Author's response to reviews

Title: Physical activity and clustered cardiovascular disease risk factors in young children: a cross-sectional study (The IDEFICS study)

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Author's response to reviews: see over
Dear Editor,

Please find, enclosed, our reviewed manuscript entitled “Physical activity and clustered cardiovascular disease risk factors in young children: a cross-sectional study (The IDEFICS study)” which we would like to resubmit, after the response to the reviewers’comments, in the BMC Medicine as a Research Article.

The authors of this manuscript really thank to the reviewers and editor for giving us the possibility to improve the quality and understanding of this paper. We addressed all the suggestions and comments of the reviewers and provide a point-by-point response (see below). After that, we consider the manuscript has considerably improved.

On behalf of the co-authors I affirm that the data have not been published elsewhere and that the manuscript is not under consideration for publication by any other journal. Other aspects of the IDEFICS study have been published as full articles, and these have been referenced in the current article.

The funding has been that of the European Community, and has been acknowledged in the appropriate section of the text. There has not been any other funding such as that of pharmaceutical companies or any other body that may have any financial interest in the outcomes of the study. This, as well, has been stated in the manuscript.

We have employed the services of a professional medical writer, but only for the purposes of editorial assistance and English language verification. The payment for these services has been internal and does not involve sources with any vested interest in the findings of the study.

All co-authors have read and agreed with the current manuscript and affirm that their contributions are sufficient to justify co-authorship. All co-authors have no conflict of interest.

Specific contributions of the authors:

DJP, YP and LAM contributed to the concept and design of the study.

DJP, WA, HP, AS, LI, CH, DM, SDH, YP and LAM contributed to the conduct of the study DJP, KK, PB and LAM contributed to the analysis and interpretation of data.

DJP, KK, PB, YP, and LAM contributed to drafting the manuscript.

DJP, WA, HP, CH, AS, LI, DM, SDH, YP and LAM critically reviewed the manuscript.
All authors have read the manuscript and have had important critical input before the final approval.

DJP is the guarantor.

We look forward to your opinion as to the suitability of our manuscript for inclusion in the *BMC Medicine*.

Yours sincerely,

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Physical activity and clustered cardiovascular disease risk factors in young children: a cross-sectional study (The IDEFICS study)

The authors thank the reviewers for the positive comments given to the manuscript. All the suggestions have been taken into consideration, and the manuscript has been modified accordingly. Please, find below answers to the reviewers’ comments. All the changes in the manuscript have been highlighted in yellow background. Consequently, authors consider that the manuscript has considerably improved.

Summary of Responses to Reviewer Comments and Changes Made

Reviewer 1 (Robert McMurray) Comments and Author

1.- This is an interesting article examining the relationship between physical activity levels and a combined score for cardiometabolic risk (CMR) factors. In addition, it is one of the first to develop PA guidelines based on a health outcome. The sample is sufficient and obtained from a diverse geographic area in Europe. The age range of the sample is also novel: a group in need of study and evaluation. The use of accelerometry to estimate physical activity levels and the methods to obtain the various risk factors are appropriate.

Response: the authors really appreciate the reviewer’s comment.

2.- There are several items that should be taken into consideration to strengthen the manuscript. First and foremost, although the sample size is quite large, the sample appears to be quite health and the reader is not provided any information on how many, or what percentage of the children are actually at risk. For example, the low mean and standard deviation of the HOMA scores suggests that there were really no children “at risk” for insulin resistance. Similar comments could be made about BMI, blood pressures and triglycerides. This suggests that even those children in the highest quintile of “risk” may not be truly “at risk”. This reviewer recommends some comment on this issue in the discussion section, or state as a limitation in that section of the discussion.

Response: Thank you for this suggestion. We agree with this reviewer, in fact, as the sample was potentially health we defined individuals >1 SD away from the mean in the clustered risk scores as being “at risk” according with the cut-off used by Andersen LB et al. in Lancet 2006 [1] as stated in the statistical section. In this sense, we identified around 15.5% of the overall sample included in the current manuscript as being at risk (based on the cluster) which is in line with the proportion found in the study of Andersen LB. Now, additional information on the population at risk has been included in the discussion as well as the limitation of a healthy population has been acknowledged.
3.- Second, the introduction starts out like a treatise on obesity. Since obesity is one of the CMR factors, this reviewer suggests starting the introduction focusing on the issue of the CMR factor of which obesity is one. Also, please define CMR factor for the reader.

Response: Thank you very much for this suggestion. The first paragraph of the introduction section has been now re-written.

4.- Third, terms “Score A” and “Score B” could be easily confused and the reader has to refer back to methodology. Could better terminology be used that are more suggestive of the score? For example “CRF” and “CRF+VO2max”.

Response: Thank you very much for this comment. The terms “Score A and Score B” have been changed by CRFs and CRFs+Fit, respectively.

5.- Since the study involved several countries and several locations, was there any attempt at “quality control” for those research assistants making the measurements?

Response: Thank you very much for this comment. This is an important issue that in the present IDEFICS project has been considered in order to avoid inter-evaluator bias [2, 3]. Now the following paragraph has been added to the methods section (end of page 6 and beginning of page 7):

“For the quality management, all measurements followed detailed standard operation procedures that were laid down in the general survey manual and finalised after the pretest of all survey modules [3]. Field personnel from each study centre participated in the central training and organised local training sessions thereafter. The co-ordinating centre conducted site visits to each study location during both field surveys to check adherence of field [2].”

6.- Fourth, this reviewer found it very interesting that CR fitness was included as a risk factor and a dependent variable like the PA. One wonders about collinearity issues with PA one side of the equation and CR fitness on the other side?

Response: Thank you for the comment. In the present study we study the association of the levels of PA (independent/predictor) with a cluster of CVD risk factors (outcome/dependent). This cluster is composed based on one previously published in Lancet [1] and included a set of factors which are known to be related with CVD. In this sense, cardiorespiratory fitness is included as it has been clearly found that a low fitness implies a high risk of CVD/mortality [4-6]. We expected that PA could be related with the cluster of CVD risk factors as an index but relationships with individual factors are also possible. Then, we understand that there is not collinearity effect between independent variables.

7.- In the Methods there was mention of a scale of 0-6 for SES. Please provide the reader with the direction of the scale; e.g. 0=low SES and 6=high SES.

Response: Thanks. This information has been added (see page 7, second paragraph).
8.- A couple of clarifications on accelerometry are needed in the methods. The authors state that two different accelerometers were used. Is there any data regarding a cross-validation between the two units and was one specific model used for the children and the other for the parents? Since there were so many sites and children and not all accelerometers provide the same counts for a given task, the authors should provide any information concerning cross-validation between specific accelerometers. Also, the authors should provide a rational for the “average PA” score and what that score tells the reader.

Response: Thank you for this suggestion. The authors included additional information for a better understanding of the accelerometers used and the term “average PA” (see page 8 paragraph 1). Briefly, the rationale to use ActiGraph in younger and Actitrainer in older children was to record, when possible, the heart rate. However, in the current study only data from accelerometers were used and cross-validation was not necessary as both accelerometers have the same model of ActiGraph integrated. Finally, the term “average PA” is widely used as an indicator of the average total PA of the children per day, then in order to avoid confusion this term has been replaced by “Total PA” and explained in the method.

9.- There may be some concern with only six hours of accelerometry data representing a day. Why was this (minimum 6 hr) used? Could it be a limitation? Finally, what was the methodology used to develop the recommendations for the minutes of MVPA?

Response: Thank you for these suggestions. The criteria and validation of using 6h/d of monitoring by accelerometers have been previously published in detail [7]. Briefly, the reliability analysis of accelerometer outcome variables indicated that a minimum duration of 6 h per day of monitoring was required to achieve 80% reliability in the validation cohort. The authors have added a short comment on that in the PA method section. See page 9, paragraph 1.

Regarding the recommendations for the minutes of MVPA showed in table 4, the criteria were based on the results derived from the logistic regression in the previous tables. Then, as being at the highest quintile of PA intensities showed to be related with a low risk of having a high score of CVD risk factors, we performed descriptive analyses to stand out the mean and SD time corresponding at each quintile among the different PA intensities segregated by age and gender. Finally, the mean and SD at the highest quintile (Q5) of PA was selected as potential recommendation as other did before [1]. See page 11, last paragraph.

