Author's response to reviews

Title: Cardiorespiratory fitness and the incidence of type 2 diabetes: a cohort study of Japanese male athletes

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Author's response to reviews: see over
Dear Dr. Pafitis,

Re: Manuscript reference No. 6031906101220558

Please find attached a revised version of our manuscript “Cardiorespiratory fitness and the incidence of type 2 diabetes: a cohort study of Japanese male athletes”, which we would like to resubmit for publication as a Research Article in *BMC Public Health*.

Your comments and those of the reviewers were very insightful and enabled us to improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using yellow highlight for additions, and strikethrough font for deletions. In accordance with Reviewer 2’s suggestion, we observed Reviewer 1’s suggestion about cardiorespiratory fitness and Reviewer 3’s suggestion about “current” covariates in statistical analysis in this letter.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *BMC Public Health*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comment of Reviewer #1

1. The authors talk of cardiorespiratory fitness; however, they make no attempt to define peak oxygen uptake and define it based on time for the 1500m run. This is problematic and they definitely should try to define it in terms of ml/kg/min especially since they have body weight and they can derive running speed.

Response: We attempted to define peak oxygen uptake (mg/kg/min) from the time of the 1,500-meter endurance run by using a calculation equation [Lacour JR et al., Assessment of running velocity at maximal oxygen uptake. *Eur J Appl Physiol Occup Physiol*. 1991; 62(2):77-82.] and body weight. However, the highest estimated $\dot{V}O_{2\text{max}}$ was 107.6 mg/kg/min, which was higher than the world record (94 mg/kg/min). This calculation equation was demonstrated with runners from regional to international levels. We thought this calculation equation overestimated $\dot{V}O_{2\text{max}}$ for the subjects of this study and for people who are not international-level athletes. Therefore there is a need to use other equations for subjects with a wider range of fitness levels. We also attempted to define it by using other calculation equations [Berthon P et al., A 5-min running field test as a measurement of maximal aerobic velocity. *Eur J Appl Physiol Occup Physiol*. 1997; 75(3):233-8.]. However, we thought that this calculation equation also overestimated $\dot{V}O_{2\text{max}}$ (highest estimated $\dot{V}O_{2\text{max}}$ was 102.6 mg/kg/min). Berthon et al. also reported the need to validate these findings on greater number of subjects as there were only 48 volunteers in their study. Therefore, we did not use either of these calculation equations because we decided that they needed to have clearer validity for a Japanese population.

However, it was demonstrated that between the 1,500-m endurance run time and maximal oxygen consumption or maximal oxygen uptake there was an inverse relationship, which is mentioned in our section on limitations. Therefore, we used the time of the 1,500-m endurance as an index of cardiorespiratory fitness in the present study.

2. Methods are poorly described. The authors need to do a better job of describing the flow chart in fig 1.

Response: We amended the flow chart in Figure 1 and added a more detailed description in the Methods (last sentence, Methods, Subjects).
Responses to the comment of Reviewer #2

1. Title: Authors should remove "long" (throughout the paper). In general, we don't use "long" or "short" in relation to a cohort study. This study is small rather than long.
Response: We removed “long” cohort in the title and throughout the text.

2. Abstract- Methods: Authors should provide the median of the follow-up period or the observed man-years.
Response: We mentioned the median of the follow-up period in the Results subsection of the Abstract (2nd sentence, Results subsection, Abstract:).

3. Abstract- Results: Authors should remove "lifestyle". There are few lifestyle covariates in their models.
Response: We changed “lifestyle” to “age, year of graduation, BMI, smoking, and college sports club participation”, which are the covariates in this study.


5. Result: Authors should provide the median of follow-up period.
Response: We mentioned the median of the follow-up period in the Results (1st sentence, paragraph 1, Results section).

6. Discussion- Paragraph 2: I suggest changing "incidence" to "prevalence". Because these studies are cross-sectional.
Response: We changed “incidence” to “prevalence” in paragraph 2 of the Discussion.

