Author's response to reviews

Title: Low bone mineral density a significant risk factor for low-energy distal radius fractures in middle-aged and elderly men: A case-control study

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Author's response to reviews: see over
Dear Editor of BMC Musculoskeletal Disorders,

Re: MS ID: 1252827154754727 entitled: Low bone mineral density is strongly associated with low-energy distal radius fractures in middle-aged and elderly men. A case-control study.

Revised title: Low bone mineral density a significant risk factor for low-energy distal radius fractures in middle-aged and elderly men: A case-control study

We thank you for valuable and constructive comments to our manuscript and we appreciate that you are willing to consider for publication a revision of the manuscript. The manuscript has now been thoroughly revised according to the suggestions and comments from associate editor and the two reviewers. Please see below our response to associate editor and the two reviewer’s comments.

We believe that the manuscript after revision has improved in quality.

We hope you will find the revised manuscript suitable for publication in BMC Musculoskeletal Disorders.

Enclosed:

- The revised manuscript.
- The revision of the manuscript with alterations shown in the manuscript.
- Responses to reviewer’s comments.

Sincerely

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There are 2 main concerns for this manuscript. First, there several risk factors listed in Table 1 for which there are <5 observations for cases and/or controls. Any inferences made that are based on analyses of such small numbers are questionable.

**Our reply:**
We fully agree with the associate editor’s comment on this. In the discussion this limitation was also highlighted by us. In the revised version this limitation has been further emphasized in the discussion by adding the sentence: “Thus, our results should be interpreted with cautionousness.”

Second, as described, the statistical analysis is inadequate. Since cases and controls were matched on age, it is inappropriate to examine age as a risk factor for fracture. Furthermore, because it is a matching factor, age must be adjusted for in analyses of any other risk factors, and the title of Table 2 suggests that all analyses are unadjusted.

**Our reply:**
We agree and we have removed age from table 2.

For the second comment we are more doubtful that testing association between variables and risk of fracture should also be adjusted for age as long as cases and controls in fact were matched for age and thus in principle is adjusted for age.

As you can see from the table 2 below adjusting the variables for age, no substantial differences from the unadjusted analyses were revealed as expected. We thus argue to keep the unadjusted analysis in table 2. However if associate editor has a different opinion we will change table 2 and replace it with the table below.
Table 2. Odds ratios (OR) with 95% confidence interval (CI) adjusted for age searching for associations between selected variables and low-energy distal radius fracture in men.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR*</th>
<th>CI 95%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1.00</td>
<td>0.93-1.06</td>
<td>0.891</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.95</td>
<td>0.91-1.00</td>
<td>0.064</td>
</tr>
<tr>
<td>Education &lt;13 years</td>
<td>0.63</td>
<td>0.17-2.24</td>
<td>0.471</td>
</tr>
<tr>
<td>Living alone</td>
<td>102836.7</td>
<td>0.00-2.3E+088</td>
<td>0.126</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.06</td>
<td>0.53-8.03</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inflammatory diseases</td>
<td>1.22</td>
<td>0.07-20.51</td>
<td>0.889</td>
</tr>
<tr>
<td>Endocrine diseases</td>
<td>0.44</td>
<td>0.02-13.05</td>
<td>0.632</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>0.75</td>
<td>0.22-2.63</td>
<td>0.656</td>
</tr>
<tr>
<td>Glucocorticosteroids:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>2.06</td>
<td>0.34-12.51</td>
<td>0.431</td>
</tr>
<tr>
<td>≥ 3 months</td>
<td>1.31</td>
<td>0.18-9.50</td>
<td>0.788</td>
</tr>
<tr>
<td>Calcium supplement</td>
<td>1.39</td>
<td>0.27-7.17</td>
<td>0.691</td>
</tr>
<tr>
<td>Vitamin-D supplement</td>
<td>0.92</td>
<td>0.33-2.53</td>
<td>0.864</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>3.74</td>
<td>0.32-43.25</td>
<td>0.291</td>
</tr>
<tr>
<td>Loss of height (≥ 3 cm)</td>
<td>1.58</td>
<td>0.22-11.45</td>
<td>0.605</td>
</tr>
<tr>
<td>Previous fracture</td>
<td>1.01</td>
<td>0.24-11.45</td>
<td>0.994</td>
</tr>
<tr>
<td>History of hip fracture in a parent</td>
<td>0.87</td>
<td>0.10-7.99</td>
<td>0.904</td>
</tr>
<tr>
<td>Falls (≥ 1 fall last year)</td>
<td>1.49</td>
<td>0.31-7.26</td>
<td>0.619</td>
</tr>
<tr>
<td>Osteopenia**</td>
<td>5.82</td>
<td>1.28-26.40</td>
<td>0.023</td>
</tr>
<tr>
<td>Osteoporosis***</td>
<td>10.02</td>
<td>1.54-65.32</td>
<td>0.016</td>
</tr>
</tbody>
</table>

