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How "healthy" should children be when selecting reference samples for spirometry?

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Abstract

Question—How 'healthy' do children need to be when selecting reference samples for spirometry?

Methods—Anthropometry and spirometry were measured at school in an unselected, multi-ethnic population of London children aged 5-11yrs, with follow-up assessments 1yr later. Parents provided information on children's birth data and health status. FEV_1 and FVC were adjusted for sex, age, height and ethnicity using the GLI-2012 equations, and the effects of potential exclusion criteria on the z-score distributions were examined.

Results—After exclusions for current and chronic lung disease, acceptable data were available for 1901 children on 2767 occasions. "Healthy" children were defined as those without prior asthma or hospitalisation for respiratory problems, born full-term with birthweight ≥2.5kg and asymptomatic at test. Mean(SD) z-scores for FEV_1 and FVC approximated 0(1) indicating the GLI-2012 equations were appropriate for this "healthy" population. However, if children born preterm, or with low birthweight, prior asthma or mildly symptomatic at test were included in the reference, results overall were similar to those for "healthy" children, while increasing the sample size by 25%.

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Competing interests
None

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Answer—With the exception of clear-cut factors such as current and chronic respiratory disease, paediatric reference samples for spirometry can be relatively inclusive and hence more generalisable to the target population.

Introduction

The inclusion and exclusion criteria applied to subjects in population-based studies of lung function vary according to the underlying question and study design [1]. Excluding subjects with prior potentially adverse exposures may be appropriate when establishing normative data for reference equations [2,3], but less so in studies exploring the early determinants of lung function during childhood [4]. Furthermore, when collecting data in schools, it may be more efficient to include all children and subsequently exclude some, rather than exclude children on 'health' grounds at the outset, which may cause embarrassment and upset. Similarly, although paediatric research studies often exclude lung function measurements within 3 [5] or 6 weeks [2] of upper respiratory infections, children frequently suffer from such symptoms and their impact of such symptoms on the results is unclear. Reassessing the child when they are symptom-free is less easy for school-based studies than for laboratory studies [5].

The aim of this study was to examine the extent to which exclusions due to current upper respiratory symptoms or a history of potential adverse events such as low birthweight (LBW), preterm birth or prior wheezing/asthma impact on the distribution of spirometric z-scores in the context of a large population-based study.

Methods

The Size and Lung function In Children (SLIC) study was designed to explore ethnic differences in lung function and body physique in a multi-ethnic population of London school children aged 5-11 years recruited from 14 London primary schools (2010-2013) (www.ucl.ac.uk/slic) [6]. Schools were sampled by education performance within boroughs to ensure a wide range of socio-economic circumstances. Anthropometry and spirometry (Easy-on-PC, ndd, Switzerland) were performed in school according to international standards adapted for children [7,8]#with follow-up assessments 12 months later. All assessments were undertaken by the same team of paediatric respiratory physiologists, using identical equipment and standardised protocols, with subsequent over-read by a senior respiratory physiologist to ensure appropriate quality control. Spirometry results were expressed as z-scores using the ethnic-specific GLI-2012 equations, which adjust for, sex, age, height and ethnicity, for forced expired volume in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC [9]. Parents completed questionnaires about their child's ethnicity, birth data, and current and prior health status. Ethnicity was coded as White, Black (Black-African or Black-Caribbean), South-Asian (Indian sub-continent), or Other/mixed. The study was approved by the London-Hampstead research ethics committee. Parents' written consent and children's verbal assent were obtained prior to assessments. Some results from this study have been reported previously [10,11]. This study explores the impact of different exclusion criteria on mean spirometry results. Five exclusion criteria were considered:

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1. current or chronic lung disease (e.g. sickle cell disease; cystic fibrosis; current asthma [either doctor-diagnosed or asthma medication in the past 12 months, with or without current symptoms/wheeze])
2. congenital abnormality likely to impact on lung development
3. born preterm (gestational age < 37 weeks) or birthweight < 2.5 kg
4. prior doctor-diagnosed asthma or hospitalisation for respiratory problems
5. symptomatic (cough or cold) at test.

The first two exclusions were considered mandatory, while the impact of applying the remaining three was tested by comparing the overall results with and without them.

