Author’s response to reviews

Title: A cross-sectional and 6-year follow-up study of associations between leisure time physical activity and vertebral fracture in adults

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Author’s response to reviews:

We thank the reviewers for very thorough and helpful comments. We have made our best efforts to address the comments and we believe that the revisions have improved the manuscript. We hope that marking of the changes is not confusing, as we have used two methods. Changes to the content of the manuscript are marked with yellow. Track changes were used when improving the text flow and paragraphs.

Editor Comments:

Firstly, I wish to profusely apologise for the delay in getting a decision to you. I have now fast-tracked this submission for any future correspondences and/or revisions. Having discussed this manuscript with one Section Editor, we believe that it is essential that you verify that fractures only happened after baseline. You should address this in your cover letter to the Editor.

As well as that, please see to you Section Editor's report:

"The authors present an interesting paper, which describes the cross-sectional and longitudinal associations between leisure-time physical activity and vertebral fractures. Overall, the authors found statistically null results; however, the confidence intervals around the odds ratios are large because of the small number of fractures among some of the groups (n = 12 to 15). The null findings are also hard to interpret because of the use of a single-item assessment of self-reported physical activity and it being unclear if baseline fractures could be ruled out (these concerns are appropriately acknowledged in the Discussion).
Methods, Design & Subjects (last line): Please clarify when the sub-cohort was >=50 years of age (2001 or 2007-2008)

In 2007-2008. This is now added to manuscript.

Assessment of physical activity: Please provide evidence for the validity of the physical activity questions (besides the first question, which was validated by Emaus). If the other questions have not been validated then it may be prudent to remove them from the paper.

The other questions regarding frequency, intensity and duration are validated in another Norwegian population based study (the HUNT study). We have added this to manuscript.

Ascertainment of vertebral fractures: The prospective study is limited by the lack of imaging at the 2001 visit. Please clarify if the VFA method can distinguish more recent incident fractures from older fractures that were prevalent prior to 2001.

No, unfortunately it is not possible to distinguish the fractures prevalent prior to 2001 from the 2007-2008 survey DXA-scans with VFA. We have added this to discussion under limitations in addition to what we had stated earlier.

Statistical analyses: The cross-sectional and longitudinal analyses are important but don't clarify if the PA change antedated the fractures. Hence, one concern is that some people changed PA levels because of the fracture. It may be beneficial to test whether 2001 PA is associated with fractures at 2007-2008. Note, this analysis is unnecessary if it is impossible to rule out fractures prior to 2001.

As the reviewers point out, it is impossible to rule out fractures prior to 2001 since we only have DXA-scans from the 2007-2008 survey. Some participants might have changed their PA levels due to fracture, but unfortunately we do not know the date/timeline of the VF. We have now added this important point to our manuscript.

Table 4 & 5: Please clarify the frequency of vertebral fracture in each category (e.g., PA duration's 3 levels)"

Number of vertebral fracture in each category is added to the table 4 and 5 in the manuscript.
Reviewer reports:

Gustavo Almeida (Reviewer 1): Dear authors,

The manuscript reports on an important topic identifying the associations between leisure time physical activity and vertebral fracture in adults. However, it is somehow difficult to follow the message you are trying to convey.

This reviewer suggests that you seek assistance from a professional scientific writer to help out with the flow of the text and clarify some paragraphs. Furthermore, the discussion section needs more work. The discussion would benefit tremendously if you elaborate on reasons that may have led to your findings. For example, what are your thoughts in regards to the lowest prevalence of fractures being present in men's sedentary group? Don't you think that this finding is counterintuitive? Do sedentary men have less fractures because they do not move around and, therefore, are not exposed to possible injuries?

We thank the reviewer for insightful advice. Regarding the clarity of the manuscript, one of our authors has published close to 100 scientific articles/other scientific publications in English since 2000. Also, our other authors have published dozens of scientific articles in English and have taught scientific writing at the university level. With their expertise in scientific writing, we have tried to make the manuscript as clear as we possibly can. We also extended the discussion section.

Please see my point-by-point comments below:

ABSTRACT

PG 2, line 27: should read: prospective follow-up data (2001 to 2007)

We have added “to 2007”.

PG 2, line 30 and 34: please spell out DXA and BMD

DXA (line 31) and BMD are now spelled out.
INTRODUCTION

PG 3, line 54: It is not clear what increase the risk of future fractures? "This" what?

Our apologies, we have now clarified the sentences as follows: "Moreover, having a vertebral fracture increases the risk of new fractures...."

PG 4, line 68: the burden? You mean, economic burden? Please clarify.

Starting from the individual burden (reduced quality of life etc.) and continuing to the economical burden for the society, the burden refers to both, the overall burden of the vertebral fractures. By preventing the individual burden, will also the economic burden be reduced. We had added the word overall in the sentence now.

METHODS


Typo has been revised.

PG 9, lines 182-183: please describe/clarify what phantom measurements are.

All DXA scanners provide phantoms for system testing and calibration. Our manufacturer currently provides a QA (quality assurance) block made up of a material with a specific density and a spine phantom. The phantoms are used to ensure the reliability of the DXA measurements between and within patients. The QA block is used ("measured") every day to ensure optimal calibration and reduce error margin of the measurements. Unfortunately, the spine phantom was not available in the 2007-08 examination.

This is now revised in the manuscript.

RESULTS

PG 12, line 240-243: were the results on highest and lowest statistically significant? please state.

Significance was not tested on characteristics. We are only stating in the manuscript what we can observe of the characteristics table.
The statement "similar prevalence in all physical activity groups in women" is not true. According to Table 2, prevalence was only similar for sedentary and highly active. Please revise.

