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One Size Does Not Fit All - Why do pediatric spirometry estimates vary across populations "down under"?

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Spirometry is the reference standard technique to estimate airflow and lung volumes, which may be reduced in individuals with obstructive or restrictive lung diseases. To classify spirometry indices, we need to define upper and lower limits of normal (ULN, LLN) usually set at +/- 1.645 z-score. The Global Lung Function Initiative (GLI) developed reference equations that allow standardized interpretation of spirometry results.[1] GLI references account for known drivers of physiological lung function variability: age, sex, height, and ethnicity including White, Black, North East Asian, South East Asian, and other or mixed ethnicities.[1] Main reasons for ethnic differences in lung function include genetic and anthropometric factors such as height, sitting-height standing-height ratio (Cormic index), weight, and body composition.[2-4] However, not all ethnic groups were included in the GLI population and it is recommended to validate the equations locally.[5] If GLI equations do not appropriately fit a given population, over- or underestimation of predicted spirometry values may occur and individuals may be misclassified as either having falsely normal or abnormal lung function.

In this issue, Collaro et al. studied if the Cormic index differed between 619 First Nations Australian children and 907 White North American children, and whether this difference was associated with lower lung function in First Nations than in White children.[6] This study sheds further light into possible ethnicity-driven differences in lung function between First Nations and White children. They found an 8 to 10% predicted lower forced expiratory volume in 1s (FEV_1) and forced vital capacity (FVC) in First Nations than in White children. First Nations children also had lower Cormic index than White children, which explained differences in FEV_1 and FVC among 8-11-year-old children by 14% and 15%, respectively, and among 12-16-year-old adolescents by 26% and 31%. Predicted GLI reference values for other or mixed ethnicities are lower than those for Whites, and Blake et al. showed that they provided good fit to the lung function of contemporary First Nations children.[7] Results of Collaro et al. suggest that reasons for the lower lung function in Fist Nations children compared to White children must include other intrinsic or extrinsic determinants besides anthropometric factors like height and Cormic index. This has potentially relevant implications for clinical care and public health programs, as it may affect spirometry interpretation.

Intrinsic factors like pubertal status and anthropometric measurements other than Cormic index were not assessed in participants of the study by Collaro et al., as is the case in many other epidemiological studies. During puberty, there is a dysanaptic growth of the lungs and airways, and timing of puberty may vary between ethnic groups.[3,8] This can affect spirometry outcomes, although part of the differences in lung function between ethnic groups due to pubertal status may be partially explained by changes in the upper segment of the body, which is included in the Cormic index.[3] Other anthropometric factors like weight or body composition such as fat mass may also systematically differ between ethnic groups. Some studies indicate that body composition can influence lung function in children and adults[4,9,10] while others suggest that this effect is negligible.[11] Collaro et al. frankly acknowledged that samples of White and First Nations children were collected 20 years apart, and secular time trends are known to affect timing of puberty, anthropometric characteristics and lung function.[12]

Extrinsic conditions like socioeconomic deprivation and environmental exposures such as pollution, can lead to reduced lung function and lung growth in children. Some populations may be exposed to unfavorable living conditions more often.[10] Children exposed to socioeconomic disadvantage and environmental risk factors may have lower lung function than those unexposed.[4] For example, Sonnappa et al. found that lung function of healthy urban children living in India was comparable to that of healthy Indian children living in the UK, but higher than that of healthy rural and semiurban children living in India.[4] Those living in rural and semiurban areas were exposed to tobacco and biomass smoke more often than those living in urban areas. In addition, muco-obstructive lung diseases such as protracted bacterial bronchitis or bronchiectasis are more prevalent in First Nations children, than in White children and adults.[11,13] Both questionnaires on symptoms and spirometry may underestimate the presence of muco-obstructive lung disease. This could contribute to systematically lower lung function in First Nations children at the population level, although at the individual level some children with muco-obstructive lung diseases may still have normal spirometry values. Yet, multi-slice chest imaging to rule out subclinical muco-obstructive lung disease is rarely done,[11] and may not be feasible in pediatric epidemiological studies.

We would like spirometry reference values to account as good as possible for intrinsic variability between ethnic groups. This is however complex, since ethnicity is a social construct that is difficult to measure, populations often are ethnically mixed, and different ethnic groups may be exposed to extrinsic factors in diverse ways. In addition, there is no uniform consensus on how to select healthy participants in studies done to create or asses fit of reference equations.[14] Heterogeneity in health status across studies hamper comparability between studies and collation of data.[15] Furthermore, disentangling sources of differences in physiological estimates between ethnic groups is a challenge not only for pediatric spirometry, but also for echocardiography, since the growth of the lungs and heart progresses non-linearly through time.[16]

In conclusion, we need to be cautious when collecting, interpreting and collating normative physiological data across diverse populations. Investigating determinants and potential confounders of physiological estimates across diverse populations will ensure appropriate interpretation of the dynamic physiology in children.

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