Author's response to reviews

Title: Resting heart rate: Its correlations and potential for screening metabolic dysfunctions in adolescents

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Author's response to reviews: see over
The relationship resting heart rate has with different diseases is starting to be investigated. Preliminary research suggests that having a higher resting heart rate is related to some chronic diseases and could possibly be used as a predictor of future diseases like type 2 diabetes. This study investigates the relationship between resting heart rate and metabolic dysfunction in an adolescent population. A large sample of adolescents from an area of Brazil was measured for their resting heart rate, and metabolic parameters (lipids, glucose, etc). The results indicated that resting heart rate was positively related with triglycerides and glucose. Logistic regression indicated that those in the highest resting heart rate group (> 86) were more likely to have low HDLC or high glucose values compared to those with the lowest group. AUC analysis indicates that resting heart rate could be a predictor or high glucose and triglyceride levels.

This study is examining an area that has had limited study. The results support what the previous evidence has suggested. High resting heart rate is related to adverse health outcomes; however, this study extends findings to an age group that has not been examined and to different health outcomes (lipids). While this study contributes to the current literature base, there are some factors that need consideration before publication.

Major Compulsory Revisions
1. short title: change the word tachycardia. There is no evidence from this paper that tachycardia is related to metabolic function.
   Answer: We adjusted this term. The word “tachycardia” was replaced by “high heart rate” in the short title.

2. This issue is throughout the paper. The highest grouping for the OR is >86 and tachycardia is defined as a heart rate >100 bpm. Further, the results do state what exact heart rate is idea to use as a screening value. Everywhere the authors talk about tachycardia it needs to be changed.
   Answer: As suggested, the term “tachycardia” was excluded of the manuscript (replaced by “high resting heart rate”).

Abstract
3. Page 2 abstract - results. Is heart rate used categorically or continuously? Is resting heart rate positively or negatively related with sleep and VO2? What level of resting heart rate is associated with HDL and glucose (OR data)?
   Answer: The text was adjusted. As suggested, additional information were included.

4. Page 2 abstract – conclusion: cannot say tachycardia, no evidence given to support this. What type of dysfunctions are being referenced?
   Answer: According to suggestion, the conclusion was adjusted.
Methods
5. Page 5 inclusion criteria: self-report of health. Did they just have to self-report health to be in the study or were certain diseases excluded?
   *Answer:* Self-report of health refers the presence of previously detected chronic diseases (e.g. high blood pressure/diabetes with medicine use).

6. Page 6 resting heart rate: Provide a rational for why ref 9 is being used for the quartiles values.
   *Answer:* Initially, the quartiles were adopted because there are not widely accepted RHR cutoffs. These quartiles were generated in a dataset constituted by Brazilian children and adolescents and have been associated with high blood pressure independently of obesity status.

7. Why was fitness not considered a confounder for the logistic analysis?
   *Answer:* As suggested, cardiorespiratory fitness was inserted at multivariable models.

8. It would be interesting and important to run the analysis stratifying by those having high aerobic fitness and those with low aerobic fitness, since fitness is going to have an important impact on resting heart rate and also the metabolic factors. OR at the very least control for fitness in the analysis.
   *Answer:* The inclusion of the cardiorespiratory fitness as confounder had significant burden in the multivariable models, which became non-significant. As suggested, these additional analyses were performed, but no significant finding was found.

Discussion
9. 2nd paragraph: in the statistical analysis section there was no mention of adjusting for obesity, but it is mentioned here. Which is correct?
   *Answer:* Obesity adjusted only linear regression (Table 1) and not binary logistic regression.

    *Answer:* Thank you for the suggestion. The reference suggested was included in the Discussion section.

Tables/Figures
11. It would be very helpful to have a table describing the sample. Mean age, lipid values, glucose, %BF, etc.
    *Answer:* According to suggestion, a table with general characteristics of the sample stratified by RHR values was inserted.

12. Table 2: why was the linear regression not run for LCL and HLD?
    *Answer:* Linear regression analyses were performed only with independent variables significantly related to RHR in Pearson correlation.

