# Global Lung Function Initiative reference equations better describe a middle-aged, healthy French population than the European Community for Steel and Coal values

*To the Editor*:

Spirometry plays a pivotal role in the clinical evaluation and management of respiratory diseases. Pulmonary function varies with age, height, sex and ethnicity, and test results need to be compared with predicted values and lower limits of normal (LLN) and upper limits of normal (ULN), that are appropriate for the individual being tested [1]. The European Community for Steel and Coal (ECSC) first published reference spirometric values for healthy non-smokers in 1983 based on a collation of regression equations [2]. In 2012, the Global Lung Function Initiative (GLI) presented prediction equations derived from measured values of a large population [1]. These newer statistical procedures provided us for the first time with a single equation for ages from 3 years through to 95 years. Measured values are converted to z-scores which describe how many standard deviations a measured value differs from the predicted value and these are independent of sex, age and height.

BACKMAN*et al.* [3] have recently shown that the GLI reference values were better suited than the ECSC reference values to the Swedish population but less relevant than local population-specific reference values. In particular, forced volume capacity (FVC) and forced expiratory volume in 1 s ($FEV_1$), expressed as percentages of predicted values, tended to be overestimated among women to a greater extent by the ECSC reference values than the GLI values. These authors pointed out the "[…] importance of validating the GLI reference values in different countries". Other authors have also shown a better fitting of GLI reference values for their specific population [4, 5]. To our knowledge, no published study has yet applied these two sets of reference equations to a large French population. Here we present a comparison of z-score distributions obtained using ECSC to that using GLI reference equations applied on data from middle-aged healthy adults of a sample of the general population from northern France.

The ELISABET (Enquête Littoral Souffle Air Biologie Environnement) study is a cross-sectional study of a representative sample of 3276 adults, aged between 40 and 65 years, living in two northern, urban areas of France, and an urban (Lille) and an industrial (Dunkerque) zone [6]. All participants answered a questionnaire and performed spirometry testing. Subjects with respiratory disease were identified by self-reporting a history of respiratory disease, asthma attacks, respiratory medication or respiratory symptoms using the standardised Medical Research Council questionnaire. Spirometry testing was performed according to the 2005 ATS/ERS guidelines [7]. For each participant, the spirometry test was repeated (up to seven times) until three acceptable flow–volume loops were obtained, following the same guidelines. The spirometers (Micro 6000 spirometers; Medisoft, Sorinnes, Belgium) were calibrated weekly. Results were expressed as z-scores that were derived using prediction equations from both the ECSC and GLI. The LLN was defined as the lower fifth percentile (*i.e.* z-score=−1.645) and ULN as the upper fifth percentile (z-score=1.645). The proportion of subjects having z-score <LLN or >ULN was calculated using both ECSC and GLI equations. Comparisons between sexes were performed using the t-test and the Chi-squared test. Comparisons of proportions of subjects having the same spirometric index were performed between the ECSC and GLI reference sets using the Bhapkar'test.

A single expert analysed all spirometry results and excluded 235 subjects because of unacceptable spirometry (n=224) or missing data (n=11). At least three acceptable spirometry tests were obtained for each included subject (n=3041). Amongst these 3041 subjects, 1971 subjects were without respiratory diseases and retained for use in this study. The number of subjects in each age group was similar between men and women (table 1).

All z-score means were further from zero using the ECSC equations than when GLI equations were used, except for the ratio $FEV_1$/FVC (table 1). Again except for the $FEV_1$/FVC ratio, distributions below the LLN