7. Discussion- Paragraph 6: Authors should describe the "maximal oxygen consumption" instead of "Vo2max".
Response: We replaced “Vo_{2max}” with “maximal oxygen consumption” and used reference [16] to describe the correlation of maximal oxygen consumption and field tests.
8. Discussion- Paragraph 6: Authors should discuss the possibility of "recall bias" in the study limitations.
Response: We mention “recall bias” in the limitations (Last two sentences, paragraph 6, Discussion).

9. Conclusions: Delete the space before "age".
Response: We deleted the space before “age” in the Conclusions section.
Responses to the comments of Reviewer #3

1. Please use “long-term” or “longitudinal” instead of using “long” cohort.
Response: We removed “long” in the title and throughout the text.

2. English grammar problems in this manuscript:
   · Verb tense: Many sentences should be used with simple past rather than present perfect tense (e.g., in page 4 (2nd last sentence) “investigated” rather than “have investigated” and many other places in the manuscript). Some confused in using active vs. passive voice (e.g., in discussion part- “showed” rather than “were shown” in “In particular, former male endurance athletes, ----, were shown to have a low incidence of type 2 diabetes”)
   · Preposition (“in” rather “at” 2007) and subject - verb agreements (singular or plural form).
   · Unclear writing in many compound sentences led to hard to read
Response: We apologize for these errors. We have had the manuscript edited by a professional language editing service.

3. Would be useful to have figure legends and table footnotes in more details
Response: We added more detailed figure legends and table footnotes.

4. Covariates at “current” study should be adjusted
Response: We understood that current variables from college-age BMI and smoking habits were important risk factors of diabetes according to Reviewer 3. However, we obtained these data from follow-up questionnaires, and they were cross-sectional data. Therefore, we could not get reliable data for the cause and effect relationship between current BMI, smoking habits and diabetes, because the incidence of disease and a doctor’s advice after diagnosing a disease are very likely to have an effect on present body weight and smoking habit. Therefore, we did not include these data among the covariates.

5. Abstract: Abstract didn’t prepare well, especially in methods and result section— more details would be useful. The last sentence of the abstract is unclear and should include 95% confidence intervals of hazard ratio.
Response: We substantially revised the manuscript, with particular focus on the Abstract, Methods, Results and Conclusion.
6. Introduction: Are you sure--- athletes in Japan were genetically selected group? Howto? It’s not clear to me (last paragraph of the introduction; p5)
Response: We have revised this to “top athletes are a biologically selected group given particular training”, and removed “genetically” to avoid ambiguity.

7. Introduction: About cross-sectional studies in Caucasian populations, please provide references, especially these studies reported a conflict finding that led you to this study.
Response: We revised this to say that “in these studies, top athletes were grouped according to the type of sports they played rather than according to measured data of their cardiorespiratory fitness levels. As these studies have been carried out only in Caucasian populations, it was not clear whether a higher level of cardiorespiratory fitness at a young age can prevent the incidence of type 2 diabetes in Asian athletes, who are generally not overweight.

8. Methods- Subject: Figure 1 is good. However, the text should summarize inclusion criteria clearly that would be useful. Describing cohort is also useful if this cohort has not been described previously.
Response: We added descriptions of the cohort and the selection of subjects.

9. Cardiorespiratory fitness test: ok for details but not necessary unless you want to compare different types. Would be useful if you provide how many years alumni had been taking the CR fitness test annually.
Response: We deleted the details of the cardiorespiratory fitness test, and describe the data used (Cardiorespiratory fitness test, Methods). Alumni participated in cardiorespiratory fitness tests annually during college (4 years). However, not every alumnus participated every year. We used the data from the last participation in the test.