13. Figure 1: the presentation of the AUC data is odd. Why not present the actual curves and give the sensitivity and specificity so the reader can determine what resting heart rate is idea to use as a cut-off value for screening purposes.
Another Reviewer solicited the exclusion of the Figure 1. However, in this new version of the manuscript all data are presented in a table.

Minor Essential Revisions

Background
14. Page 3 2nd paragraph: with the Freitas et al [11] study what direction is the relationship between RHR and lipid values?
   Answer: The direction of the relationship was inserted (positive).

15. The last sentence is awkward and unclear, this needs to be re-written.
   Answer: According to suggestion, the sentence was adjusted.

Methods
16. Page 7 statistical procedures & page 9 2nd paragraph in discussion: change wording of maturational status to pubertal stage.
   Answer: As suggested, this change was done.

Discussion
17. Page 9 1st paragraph: the 1st sentence is awkward, re-word.
   Answer: After changes in the Discussion section, the first paragraph was excluded.

18. Format for the references changed in the 2nd paragraph.
   Answer: We correctly formatted the reference.

19. Last paragraph: reference 7 was this study in adults or children?
   Answer: The reference 7 is related to adult population (the information was inserted at Discussion section).

Discretionary Revisions

Methods
20. Move potential confounders section to before statistical procedures
   Answer: As suggested, this change was done.

Results
21. Page 8 2nd paragraph r and p values not needed as all this information is in the table.
   Answer: As suggested, the r and p values were excluded.

Tables/Figures
22. Table 1 and 2 could be combined into 1 table
   Answer: Tables 1 and 2 (now tables 2 and 3, respectively) were not combined because both multivariable models are very different. For example, relationships between RHR and lipid variables are adjusted by three potential confounders (Table 3). While the multivariable model elaborated in Table 2 had the three potential confounder plus all independent variables significantly related to RHR.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interest
Reviewer's report

Title: Resting heart rate: Its correlations and potential for screening metabolic dysfunctions in youth

Version: 2 Date: 28 November 2012
Reviewer: Rima Chedid

Reviewer's report:

Major Compulsory Revisions:

1- In the abstract, 4th line, the authors talk about “screening metabolic dysfunction”. In the abstract last line “the development of dysfunctions” is used. These terms are too wide and encompass many diseases. Specially that in the objective of the study, Background section, the end of the second paragraph, the authors talk about “increased cardiovascular risk” The authors should narrow down the term “metabolic dysfunction” in order to be more specific.

Answer: According to suggestion, the text was adjusted and only the terms “dyslipidemia” and “high blood glucose” were used throughout the manuscript.

2- In the Background section, the end of the second paragraph is unclear “The above mentioned data is promising…..of RHR in these populations”. It should be reformulated again, as this is the key sentence in the objective of your study. Did you mean:

“The above mentioned data is in favor of the use of RHR as an index in screening pediatric population for increased cardiovascular risk. However, since pediatric populations have not been thoroughly studied in epidemiology, the determinants of RHR in children need to be more clarified”?

Answer: As suggested, the second paragraph of the Background was changed.

3- In the Methods section, Sample paragraph, the authors mention a high human development index in South Brazil and state a figure. Indicate in the reference section where you took this figure from.

Answer: The citation was inserted.

The sentence “The minimum sample size was estimated using an equation for correlation coefficients, adopting a power of 80% and alpha error of 5% (Z=1.96).” is unclear. Try to explain it or cite a reference.

The sentence “Among obese youth, Freitas Junior et al. [11] identified that RHR was significantly related to triglycerides (r= 0.21; p= 0.004) and total cholesterol (r= 0.18; p= 0.011).” is not relevant here. Move it to the Discussion section where you discuss the significance of triglycerides and TC values in your study population.

Answer: As suggested, the changes were performed.

4- In the Methods section, there are too many details on how you proceeded with your sample size. Try to summarize it in a couple of lines.

Answer: According to suggestion, the text was adjusted.

5- In the Methods section, the Independent variables paragraph, did the authors also compute the coffee intake, as well as cola and energy drinks as these also affect RHR? If not, specify it in the limitations to your study, Discussion section.

Answer: As suggested, this limitation was inserted in the Discussion section.