As prevalence is often expressed by percentage, we have done it as well. The sedentary and the highly active groups have less women (smaller n) that the moderate active group, so that number of vertebral fracture is higher on the moderate active group. But if we take the total number into consideration and look at the percentage, all groups have similar (not exactly the same) prevalence (9.9-9.4-9.9%)

**PG 12, Table 2:** How about performing a test statistic to compare subgroups (i.e., sed, mod active and highly active)?

Whether to test the significance of differences between groups regarding participant characteristics is a matter of choice. As our research question (to examine associations between leisure time physical activity and vertebral fracture) would not be answered by such significance testing, and we did not have any hypotheses on baseline characteristics, we chose not to test the significance in table 2. We are however prepared to do that if the reviewers find that this will add to the overall message of the study.

**PG 13, line 254:** "two years younger than moderately and highly active subjects" - was this statistically significant? Please state.

Please refer to the above answer. We are only stating in the manuscript what we can observe of the characteristics table.

**PG 13, Table 3:** How about performing a test statistic to compare subgroups (i.e., sed, mod active and highly active)?

Please refer to the above answer on table 2.

**PG 14, line 262:** Results on Fig 1 need a better description: were those changes statistically significant? if yes, it needs to be stated.

Please refer to the above answer on table 2.
Did women change more than men? What happened to 6.3% of the women and 8.1% of the men that were left out of the changes in physical activity? The sum of the percentages does not add up to 100%... why?

We understand the confusion and have revised as follows: The proportion of women who remained physically active was 63.8% and 6.3% remained sedentary, whereas 14.3% of the women reduced and 15.6% increased their activity levels. In men, 51.9% remained physically active and 8.1% remained sedentary, while 18.6% reduced and 21.4% increased their physical activity level.

DISCUSSION

PG 17, line 304: the statement "even fewer longitudinal studies" should be revised. It appears to me that there is a good amount of longitudinal studies, which surpasses the number of cross-sectional studies cited in the discussion...

The statement “and even fewer longitudinal studies” is removed from the manuscript.

PG 18, line 310-312: How about discussing the results on women in the "moderately/ high intensity" group being less likely to have a vertebral fracture as compared with women in the "low intensity group". Isn't that important to highlight? Clinically relevant?

These results were only in the age-adjusted model so we didn’t think that it was important to highlight as the other analyzes (i.e. total level of PA) gave us no finding. This may or may not be clinically relevant, but in our opinion, highlighting it would be too speculative.

PG 18, line 321-326: So these are conflicting findings - with the study in Chinese stating that a more active occupation is associated to less fractures, while the study in Asian showing that a labor intense occupation, such as farmer, is associated with more fractures. I believe that is the main message that you have to put in perspective here and discuss about it.

This was briefly mentioned in the following sentences (line 326-328), but we have now added some discussion on this topic to our manuscript.

PG 19, line 328: larger than what? Than the previous studies or your study?
Our study since she was using the same 2007-2008 data as we are, only a larger cohort as Waterloo et al. was focusing on other issues. We have now clarified this in our manuscript.

PG 19, line 330: what were the results that support the present study?

Waterloo et al. studied independent risk factors (including high vs. low physical activity) for vertebral fracture and found that physical activity was not a risk factor. This is now explained in the manuscript.

PG 19, line 341: This is a very important topic for discussion. How would you elaborate on how these confounders played a role in the analysis clinically speaking?

The fact that the model was no longer significant after controlling for multiple confounders indicates that the relationship of physical activity intensity with reduced risk of vertebral fracture is complex and possibly mediated by other factors. Age, in particular, appears to mediate the relationship. As one may notice that when corrected for age (see age-adjusted model) the previously significant relationship of physical activity with risk of vertebral fractures was no longer significant. Ageing is indeed known to associate with decreasing physical activity levels, which (along other factors) might contribute explaining increased risk of risk of vertebral fracture in women. This has now been added to discussion.

PG 19, line 346-347: This info goes along with the Asian study in farmers. And why is that? What are your thoughts on why heavy physical activity would increase the risk for fractures?

We carry naturally lot of our weight on vertebra. Adding extensive amount of external weight by for example farm labor will add to that load and cause compression to vertebra and makes it to collapse. Traditionally we think that PA will make bones stronger, but the fracture mechanism on vertebra is often different from long bone i.e. compression leads to vertebral fracture without trauma.

PG 20, lines 364: A discussion on this surprising finding should be expanded. Why do the authors think that there was no association between physical activity and fractures in older subjects?
The participants were mainly older subjects in the main analysis as well. So, maybe the sub-analysis didn’t change the characteristics substantially. We have now added this to our manuscript.

Also, type of PA might pay a role in this. For example running and weight bearing PA is generally set as beneficial for bone health and preventing fractures, whereas cycling and swimming seem not to contribute as much for the osteogenic stimulus that is needed for improving bone health. This is discussed briefly under limitations and we have now added discussion on that section in the manuscript.

PG 20-21, line 372-373: how many years would be ideal? I believe that 6 years of follow-up from your study was fair enough.

We believe that we would have gained more information if the vertebral fracture data had been available for the 2001 survey. That way we would have known how many fractures occurred during the follow up time and who got the fractures. We have now removed the sentence "Additionally, the study might have benefited from a longer follow-up time”.

PG 21, line 385: why would those confounders be important? How would they have changed the results of your study?

Probably not, it was more matter of choice when it came to confounders. So, just to highlight other existing options. For example dietary factors like vitamin D and calcium intake are confounding factors for vertebral fracture, and dietary habits for physically active people may vary based on PA level. Fall at baseline affects PA habits and may cause fracture, and general health status can as well have impact on both, PA and VF development.