Author's response to reviews

Title: Atrial fibrillation and cycling. Six year follow-up of the Taupo Bicycle Study

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Author's response to reviews:

Dear Editor

Thank you for the opportunity to revise and improve the paper.

We have listed below the comments from the reviewers, followed by an explanation of the changes we have made, or the reasons we provide for not making changes.

Consent

“Informed consent must be documented. If you considered participation in the survey to constitute implied consent, please state this clearly. Alternatively, if the questionnaire included a question regarding consent, please state this clearly. Please also update your manuscript to indicate whether parental consent was obtained for study participants under 18 years of age. If the ethics committee did not require parental consent for this age group, please state this clearly.”

We have added text (see highlighted section below) in the methods section to make clear that we explicitly sought consent (it was not assumed) and that the ethics committee did not require parental consent for individuals aged 16 years and over.

Briefly, we sent email invitations, containing a hyperlink to the study information page, to 5653 entrants who provided their email addresses at registration for the event. At the bottom of the page, entrants could click a button agreeing to take part in the study. (The ethics committee did not require parental approval for those aged 16 years and over.) Those who agreed to take part filled in a web questionnaire that included....

Reviewer 1 – Brian Olshansky

1. “The participation rate was 43% of the group. It is unclear if this is a representative cohort of the entire cycling.”
We have added the following paragraph to the Discussion.

We do not claim that the study sample is representative of all who participated in the Taupo event nor of all New Zealand cyclists in general. What is material to this paper is whether the relation between the exposure (amount of cycling) and risk of AF is different in the study group than amongst the wider group of cyclists. We see no reason why this should be the case.

2. “It is unclear how much exercise the national population in the same area accomplishes. There is no real mention of this here.”

We have added a sentence that describes the frequency of physical activity in the adult New Zealand population.

Amongst participants in the Taupo Cycle Challenge study, the rate of first hospital admission for AF was almost identical to that for the adult New Zealand population at large, amongst whom about 50% do not meet the physical activity guideline of “at least 30 minutes of moderate-intensity physical activity on most if not all days of the week” [SPARC, 2008]

3. “These data do not prove that cycling was not associated with atrial fibrillation. This these to be clarified in the manuscript. All it shows is that for these individuals who participated, there is no increased risk for atrial fibrillation hospitalization. However, it is important to recognize that atrial fibrillation can be asymptomatic”

We accept this point. We have noted already that AF may be asymptomatic (page 11, line 3), but have altered the abstract and the conclusion to make it clearer that the outcome in this analysis is admission to hospital not incident cases of AF.

On the basis of the data to hand we conclude the level of physical activity undertaken by this cohort of cyclists did not, on average, influence hospital admissions for AF.

4. “It is also unclear for both groups how many have atrial fibrillation and are either symptomatic or asymptomatic but do not recognize that they have atrial fibrillation. Therefore, the authors have not proven by any means that cycling at this level does not cause atrial fibrillation.”

We agree we have not “proven” this proposition, but hold that it is a reasonable conclusion. We have already acknowledged in the paper that some occurrences of AF do not lead to hospital admission: “we cannot determine from this the study the absolute incidence of AF” (page 11, line 5). But we go on to point out (lines 8 to 18) that the important issue here is whether under-estimation varies between the Taupo participants and the population at large, or within the Taupo group, whether under-estimation is related to amount cycled. We speculate that ascertainment may or may not be more complete in a better educated group (depending on use of private practice for instance). But we see no reason why ascertainment should be biased by physical activity.
5. “this manuscript adds to the literature in the sense that this level of activity does not appear to be particularly associated with atrial fibrillation. That does not mean that more intense endurance activity would not be associated with atrial fibrillation. These caveats need to be in the manuscript.”

We agree with the need for such a caveat, but think the point is already made in the introduction, where we say “while it does appear there is a relationship between occurrence of AF and elite endurance athletic training, the relationship between more modest athletic training and AF is less certain” (page 5, lines 5-7).

Reviewer 2 – Norman Sharpe

1. “the authors have realized the excellent opportunity provided by a large scale cycling event to link survey questionnaire data from a sample of participants with hospital discharge data related to atrial fibrillation”

Thank you

2. “The followup period was relatively short however and it remains plausible that AR might be increased either with longer duration of exposure …and/or more prolonged followup”

We agree it is plausible that an effect may become apparent in the future, and intend to extend the period of followup, as indicated in the paper (conclusion line 11).

Reviewer 3 – Dag Steinar Thelle

1. The reviewer points out relevant publications that we have not cited. We have added the one we think is most apt (Thelle et al, 2013) as well as Drca et al (2014) which was published after we submitted our paper. (see below)

2. “Little emphasis has been put on the heterogeneous nature of atrial fibrillation as an end-point, and the influence of confounding variables”

We have added a sentence in the section of study limitations, to acknowledge the point about the different forms of AF, and only a fraction of all cases being sensitive to strenuous physical activity (though this fraction may be large in a relatively young population such as the Taupo cohort with little co-morbidity).

The study reports hospital admissions for all occurrences of AF, which is a heterogeneous group of conditions, and it has been proposed that some sub-types are particularly sensitive to levels of physical activity (Thelle et al, 2013). Moreover it is unlikely the data presented here capture all occurrences of AF…

In our analysis we have controlled for age, gender and height, which we think are the major confounding variables in this context.

3. “the lack of association … may be due to misclassification (all atrial fibrillation
cases are included, disregarding underlying other causes) and thereby low power”

We agree this is possible, and acknowledge in the conclusion the importance of continuing followup to accumulate more cases.

4. “the authors are recommended to use the STROBE statements”

We thank the reviewer for reminding us of this resource. We have checked our paper against the STROBE checklist of 22 items that should be included in reports of cohort studies. Item 13 (recruitment of participants) is not described in full in this paper, because the detail is provided in earlier papers (references 11 and 12). Item 14b – we have not shown the number of participants with missing data for each variable because of space constraints. These numbers are small: overall, 95% of participants have complete data. Item 16c – we have not translated relative risk estimates into absolute risk quantities (we judged it was not necessary in this situation). Otherwise all items on the STROBE list are included.

Reviewer 4. Luis Mont

1. “they found no association at variance of the majority of published studies”

We accept the findings of the literature are mixed. For instance, the very good paper by Drca et al (2014), cited by the reviewer, published since our paper was submitted, and discussed in the revised version (see below), found a positive association with AF of leisure time walking and cycling at age 30, but not at ages 15 or 50. The same study found a protective effect of walking and cycling more than an hour a day at older ages (which fits with our findings, although the estimate in our case was imprecise). We suspect there may be competing forces acting here – heavy activity at a young age may provide the substrate for arrhythmias that appear later in life (possibly via atrial remodelling and micro-fibrotic changes), while strenuous activity in older years may have a net protective effect, via other pathways (such as lowering blood pressure). We have added the following sentences to the discussion, accordingly.

How to reconcile the mixed results reported in the literature? We propose there may be competing forces on the incidence of AF. Heavy activity at a young age may provide the substrate for arrhythmias that appear later in life (possibly via atrial remodelling, increased autonomic tone and micro-fibrotic changes in the atrial wall), while vigorous activity in older years may tend to reduce occurrence of arrhythmias via other pathways (such as lowering blood pressure). In a large cohort of Swedish men Drca et al (2014) found a positive association with AF of leisure time walking and cycling at age 30, but not at ages 15 or 50. The same study found a protective effect of walking and cycling more than an hour a day at older ages.

2. “I think the most probable explanation for the findings is an unwanted and undetected selection bias”
Please note our response to reviewer 1, points 1 and 4. It is possible that the relation between physical activity and the occurrence of AF differs between our study sample and the population at large, but we think this is unlikely. We can think of no explanation for such a differential effect. Differences between participants and non-participants in terms of social class or education would be important if we were studying the characteristics of cyclists, but are not so relevant to an investigation of relationships between particular exposures (such as level of physical activity) and disease outcomes.

3. “there are many more studies supporting the positive association of endurance training and AF and flutter and the discordant results of the present work should be interpreted with caution”

We agree the results should be interpreted with caution, and hope the revised draft makes this clear. We have added text (as outlined above in our response to point 1), and included additional references.

4. “the authors should rephrase the title”

We accept the title may be too colloquial, and have amended it to
Atrial fibrillation and cycling. Six year follow-up of the Taupo Bicycle Study

5. “the introduction is too long”

We agree that shorter is better, as long as important detail is not excluded. In this case, the reviewers mostly thought there should be a fuller description of the literature, so we have not made cuts.

6. “page 3, line 2, most of the papers in the metanalisis are case-control studies and the incidence of AF does not refer to the general population but to controls”

We note that different approaches to control selection were adopted in the studies included in this meta-analysis, but the intent in each case was to sample the range of exposures in the general population from which the cases arose. We have amended the text to read

One systematic review and meta-analysis estimated the risk of AF in athletes was more than 5 times that in the general population.[5]

Yours sincerely

Alistair Woodward (on behalf of the authors)