10.- The authors used VO2max as their indicator CR fitness. This methodology includes weight and therefore fat mass. Thus, the inclusion of VO2max and adiposity are collinear and results in an overestimation of the significance of adiposity. Why not use laps completed for the fitness measure? This was directly measured and reduces the inaccuracies that occur with the use of the prediction equation and eliminates any colinearity with obesity.

Response: Thank you for this suggestion. Authors totally agree with that point, then the score “CRFs+fit” has now been recalculated using the final stage instead of VO2max in order to avoid potential collinear effects. The result did not substantially change but the
Table 3 showing logistic regression on this score has been updated. Moreover, descriptive values for the final stage have been included in Table 1.

11. Finally in the methods, please provide a rational for using one standard deviation above the mean to indicate CMR. If you examine the data provided in Table 1, one SD above the mean for any of the risk factors would still be considered “within normal limits”.

Response: Thank you for this suggestion. As it has been explained in the response of previous comments (see response to comment number 2) the sample was potentially health, then we defined individuals above 1 SD away from the mean in the clustered risk scores as being “at risk” according with others [1, 8] which previously used the same criteria for apparently healthy population (only 15% at risk).

12. The Results section states that there were significant differences between the sexes for most characteristics and CMR factors. However, when you view the data there is actually little numerical differences. Could it be that the statistical results are simply related to sample size and there is not any clinical relevance?

Response: Thank you very much. The authors agree with this reviewer that in some cases the differences between genders could be influenced by sample size, however, in other cases such as most of the remained significant after multiple tests correction (See next comment) these seem to be biologically relevant. Especially interesting are the differences in PA intensities by gender as independent variables of the present work. If this reviewer agrees with the inclusion of the Bonferroni correction (see next comment) the results from Table 1 can be better interpreted otherwise the reviewer consider to add some additional issue.

13. Similarly, there were 19 statistical tests for each age group (Table 1). A correction factor for multiple tests is recommended. Likewise, the partial correlation were statistically significant, but how meaningful is an r = 0.086 which accounts for < 1% of the variance? This should be addressed in the Discussion section.

Response: Thank you for these comments. The authors agree with the numbers of tests in table 1, then the Bonferroni correction for multiple tests was applied and the remained significant differences were mentioned in the result section and Table 1. See page 12 paragraph 1 and page 15 last paragraph.

14. With regard to the PA results, some information (minutes) regarding the limits of each quintile would be of great benefit for the reader. Table 4 does provide information on counts/minute but most readers will not be sufficiently knowledgeable to interpret the counts. This reviewer also recommends placing the PA results before the logistic regression analyses.

Response: Thank you for the suggestions. As the reviewer suggest the Table 4 has been completed with the limits (range) for each quintiles across the four variables of PA. All the units are provided in “min”, except to “Total PA” which is in “counts” as it is the common way to show for this variable. Finally, the authors consider adequate to place the Table 4 at the end given that we based on the logistic results for the selection of PA recommendations (see previous response number 9 for more information).
15.- As presented the discussion provides little information beyond the results. There should be some discussion of the differing age-group results beyond the one sentence provided (I counted the same sentence four times in the Discussion that said this was novel but provided nothing beyond that statement). Some discussion could provide new and relevant information.

Response: Thank you for this comment. The discussion has now been properly completed and attention has been paid to the differences between age-group.

16.- Also, the CMR factors appear normal (Table 1), a reader (and this reviewer) would be interested in knowing which of the CMR factors is/are causing the elevated risk score?

Response: Thank you for this comment. The authors decided to use the clustering of individual risk factors as it has been suggested as a good method to assess CVD risk level in apparently healthy children, given that it describes a state in which several risk factors are high simultaneously in the same individual [8]. Moreover, the clustered z-score is based on the assumption that all included individual CVD risk factors are equally important in defining CVD risk, which may not be the case. However, there is no evidence suggesting how risk factors should be weighed, and we may never get that in children, because CVD is not usually manifested in children [8]. Then, the authors do not feel able to determine the particular weight of each risk factor.

