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Interpretation of pediatric lung function: Impact of ethnicity

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SUMMARY

Rationale—To evaluate the appropriateness of spirometric and plethysmographic reference equations in healthy young children according to ethnic origin.

Methods—Spirometry data were collated in 400 healthy children (214 Black and 186 White) aged 6 to 12 years. Of these children, 68 Black and 115 White children also undertook plethysmography. Results were expressed as percent predicted according to commonly used equations for spirometry and plethysmography.

Results—Black children had lower lung function for a given height compared to White children. The magnitude and direction of these differences varied according to specific outcome. In the studied age range (6–12yrs) the ethnic-specific Wang equations were adequate for spirometry (mean results approximating 100% predicted in both ethnic groups). By contrast, significant differences were found between observed and % predicted plethysmographic lung volumes according to published equations derived from White children: Among the Black children, FRC and TLC for were, on average, 14% and 6% lower than predicted, whereas mean RV and RV/TLC were 4% and 10% higher. Among White children, the Rosenthal equations gave the best fit, with the exception of FRC which was, on average, 9% lower than predicted.

Conclusion—Spirometry equations may suffice in Black children; however interpretation of static lung volumes in Black children is limited due to inappropriate reference equations. More appropriate plethysmographic reference equations that are applicable to all ethnic groups across the entire age range are urgently needed.

Keywords

Child; Ethnicity; Plethysmography; Reference values; Spirometry

INTRODUCTION

Lung Function tests such as spirometry and body plethysmography are widely used to identify obstructive and restrictive lung defects.[1] Commercial equipment which adheres to standardized international specifications for both spirometry[2] and plethysmography[3] potentially allow such measurements to be used in multi-center trials of children with

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suspected lung disease.[4] Sickle Cell Disease (SCD) is a genetic disorder which predominantly affects children of Black African and Afro-Caribbean origin, and frequently results in significant respiratory morbidity.[5] Studies suggest SCD progresses from an obstructive lung defect in childhood[6] to a predominantly restrictive defect in adulthood.[7] Measurements of spirometry and plethysmography in children with SCD could therefore play a potentially important role in the clinical management of children with SCD. However, since ethnic differences in lung function are known to exist,[8] appropriate interpretation of these measurements is not feasible in children with SCD, or indeed in Black children with any other suspected lung disease without using appropriate reference data.[9]

Availability of ethnic-specific reference equations is limited in comparison with those for White subjects. For spirometry, the most comprehensive reference equations to date are the "all-age" equations by Stanojevic et al.[10] At the time of writing these equations were, however, limited to the White population only. The spirometry equations by Wang et al include equations for Black children aged 6 to 18 years,[11] but are not continuous equations and do not include either the preschool years or adults. In addition, the NHANES III spirometry reference data included African-American subjects, but did not extend below eight years of age.[12] For plethysmographic lung volumes, reference data in children are extremely limited and ethnic differences poorly defined.[1] In the USA, the Zapletal equations are most commonly applied,[13] whereas in the UK, the British Thoracic Society recommend reference equations by Rosenthal et al.[14] To our knowledge, no static lung volume equations have been published specifically for Black children. The ATS/ERS 2005 Interpretative strategies for lung function tests suggest ethnic adjustment factors of 0.88 for TLC, FEV_1 and FVC and ~0.93 for FRC to reduce the predicted values based on White children by 12% and 7% respectively when interpreting values for Black children.[1] Previous attempts to correct for ethnic differences in lung function in this way have been shown to be oversimplistic. [15, 16] The aim of this study was to evaluate the appropriateness of spirometric and plethysmographic reference equations in healthy young children according to ethnic origin.

MATERIALS AND METHODS

Subjects

Spirometry and plethysmography data from healthy Black (primarily African and/or Caribbean descent) children aged 6 to 12 years were collated from two studies (the Size and Lung function in Children study (SLIC study) and the Sleep, sickle cell and Asthma Cohort study (SAC study) across three sites (London schools, London laboratory and St Louis, USA laboratory, see OLS). In addition, data collected from healthy White children (primarily of White European descent) of the same age from recent and on-going research projects based at the UCL Institute of Child Health, London[4, 17, 18] were evaluated to determine the appropriateness of commonly used pediatric lung function reference equations and the impact of ethnicity on spirometry and plethysmography outcomes. Asian children or "other"/mixed ethnicities were not included in this study. Children with Cystic Fibrosis or SCD were excluded as were those with a history of asthma (doctor diagnosis or current (within last 3 months) bronchodilator therapy); prematurity (less than 37 completed weeks of gestation), previous hospitalization with a respiratory complaint, or a past history of pneumonia, tuberculosis or whooping cough. Measurements were postponed if the child had had a respiratory infection within 3 weeks of the appointment. The study was approved by the local research ethics committee for each center and written informed consent/assent was obtained from all parents and children participating in the study.