OR and 95% CI was calculated using conditional logistic regression analysis. ** At femoral neck, total hip and/or lumbar spine L2-4 but no osteoporosis. *** At femoral neck, total hip and/or lumbar spine L2-4.

**Associate Editor's comments:**
There are two other important points that should be addressed:

First, the timing of ascertainment of controls is important, yet it is not described in the manuscript. Second, the analysis comparing the FRAX scores between cases and controls is not described in the methods section.

**Our reply:**
Both issues have now been addressed and described.

**Associate Editor's comments:**
Finally, given the small number of subjects and the wide confidence intervals for the odds ratios, it is somewhat of an overstatement to conclude that "reduced bone density is the most important alterable risk factor" for wrist fractures in men. Conclusions should be tempered.
Our reply:
The conclusion has now been tempered both in the abstract and at the end of the discussion. As a consequence of this we have also changed the title of the manuscript.

Reviewer 1:

Item 1:
Bisphosphonate has now been spelled correctly.

Item 2:
In table 2 we now also describe that conditional regression models was used for Odds ratio calculation with 95% CI.

Reviewer 2:

BACKGROUND:

Reviewers comment:
Ref 16 should be added.
Our reply:
Reference 16 (Atroshi et al) has now been added and is reference 6 in the updated reference list.

METHODS:

Reviewers comment:
Some description of the population is needed, population size, urban/rural?
Our reply:
Additional information as requested for the recruitment area has now been added.

Reviewers comment:
Why did the authors choose to include only one age-matched control man per patient (considering that some important differences, e.g. weight, were subsequently found)? A supporting reference for this choice would be appropriate here.
Our reply:
We used the same matching for men as we did for women 1:1 in this study. Ideally for men due to the relatively low number we should have included more controls to improve the power of the statistics.
STATISTICS:

**Reviewers comment:**
It is unclear how the logistic regression was performed, which variables were included in the model that estimated the odds ratio for osteoporosis? In Table 2 it seems too many variables have been analyzed considering the small number of patients.

**Our reply:**
In table 2 only unadjusted analysis have been performed that means each variable is tested separately and is not adjusted for by any other variables. Associated editor has also addressed questions related to the statistics we applied; please also see these comments above.

We agree with the concern that multiple comparison increases the risk of finding associations which in fact may not be true and that such a finding has only become statistically significant by chance. The large number of variables thus is a limitation indeed in our small study however is also a strength of the study as many potential variables has been tested. If our findings would have been in conflict with previous reports the reliability of the results would of course have been more doubtful.

RESULTS:

**Reviewers comment:**
How many fractures were excluded (e.g. high energy, etc)?

**Our reply:**
Unfortunately we have not recorded the number on how many distal radius fracture patients were excluded due to high energy trauma.

**Reviewers comment:**
Could the authors analyze whether patients who did not attend BMD measurement differed from the participants in characteristics other than age?

**Our reply:**
We also recorded information on whether the fracture occurred indoor or outdoor but the number is too small to compare the two groups.

DISCUSSION:

**Reviewers comment:**
Page 9, paragraph 3, second sentence “In one of these studies …” it seems the citation is incorrect because this is not what reference 16 reported.

**Our reply:**
We are sorry for this mistake it should have been reference 2 (Tuck et al).

**Reviewers comment:**
The authors state that falls in last year were not associated with fracture risk but the difference (41% of the patients vs 18.5% of the controls) although statistically not significant is a relatively large difference suggesting inadequate power. It would be interesting to discuss possible explanations to why “living alone” was associated with fracture.
**Our reply:**
**Falls:** We agree with the reviewer and this has now been addressed and discussed.
**Living alone:** We now in the revised version discuss potential reason why living alone may be associated with distal radius fracture.

**Reviewers comment:**
A few minor language corrections needed.

**Our reply:**
We have once more thoroughly read the manuscript and we hope the language issues have now been improved.