17.- This reviewer recommends moving the limitations section toward the end of the discussion and include the overall healthy sample as a limitation as mentioned above.

Response: Thanks you for this comment. The limitation section has been moved and the overall healthy sample has been included as limitation.

18.- The authors are also directed to an article in Dynamic Medicine in 2008 by McMurray et al., that discusses the importance of PA and VO2max in predicting METs in youth. The section on comparisons with other studies could be reduced to allow for more discussion of the points mentioned above.

Response: Thanks. The discussion has now been completed in order to address the point raised in comments 15 and 18.

19.- Couple of minor points:

• “Body mass” not “weight” was measured.

Response: Thanks. Done.

• The abstract needs a statement regarding what variables were included in the CMR factor score.

Response: Thanks. Done.
- Please check the metrics under CR fitness. The “-1” should be to the power and not subtracted.

响应: 谢谢这个建议。在生成簇中，除了心血管和呼吸健康外的所有风险因素，都对CVD风险有正向影响。这意味着风险代谢的随着值的增加而增加。因此，心血管健康被乘以“-1”以将方向反转为与其它包含在簇中的因素相同。

- With the blood draw, was the overnight fast verified or checked?

响应: 谢谢。在抽血前，调查问卷确认了过夜禁食。这个信息已被添加。见第9页，第1段。

20.- In the Results section, why mention tertiles? As stated this suggests the authors are “double” publishing the results. If so the first publication should be noted in the Introduction or Methods sections.

响应: 非常感谢您的建议。作者们同意这个表述不清晰。然而，没有前文提到过这些结果。这个句子旨在说明在使用5组而不是3组进行敏感性分析后，结果没有变化。参考文献33是为替代切口在敏感性分析中使用的标记。现在，它已在结果部分进行了澄清。见第12页，第1段。

21.- Please be consistent with “cardiorespiratory”. Sometimes it is spelled as one word and sometimes it is hyphenated.

响应: 谢谢。术语“cardiorespiratory fitness”已被用于保持与参考文献中原始单词的一致。

22.- In the Conclusion, what is meant by “In younger children it seems that this role of PA is not such evident”?

响应: 非常感谢您的评论。尽管PA与CVD风险因素的关联在两个年龄组中被发现，但在2到6岁的年轻儿童中似乎不那么明显，因为关联数较少。现在，句子已经重写以说明这一点。见第17页，结论段如下：“在2至6岁的年轻儿童中，PA的作用似乎不如在6岁以上儿童中那样明显，因为显著关联的数量较少”。

23.- Table 2 and figures: Please indicate what quintile is what; Q1 lowest, Q5 highest or the reverse.

响应: 谢谢您的评论。Q5已被标记为五分位的基准，指示最高的PA值通过表格和图例。
Reviewer 2 (José Ribeiro) Comments and Author

1.- This is an interesting paper about physical activity and the clustering of CVD risk factors. The aims of the study are well defined and the methods used are clear and detailed. The study design is adjusted to the aims of the research, and data is adequately presented. The conclusions and discussion of the paper is based on the main results of the research, and supported by the data presented. Although the manuscript is well written and clear, a few points need to be clarified by the authors, and we suggest these Minor Essential Revisions.

Response: the authors really appreciate the reviewer’s comment.

2.- In the physical activity methods section, we suggest the author to clarify a few points:

How did the handle the consecutive amounts of zeros (more than 60 minutes represent not wearing the unit?); although several studies have reported similar methods of research, we suggest the authors to insert a comment about the placement of the unit (waist, wrist, left side or right side, etc.).

Response: The authors thank the reviewer’s comment. Several validation studies were performed in relation with the accelerometry usage. Particularly, in the study of Ojjiambo et al. [7] this issue is addressed. Thus, the following information has been added to the method section (page 9, paragraph 1): Non-wear time was excluded from the data my means of an automated method which use an algorithm developed using R (version R 2.9.0., R Foundation for Statistical Computing, Vienna, Austria; http://www.R- project.org). Thus, periods of 20 min or more consecutive zero counts were replaced by missing data code before further analysis[7].

