Reviewer’s report


Version: 0 Date: 10 Sep 2019

Reviewer: Helena Backman

Reviewer's report:

Thank you for letting me review this interesting study titled "Validation of the Global Lung Initiative 2012 Multi-Ethnic spirometric reference equations in healthy urban Zimbabwean 7-13-year-old school children: a cross-sectional observational study". As per information available in the abstract, the aim of the paper was to evaluate the fit of the ERS/GLI2012 reference values for a population of healthy urban Zimbabwean school children (7-13 years). I think this is an important study aim and that evaluations of reference values should be performed on healthy subjects in the population they are applied on in order to identify the overall fit and possible consequences of lack of fit.

I find the paper important and interesting but have some major comments:

Main comments:

The aim of the study, as stated in the end of the introduction, seems to be to "evaluate the performance of the ERS/GLI2012 equations among urban and peri-urban Zimbabwean children aged 7-13 years against a standard normal distribution". I don't think that this is what the authors have done in the current study. The first part of this sentence is correct but the ending "against a standard normal distribution" seems questionable to me and should either be justified or omitted. I also hesitate to agree with the authors on their conclusion that evaluation of restrictive and obstructive spirometry should be based on the GLI reference values. I agree that the overall fit is evaluated in this paper, but we have no clinical data suggesting that these reference values identify obstructive or restrictive spirometry. This is a separate study.

In the Introduction (second page), line 12: I would like the authors to justify, as a response to this comment and perhaps not necessarily so in the manuscript, their claim that "However, the FEV1/FVC ratio has consistently demonstrated a better fit across populations than the other lung function measurements". I am not convinced that this is true. And in the following sentence the authors list possible reasons for poor fit of spirometry reference equations such as air pollution, malnutrition and low socioeconomic status. This statement is in one way true but on the other hand it is sort of incomplete and "one-eyed". The reasons for poor fit can also be due to the reference equations per se (and not only because of the harmful exposures and other factors in the population they are applied on) such as inappropriate modelling of the reference equation per se, inappropriate sample that the reference equation is based on, and so on. The population that the reference equations are applied in may also be healthier, less exposed and of higher socioeconomic status than for instance the GLI population, possibly resulting in "poor fit" or "erroneous estimations" as stated on line 22. I think this aspect should be considered better not only in the introduction, but throughout the manuscript.
I am not sure I agree that this is a random sample as stated in the last part of the discussion. It does not necessarily mirror the distribution in the Zimbabwean society. Instead, in the last part of the discussion where strengths and weaknesses are described, please clarify that these children are from three schools randomly selected from three areas with different socioeconomic standard. And further on this topic I would prefer that the conclusion is adjusted with the clarification that these children all come from the region of Harare, and are not randomly selected from the general population of Zimbabwe, as the current wording could implicate.

I find the methods regarding data collection and spirometry sufficiently described. However, it should be clarified if all included children were indeed Zimbabwean and if other "ethnicity/race" was an exclusion criterion.

Minor comments:

The abbreviation ECSC stands for "European Coal and Steel Community" and not "European Coal and Steel Company".

In the Introduction (first page), line 15: Please consider replacing the word "are" with "can be".

In the Introduction (first page), line 45: Please consider replacing the word "are" with "can be". The GLI task force recommends the use of the 2.5th percentile as LLN for epidemiological studies, and thus the 5th percentile is not always and per definition the golden standard.

In the second page of Results, line 11: consider changing the word "centile" to percentile". On the same page on line 19, consider replacing the the word "normality" with "the GLI distribution" or similar. And further on the same page, line 33-35, the authors state that "...the strengths of associations (β coefficients) from linear regression were within ±0.2 (Supplementary File 2).". This statement should be changed as the absolute value of β coefficients says nothing about the strengths of associations. The strength of association cannot be evaluated by the value of β alone, but rely heavily also on the values of the X-variable. For instance the value of β is affected substantially if e.g. height would be an X-variable included measured in centimetres or meters.

Please consider adding the words "With perfect fit" before the sentence "The z-scores developed from the ERS/GLI..." at the second page of Discussion, lines 37-38.

The reference list is not appropriately formatted. Some references are duplicated and sometimes the journal names are missing. Please revise.

On the third Discussion page, please consider replacing the word "better" by the word "higher" on line 25. On the same page, please consider revising the sentence on lines 35-38 as previously commented on.

Please clarify the statement "Using the LLN as compared to the Polgar fixed cut-offs of 70%..." on the third discussion page, lines 52-57. I don't think that the fixed cut-off of FEV1/FVC<0.7 is generally referred to as the "Polgar fixed cut-off" but more commonly it is stated that this cut-off is generally used on many clinics due to simplicity and that this cut-off is recommended by GOLD. This could be corrected.

Finally, I suggest adding mean and SD to the captions for Figures 3 and 4.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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