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Global Lung Function Initiative 2012 reference values for spirometry in South Italian children

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ABSTRACT

Rationale: Despite the widespread use of the Global Lung Function Initiative (GLI) 2012 reference values, there is still the need of testing their applicability in local areas.
Objectives: The aims of this study are to evaluate applicability of GLI reference equations in a large population-based sample of normal schoolchildren from Sicily, and to compare GLI and previous prediction equations in terms of spirometry test interpretation.
Methods: GLI equations were evaluated in 1243 normal schoolchildren, 49% males, aged 7–16 years, height 116–187 cm. Normality assumptions for the GLI z-scores (FEV_1, FVC, FEV_1/FVC) were tested, and *bootstrap* confidence intervals for the mean (0 expected) and the variance (1 expected) were derived. GLI and other reference equations were compared in terms of probabilities to fall below the lower limit of normal (LLN).
Results: The GLI z-score normality assumption held for males but not for females ($p < 0.001$). According to the mean z-score, predicted values were: slightly underestimated for FEV_1 (0.15 in males, 0.07 in females); overestimated for FVC (−0.27 in males, −0.32 in females); highly underestimated for FEV_1/FVC (0.75 in males, 0.81 in females). Variability was correctly estimated. The probability of FEV_1<LLN correctly approached 0.05 when using GLI, Hankinson and Quanjer equations. Wang equations yielded correct probabilities of abnormal FVC; Pistelli equations yielded correct probabilities of abnormal FEV_1/FVC for females.
Conclusions: GLI 2012 references underestimate FEV_1/FVC predicted values in a sample of normal South Italian children. Physicians interpreting spirometry should be aware to test reference values prior to their use in a local area.

1. Introduction

In 2012, the European Respiratory Society Task Force for Global Lung Function Initiative (GLI) published reference values for spirometric parameters for five ethnic groups, in the 3–95 years age range [1]. In view of their characteristics (different ethnicities, large age range and sample size), the American Thoracic Society (ATS), the Australian and New Zealand Society of Respiratory Science and other international respiratory societies encouraged their use and implementation into spirometric devices [2]. As a consequence, a progressive replacement of previously used reference equations [3,4] occurred.

Recently, some concerns about GLI applicability derived from studies in European [5] and North African [6] population-based samples of healthy adults, highlighting the importance of a local assessment. In particular, the evaluation of applicability is needed in those individuals not represented in the GLI collated dataset, such as South Italian children. Since applicability studies require large population-based samples (at least 300 healthy controls) [7], only few previous studies demonstrated GLI applicability in healthy

Abbreviations used: GLI, Global Lung Function Initiative; LLN, Lower limit of Normal; FEV_1, Forced Expiratory value in 1 second; FVC, Forced Vital Capacity; CI, Confidence Interval.

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populations of children [8–11] and adolescents [12].

The consequences of adopting GLI reference equations as the gold-standard for spirometric parameters were early investigated in data from outpatient and inpatient children, including patients with cystic fibrosis, highlighting some interpretative differences induced by the replacement of previous references [13–15]. On the contrary, only few comparative studies between GLI and other published reference equations were performed on population-based sample of healthy children [1,16]. Indeed, such studies can be useful to identify the most suitable reference values for a local area.

The aims of this study on a large population-based sample of healthy schoolchildren from Sicily (Southern Italy) are: i) to assess the applicability of GLI reference equations in a local, Mediterranean area; ii) to compare GLI and previous prediction equations for paediatric age in terms of spirometry test interpretation. Some results of this study were previously reported in the form of an abstract [17].

2. Materials and methods

2.1. Study population

3804 Caucasian children from primary and lower secondary schools, aged 7–16 years, were pooled from five cross-sectional studies performed in Sicily between October 2004 and April 2012. The aforementioned studies were: *i*) "Palermo Junior High School" (PJHS I) [18], n = 1,050, 8 schools; *ii*) "Palermo Junior High School" (PJHS II) [19], n = 2,150, 16 schools; *iii*) CCM Project [http://www.ccm-network.it], n = 343, 8 junior high schools; *iv*) SINPHONIE Project [http://www.sinphonie.eu], n = 39, 2 primary schools; *v*) RESPIRA Project [http://www.keep.eu], n = 222, 12 junior high schools. All studies were approved by the Ethic Committee of the University Hospital of Palermo with the exception of the RESPIRA Project, which was approved by the Ethic Committee of the Provincial Health District of Caltanissetta (Italy). Parents of the invited schoolchildren signed a written informed consent. According to the Italian law, respect of individual privacy concerning clinical data was guaranteed.

