Author’s response to reviews

Title: Feasibility study and reference values of FibroScan 502 with M probe in healthy preschool children aged 5 years

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you very much for your comments and thoughtful suggestions on our manuscript (BPED-D-18-01024R1). We have tried our best to revise and improve the manuscript and have made careful modifications to the manuscript based on the reviewers’ comments. We hope that the corrections will meet with approval. We did not list the changes here but marked them in red in the revised paper. Thank you again for your time and consideration.

Below you will find our point-by-point responses to the reviewers’ comments:

Responses to the reviewer’s comments:

To Mi-Jung Lee (Reviewer 1):

1. The title was expressed as preschool children, and only five-year-olds were actually included, so it needs to be corrected throughout the manuscript.
Response: Thank you very much for pointing out this issue. Actually, our study only focused on five-year-old individuals. We will continue to discover the normal range at other age levels in the future studies based on this ongoing perspective birth cohort. Per the reviewer’s instructions, we corrected the title to “Feasibility study and reference values of FibroScan 502 with M probe in healthy preschool children aged 5 years”.

2. I think it's also meaningful to review the causes of measurement failures in the healthy children. It would be nice to add an analysis/description on this part (whether because of moving or because of too narrow ribs, etc.).

Response: We agree with the reviewer’s suggestions that reviewing the causes of measurement failures in the healthy children is very important. In our study, 452 participants were enrolled into the TE study, and a total of 16 children were excluded due to TE measurement. Among these, 10 children failed because of intercostal spaces that were too narrow, 4 children failed because of moving, and the remaining cases failed because of unknown reasons. We have added these to the revised manuscript. Thank you very much for the suggestion.

3. Additional explanation of statistical analysis and specific results are required.

(1) It seems to be distracting to mix the results of parametric and nonparametric tests. You need to check if there are any statistical advice on this part.

Response: We very much appreciate the reviewer’s advice. Parametric tests deal with the estimation of population parameters, whereas the nonparametric parameters are distribution free methods and rely on ordering (ranking) of observations. If the populations are normally distributed, then we use parametric tests. If we are not sure or we suspect that they do not behave normally, then we use nonparametric methods. Table 1 and Table 2 include all characteristics of these healthy preschool children. The results apply both parametric and nonparametric tests based on the data distribution, and we put them into one table to be intuitive and clear.

(2) For correlation, I think Pearson is more appropriate.

Response: Thank you very much for the suggestions. The Pearson correlation in statistics is a measure of the linear correlation between two variables X and Y, giving a value between +1 and −1 inclusive. It is widely used in the sciences as a measure of the degree of linear dependence between two variables. A Spearman correlation is applied when the two variables being compared are monotonically related, even if their relationship is not linear. When the data are roughly elliptically distributed and there are no prominent outliers, the Spearman correlation and Pearson correlation give similar values. If there are no repeated data values, a perfect Spearman correlation of +1 or −1 occurs when each of the variables is a perfect monotone function of the other. Spearman’s coefficient is appropriate for both continuous and discrete ordinal variables. As the distribution of CAP values is non-normal, we think that the Spearman’s rank correlation coefficient test may be more sensitive than Pearson's test in showing the associations.
(3) The results of the piecewise linear regression requires confirmation that no numerical interpretation exists. This is an unfamiliar statistic, so further clarification is required.

Response: Thank you very much for pointing out this issue. We agree with the reviewer’s suggestions that some numerical interpretation should exist to help us understand the analysis results. We have added this to the revised manuscript (see Table 4). Thank you very much for the suggestion.

(4) Are there both univariate and multivariate results in Table 3? Table format is ambiguous and inconsistent. Please check.

Response: Thank you very much for pointing out this issue. The final univariate and multivariate analyses of factors related to CAP are shown in Table 3. Factors <0.05 in univariate analysis were included in the multivariate analysis. As the reviewer mentioned, we found that the inconsistency in line break may lead to the ambiguous format. Table 3 has been modified to avoid ambiguity in the revised manuscript. Thank you very much for the suggestion (see Table 3).

4. It would be better to unify the results in one decimal place, consistent with existing studies.

Response: We appreciate the reviewer’s advice. Thus, we have made corrections according to the reviewer’s instructions in the revised manuscript. Thank you very much for the suggestion (see Table 1 and Table 2).

5. line 165-166: LDL-C was also different between the two groups.

Response: Thank you very much for pointing out this issue. As the reviewer mentioned, LDL-C was also different between the two groups (P = 0.004). We have added this in the revised manuscript.

6. line 216-217: Reference 16 and 17 do not include the part of steatosis. Please check and delete it.

Response: Thank you very much for pointing out this issue. We have rechecked and reconfirmed these references’ contents. As the reviewer mentioned, references 16 and 17 include fibrosis but do not include steatosis. The error has been corrected. Thank you very much.

7. line 227: Daisuke et al -> Tokuhara et al

Response: As suggested by the reviewer, the “Daisuke et al” has been corrected to “Tokuhara et al”. Thank you very much.
8. line 232: Engelmann G et al -> Engelmann et al

Response: As suggested by the reviewer, the “Engelmann G et al.” reference has been corrected to “Engelmann et al.”. Thank you very much.

9. line 233: So, they concluded that... -> The "they" means Daisuke et al, not Engelmann et al, doesn't it? It is confusing. Please clarify it.

Response: Thank you very much for pointing out this issue. We have rechecked and reconfirmed the contents of these two references. As the reviewer mentioned, the “they” actually means Tokuhara et al. Our statement maybe lead to ambiguity. We have corrected the statement in the revised manuscript.

10. line 275-277: The cutoff values of 75th and 95th percentile need references.

Response: Thank you very much for pointing out this issue. Any claim on the clinical predictive value of these CAP values needs references. As CAP values were correlated with parameters of body composition, namely, fat mass content, waist circumference and percent of body fat, CAP may become a useful tool to assess hepatic fat content and screen for fatty liver in children. However, all children in the cohort had been specifically selected for being healthy, and the children whose CAP values exceeded 75% or 95% were still in the normal range. Based on the normal range of the CAP values in these preschool children, how can fatty liver be diagnosed? This is a question that has not yet been solved. Therefore, we made the assumption that the doctors would be careful to prevent fatty liver when the CAP values exceed the 75th percentiles, and the doctors would be aware of fatty liver as the CAP value exceeds the 95th percentiles. However, in the absence of other supporting data supported, these statements seemed slightly arbitrary. We have corrected the statements in the revised manuscript. We will continue to discover the normal ranges at other age levels and the range for the prevention, diagnosis, and treatment of fatty liver disease in children in future studies based on this ongoing perspective birth cohort. Thank you very much.

11. line 302-303: This study does not support that TE is "rapid" or "reproducible".

Response: Transient elastography (TE) gives a quantitative one-dimensional (i.e., a line) image of tissue stiffness. This technique is used mainly with the Fibroscan system, which is used for liver assessment. During detection, the acquisition of information lasts a tenth of second and the calculation is complete in a few seconds when the result of one measurement is displayed. This method is noninvasive and avoids the pain and risk of infection and bleeding from a biopsy and does not destroy tissue, so the same site can be tested again and again. Therefore, this approach is as rapid and reproducible as its own characteristics. We have modified the statement to be more accurate in the revised manuscript. Thank you very much for pointing out this issue.
12. Figure 2: Frequency -> Frequency, LS -> LSM (It also needs to be explained the abbreviation of LSM and CAP)

Response: Based on the reviewer’s suggestion, we have corrected these statements and supplemented the explanation of the abbreviation of LSM and CAP in the revised manuscript. Thank you very much for the suggestion (see Fig. 2).

13. Figure 2 and 3: The quality of the images is reduced. Modification is required.

Response: The quality of the images is low due to overcompression. The images have been modified in the revised manuscript. Thank you very much for pointing out this issue.

To Imeke Goldschmidt (Reviewer 2):

1. First and foremost, the manuscript needs a thorough revision with regards to English grammar and style.

Response: We have revised the whole manuscript carefully and tried to avoid any grammar or syntax errors. Additionally, we have asked colleagues who are skilled authors of English language papers to check the English. We hope that the language is now acceptable for the next review process. Thank you very much.

2. Presentation of the data appears appropriate; however, all tables need to be checked for consistency in line break. For parameters such as height, weight and BMI, it would be useful not only to present absolute values, but also centiles or z-scores.

Response: Per the reviewer’s instructions, we have checked and ensured the consistency. We agree with the reviewer’s suggestions that presenting the percentiles or z-scores is also important as BMI% can be used to divide subjects into the following fatness categories. We have added the data to the revised manuscript. Thank you very much for the suggestion (see Table 1).