The Peak Height Velocity ideal age of prediction works best between 9 and 13
for girls and 12 to 16 for boys, whereas your population age ranges from 11 to 17. This should be mentioned in the limitations to your study as the Pubertal Stage, which is directly derived from this value, is used as a potential confounder in the multivariate models.

**Answer:** According to suggestion, this information was inserted as limitation of the study.

6- In the Methods section, Resting Heart Rate paragraph, explain more about the 2 types of cut offs which were used according to the arm circumference. State figures or cite a reference as RHR is the key word and issue of your manuscript.

**Answer:** The word “cutoffs” was replaced by “cuffs”. Additional information about arm circumference measures was inserted.

7- In the Discussion section, 4th paragraph, the authors state that “Adolescents are prone to perform many activities at night (TV viewing and computer usage) and thus they are more exposed to shorter periods of sleep.” As compared to whom? Do they mean that they are more exposed than children?

**Answer:** The adolescents were compared to children.

8- In the Discussion section, 4th paragraph, the authors talk about pro-inflammatory agents which increase in people with short sleep periods. Did you measure any of these agents in adolescents affected with short sleep pattern in your sample population?

**Answer:** Unfortunately, there were not measures of inflammatory agents in our sample. The absence of these data was indicated in the text as a limitation of this study, because are relevant in the process.

9- In the Discussion section, last paragraph, the authors admit that there are not widely recognized RHR cut offs values. It will be interesting to establish their own RHR cut offs from their study population. It can be easily done first because the sample size has been carefully selected and is large enough, and second because they already plotted the ROC analysis curves. The article will be richer and more attractive.

**Answer:** As suggested, a new table was inserted with this data.

10- In the Discussion section, last paragraph, the authors recommend to measure adipokines and insulin resistance in future investigations. This could be easily done on the same population if some serum stored at -80 degrees is left.

**Answer:** Unfortunately, this will not be possible today. The absence of these data was indicated in the text as a limitation of this study, because are relevant in the process.

11- In the Discussion section, last paragraph, last sentence, be more specific and explain what do you mean by “low magnitude”: as compared to what? Moreover, state the other putative variables that might interfere in the outcome.

**Answer:** Low magnitude compared to the maximum value of the coefficient (a reference was inserted). Moreover, other variables were cited.

Minor Essential Revisions:

1- In the Abstract, the Objective section, use the word “impact” instead of
“potential”. In the Results of the Abstract, add the word “curve” after “The receiver operating characteristic”.

Answer: As suggested, these changes were done.

2- In the Methods section, statistical procedures, the 4th sentence is unclear. Do you mean: “Gender, age and maturational status were adjusted for in both multivariate models”?

Answer: The phrase was rewritten: “Gender, age and pubertal stage adjusted both multivariable models (linear regression and binary logistic regression)”. All models were adjusted simultaneously by these three variables.

3- In the Methods section, the blood sample paragraph, use the word “measured” instead of “evaluated” when you talk about the biochemical parameters.

Answer: As suggested, the change was done.

4- In the Results section, first paragraph, first line, be careful with the word Youth that admits no plural and generally refers to young men.

Answer: As suggested, the word “youth” was excluded of the manuscript when referring children and adolescents.

5- In the Discussion section, 3rd paragraph, “in an intervention protocol of eight months […] with obese children”, are the words “physical training” missing here?

In the same paragraph, “The positive effect of sports practice in RHR was mediated by cardiorespiratory fitness”, it is better to replace the verb “mediated” by “estimated”.

Answer: As suggested, the changes were done.

6- In the Discussion section, 4th paragraph, “as a stressor in the acute and chronic setting”, the word setting is unclear.

Answer: The word “setting” was excluded and the phrase rewritten.

7- In the Conclusion section, replace “the development of RHR cutoffs” by “further studies of RHR cutoffs.”

Answer: According to suggestion, the phrase was adjusted.

8- In Tables 1 and 2, add at the end of both charts the sentence: “Statistical significance was set as p#0.05”. In Table 1, the footnote VO2=maximum oxygen uptake is not necessary as it is not mentioned as a variable in the Table. In Table 3, draw physical lines between every series of RHR. The Table will look more reader friendly. Mention why you used bold font as you did in the Results section (“highest quartile was associated with increased values of glucose and decreased values of HDL-C.”).