A self-administered standardized questionnaire, the SIDRIA parent questionnaire [20], was filled by parents/caregivers at home. "Healthy" children were defined as: i) negative answers given by parents to all the following questions: "*Has your child ever had wheezing or whistling in the chest at any time in the past*?"; "*In the past 12 months, has your child's chest sounded wheezy during or after exercise*?"; "*In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection*?"; "*Has your child ever had asthma diagnosed by a doctor*?"; "*In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu*?"; ii) no respiratory tract infections reported in the 6 weeks preceding the study; iii) never smokers. Out of the 3804 children there were 1599 "healthy" children. Moreover, "normal" children were defined as those without the following conditions: i) birth-weight<2000 g; ii) absolute BMI-for-age z-score≥2 [21]; iii) both non-European parents. A total of 356 children were excluded, ending up to 1243 "normal" children. The flow-chart of the study sample is depicted in Fig. 1.

2.2. Pulmonary function test

All pulmonary function tests were performed through standardized spirometric procedures by well trained physicians (F.C, S.L.G). In detail, spirometry was carried out in the morning at school under standard environmental conditions, after at least 30 min and 2 h from, respectively, exercise and eating. Height (in cm) and weight (in kg) were measured in standing position without shoes, using a stadiometer (Wunder HR1, Italy) and an electronic weighing scale (Seca, Hamburg, Germany). Spirometry was performed through the Micro Medical MicroLab 8 v2.29 Spirometer (MicroLoop, CareFusion UK 306 Ltd The Crescent Jays Close Basingstoke RG22 4BS United Kingdom), a portable spirometer that has been tested to meet the ATS/ERS recommendations [22] for accuracy and precision in measuring both FEV_1 and FVC. According to the guidelines, out of three technically acceptable tests, the best FVC and FEV_1 were retained, and the FEV_1/FVC ratio was computed.

2.3. Statistical analyses

To test for the GLI applicability, the corresponding z-scores for FEV_1, FVC and FEV_1/FVC were computed for each subject, and 95% percentile *bootstrap* confidence intervals (CIs) [23] were derived for their mean and variance (yielding 10,000 samples with replacement). The normality assumption was tested through the Jarque-Bera test [24], to detect possible lack of symmetry (skewness, if larger or lower than 0) or heavy/thin tails (kurtosis, if larger or lower than 3) of the z-score distribution. If the GLI prediction equations perfectly fit a sample, the z-scores should be normally distributed with mean equal to 0 and standard deviation equal to 1.

The Lower Limit of Normal (LLN) was computed for FEV_1, FVC and FEV_1/FVC using reference equations originating from other studies on children with age and height ranges comparable to those of the present study population (Table 1): Polgar [25], Zapletal [26], Knudson [27], Rosenthal [28], Wang [29], Quanjer [30], Hankinson [3], Pistelli [31]. The LLN is defined as the lower fifth percentile of a distribution for normal subjects. For all reference equations, standard [32] 95% CIs for the probability of a child to fall below the LLN were computed. Such "abnormality probability" should approximate 0.05 by definition, in a "normal" sample [33]. It is expected that the better the fitting of a reference equation, the closer the relevant confidence interval should be to the target value of 0.05. Corresponding p-values for the null hypothesis of "no deviation from the target value" were also used to assess the goodness of fit: lower p-values (the usual threshold of 0.05 can be used) indicate higher deviation of the abnormality probability from the 0.05 target value. In particular, the fitting of a reference equation was defined as "good" if $p = 0.05$, "not very bad" if $0.001 \leq p < 0.05$, "very bad" if $p < 0.001$. All statistical analyses were performed using the R statistical software version 3.2.0 [https://cran.r-project.org].

3. Results

3.1. Demographic characteristics of normal children

The study sample consisted of 603 males (49%) and 640 females (51%). The age range was 7–16 years for both males and females; the height range was 120–187 cm for males and 116–176 for females, whilst the BMI range was 14.47–25.47 kg/m^2 for males and 13.23–27.18 kg/m^2 for females.

3.2. Applicability of GLI 2012 reference equations

The results of the Jarque-Bera test are summarized in Table 2. Normality hypothesis was always rejected for females; in particular, z-score distributions for FEV_1 and FVC were symmetric, but they exhibited thinner tails with respect to the normal distribution (kurtosis>3), while z-score distributions for FEV_1/FVC showed negative (left) skewness.

Fig. 2 shows CIs for mean z-scores of FEV_1, FVC and FEV_1/FVC by sex. Both in males and females, mean FEV_1 z-scores were slightly