10. “These records were stored by the University since 1971”. How were the data before 1971 treated?
Response: The university only carried out and stored the cardiorespiratory fitness tests after 1971. In the present study, we included alumni for subjects who answered the questionnaire (the alumni who received questionnaires graduated between 1956 and 1991), and who had cardiorespiratory fitness data (the alumni who graduated after 1971). Therefore, the subjects of this study were selected male alumni who graduated between 1971 and 1991.
11. It's helpful if information of “3539 male alumni……. between 1956 and 1991….”) from the Investigation of diabetes prevalence to subject selection because this information is good there and didn’t seat well here.
Response: We removed reference to the investigation of diabetes prevalence among subjects, and revised the information about the subjects themselves.

12. “smoking habits” was defined yes/no at time of college is not enough –
Suggestion: asking smoking habit from the time of college to current and stratifying as “none”, “smoker” or “ex-smoker”
Response: We could not use the variation in smoking habits from the time of college to the present because of response 4. Furthermore, we did not have more detailed data of smoking habits at college age.

13-1. Statistical analysis: Figure 1. Alumni who “received “(not “mailed”) follow-up questionnaire.
Response: We have changed this to “were mailed”.

13-2. Statistical analysis: got confused – “duration of follow-up was counted from the year of graduation (1975-1991) until…..” where as you abovementioned that male alumni who graduated between 1956 and 1991. Less getting confused and easier to follow if you focus on your selected sample of 570 male alumni, and other related information can be explained in few sentences describing cohort instead of mentioning these data in several places. Alternative, cohort characteristics may be included in figure legend of figure 1.
Response: The graduation year was incorrect (it should have been 1971–1991 rather than 1975–1991). In this study subjects were male alumni who graduated between 1971 and 1991. The details are explained in reference to response 10. We described the study subjects in the Methods and the legend of Figure 1.

13-3. Statistical analysis: Statistical test used is acceptable. However, as mentioned earlier, “current” covariates should be taken into account.
Response: We could not use “current” covariates for the reasons cited in response 4.

14-1. Results: 3rd sentence of results: median age of subjects at BASELINE was 23 years and what was their median (IQR) age at time of study?
Response: The median age at time of follow-up questionnaire was 49 years (IQR: 45–52 year). We wrote the age at the time of the follow-up questionnaire in the text of the Results section.

14-2. Results: Would be smoother if having one sentence to define baseline (e.g., baseline was defined as ….)
Response: We removed “at baseline”, and integrated the phrase “at the time of college” to avoid confusion.

14-3. “current” variables such as BMI, age, smoking habit are stronger factors impacting on developing type 2 diabetes. Please consider adjusting them in your multivariate models. Table 1 indicated they were all healthy with BMI of 22.1 (21.1-23), but may be different if having “current” variables time of study.
Response: Adjustments were all at the time of college as mentioned earlier for the reasons cited in response 4. For age at the time of the follow-up questionnaire, we adjusted for graduation year instead of age.

14-4. Again, smoking variable is not clear
Response: We could not use the “current” smoking variable for the reasons indicated in responses 4 and 12.

14-5. Table 1 should be kept consistent format as table 2 & 3 & should be added “current” characteristics that may be associated with diabetic risks, such as age and BMI, etc.
Response: We made the format consistent in all tables. “Current” characteristics, except for age, could not be used in this study for the reasons cited in response 4.

14-6. Table 2 should be included univariate and multivariate Cox models as well as indicate what covariates were included in the models in table footnotes. Table 2 showed not significant finding because of data from “young and healthy” people. Again, would be useful to have “current” data taken into account.
Response: We added the covariates in table footnotes. We thought that subjects in this study were young and healthy at college age, and needed to demonstrate variations in their lifestyle that would affect the incidence of diabetes. However in this study, “current” characteristics except for age were not used for the reasons indicated in response 4.
14-7. Adjust for age and BMI at what time-- time of college or study?
Response: We adjusted for age and BMI at college age for the reasons noted in response 4.

15. Discussion: overall is good. However, limitation of female didn’t mention.
Response: We mentioned the lack of females as subjects and indicated it as a limitation (7th sentence, paragraph 6, Discussion).