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Eur Respir J 2016; 47: 1288–1290 | DOI: 10.1183/13993003.02185-2015 | Copyright ©ERS 2016

Inclusion of children with airway disease for the development of spirometry reference data

To the Editor:

When establishing normative data for the development of spirometric reference equations, generally measurements have to fulfil internationally accepted criteria [1, 2] and should be derived from data taken from healthy subjects. In their recent publication Lum *et al.* [3] discussed how "healthy" children should be when selecting reference samples for spirometry. They investigated this in the context of a study designed to explore ethnic differences in the lung function of school children aged 5–11 years from London. They recommended including children with current respiratory tract infection, a history of prior asthma or minor pre-existing risk factors, such as prematurity and low birth weight in normative analysis.

In contrast, we have come to a different conclusion, and we advocate that recommendations for patient samples should be less inclusive in the development of reference data. Our group analysed data from our LUNOKID study (LUng function NOrmal values for KIDs in Germany), where we measured lung function (N=5104; aged 4–18 years) between 2007 and 2009 in three German communities under field conditions [2, 4, 5]. Spirometric reference values were developed with the same regression model used by the Global Lung Initiative (GLI) [6]. For the reference data set, the following subgroups (not overlapping) were excluded. 1) Subjects with asthma diagnosis ever (n=417); a) with no current asthma medication (n=195) and b) with current asthma medication (n=222). 2) Upper respiratory tract infection (RTI) on the day of the investigation (n=734) (without asthma). 3) lower RTI within 6 weeks prior to testing (n=180) (without asthma and without upper RTI). 4) Children who have ever been diagnosed with wheezy bronchitis ("obstructive", "asthmatic" or "spastic bronchitis") (n=629) (without asthma and either an upper or lower RTI).

From the total group, 3205 children fulfilled American Thoracic Society (ATS)/European Respiratory Society (ERS) quality criteria. Compared to healthy children, the proportion of visually acceptable manoeuvres was lower in children with upper RTIs on the day of investigation (72% and 62%, respectively; $p<0.01$), whereas it was higher in asthmatics (80%; $p<0.01$). No further statistically significant differences related to the fulfilment of quality criteria were observed.

Using all acceptable tests, mean z-scores were then calculated for the subgroups (table 1). As suggested by Hall *et al.* [7] and Thompson *et al.* [8] a difference in z-score of 0.5 was considered relevant. The mean LUNOKID based z-scores for the healthy reference children are zero by definition [4]. Children with a history of physician diagnosed asthma had relevantly lower mean z-scores for forced expiratory volume in 1 s (FEV_1)/forced volume capacity (FVC) irrespective of current treatment (−0.52 and −0.66). Furthermore, the standard deviation for this group was higher than the expectation (=1), and it was higher than in the other groups. No relevant mean differences were found for the other subgroups or for the total study population when all subgroups were included. These findings are in accordance with the observations

TABLE 1 Distribution of LUNOKID-based z-scores in groups defined by airway disease

Airway disease	Spirometric test	Subjects	z-score	p-value[#] H_0: mean z∉ (−0.5, 0.5)	⩽LLN %
Asthmatics without medication	FEV_1	129	−0.17±1.22	0.006	10.85
	FVC	129	0.24±1.08	0.011	2.33
	FEV_1/FVC	129	−0.66±1.23	0.891	17.05
Asthmatics with medication	FEV_1	150	−0.16±1.30	0.004	10.67
	FVC	150	0.14±1.29	0.003	8.00
	FEV_1/FVC	150	−0.52±1.26	0.579	19.33
Infection on the day of investigation	FEV_1	393	0.15±1.15	<0.001	5.09
	FVC	393	0.25±1.12	<0.001	4.33
	FEV_1/FVC	393	−0.24±1.00	<0.001	9.67
Infection in the last 6 weeks	FEV_1	109	0.15±1.16	0.004	5.50
	FVC	109	0.21±1.15	0.015	4.59
	FEV_1/FVC	109	−0.17±1.00	0.002	6.42
Ever diagnosed with wheezy bronchitis	FEV_1	394	0.04±1.14	<0.001	7.61
	FVC	394	0.13±1.10	<0.001	5.08
	FEV_1/FVC	394	−0.19±1.11	<0.001	9.39
All subjects[¶]	FEV_1	3205	0.11±1.11	<0.001	5.05
	FVC	3205	0.15±1.07	<0.001	4.02
	FEV_1/FVC	3205	−0.10±1.09	<0.001	7.93

Data are presented as n or mean±SD, unless otherwise stated. LLN: lower limit of normal; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: two one-sided tests for equivalence were performed to test on equivalence between the mean z-scores of the LUNOKID (LUng function NOrmal values for KIDs in Germany) reference population (=0) and groups of children with airway disease. A good fit was reached if the null-hypothesis of a mean z-score outside of the interval (−0.5, 0.5) was rejected at the 5% significance level. [¶]: including all groups above, healthy subjects and subjects with missing information about respiratory health.

of Lum *et al.* [3]. However, the percentage of values below the lower limit of normal (LLN) for FEV_1/FVC is larger than the expected 5% in the total group, if these additional subgroups are included.

