3.54 (0.38)	95.55 (13.34)	-0.23 (0.58)
FEV1/FVC%	89.79 (0.09)	98.36 (8.05)	-0.25 (1.05)	90.39 (0.06)	99.80 (7.11)	-0.06 (0.91)
FEF25-75(L/s)	4.51 (0.60)	101.64 (21.25)	**-0.02** (0.71)	3.56 (0.36)	104.70 (22.19)	0.08 (0.73)

*Standard deviation, results in bold indicate best fit, FEV1: forced expiratory volume in the 1st second, FVC: forced vital capacity, FEF2575: mid forced expiratory flow rates.

Table 3. Frequency of adolescents below LLN produced by different studied equations. Data presented as count (%).

	GLI Caucasian		**GLI other**		**Al-Riyami et al**		**Sliman et al**	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
FEV1	15 (2.70%)*	22 (4.60%)	3 (0.50%)**	3 (0.60%)**	4 (0.70%)**	5 (1.00%)**	0 (0.00%)	2 (0.40%)**
FVC	34 (6.10%)	31 (6.50%)	5 (0.90%)**	8 (1.70%)**	15 (2.70%)*	4 (0.80%)**	3 (0.50%)**	3 (0.60%)**
FEV/FVC	28 (5.0%)	19 (4.0%)	36 (6.40%)	41 (8.60%)**	–	–	50 (8.90%)**	29 (6.10%)
FEF25-75	12 (2.10%)**	25 (5.20%)	7 (1.30%)**	14 (2.90%)*	10 (1.80%)**	26 (5.50%)	9 (1.60%)**	9 (1.90%)**

Significant difference from 5% (*p<0.05, **p<0.01), FEV_1: forced expiratory volume in the 1st second, FVC: forced vital capacity, FEF2575: mid forced expiratory flow rates.

Table 4. Linear regression of z scores produced by studied equations.

Variable	Equation	Sex B (p-value)	Height B (p-value)	Age B (p-value)
FEV1	GLI Caucasian	-0.35(<0.01)	-0.01(0.02)	N/S
	GLI other	-0.36 (<0.01)	-0.01(0.02)	N/S
	Al-Riyami et al	-0.44(<0.01)	-0.05(<0.01)	0.19 (<0.01)
	Sliman et al	-0.43 (<0.01)	-0.02 (<0.01)	0.1(<0.01)
FVC	GLI Caucasian	-0.27(<0.01)	-0.01(0.02)	N/S
	GLI other	-0.34 (<0.01)	-0.01(0.02)	-0.08(0.04)
	Al-Riyami et al	N/S	-0.05(<0.01)	0.15 (<0.01)
	Sliman et al	N/S	-0.02 (<0.01)	0.08 (<0.01)
FEV1/FVC	GLI Caucasian	N/S	N/S	N/S
	GLI other	N/S	N/S	N/S
	Al-Riyami et al	_	–	–
	Sliman et al	N/S	-0.01 (<0.01)	N/S
FEF25-75	GLI Caucasian	N/S	N/S	N/S
	GLI other	N/S	N/S	N/S
	Al-Riyami et al	-0.6 (<0.01)	-0.02 (<0.01)	0.13 (<0.01)
	Sliman et al	N/S	-0.02 (<0.01)	0.11 (<0.01)

N/S: not significant, B: Unstandardized coefficient, FEV_1: forced expiratory volume in the 1st second, FVC: forced vital capacity, FEF2575: mid forced expiratory flow rates.

Figure Legends:

Figure 1. Recruitment chart flow