3. In the discussion, the authors claim that due to the observed correlation of CAP results with parameters of body composition, namely fat mass content, waist circumference and percent of body fat, CAP may be a useful tool to screen for fatty liver. Given that CAP was specifically developed to assess hepatic fat content and that the latter depends on body composition, the observed correlation is rather reassuring, but not really a surprise. I am concerned however about the conclusion that CAP values exceeding the 75th centile should prompt measures to prevent fatty liver, and that CAP values exceeding the 95th should raise awareness of fatty liver. I feel that in a cohort that has specifically been selected for being healthy, with obese children excluded a priori, normal plasma lipids and with normal growth parameters, i.e. without any children at risk for developing fatty liver, the claim that 25% are at risk of developing fatty liver
cannot be made without more evidence. In contrast, describing normal values suggests that CAP values above the 75th centile are exactly that - normal - in 25% of the population. Any claim on the clinical predictive value of these CAP values needs more basis in facts, including liver ultrasound (despite its limitations correctly mentioned in the discussion), liver histology and additional markers of fatty liver disease.

Response: We agree with the reviewer’s suggestions that any claim on the clinical predictive value of these CAP values needs more basis. As the reviewer mentioned, all children in the cohort had been specifically selected for being healthy and had normal growth parameters, while obese children excluded. Therefore, we obtained the normal LSM and CAP value ranges. Therefore, the children whose CAP values exceeded the 75% or 95% percentiles were still in the normal range. As CAP values were correlated with parameters of body composition, namely, fat mass content, waist circumference and percent of body fat, CAP may become a useful tool to assess hepatic fat content and screen for fatty liver in children. Based on the normal range of the CAP values in these preschool children, how can fatty liver be diagnosed? This is a question that has not yet been answered. Therefore, we assumed that the doctors would be careful to prevent fatty liver when the CAP values exceed the 75th percentiles and that the doctors would be aware of fatty liver as the CAP values exceeds the 95th percentiles. However as no other supporting data exist, these statements seemed slightly arbitrary. We have corrected the statement in the revised manuscript. We will continue to discover the normal range at other age levels and the range for the prevention, diagnosis, and treatment of fatty liver disease in children in future studies based on this ongoing perspective birth cohort. Thank you very much.

4. With regards to transient elastography, please be aware that the manufacturer’s recommendation for use of the S probe goes up to 75 cm chest circumference, not 45 - if it didn't, using the M probe in children with a mean of around 50 cm chest circumference would not be so exceptional. Also, there is data in the literature that in paired comparison, using the M probe will yield lower values than the S probe. This should be mentioned when the authors discuss their results compared with the existing literature.

Response: We appreciate the reviewer’s advice, which will be very helpful for our future studies. The FibroScan probe types include S type (S1 and S2), M type and XL type according to different detection populations. The M probe has a transducer with a diameter of 7 mm and can measure 35 to 75 mm liver depth, whereas the S1 and S2 probes have transducers 5 mm in diameter and are designed to measure 15 to 40 and 20 to 50 mm liver depth, respectively. Therefore, the manufacturer recommended a single suitable probe for the patients’ thoracic perimeter including an S1 probe for 45 cm, S2 probe for 45–75 cm, and M probe for >75 cm. The main reason for the manufacturer to design several types may be to get accurate data in different groups. As some health centers cannot afford both the M probe and S probe considering the total cost, we also found that the M-probe had been used in school-age children whose thoracic perimeters were less than 75 cm in some studies. As the reviewer mentioned, there was data in the literature that showed the S2 probe would have overestimated the stage of fibrosis compared with the M probe. If the detection method of operation is correct and the results are accurate, could we find an association between the measurements of M probe and S probe? This is also a question that has not yet been answered. Hopefully, our results will provide a useful
reference, and we will conduct further research on the feasibility and reliability of the FibroScan S probe compared with the M probe for LSM and CAP values. We have made corrections and added the published paper to the revised manuscript. Thank you very much for pointing out this issue.

5. In summary, while reference values are useful for clinicians using TE and CAP in their daily practice, there is nothing particularly new or original about publishing these reference values. I feel that they should nevertheless be published, but I would argue against over-interpreting the results. In any case, the discussion needs to be streamlined and revised, and some thorough language polishing is required.

Response: The results in our study show the normal ranges of LSM and CAP values using the M probe in preschool children. Based on the reviewer’s suggestion, we have revised the whole manuscript carefully and tried to avoid any grammar or syntax errors. We have corrected the results and the discussion to be more concise and clear in the revised manuscript. These are some questions that may have not yet been answered and need to be explored. Further studies should explore how can fatty liver be diagnosed based on the normal range in these preschool children and find the association between the measurements obtained using the M probe and S probe. Additionally, we have asked colleagues who are skilled authors of English language papers to check the English. We hope that the language is now acceptable for the next review process. Thank you very much.

Once again, thank you very much for your comments and suggestions.

We look forward to your information about our revised papers.

Thank you very much and best regards.

Yours sincerely,

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