Lung function testing in children: Importance of ethnic specific reference equations

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Asthma affects as many as 334 million people of all ages in all parts of the world and is the commonest long-term respiratory condition affecting children in developed countries, the prevalence and morbidity varying by ethnic group[1]. Accurate diagnosis and effective management of respiratory diseases such as asthma requires objective measures of lung function, but reliable use of such measures is only possible if appropriate normative ranges are available to distinguish the effects of disease and treatment from those of growth and development.

Evidence for ethnic differences in lung function

Ethnic differences in lung function have been well documented[2]. In the past, attempts to interpret observed ethnic differences in lung function were often confounded by selection bias related to use of small population samples that were not necessarily representative or generalizable, use of different methods, equipment and quality control (QC) criteria, failure to adjust for other important determinants of lung function, including socio-economic circumstances and/or inappropriate statistical analyses. In recent years, many of these problems have been addressed by applying standard methodology, inclusion criteria and QC to large, ethnically homogenous groups. Current research shows that after adjusting for age, sex and standing height, forced expired volume in 1 sec (FEV_1: a measure of airway calibre) and forced vital capacity (FVC: a measure of lung size) are both reduced by approximately 14% in individuals of African ancestry (Black) across the entire life span when compared with those of European ancestry (White)[3-6]. Similar though smaller reductions have been observed among South Asian (from Indian subcontinent)[7-9] and South-East Asian (e.g. China, Thailand, Malaysia etc)[6] subjects. Since these "ethnic" reductions in FEV_1 and FVC are generally proportional, the FEV_1/FVC ratio, which is the most commonly used outcome to assess airways obstruction, is usually independent of ethnic background[5-7], suggesting that there are no structural or functional ethnic differences in lung design. Thus the observed ethnic differences in lung function appear to be primarily limited to lung size rather than airway or dynamic respiratory characteristics. However, the same adjustment factor cannot be used for all lung volume outcomes. For example, there is evidence that the lower FVC found among Black children can be attributed at least in part to a relatively high residual volume, suggesting that factors such as anatomic differences in diaphragmatic position or respiratory muscle strength might contribute to some of the observed differences[5]. Furthermore, lung function indices that are internally adjusted for the size of the individual's resting lung volume, such as the Lung Clearance Index (LCI: a measure of gas mixing efficiency)[10,11] or specific airways resistance (sRaw: a

measure of airway calibre adjusted for lung volume)[11] do not appear to be influenced by ethnic background. Nevertheless, since larger sample sizes will be required to confirm these findings, data interpretation of LCI and sRaw from non-White subjects should currently be undertaken with caution.

GLI-2012 equations

Recently, the Global Lung function Initiative (GLI) collated results from >74,000 healthy non-smokers aged 3-95 years to create the first all-age, multi-ethnic reference equations for spirometry with appropriate age dependent lower limits of normal[6]. Prediction equations were derived using the LMS method, which allows simultaneous modelling of the mean (mu), the coefficient of variation (sigma) and skewness (lambda) of the distribution and reference equations were derived for Caucasians (White); African-Americans (Black), North- and South-East Asians. These equations enable assessments to be evaluated over the entire age range using a single reference data set, thereby avoiding the errors that can occur when switching between equations, particularly during the transition between paediatric and adult care[12].

Defining ethnicity

Ethnicity is extremely difficult to define. Self-assigned ethnicity may differ from observer-assigned ethnicity and in certain countries it is against the law to record ethnic origin for any purpose. Furthermore, in recent censuses in both the UK (2011) and US (2010), mixed-race populations have been shown to be the fastest-growing ethnic group. Thus, classifying ethnicity may become an increasingly complex task!

Could differences in body proportions explain the ethnic differences in lung function?

Standing height is a major determinant of lung volumes, reflecting the fact that lung size is adapted to our metabolic needs. However this is not ideal since the size of the lungs is more closely related to thoracic size than leg length and differences in body proportions may underpin much of the observed ethnic variation in lung function. The Size and Lung function In Children (SLIC) study was designed to improve normative reference ranges for lung function by taking differences in body physique into account to facilitate early diagnosis and treatment of lung disease in all children, irrespective of ethnic background[7]. However, of the numerous additional anthropometric measurements undertaken to quantify body physique, only sitting height and chest width significantly contributed to the prediction of spirometric lung function. Chest dimensions and lean mass also significantly predict FEV_1 and FVC within each ethnic group, but did

not affect differences between groups. The persistence of ethnic differences after adjustment for sitting height, chest dimensions, body composition and socio-economic factors may reflect the fact that some factors affecting chest size such as diaphragmatic position or muscle strength cannot be assessed by anthropometry, and emphasises the importance of taking ethnicity into account when interpreting spirometry data[7].

Impact of socio-economic factors on ethnic differences in lung function

While some studies have shown an association between socio-economic conditions (SEC)[13,14] and lung function and suggested that this is a key factor in explaining ethnic differences in lung function[15] , there is increasing evidence that the contribution of SEC to variability of lung function is very small except under the most adverse of conditions[7,14,16]. A recent study in India[8], using identical equipment and techniques as those used in the SLIC study found that while average FEV_1 and FVC in urban Indian children were similar to those in Indian children residing in the UK, they were significantly higher than in semi-urban and rural Indian children (by ~6% and 11% respectively). These results probably reflect the marked differences in the degree of social deprivation between the UK and India[7,8] and suggest that there may be a threshold effect of poverty on lung function. Adjusting for sitting height has been shown to reduce the contribution of SEC to ethnic variability[7,14].

Data interpretation and ethnic adjustments

The use of inappropriate reference equations and misinterpretation can lead to serious errors with respect to both under- and over-diagnosis. In the past, attempts to correct for ethnic differences, if made at all, tended to apply the same fixed adjustment factor across all ages[2], all ethnic groups, both sexes and all spirometric outcome measures, an approach now shown to be over-simplistic[14,17].

In addition to errors relating to ethnic differences in lung function, misdiagnosis may also occur when fixed cut-offs, such as 80% predicted FEV_1 or 0.7 FEV_1/FVC are used; particularly in young children and elderly adults. While %predicted has historically been used to interpret lung function results, z-scores are more appropriate as they take into account the between-subject variability of measurements for any given outcome at any given age, as well as the predicted value[17]. Similarly, use of <0.7 as a fixed threshold for abnormal FEV_1/FVC can lead to gross under-diagnosis of airway obstruction in the young and over-estimation in the elderly[17].

Conclusions and recommendations

With exception of extreme deprivation, ethnic differences in lung function cannot be explained by socio-economic factors. After adjusting for confounders, genetic factors do contribute to ethnic differences in body physique and lung function. Given the marked ethnic differences in lung function, the magnitude of which are similar across the entire life span, it is essential that lung function results in children are interpreted using ethnic specific equations whether in clinical practice or epidemiological research.

Although GLI-2012 do not and never will cover all ethnic groups, appropriate use of age, height and sex adjusted values of FEV_1/FVC ratio derived from these equations (which is consistent across all ethnic groups) will facilitate better identification of airway obstruction in children irrespective of ethnic background. Failure to adjust lung function for ethnic differences will result in overestimation of both the severity of airway obstruction and the severity and prevalence of restrictive lung disease.

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