Statistical analysis

Results are presented as frequencies (%) for categorical variables and as mean (SD) or median (range) for continuous outcomes. Student's *t* test was used to compare mean differences in lung function between groups. The impact on the distribution of spirometry z-scores with different exclusion criteria was examined by comparing the mean and SD of the z-scores.

Results

Assessments were attempted in 2171 children on 3302 test occasions (including those from an initial feasibility study in two schools [6]). Of these, 125 children were excluded on technical grounds (124 who failed spirometry on all 279 test occasions, and one with missing height). A further 145 children (255 test occasions) were excluded under exclusion criteria 1 or 2: current or chronic lung disease, or congenital abnormality (Table 1). Technically satisfactory spirometry was obtained for the remaining 1901 children on 2767 test occasions (46% boys; 35% White, 29% Black, 24% South-Asian, 12% other/mixed ethnicity; mean (range) age 8.3 (5.2-11.9) years). Technically acceptable spirometric data could not be obtained on 7.5% of all test occasions in "healthy" children, this failure rate being significantly higher among children with congenital abnormalities [% mean difference (95% CI): 18% (6.6%; 35%)], current asthma [5.2% (2.5%; 8.5%)], or those who were symptomatic at time of test [26% (21%; 31%)].

Table 2 shows the 1901 children without chronic disease split into groups by identifying those meeting each of the exclusion criteria 3 to 5, while the remaining 1520 children constitute the "healthy" group. Among the children born preterm and/or low birthweight, the median [range] gestational age was 36 [23-41] weeks, with only 5 (2.7%) being born before 28 weeks gestation representing 0.3% of the reference population. Similarly the mean [range] birthweight for this subgroup was 2.27 [0.73-4.0] kg, with only 3 (1.6%) children having a birthweight <1kg. There was some overlap across the three exclusion groups, with between 6% and 13% of children per group meeting more than one exclusion criterion. The proportions of children meeting the various criteria were similar across ethnic groups [6].

The mean (SD) of the FEV_1 and FVC z-scores ($zFEV_1$ and zFVC respectively) approximated 0 (1) in the "healthy" group, indicating that the GLI-2012 reference equations

were broadly appropriate for this multi-ethnic population (Table 2). Although there were no significant differences in zFVC between the four groups, $zFEV_1$ and $zFEV_1$/FVC were significantly lower in those with "prior asthma" or "symptomatic at test" by up to 0.3 z-scores for FEV_1 (equating to ~ 3.5% if expressed as % predicted) and 0.5 z-scores for FEV_1/FVC (Table 2). Similar results were observed for FEF_{25-75} but since FEF_{25-75} was no more discriminative in detecting children with lung function abnormalities than FEV_1/FVC (data not shown) [13,14], this outcome was not reported for subsequent analyses.

Impact of health status on lung function

Relaxing the exclusion criteria to progressively include a) children born preterm and/or LBW, b) those with prior asthma and c) those symptomatic at test, had only minor effects on the z-score distributions of FEV_1, FVC and FEV_1/FVC for the entire group (Table 3). Thus, despite the significant differences between the groups seen in Table 2, the fact that the exclusion groups were relatively small meant that including them with the "healthy" group made little difference to the combined z-score distributions, but increased the reference sample size by 381 children or 25%. Furthermore, the decrement of lung function among those with current asthma or chronic lung disease could still be distinguished from the "reference sample" (e.g. mean difference (95%CI) [Reference Population-Current Asthma] $zFEV_1$: 0.26 (0.10; 0.41); $zFEV_1$/FVC: 0.53 (0.39; 0.67)).

The 568 tests on the 381 "unhealthy" children constituted 20% of the total reference population. To explore how sensitive the conclusions were to this specific proportion, corresponding results were calculated by doubling the size of the "unhealthy" group, i.e. assuming a 60:40 split between the "healthy" and "unhealthy" test results, rather than the observed 80:20. In practice this had only a small effect on the distribution, reducing the means for $zFEV_1$ and $zFEV_1$/FVC by 0.04 and 0.05 respectively (no change noticed for mean zFVC), while increasing the SDs by 0.01 (changes which happen to match the actual differences between the healthy and combined groups (columns 1 and 4 in Table 3). Thus the conclusions do not depend critically on the proportion of "unhealthy" children recruited from a large population sample, provided the sample is unselected and that there is no gross reduction in lung function among such children.

Discussion

Our study shows that, with the exception of children with clearly defined current or chronic disease, reference samples for paediatric spirometry can be relatively all-inclusive and thus more representative of the general population. While factors such as low birthweight, preterm delivery, prior asthma and symptoms at test introduce bias in individuals, they do not have a substantial impact in large epidemiological studies due to the relatively small proportion of affected children, and the relatively mild reductions in lung function observed when recruiting an unselected population. Using this approach, the expanded sample in our study was not only more representative of the underlying population but also 25% larger, thereby increasing cost effectiveness.

A major strength of our study is that all the assessments were undertaken by the same team using identical equipment and standardised protocols, with subsequent over-read by an

experienced physiologist to ensure a high degree of quality control and reliability. As recently reported by others [13,14]. we found very little discordance between FEF_{25-75} and FEV_1/FVC when classifying test results, suggesting forced expiratory flows do not contribute to clinical decision making in either children or adults. We recommend limiting the reporting of spirometry outcomes to FEV_1, FVC and FEV_1/FVC as recommended by the ATS/ERS guidelines [15].

The study was designed to assess children in school without parents needing to be present. This maximised recruitment and reduced bias that may have occurred had parents had to take time off work, wherein those with potential anxieties about their child's lung health may have been more willing to enrol. The proportions of preterm children and those with a diagnosis of asthma in the study were small, and similar to those reported for England and Wales (6% for GA<37; 0.4% for GA <28w and 9% for asthma) [16,17]. The study sample was also representative of an inner city population of multi-ethnic school children [18]. For the purposes of this study, any child born < 2.5 kg or < 37 weeks gestation was classified as low birthweight or preterm respectively, but the vast majority of such children were relatively mature (71% of this group being ≥ 35 weeks GA and 67% ≥ 2kg birthweight), when any deficiencies in lung function are likely to be relatively minor [19].

The fact that neither prematurity nor low birthweight adversely affected the results in this 'unselected' study where such children represent only 8% of the population, does not diminish their potential impact in individual children, especially those who are born extremely preterm or of very low birth weight, as clearly indicated by focussed studies (e.g. with a 50:50 mix), where mean reductions in FEV_1 by up to 1 z-score (i.e. over 10%) have been reported [4,20,21]. Similarly, the need to record relevant prior medical history including birth status, and using such information when interpreting results, remains of paramount importance during both research studies and the clinical management of individual patients with respiratory disease at any age [22].

It was reassuring that current upper respiratory symptoms did not influence the sample distribution of spirometry, since not all epidemiological studies record symptoms during lung function testing [23] and such symptoms can be very subjective. It must however be emphasised that these findings apply only to spirometry, which is expected to be relatively independent of upper respiratory symptoms. Furthermore, the failure rate was almost five times higher in those with than without symptoms, suggesting a degree of 'self-exclusion', with technically acceptable data being achievable only in children with relatively mild symptoms.

To assess the potential impact of including a higher proportion of "unhealthy" children on population estimates of spirometry, we modelled the effect of doubling the size of this group. Given that the proportions of children with prior asthma or those born preterm/LBW are unlikely to be higher than the unselected population sample from which they were recruited (15% of total), the effect of doubling the sample size of 'unhealthy' children was just a crude approach to show that it makes little difference to the results, providing the mean deficit within such groups is minimal. The mean values fell slightly and the SDs rose minimally, but in practice the impact was minimal, due both to the fact that the proportion of

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healthy children remained in the majority and that there were relatively small group differences in lung function between the healthy children and those with symptoms who were well enough to attend school and produce technically satisfactory results. It should be noted that since a 1 z-score change for FEV_1 in 8 year old children is equivalent to ~12% of predicted FEV_1, a difference of 0.04 z-scores when doubling the proportion of "unhealthy" children only represents a change of 0.5% in predicted FEV_1.

Our results suggest that where a *genuinely* "healthy" population sample of children is required to address a research hypothesis with spirometry as the primary outcome, i.e. where all five exclusion criteria apply, the target sample size needs to be increased by at least 30% to cover exclusions.

In conclusion, we found that the mean and SD of spirometry in our study was not materially affected by exclusion criteria such as mild current symptoms, prior wheeze or LBW. While inclusion/exclusion criteria will always need to be considered carefully according to the specific hypotheses under examination, these findings have potential implications for epidemiological studies with respect to the cost, efficiency and generalisability of population studies with spirometric lung function as a primary outcome.

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References

1. Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. Eur Respir J. 2010; 36:12–9. [PubMed: 20595163]
2. Muller-Brandes C, Kramer U, Gappa M, Seitner-Sorge G, Huls A, von Berg A, Hoffmann B, Schuster A, Illi S, Wisbauer M, Berdel D. LUNOKID: can numerical American Thoracic Society/ European Respiratory Society quality criteria replace visual inspection of spirometry? Eur Respir J. 2014; 43:1347–56. [PubMed: 24232698]
3. Schwartz JD, Katz SA, Fegley RW, Tockman MS. Analysis of spirometric data from a national sample of healthy 6- to 24-year-olds (NHANES II). Am Rev Respir Dis. 1988; 138:1405–14. [PubMed: 3202495]
4. Stocks J, Sonnappa S. Early life influences on the development of chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2013; 7:161–73. [PubMed: 23439689]
5. Lum S, Kirkby J, Welsh L, Marlow N, Hennessy E, Stocks J. Nature and severity of lung function abnormalities in extremely pre-term children at 11 years of age. Eur Respir J. 2011; 37:1199–207. [PubMed: 20947682]
6. Lum, S.; Sonnappa, S.; Wade, A.; Harding, S.; Wells, J.; Treleaven, P.; Cole, TJ.; Griffiths, CJ.; Kelly, F.; Bonner, R.; Bountziouka, V.; Kirkby, J.; Lee, S.; Raywood, E.; Legg, S.; Sears, D.; Stocks, J. Exploring ethnic differences in lung function: the Size and Lung function In Children (SLIC) study protocol and feasibility. UCL Institute of Child Health; London, UK: 2014.

7. Kirkby J, Welsh L, Lum S, Fawke J, Rowell V, Thomas S, Marlow N, Stocks J, Group EPS. The EPICure study: comparison of pediatric spirometry in community and laboratory settings. Pediatr Pulmonol. 2008; 43:1233–41. [PubMed: 19009621]
8. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. Eur Respir J. 2005; 26:319–38. [PubMed: 16055882]
9. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012; 40:1324–43. [PubMed: 22743675]
10. Lum S, Sonnappa S, Cole TJ, Bountziouka V, Bonner R, Kirkby J, Lee S, Cottam P, Stocks J. How should we define a reference population when assessing lung function? Am J Respir Crit Care Med. 2014; 189:A3229.
11. Bonner R, Lum S, Stocks J, Kirkby J, Wade A, Sonnappa S. Applicability of the global lung function spirometry equations in contemporary multiethnic children. Am J Respir Crit Care Med. 2013; 188:515–6. [PubMed: 23947526]
12. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. Stat Med. 1998; 17:407–29. [PubMed: 9496720]
13. Boutin B, Koskas M, Guillo H, Maingot L, La Rocca MC, Boule M, Just J, Momas I, Corinne A, Beydon N. Forced expiratory flows' contribution to lung function interpretation in schoolchildren. Eur Respir J. 2015; 45:107–15. [PubMed: 25186269]
14. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25-75% and FEF75% does not contribute to clinical decision making. Eur Respir J. 2014; 43:1051–8. [PubMed: 24072211]
15. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26:948–68. [PubMed: 16264058]
16. Moser, K.; Stanfield, KM.; Leon, DA. Birthweight and gestational age by ethnic group, England and Wales 2005: introducig new data on births. Office for National Statistics; London: 2008.
17. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. J R Soc Med. 2010; 103:98–106. [PubMed: 20200181]
18. Whitrow MJ, Harding S. Asthma in Black African, Black Caribbean and South Asian adolescents in the MRC DASH study: a cross sectional analysis. BMC Pediatr. 2010; 10:18. [PubMed: 20334698]
19. Kotecha SJ, Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. Thorax. 2012; 67:54–61. [PubMed: 21953066]
20. Lum S, Kirkby J, Welsh L, Marlow N, Hennessy E, Stocks J. Nature and severity of lung function abnormalities at 11 years of children born extremely preterm. Eur Respir J. 2011; 37:1199–207. [PubMed: 20947682]
21. Hacking DF, Gibson AM, Robertson C, Doyle LW. Respiratory function at age 8-9 after extremely low birthweight or preterm birth in Victoria in 1997. Pediatr Pulmonol. 2013; 48:449–55. [PubMed: 22826206]
22. Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L, Stocks J, Walshaw MJ. Are early life factors considered when managing respiratory disease? A British Thoracic Society survey of current practice. Thorax. 2012
23. Aresu, M.; Mindell, J.; Stocks, J. Lung Function in Children. In: Health NHST. Social Care Information C. , editor. Health Survey for England - 2010: Respiratory health. NHS information Centre; London: 2011. p. 1-17.

Take home message

Apart from exclusions for current or chronic lung disease, population samples for children's lung function can be relatively inclusive.

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Table 1

Group characteristics and lung function of 145 children excluded from analysis by criteria 1 and 2.

	Congenital abnormality*	Sickle cell disease	Current asthma	Total
Subjects (n)	9	12	124	145
Boys (%)	78%	17%	56%	54%
White (%)	56%	17%	32%	32%
Test occasions# (n)	8	18	192	218
Age at test (y)	8.6 (1.88)	8.4 (1.83)	8.7 (1.55)	8.7 (1.58)
zHeight§	−0.17 (1.87)	0.51 (1.03)	0.27 (1.29)	0.28 (1.3)
$zFEV_1$	0.19 (2.68)	−0.50 (1.01)	−0.27 (1.04)	−0.27 (1.13)
zFVC	0.27 (2.82)	−0.37 (1.00)	0.22 (0.99)	0.17 (1.10)
$zFEV_1$/FVC	−0.05 (0.90)	−0.29 (1.04)	−0.85 (0.96)	−0.77 (0.98)

Data presented are Mean (SD) unless otherwise specified.

§according to the British 1990 reference[12].

*6 children with congenital or neurological abnormalities and 3 with growth abnormalities.

#Test occasions with technically acceptable spirometry results.

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Table 2

Group characteristics and lung function according to health status[¥] in 1901 children on 2767 test occasions.

	Healthy	Exclusion criterion 3: Preterm/LBW	Exclusion criterion 4: Prior asthma	Exclusion criterion 5: Symptomatic at test
Subjects (n)	1520	186	158	111
Boys(%)	45	46	57	47
White (%)	37	24	33	38
Test occasions[#] (n)	2199	232	208	141
Age at test (y)	8.5 (1.7)	8.7 (1.6)	8.4 (1.7)	8.4 (1.5)
zHeight[§]	0.48 (1.05)	0.23 (1.16)	0.41 (1.14)	0.45 (1.01)
$zFEV_1$	0.03 (0.90)	−0.11 (1.00)	**−0.27 (0.96)** ***	**−0.29(1.12)** ***
zFVC	0.17 (0.92)	0.11 (0.97)	0.12 (0.87)	0.02 (1.10)
$zFEV_1$/zFVC	−0.27 (0.95)	−0.41 (1.00)	**−0.72 (1.02)** ***	**−0.55 (1.11)** ***

Data presented are mean (SD) unless otherwise specified.

[¥] exclusion criteria not mutually exclusive

[§] according to the British 1990 reference[12]. LBW: Low birthweight (<2.5kg)

*** p <0.001 compared to lung function from “Healthy” children.

[#] Test occasions with technically acceptable spirometry results.

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Table 3

Impact of health status on lung function

	Healthy	+ Preterm/LBW	+ Prior asthma	+ Symptomatic at test
Subjects (n)	1520	1676	1825	1901
Boys (%)	45%	45%	46%	46%
Test occasions[#] (n)	2199	2431	2626	2767
$zFEV_1$	0.03 (0.90)	0.02 (0.90)	0.00 (0.91)	−0.01 (0.92)
zFVC	0.17 (0.92)	0.17 (0.92)	0.17 (0.92)	0.16 (0.93)
$zFEV_1$/FVC	−0.27 (0.95)	−0.28 (0.95)	−0.31 (0.96)	−0.32 (0.97)

Footnote: Data presented are mean (SD) unless otherwise indicated. LBW: Low birthweight (<2.5 kg).

[#]Test occasions with technically acceptable spirometry results.