Many children with an upper RTI on the day of testing were excluded from our reference population because they had not been able to produce technically acceptable manoeuvres. This finding is in accordance with the findings of Lum *et al.* [3] who also showed that children who were symptomatic on the day of investigation had a higher failure rate in performing technically acceptable manoeuvres. Acceptable tests, however, were indeed not different from our healthy reference population.

We agree that in order to establish the reference data the reference population should be as large as possible. Lum *et al.* [3] propose to include children with current upper respiratory symptoms and/or a history of asthma. Our data confirm that spirometry data from children with upper RTIs and no asthma diagnosis may not be different from healthy children's data in cases where the ATS/ERS quality criteria (including careful visual control) are fulfilled. Statistically, there is also no reason to exclude children without an asthma diagnosis but a history of lower RTIs within 6 weeks of testing, or a history of wheezy bronchitis from the reference population. However, clinical assessment may differ between investigators, thereby potentially influencing the results. The correct diagnosis of an RTI as upper or lower, with or without obstruction, may be difficult for field staff to ascertain; therefore, strict criteria to define a healthy population should be adhered to. While success rates in children with a history of asthma may be higher, the differences in results (especially FEV_1/FVC) are clinically relevant.

Although the mean reference data would only slightly change when including asthmatics because of the low prevalence of asthma, for clinical reasons, we would like to challenge the recommendation generated by Lum *et al.* [3] to include children/adolescents with a present or past history of asthma or current respiratory tract infection in a reference population for spirometry. Inclusion will result in higher standard deviations and lower LLNs, which may finally negatively affect diagnostic accuracy.

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Children/adolescents with asthma or current respiratory tract infection should not be included in a reference population for spirometry http://ow.ly/VBVe8

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Received: Sept 03 2015 | Accepted after revision: Nov 22 2015

Support statement: Funding for has been provided by GlaxoSmithKline GmbH & Co. KG, Munich, Germany; Aerocrine AB, Solna, Sweden; MSD Sharp & Dohme GmbH, Haar, Germany; AstraZeneca GmbH, Wedel, Germany; Novartis Pharma GmbH, Nuernberg, Germany; Astellas Pharma GmbH, Munich, Germany; Deutsche Atemwegsliga; Ndd Medizintechnik AG, Zürich, Switzerland. Funding information for this article has been deposited with FundRef.

Conflict of interest: None declared.

Acknowledgements: The authors would like to thank the children and their families for taking part in this study. The authors would also like to thank the following people for their technical assistance: Christina Beckmann, Julia Bienen, Cornelia Bisdorf, Irene Groß, Christina Müller, and Sandra Werth (Children's Hospital and Research Unit, Marien Hospital, Wesel, Germany); Heike Beermann and Marion Kliemt (Paediatric Pulmonology, Allergology and Neonatology, Hannover Medical School, Germany); Sabina Illi (University Childreńs Hospital, LMU, Munich, Germany); Özgü Altin, Gisela Bartkowiak, Ursula Pfeiffer and Michaela Strempel (University Hospital, Heinrich-Heine University, Düsseldorf, Germany).

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Eur Respir J 2016; 47: 1290–1292 | DOI: 10.1183/13993003.01465-2015 | Copyright ©ERS 2016

From the authors:

We wish to thank A. Hüls and colleagues for their interest in our recent paper [1], and the opportunity to clarify the rationale behind the conclusions we reached, which differ from their own. Despite the title of their letter, it is important to emphasise that we did not recommend inclusion of symptomatic children, those with a prior history of adverse exposures, or those with a current respiratory illness such as asthma, when establishing spirometric reference equations, where international standards regarding definition of health may need to be adhered to. Indeed we state clearly in the discussion that under such circumstances the target sample size may have to be increased by at least 30% to account for such exclusions, a proportion not dissimilar to that reported by Hüls *et al.* [2] What was demonstrated by our results is that when carrying out epidemiological studies such as the SLIC study (Size and Lung function In Children)[3], the primary aim of which was to ascertain the extent to which ethnic differences in lung function can be attributed to differences in physique and socioeconomic factors, inclusion criteria can be broader without biasing results. This not only renders the results more generalisable but has considerable practical and economic benefits.

Although the authors compared their data from the LUNOKID study (LUng function NOrmal values for KIDs in Germany), with our results, there are differences regarding the definition of "current asthma"