Lung function assessments

All assessments were performed by specialized pediatric respiratory physiologists, using identical protocols, and a central over-read system was established (details on the OLS). Prior to lung function assessments a respiratory questionnaire was conducted to ensure the child was eligible for the study and standard anthropometric measures were obtained: Height was measured to the nearest 0.1cm without shoes using a calibrated stadiometer, and weight was measured in light clothing and without shoes to the nearest 0.1kg using calibrated scales. To adjust for sex and age at time of testing, height, weight and body mass index (BMI) were converted to Z-scores based on CDC growth charts, which combined ethnic minorities in one set of equations stating "there are differences in size and growth among the major/ethnic groups in the United States, but these appear to be small and inconsistent."[19]

Spirometry measurements were obtained using identical spirometers and software in all sites (Jaeger Masterscope, LabManager version 4.65), calibrated in accordance with ATS/ERS recommendations.[2] The protocol was based on the 2005 ATS/ERS guidelines for spirometry[2] modified for children as described previously.[20] Spirometric outcomes (FEV_1, Forced Vital Capacity (FVC) and FEV_1/FVC ratio) were adjusted for age, height and sex using published reference equations for White[10] and Black[11] children and, for the purpose of this paper, are presented as percent predicted.

Plethysmographic lung volumes were performed according to a protocol based on the ATS/ERS 2005 recommendations,[3] using either the Jaeger Masterscreen body box (V.5.02) or the Sensormedics V07-2B Box (V6200). Functional Residual Capacity (FRC) was calculated from the mean of 2–5 technically satisfactory FRC measurements (each of which consisted of at least two respiratory efforts at a breathing frequency of 30–90 breaths/min against the occlusion, with closed, super-imposable loops free from artefact/drift). Residual Volume (RV) was calculated as FRC minus the mean of the technically acceptable Expiratory Reserve Volume measurements, and Total Lung Capacity (TLC) as the reported value for RV plus the largest technically acceptable Inspired Vital Capacity (IVC). The optimal repeatability criteria were 3 FRC measures within 5% or 100ml, although 2 FRC measurements within 10% were accepted (albeit with a lower quality control score, see OLS) if both were technically acceptable. Plethysmographic lung volume outcomes (FRC, TLC, RV and RV/TLC ratio) were adjusted for height and sex and presented as percent predicted according to two published reference equations for children.[14, 21]

Statistical analysis

A sample size of 64 children in each group was required to determine differences in outcomes equivalent to 0.5SD (which equates to ~5–6% predicted in FEV_1 and FVC, 6% predicted in FRC, 10% predicted in RV and 5% predicted in TLC) with 80% power at the 5% significance level Statistical analyses were performed using SPSS V18, and Graph-Pad Prism 5. Independent t tests and Bland and Altman analyses were used to assess within-subject agreement according to different reference equations.[22]

RESULTS

Demographics

Spirometry measurements were successfully obtained in 214 healthy Black and 186 healthy White children aged 6 to 12 years. Subject demographics from children enrolled in different sites are presented in the OLS. Black children were slightly older than their White peers. After correcting for age and sex, Black children were also slightly taller and heavier than their White peers (Table 1).

Spirometry

Table 2 shows spirometry results calculated according to Wang et al,[11] using the Black or White equations as appropriate, and the Stanojevic All-Age equations, which are based on White children only.[10] Both Wang and All-Age equations described the White population well, with Bland and Altman analysis revealing close agreement between the two equations ($FEV_{1:}$ mean difference (95% limits of agreement (LA)): 2.1% (−3.8 to 8.0)). The Wang equations also described the Black population well, with both mean FEV_1 and FVC centered on 100% predicted. When compared with their White peers using the All-Age equations, results from Black children were ~15% lower for FEV_1 and ~13% lower in FVC (Table 2).

Plethysmography

Background characteristics in the subset of 68 healthy Black children and 115 healthy White children undergoing plethysmography were similar to those in whom spirometry was undertaken (Table 1 and Table E3 OLS) and there were no differences in lung volume outcomes according to measurement site (Table E4 OLS). Lung volume data calculated according to Zapletal[13] and Rosenthal,[14] both of which were derived from White children, are summarised in Table 3.

Absolute lung volumes against height can be seen in the OLS (Figure E1) which shows that for any given height, White children have larger lung volumes in comparison with Black children over the age range studied. With the exception of RV, there were significant differences between Black and White children for all lung volume outcomes, but the magnitude and direction of these differences varied markedly according to outcome and equation selected (table 3). Thus, while there were no ethnic differences in RV by either equation, FRC was 6–9 % lower in Black children, whereas % predicted RV/TLC ratio was ~ 12% higher among Black children. Even among the White children, when results were compared to those predicted by Zapletal, there was a significant bias which exceeded 5% for all outcomes except TLC (see OLS for further details). By contrast, with the exception of FRC, where mean values were 9% lower than the expected mean of 100%, the Rosenthal equations provided a reasonable fit for the White children.

DISCUSSION

Results from this study highlight some of the challenges surrounding interpretation of lung function in Black children, in that not only do Black children have different lung function results for a given height when compared to their White peers, but the magnitude and direction of these differences vary according to the specific outcome. While the spirometry equations developed by Wang et al for Black children appear to remain appropriate for those above 6 years of age, previous attempts to apply a fixed adjustment factor of 0.88 to reduce predicted plethysmographic lung volumes derived from White children by 12% when interpreting results from Black children could lead to misdiagnosis, with associated risks of over- or under-treatment.

The strengths of this study include the fact that standardized protocols and equipment were used for all measurements allowing direct comparison of the impact of ethnic differences, and that measurements were made over three different sites, in two continents, thereby increasing their generalizability. Results from this study emphasized the importance of strict adherence to protocol, within-center biological controls and prospective over-reading as this appeared to minimize bias between results collected in different laboratories in the USA and UK. There was also no bias between spirometry results collected in London schools when compared to those measured in a specialized pediatric lung function laboratory. A potential limitation was the restricted age range (6 to 12 years), which was a consequence of

recruiting children mainly from primary schools. Although pubertal staging was not included in the original part of the protocol, it is likely that some of the children would have entered puberty, and the impact of puberty and further comparisons of teenage children needs further investigation as the relationships between lung and somatic growth may change dramatically during puberty.[23] Although now our standard practice, at the time when most of these measurements were undertaken we did not measure the ratio of sitting to standing height which may contribute to ethnic differences in lung function.[24]

Ethnic differences in lung function have been described previously,[8] with lung function reported to vary between 10% to 25%.[25] The ATS/ERS 2005 Interpretative strategies for lung function tests suggest ethnic adjustment factors of ~12% reductions for TLC, FEV_1 and FVC and ~7% for FRC in Black subjects,[1] but most commercial lung function provide a simple fixed adjustment of 12% for all parameters leaving the operator to decide whether to use an adjustment or not. Results from this study demonstrate this blanket 0.88 ethnic adjustment is clearly inappropriate, and adjustments of 0.86 (FRC), 1.04 (RV), 0.94 (TLC) or 1.10 (RV/TLC) may be more appropriate. The use of such “fudge factors” however is limited due to the sample size upon which they were based, and interpretation of lung volume results in non-White children should be undertaken with extreme caution. Furthermore, the between-subject variability, although similar in Black and White children, varied markedly according to lung volume outcomes, being twice as high for RV and RV/TLC as for TLC. This has a direct impact on the calculated limits of normality, which need to be addressed in future work with ethnic-specific reference data.

Although the limitations of ethnic adjustment factors as opposed to specific race/ethnic equations have been highlighted previously,[12] the resources required to establish such equations for the more complex, laboratory-based tests such as plethysmography and Diffusing Capacity has impeded progress in this field, especially in relation to the pediatric age group. Hopefully, the current initiatives by the ERS Global Lungs Task Force to develop improved spirometry equations that are globally applicable across the entire age-range (www.lungfunction.org) can be extended to these tests in the near future.

The “All-Age” spirometry equations demonstrated excellent agreement in White children, as described previously[26, 27] but, as expected, were not appropriate for Black children. The ethnic-specific spirometry equations by Wang et al[11] proved a good fit for White and Black children respectively, mean results from our healthy children approximating 100% predicted (Table 2). The Wang equations, developed from the Harvard 6 Cities Study, included 11,630 White children and 989 Black children aged 6 to 18 years, with outcomes regressed on a logarithm of height.[11] They are, however, limited to 13 step-wise sex-specific equations for each year of age from 6 to 18 years for each ethnic group and are thus not suitable for the increasing number of preschool children now undertaking such tests.[28] The new Global Lungs spirometry equations for all ethnicities are due to be released in 2012. This should address the problems associated with fixed adjustment factors and errors which may occur when switching between reference equations.[9, 29, 30]

Plethysmographic lung volumes are considered to be the gold standard lung function test when diagnosing restrictive lung disease[1], however interpretation can vary widely depending on which equation is applied. In this study, we found significant differences in % predicted lung volumes according to Zapletal and Rosenthal, particularly with respect to RV and hence the RV/TLC ratio, which could have significant clinical implications. Given that the Zapletal equations were derived from a small sample of White children (86 boys and 87 girls) aged 6 to 17 years, measured over 40 years ago before international guidelines regarding standardized protocols had been published and using equipment that is no longer available, it is not surprising that such differences exist. The Rosenthal equations, which

were published 20 years later and are based on a much larger population (772 White children 4–18 years of age), used modern equipment and show good agreement for RV and TLC in the White children recently measured in our laboratory. However, as reported previously[18, 31] FRC was over-estimated by ~9% (i.e. mean % predicted FRC in our sample was only 91%). This discrepancy may reflect a change in protocol during recent years, whereby subjects are no longer required to pant rapidly during airway occlusions for thoracic gas volume maneuvers, a practice that may in the past have led to elevated resting lung volumes. This has important implications since clinical evidence of hyperinflation or gas trapping may be missed unless this bias is taken into account.[17, 18] The difficulties in interpreting plethysmographic lung volume data are further confounded when investigating Black children. In our study, FRC and TLC were 14% and 6% lower in Black children than predicted by Rosenthal equations.

When interpreting lung function, whether or not a result falls outside the lower or upper limits of normality (LLN or ULN) is often of greater clinical significance than the precise % predicted value. Depending on outcome, these limits of normality may be defined either as those encompassing 90% of the healthy population, in which case the LLN and ULN are based on the 5^{th} and 95% centiles (i.e. ±1.64SDs) or alternatively encompassing 95% of the population, whereby the LLN and ULN represent the 2.5^{th} and 97.5^{th} centiles (±1.96 SDs) respectively. Conventionally, a LLN derived from -1.64SDs is used for outcomes such as FEV_1 and FVC where only reductions in measured values are clinically relevant. By contrast, for outcomes such as FRC or RV/TLC where either reduced or elevated values may be clinically significant with respect to restrictive (defined by a reduction in TLC) or obstructive lung disease, then the 95% limits should apply. When results are expressed as SD (or Z) scores, it is self-evident as to whether or not a result lies outside these limits, however results expressed as % predicted are slightly more complex due to the wide range of between-subject variability (i.e. SD) according to outcome.[9, 26] For example, in this study the between subject variability (SD) for RV was ~22%, thus the limits of normality could be in the region of 56 to 144% predicted. While these thresholds may provide a useful guide until more appropriate reference equations can be developed, they must be interpreted with caution, given the relatively small numbers of children in the current study, as it has been shown that at least 300 local healthy controls (150 males and 150 females) are needed to validate published reference equations with any degree of certainty. With smaller sample sizes, differences of up to 0.5 z-scores may arise purely by chance.[32]

SUMMARY and CONCLUSIONS

Our study revealed that with standardized protocols and a central over-read process, pediatric lung function data from different sites can be combined. Ethnic differences in lung function exist and vary depending on the outcome. Consequently lung function reference equations based on White children are not appropriate for use in Black children, nor is the application of a fixed ‘ethnic’ adjustment factor for all outcomes. The Black equations by Wang et al appear to be adequate for spirometry but are limited to ages 6 to 18years. Marked discrepancies between two commonly used pediatric plethysmographic equations were found; those described by Rosenthal equations appear to be more reliable but should be applied with extreme caution, given the known ethnic differences. This study highlights the urgent need to develop ‘all-age’ equations for plethysmographic lung volumes which are applicable globally to individuals of all ethnic backgrounds and which are derived from measurements made across the entire age span using modern equipment and standardized protocols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ATS	American Thoracic Society
B	Black Children
BMI	Body Mass Index
CDC	Centre for Disease Control
CI	Confidence Interval
ERV	Expiratory Reserve Volume
FEV_1	Forced Expired Volume in one second
ERS	European Respiratory Society
FRC	Function Residual Capacity
FVC	Forced Vital Capacity
IVC	Inspired Vital Capacity
LA	Limits of Agreement
LLN	Lower Limits of Normality
NA	Not Applicable
OLS	Online Supplement
RV	Residual Volume
SAC	Sleep, Sickle cell and Asthma Cohort study
SCD	Sickle Cell Disease
SD	Standard Deviation
SLIC	Size and Lung Function in children study
TLC	Total Lung Capacity
UCL	University College London
ULN	Upper limits of Normality
W	White Children

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Table 1

Demographics of healthy children in whom spirometry measurements were obtained

	Black (B)	White (W)	Mean Difference (95%CI; B–W)
N (% male)	214 (40%)	186 (50%)	
Age (yrs)	8.9 (1.7)	8.4 (1.6)	0.5 (0.2; 0.8) *
Height (cm)	137.1 (13.0)	131.2 (10.8)	5.9 (3.5; 8.2)
Height Z-score	0.7 (1.1)	0.3 (0.9)	0.5 (0.2; 0.7) ***
Weight (kg)	36.2 (12.1)	29.7 (7.8)	6.4 (4.4; 8.5)
Weight Z-score	0.8 (1.0)	0.3 (0.9)	0.5 (0.3; 0.7) ***
BMI	18.8 (3.7)	17.0 (2.2)	1.8 (1.2; 2.4)
BMI Z-score	0.7 (1.0)	0.3 (0.9)	0.4 (0.2; 0.6) ***

Unless stated otherwise, results presented as mean (SD),

* p<0.05,

** p<0.005,

*** p<0.0005

Z-scores for weight, height and BMI were based on CDC growth charts.[19]

Table 2

Comparison of spirometric outcomes between healthy Black and White children according to two reference equations

	Black (B)	White (W)	Mean Difference (95%CI, B-W)
N (% male)	214 (40%)	186 (50%)	
Wang et al:[11]			
FEV_1 % pred.	99.9 (12.4)	104.4 (12.9)	−4.3 (−6.8; −1.8) **
FVC% pred.	103.0 (13.0)	104.4 (12.9)	−1.4 (−4.0; −1.1)
FEV_1/FVC % pred.	97.4 (7.6)	99.8 (6.9)	−2.5 (−3.9; −1.1) **
All-Age:[10]			
FEV_1 % pred.	86.6 (10.2)	102.1 (12.5)	−15.5 (−17.7;−13.3) ***
FVC % pred.	90.1 (11.2)	103.5 (12.3)	−13.5 (−15.8;−11.2) ***
FEV_1/FVC % pred.	95.4 (7.6)	97.7 (6.6)	−2.3 (−3.7; −0.9) **

Unless stated otherwise, results presented as mean (SD),

* $p<0.05$,

** $p<0.005$,

*** $p<0.0005$

Footnote: Wang et al equations have ethnic specific equations and were calculated respectively. All-age equations are based on White subjects, no ethnic adjustment was made in this table. These results are presented in more detail in the OLS (Table E6)

Table 3

Comparison of plethysmographic outcomes between healthy Black and White children according to two reference equations

	Black (B)	White (W)	Mean Difference (95%CI; B-W)
n (%male)	68 (43%)	115 (45%)	
By Zapletal:[13]			
FRC % pred.	86.6 (12.3)	95.1 (15.6)	−8.5 (−12.8; −4.1) ***
RV % pred.	109.0 (21.8)	107.8 (24.5)	1.2 (−5.9; 8.2)
TLC % pred.	88.6 (9.2)	96.9 (10.0)	−8.2 (−11.2; −5.3) ***
RV/TLC % pred.	122.5 (21.2)	110.8 (20.1)	11.8 (5.5; 18.1) ***
By Rosenthal:[14]			
FRC % pred.	86.2 (12.6)	91.2 (15.4)	−5.8 (−10.1; −1.4) *
RV % pred.	103.7 (20.0)	99.0 (23.4)	4.7 (−2.0; 11.4)
TLC % pred.	94.2 (9.8)	101.7 (11.0)	−7.5 (−10.6; −4.3) ***
RV/TLC % pred.	110.2 (19.0)	96.9 (19.0)	13.2 (7.5; 19.0) ***

Unless stated otherwise, results presented as mean (SD),

* p<0.05,

** p<0.005,

*** p<0.0005

Footnote: Equations by Zapletal and Rosenthal are based on White children. No ethnic adjustment was applied in this table.