The following sentence about the placement of the unit has been completed; Prior to data collection, parents were instructed in the correct positioning of the accelerometer, it is, to attach the accelerometer to the right hip of the child during their waking day by means of an elastic belt and adjusted to ensure close contact with the body.

3.- In our opinion it’s already available more suitable equations (than the original by Leger) to estimate the cardio respiratory fitness adjusted to children and adolescents (Barnett; Ruiz; etc.).

Response: Thank for this comment. According with the comment number 10 of the reviewer 1, cardiorespiratory fitness has been expressed as the final stage instead of VO2max and used in the clustering with this unit in order to avoid collinear effect with fat mass.

4.- In the methods section about biological samples, authors are using the Andersen et al. method to compute the CVD score, but they need to clarify why are they only using the SBP and not the DBP, and since they used a Tanita BC 420 they should have data about the percentage of body fat, and it could be more adjusted than using the sum of two skin folds!

Response: the authors thank the reviewer’s comments. As it has been mentioned we followed the standards used in the CVD score of Andersen el al [1] in which only use
SBP but not DBP. One of the reasons why we thought it was the most appropriate idea fall on the potential collinerarity and overlapping effects of including two closely related variables such as SBP and DBP into the same score.

On the other hand, although these authors understand that percentage of body fat is interesting and could also be used, we do not totally agree that could be more precise. First, we wanted to replicate the score used by Andersen et al. [1] in order to allow a future and clear comparison between studies. Secondly, the use of percentage body fat estimated from a formula implies the assumption of an error of estimation which is particular for the population of validation of this formula. Additionally, the lack of previously validated formula for the particular young age range existing in our study could increase the estimation’s error to assume. Then, we decided to use the raw data of the sum of skinfolds which can be easily compared between studies, population and age ranges as well as do not alter the overall score.

5.- I the statistical analysis they report using ANOVA to compare genders, wouldn’t it be more suitable to use independent samples T test, since the only have two independent variables?

Response: The authors thank the reviewer’s comment. Now, the T test was used instead of ANOVA and the result did not change.

6.- I results authors are reporting data about DBP, but they didn’t used it in the score, why?

Response: Thank you. The reasons to do not include DBP in the score have been described in the previous response to comment number 4. Then, it was used only for descriptive information of the population.

7.- The results about the correlations are presenting conflicting numbers regarding the sample sizes presented in tables; this aspect needs to be clarified.

Response: Thank you for the comment. This was a mistake with the update of the correct sample sizes after to apply additional criteria for selection. Please, see response to comment number 11 for more information.

8.- In the likelihood ratios, we suggest the authors to better clarify the significance levels of the OR, because, although we can find the significance values from the confidence intervals, that is not clear in the tables. We suggest including a note in the tables representing the p value.

Response: The authors really thank this appreciation. Now, the significant ORs and their confidence intervals have been highlighted in bold through the tables.

9.- In discussion authors present data about the quintiles of PA, but they didn’t presented in methods how did they did it, were the quintiles age and gender djusted?

Response: Thank you for the comment. The reviewer is right, this is information has now been included as suggested for both reviewers in the statistical analyses. See page 11, last paragraph.
10.- We suggest the authors to include the minutes of MVPA of the quintiles by gender (maybe including a new table with data for all the quintiles of MVPA by gender).

**Response:** Thanks you. The information on minutes of MVPA for boys and girls at each age group is already provided in the table 4.

11.- In table 1, regarding the PA variables we suggest the authors to correct the units for min./day instead of only min Sample sizes in table 2 and 3 are confusing, since they don’t match the sample sizes in the methods. We suggest authors to clarify.

**Response:** the authors thank the reviewer’s comment. Now, the units of PA have been corrected in table 1.

We apologize for the confusion in the sample sizes, but this was a mistake in update the final sample sizes in methods and table 1. The real sample sizes including all the variables (dependent and independent) but also confounders are those despite in tables 2 and 3. However, the sample sizes in methods and table 1 also correspond to a previous step including participants without data for some confounders such as SES, while data correspond with the real sample size. Then, we decided to include only those participants with valid data for all the variables and confounders and the sample sizes have now been updated.

**References:**