Answer: As suggested, the footnotes in Tables 1 and 2 (now Tables 2 and 3) were inserted. The Table 3 (now Table 4) was changed. Bold fonts were excluded.

9- In Figure 1 legend, write: Impact of Resting Heart Rate in screening metabolic variables…… State what the abbreviation AUC±95%CI stand for and what the reference line you drew indicate. Mention the reference figures next to
the legend of this chart listed in the Blood Sample, Methods section. Does the small vertical lines indicate the Standard Deviation? Mention it.

*Answer:* Figure 1 was excluded and all data suggested were inserted in the Table 5.

Discretionary Revisions:
1- In the Discussion section, second paragraph, the authors use the sign “to the” when indicating the references 10 and 20.

*Answer:* As suggested, the change was done.

2- I noticed some punctuation errors such as extra or missing commas. The manuscript should be carefully edited in this regard.

*Answer:* As suggested, we correctly formatted the manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests.

**Quality of written English:** Needs some language corrections before being published.

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
'I declare that I have no competing interests'
Reviewer's report
Title: Resting heart rate: Its correlations and potential for screening metabolic dysfunctions in youth
Version: 2 Date: 10 December 2012
Reviewer: Yiannis Koutedakis
Reviewer's report:
Major Compulsory Revisions

General comments
A well written manuscript which covers a relatively under-researched area. Of concern the statistical findings. Authors should discuss the clinical (or otherwise) significance of their low, yet significant, correlation coefficients; for instance, what do we learn from an $r=0.07$? Appreciate that authors have included this issue in the “limitations” section, but more is needed as these coefficients constitute the basis of the manuscript.

Answer: We’d like to thank the referees for their suggestions that surely improved our manuscript a lot. As suggested, more information was inserted about the issue.

The role of fitness in CHD development should also be briefly discussed using published information (e.g., Bouziotas et al, *Ped. Exerc. Sci.*, 13: 173-184, 2001; Boreham et al, *Med Sci Sports Exerc.*, 33:270-74, 2001) and making the link between CHD, fitness and RHR clearly visible. Perhaps the current findings are just the effects of physical activity / fitness differences.

Answer: The article of Boreham et al. (2001) was inserted as reference in the Discussion section. Moreover, the effect of the cardiorespiratory fitness was better discussed.

The term tachycardia may not be an alternative to RHR; at which point RHR becomes tachycardia?

Answer: The Reviewer is right and, therefore, the word “tachycardia” was excluded of the manuscript.

Specific comments
Abstract
….. identify its correlation ..... to “….. identify its significance ....”

Answer: This change was done.

Conclusions not exactly supported by findings; problematic use of terms?

Answer: The conclusion was changed.

Background
p.3, line 2:: replace “cheap” with “inexpensive”

Answer: This change was done.

p.5 (independent variables): Using the approach which increases the efficacy of multistage 20-meter shuttle run test (Flouris et al, *Br. J. Sports Med.*, 393: 166-170, 2005), might strengthen current findings;

Answer: The cardiorespiratory fitness was estimated using the above mentioned reference. However, the results were not changed and, therefore, the current references were maintained.
p.6 (Blood samples): I do not think that the youths of this study were actually “patients”...

Answer: This change was done. The term “patients” was replaced by “adolescents”.

p.7 (Statistical procedures): “Pearson correlation analyzed ....” should read “Pearson correlation assessed/indicated ...”, and also “Chi-square analyzed ...” should change to “Chi-square assessed/indicated ....”

Answer: These changes were done.

p.9 (Discussion): a sloppy start of discussion; rephrase

Answer: This paragraph was excluded of the discussion.

p.9: “cardiorespiratory fitness” is not synonymous to “physical fitness” (the latter incorporates “cardiorespiratory fitness”)

Answer: The term cardiorespiratory fitness was adopted throughout the manuscript.

p.12 (Conclusions): “In summary, our findings indicate ....” should read “The present data indicate ....”

Answer: This modification was done.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests