Author's response to reviews

**Title:** Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland.

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**Author's response to reviews:** see over
Response to the Reviewers Comments on Ms. No.: 5762606318969334
Reference values for the 6-minute walk test in healthy children and adolescents in Central Europe.
Silvia Ulrich and Florian F Hildenbrand

To Reviewer 1

Dear Dr. Henricson,

We thank you for reviewing the above manuscript and your valuable comments. We can address your detailed comments as follows:

1.) We agree with your concerns about our statement as in lines 76-79 and changed it accordingly. We also agree that reliability testing with repeated tests would be interesting. However, the design of our study did not allow to do repeated testing and we can therefore not directly confirm our results with the one from Geiger et al 2007. We added this drawback in a section on study limitation at the end of the discussion.

2.) As the 6 minute walk test is a self-paced test, thus we decided to give as little feedback as possible in order not to distract children and adolescents walking and in line with Gordon et al (Thorax, 1984), who hypothesized that “differential encouragement may tend to bias walking test scores”. The post exercise heart rate (taken as a possible marker for appropriate enforcement of the 6MWT) in our population was quite similar to Geiger et al (average 137.17 vs. 136.47 bpm). Thus, we believe that our study population walked as much as they could in general. However, we cannot exclude that the inter-individual effort taken was different. Although we encouraged all participants at the beginning of the test to walk as far as possible, we cannot really say what would have happened, if we would have encouraged the children and adolescents more or if we would have provided e.g. a price for the fastest walker etc. Thus, we stated this in the limitation section. Similarly, we cannot clearly differentiate, whether the plateau achieved in puberty would be biomechanical or behavioural.

3.) In a self-paced test the motivation of the participant is of great importance. But other tests which are used for evaluation of subjects’ performance status like forced expiration capacity have the same restricted informative value. Lack of motivation and understanding for the need of a 6MWT may affect performance more in adolescents than in smaller children. Moreover, potentially the motivation will differ from subject to subject in any age group. However, the flattening of the 6MWD-curve in adolescence might indicate that adolescents were less motivated. But potentially also physiological or biomechanical measures may play a role. We added this to the limitation section. This study was not designed for measuring the motivation of the participating children. A possible hint if the distance walked could be reliable according to age might be the post-test heart and the increase of heart during the test. In clinical routine we suggest repetition of the 6MWT and interpretation in a clinical context. Similarly, we do not know how our simple method of walk distance measurement would compare to other tests like stride length or cadence-based methods. Our method is simple and easy to performed and widely used.
in adults. In our experience, it also worked very well in children and adolescents. However, more sophisticated measures like actimetry in everyday life would potentially have the advantage to be closer to everyday life behaviour. We similarly added this to the limitation section.

4.) We corrected the sentence fragment line 116 and thank you for this remark.

5.) The reviewer is right that we did not assess puberty in the individuals but rather took the average of the Swiss population as we discussed with several paediatricians. However, it may well be the case that our estimate would not be correct for all subjects investigated. We hypothesize that the continuation of linear growth with stabilization that was found in the puberty age might point towards a motivational problem in this age group. However, we believe that probably not mere biological puberty, but also many psychosocial factors may play a role in this age group. Therefore we choose to make separate analysis for children above and below 12 years, as at this age frame, children change from primary to secondary schools in Switzerland and herewith change social environments, are allowed to look other films in the cinema etc.

6.) The reviewer is right that physical activity score only correlate with the 6MWD in boys and not in girls. We can only speculate about the reason for it, but believe that a behavioural aspect as stated by the reviewer might well play a role. Potentially, boys are more competitive herein. However, every single child performed the 6MWD test by its own without audience from other children. Nevertheless, competition might have played a role. Another reason could be that physical activity is more preserved in boys and therefore more reported as it than in girls, e.g. a girl that plays with elastic ropes might not perceive itself as doing exercise, whereas a boy playing football would. But as stated, these are only speculations.

7.) We added a section on limitation and relation to other studies in the field to the paper, as the reviewer suggested. We discussed the age limits and hypothesized about potential behavioural influence. We agree that simultaneous assessments of other physiological function such as lung function would have been interesting. We did not do this in the present study but agree that it could be well worth for future work.

We again thank you for your valuable comments and the interesting discussion. Silvia Ulrich & Florian Hildenbrand, on behalf of all authors
To Reviewer 2:

Dear Doctor Jansen,

We thank you for reviewing the above manuscript and your valuable comments. We can address your detailed comments as follows:

1.) We added the hypothesis and changed the abbreviation as you suggested.