TABLE 1 General characteristics of population and proportions of subjects with spirometric data below the lower limit of normal (LLN) (*i.e.* with z-score value < −1.64) and above the upper limit of normal (ULN) (*i.e.* with z-score value >1.64) in subjects without respiratory disease

| | Men | ECSC *versus* GLI | Women | ECSC *versus* GLI | Men *versus* women |
|---|---|---|---|---|---|
| **Subjects n** | 904 | | 1067 | | |
| **Age years** | 53.3±7.1 | | 52.8±7.3 | | 0.149 |
| **Age categories n (%)** | | | | | 0.580 |
| 40–45 years | 142 (15.7) | | 192 (18.0) | | |
| 45–50 years | 186 (20.6) | | 228 (21.4) | | |
| 50–55 years | 176 (19.5) | | 208 (19.5) | | |
| 55–60 years | 192 (21.4) | | 211 (19.8) | | |
| 60–65 years | 208 (23.0) | | 228 (21.4) | | |
| **Height (m)** | 0.067 (1.757) | | 0.067 (1.636) | | <0.001 |
| **BMI kg·m$^{-2}$** | 27.3±4.2 | | 26.0±5.2 | | <0.001 |
| **Mean z-scores** | | | | | |
| ECSC | | | | | |
| FVC | 0.79±1.08 | | 1.30±1.11 | | <0.001 |
| $FEV_1$ | 0.37±1.06 | | 0.51±1.00 | | 0.002 |
| $FEV_1$/FVC | −0.17±0.82 | | −0.25±0.85 | | 0.039 |
| GLI | | | | | |
| FVC | 0.18±1.00 | #,*** | 0.24±0.98 | #,*** | 0.194 |
| $FEV_1$ | 0.01±1.11 | #,*** | 0.03±1.00 | #,*** | 0.421 |
| $FEV_1$/FVC | −0.32±0.87 | #,*** | −0.40±0.80 | #,*** | 0.064 |

| Distribution of z-scores n (%) | <LLN | >ULN | ECSC *versus* GLI | <LLN | >ULN | ECSC *versus* GLI | Men *versus* women |
|---|---|---|---|---|---|---|---|
| **ECSC** | | | | | | | |
| FVC | 12 (1.3) | 189 (20.9) | | 4 (0.4) | 387 (36.3) | | <0.001 |
| $FEV_1$ | 25 (2.8) | 110 (12.2) | | 19 (1.8) | 128 (12.0) | | 0.330 |
| $FEV_1$/FVC | 42 (4.6) | 3 (0.3) | | 62 (5.8) | 5 (0.5) | | 0.456 |
| **GLI** | | | | | | | |
| FVC | 28 (3.1) | 72 (8.0) | ¶,*** | 25 (2.3) | 70 (6.6) | ¶,*** | 0.268 |
| $FEV_1$ | 45 (5.0) | 63 (7.0) | ¶,*** | 47 (4.4) | 61 (5.7) | ¶,*** | 0.417 |
| $FEV_1$/FVC | 65 (7.2) | 5 (0.6) | ¶,*** | 68 (6.4) | 4 (0.4) | ¶,* | 0.644 |

Data are presented as mean±SD or n (%), unless otherwise stated. Z-scores calculated from European Community for Steel and Coal (ECSC) and Global Lung Function Initiative (GLI) reference equations. FVC: forced vital capacity; $FEV_1$: forced expiratory volume in 1 s. #: paired t-test between z-scores obtained by ECSC and GLI equations; ¶: Bhapkar's test between distribution of z-scores. *: $p<0.05$; ***: $p<0.001$.

and above the ULN were significantly further from the 5% expected using ECSC equations, especially in women (36.3% had a ECSC z-score FVC >1.64), whereas these proportions were close to the 5% expected using GLI equations (table 1). The differences in distribution between the two references were highly significant ($p<0.001$), except for the $FEV_1$/FVC ratio of women for which the difference (while still significant) was less so ($p=0.041$). We obtained the same trends for an analysis restricted to those subjects (n=1804) who met FVC reproducibility criteria as well as three acceptable blows (data not shown) [7]. We also compared the proportion of subjects with spirometric data below the LLN (*i.e.* with z-score value < −1.64) using ECSC and GLI reference equations among the 1072 subjects with respiratory disease. This comparison showed that GLI reference equations better identified the subjects with respiratory disease than those of ECSC. Indeed, the proportions were significantly lower for all the indices using ECSC than using GLI reference equations (3.1 *versus* 8.9%, 11.2 *versus* 19.1%, and 15.9 *versus* 18.1% for FVC, $FEV_1$ and $FEV_1$/FVC respectively).