2.)
   a. Power-calculation was done by our children’s hospital statistician based on the 6MWD in adults and included in the study.
   b. We used a stepwise multiple regression analysis as provided by SPSS. In each step performed, variables are consecutively taken similar to the forward-model, and then the new variable will be checked according to the backward model. According to our statistician, this is the most popular model to date. We double-checked these models by using only forward models and this did not change the results. We specified this in the method section.
   c. Thank you for this remark. We changed this throughout the text.
   d. We added this as recommended.
   e. We did test for normality (histograms and Kolmogorov-Smirnov-tests) and all data were normal distributed. Thus, the reviewer is right that we could have used simple T-tests. However, as we mainly compared boys and girls or different age groups, the groups remained small and thus we used the more conservative non-parametric test. The results would have been similar if we would have given the simple t-test.
   f. We decided to give as little feedback as possible in order not to distract the children, as proposed by Gordon et al (Thorax, 1984) However, we clearly told this to all children before and that they should walk as fast as possible without running although the person performing the test would be there without talking. We didn’t notice any problems in the attention span in the children and we observed a good motivation.
   g. We agree with your remark and changed this to achieve a better understanding.

3.)
   a. As suggested we added the missing data. We had 496 participants and all of them completed the test in the exact same manner.
   b. We changed this as suggested.
   c. We changed the title of this subpart and added some additional values as suggested.
   d. Table 3 shows different calculation formulas to predict 6MWD. The calculated the statistical significance for every variable in the different formulas. Therefore we get so many p-values. We think the addition of different steps of the regression analysis won’t add any additional information and would increase complexity at the expense of readability.
   e.

4.)

5.)
   a. Thank you for this valuable remark. We edited the first paragraph.
b. The reviewer is right that the sex-adjusted 6MWD can be calculated from mere age. However, as shown in table 3, the anthropometrics add significantly to the estimation of the normal 6MWD. The addition of height and weight however does not add the same value in all gender-specific age group, e.g. in girls younger than 12 years, the height is more important, in the older ones, the weight. We changed the footnote of the table in order to make this clearer.

c. There are several possible explanations for this mismatch. In our opinion the most important factor is that we didn’t include children younger than 5 years. Geiger et al dealt with this age-group in different manner (e.g. they were allowed to run and jump). In this group they had a major increase in heart rate. Another possible answer is that we had a higher average baseline heart rate before 6MWT (95bpm vs 88bpm) while the average end of test heart rate was quite similar (137.17 vs. 136.47 bpm). This is why we tried to apply a more practicable and feasible approach without a resting period of 2 hours before the test (Geiger 2007). Additionally, we didn’t give any verbal commands (except the 5 minutes command), thus we didn’t abet the participants to a higher effort, which could also be an explanation.

d. Although we found that the PAS correlated with the 6MWD if the population as a whole was taken, this was no longer true for all subgroups in multivariate models. In boys, adding the PAS to a model including physiological measures such as HR and blood pressure, the PAS did no longer add to the prediction model. This was similar for girls younger than 12 years. In adolescent girls on the other side, the PAS added to the prediction equation, together with the HR and body weight. We can only speculate why this was the case, but think that potentially in girls from 13-17 years life-style and sport activity get more important in a positive and negative sense, that means, sportive adolescent girls walk longer and have less body weight, whereas adolescent girls who state not to do many physical activity walk less. The reason why this is not the case in younger children and adolescent boys is not clear, we believe that it may be a question of what is perceived as sportive activity, e.g. football during school pauses in adolescent boys may not be preserved as sport or playing outside in younger children. We hypothesised this in the paper.

As you suggested, we added a section of limitations to our study.

6.)
7.)
8.)
a. We changed from central Europe to Switzerland.
b. We changed the word to influence
c. We changed this as you suggested.
d. We described how we got the reference equations by multiple stepwise linear regression done with the SPSS statistic program
e. Weight and height add information compared with equations using only age if boys and girls are taken overall. However, if boys are devided by the age 13 in two groups (above and below this cut-off), a age related equation using different regression-coefficients than in the overall formula can be taken. If this is done, weight and height no longer add in boys (table 3). In girls, the overall formula can be taken, but a formula including weight and height will be better as this anthropometrics add
information to the equation. However, if the girls are divided by a cut-off of 12 years, weight will add information in girls above the age of 12, height will add information in girls below 12 in comparison to the formula which only takes age.

f. We clarified this in the abstract

9.)

a. We apologize for the mistakes and corrected them.

Discretionary revision:
We changed to Swiss instead of Central European throughout the manuscript.

We again thank you for your valuable comments and the interesting discussion.
Silvia Ulrich & Florian Hildenbrand, on behalf of all authors