The comparative analysis of the z-scores distributions clearly show that the GLI reference for FVC and $FEV_1$ is better adapted to our population without respiratory disease, and particularly so among women. Indeed, we found z-score means closer to zero and that sex differences disappeared when GLI equations were used (table 1). Backman *et al.* [3] showed that GLI equations better described a healthy Swedish population than the ECSC equations, but the average z-scores of each parameter were further from zero than ours when applying the GLI reference values. For example, the mean z-score was 0.41±0.92 *versus* 0.24±0.98 for FVC and 0.25±0.86 *versus* 0.03±1.00 for $FEV_1$, respectively, among women in the Swedish study *versus* women in our northern French population. We observed a higher airway obstruction rate in our population by applying GLI compared to ECSC equations and this difference was more pronounced among men. Similarly, Quanjer *et al.* [8] observed a 2.2% added airway obstruction rate in men of an

Australian and Polish population using GLI equations. It should be noted that in a normal healthy population the proportion of subjects with FEV1/FVC above the ULN will be less than the proportion below the LLN because the distribution of FEV1/FVC is skewed being censored at 1.

The proportions obtained under and above the limits of normal were less balanced using ECSC reference equations than those obtained using GLI reference equations, particularly for volumes and especially in women (*e.g.* for FVC in women: 0.4% and 36.3% respectively for ECSC *versus* 2.3% and 6.6% respectively for GLI) (table 1). The differences between ECSC and GLI predicted values might be explain by the fact that, first of all, the 1983 predicted values were not based on real measured data, but on a collation of published reference values, secondly, the selection of subjects upon which those published equations were based was much more poorly defined than nowadays, thirdly, those measurements predated the era of standardised measurements and strict quality criteria.

We have not taken into account smoking status in our study because we wanted to apply these equations to “real-life” conditions in a general population. However, the sensitivity study in nonsmokers (379 men and 702 women) showed the same trends but with a lower statistical power and mean FEV1/FVC z-scores closer to zero than those presented using the two reference equations in table 1.

Although the French data were not included when establishing the more recent GLI reference values, our results show that these GLI equations fit better than those of ECSC to our population sample and can be used for a French population aged 40–65 years.

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**GLI reference equations better describe a middle-aged, healthy French population than the ECSC values** http://ow.ly/xF773022Xhy

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## References

1 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.
2 Quanjer P, Dalhuijsen A, Van Zoramen B. Standardized lung function testing. Report working party. *Bull Eur Physiopathol Respir* 1983; 19: Suppl. 5, 1–95.
3 Backman H, Lindberg A, Sovijärvi A, *et al.* Evaluation of the global lung function initiative 2012 reference values for spirometry in a Swedish population sample. *BMC Pulm Med* 2015; 15: 26.
4 Quanjer PH, Weiner DJ. Interpretative consequences of adopting the Global Lungs 2012 reference equations for spirometry for children and adolescents. *Pediatr Pulmonol* 2014; 49: 118–125.
5 Ratomaharo J, Linares Perdomo O, Collingridge DS, *et al.* Spirometric reference values for Malagasy adults aged 18-73 years. *Eur Respir J* 2015; 45: 1046–1054.
6 Quach A, Giovannelli J, Chérot-Kornobis N, *et al.* Prevalence and underdiagnosis of airway obstruction among middle-aged adults in northern France: The ELISABET study 2011-2013. *Respir Med* 2015; 109: 1553–1561.
7 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
8 Quanjer PH, Brazzale DJ, Boros PW, *et al.* Implications of adopting the Global Lungs Initiative 2012 all-age reference equations for spirometry. *Eur Respir J* 2013; 42: 1046–1054.

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