Author's response to reviews

Title: Cross-sectional associations between prevalent vertebral fracture and pulmonary function. The sixth Tromso Study

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Author's response to reviews: see over
A. Major Compulsory Revisions.

1. The study by Morseth et al of vertebral fractures and pulmonary function has some interesting results but has issues with lack of discrimination in its design and interpretation. The cohort is good in that it is population based but the overall results are presented as negative for a significant association between vertebral fractures and lung disease. The actual incidence of fractures in the cohort is relatively small for analysis raising concerns. In such a report of nonassociations between the two conditions - the author should present key information about their estimates of power to detect true differences between groups. This is essential for readers to interpret the results properly.

Comments from the authors: Observed power was in the range of 0.55-0.96. For men, the observed power was lower (0.2) when analyzing fracture site and severity of fracture. This has been added to the Discussion section as a weakness.

2. Inadequate data is provided to evaluate their assessment of vertebral fractures. They do not give specific criteria for identifying or classifying the fractures as mild moderate and severe. The authors describe the classification of fractures into types (wedge, biconcave and “compression”) but do not provide data about the distribution of those types within the cohort and in relation to the outcome of pulmonary function. More detail regarding the assessment and types of fractures is needed.

Comments from the authors: For an overview over types and severity of fracture, we refer to Figure 1 in Lenchik L, Rogers LF, Delmas PD, Genant HK: Diagnosis of osteoporotic vertebral fractures: importance of recognition and description by radiologists. AJR American journal of roentgenology 2004, 183(4):949-958. We are currently working on permissions to reprint this Figure. Distribution of severity of fractures is presented in Table 5. We did not aim to analyze fractures according to types (wedge, biconcave, compression).
3. The authors appear to not discriminate their conceptual design based on type of respiratory disease – i.e. restrictive vs. obstructive. Recognizing the different relationships between effects of vertebral fractures on restrictive lung disease and obstructive lung disease in their study design and discussion is important. There are sufficient reports of the association of COPD to reduced bone density and fractures to suggest that the impact of vertebral fractures on restrictive lung disease is potentially a divergent process from an association to obstructive disease.

Comments from the authors: Our paper is mainly based on respiratory markers (e.g., FEV1, FVC, their ratio) and not obstructive/restrictive respiratory disease. However, we included a section regarding obstructive and restrictive disease, as we see that it is of interest (table 6). The main reason for our choice is that this is a population study and a large proportion of the subjects were healthy, and our main aim was to examine the association between lung function and vertebral fracture. The hypothesis behind this study was that vertebral fracture may inhibit lung function. We therefore chose to not pay that much attention to studies suggesting that COPD may lead to osteoporosis, as we see this as a different issue related to COPD patients.

4. This study is derived from a larger population study. I would like to see a table comparing key demographics from the main study and this sub study.

Comments from the authors: The following table shows that characteristics do not differ much between the eligible population and those who were included in this study. This table in not included in the study to avoid too many tables, but can easily be included if desired.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Eligible (n=2886)</th>
<th>Included (n=2132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>41.8 (1206)</td>
<td>41.8 (892)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.4 (9.4)</td>
<td>67.8 (7.4)</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>167.7 (9.2)</td>
<td>167.3 (9.1)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76.4 (14.1)</td>
<td>76.2 (13.8)</td>
</tr>
<tr>
<td>Smoking^a n=2834, 2132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>17.1% (485)</td>
<td>16.2% (345)</td>
</tr>
<tr>
<td>Past</td>
<td>47.9% (1358)</td>
<td>49.2% (1050)</td>
</tr>
<tr>
<td>Never</td>
<td>35.0% (991)</td>
<td>34.6% (737)</td>
</tr>
<tr>
<td>Physical inactivity^c</td>
<td>19.6% (500)</td>
<td>19.8% (367)</td>
</tr>
<tr>
<td>Cardiovascular disease^d</td>
<td>14.2% (409)</td>
<td>15.8% (337)</td>
</tr>
<tr>
<td>Lung disease^e</td>
<td>13.1% (377)</td>
<td>13.5% (288)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or % (n)
^a n=2885
^b n=2834 and 2132
^c n=2552 and 1855
^d Cerebral stroke, myocardial infarction, or angina pectoris
^e Asthma, chronic bronchitis, emphysema, or COPD
5. Although the authors discuss the issue of height reduction with age it is unclear how they used the 1994-95 height measurements in their analyses since it is described as being in a sub analysis and a subsample. Please clarify and present that data separately.

Comments from the authors: We have added the following to the methods section: “in a subsample of 859 men and 1199 women, we repeated the analyses using the subjects previous height in 1994-95 instead of current height.”

6. The authors do not present a logical framework to consider a relationship between lumbar vertebral fractures and lung function. It is similar to asking if hip fractures are associated with pulmonary function. Is there evidence or theory to support a relationship?

Comments from the authors: We have inserted a paragraph in the Discussion, suggesting an explanation for the association between some respiratory markers and lumbar vertebral fracture, according to Horie et al. (28):

“In our study, we found significantly lower FEV₁/FVC% predicted in women and men with lumbar vertebral fracture than in those without fracture. This may seem surprising, as the lumbar vertebrae are not part of the rib cage. However, according to Horie et al. [1] there may be a reasonable theory behind these findings. The lumbar vertebrae are attached to the diaphragm, which main function is to contract and expand the lungs during inspiration. Lumbar vertebral fracture may lead to reduced constriction efficiency of the diaphragm and thus decrease the expansion of the lungs [1].”

7. No information is presented about the choice of multiple regression covariates. The models appear to have a significant risk of over adjustment with collinear variables. Since models with age only are borderline in men and significant in women, additional information about selected reduced models would be helpful. Discussion should be added about the choice of models.

Specific concerns for over-adjustment are including age and height as covariates for assessing a relationship to % predicted FEV1 and FVC, given that prediction equations for those variables typically include age and height. Adjusting for cardiovascular or lung disease in the association between fractures and lung function is questionable and is not justified or discussed. Adjusting for physical activity in assessing these relationships is also curious given that it may reduce bone loss but increase fracture risk.

Comments from the authors: The multiple regression covariates are chosen based on previous research and plausible confounding effects. As expected, age was the most important covariate, and the other covariates added only minor changes to the results.
We did test for multicollinearity between independent variables, but did not find high correlation between any of the covariates. As one could expect, both women and men showed highest correlation between height and weight (0.3-0.5, P<0.001) and between lung disease (CLD) and use of corticosteroids (0.5-0.6, P<0.001). Tolerance was high (>0.6). This information has been added to the methods section.

% predicted FEV1 and FVC values are not adjusted, as the prediction formula includes age and height. We only adjusted absolute values.

Adjusting for cardiovascular and lung disease is based on the assumption that for instance CVD could be a confounder in the relationship between lung function and vertebral fracture. There are few reports of the association between physical activity and vertebral fracture, but most studies show a reduced risk of vertebral fracture with higher physical activity levels. Physical activity is also related to lung function. However, physical activity was not significantly related to lung function in our study. This discussion was added to the manuscript.

8. Odds ratios should be presented with 95% confidence intervals.

Comments from the authors: Table 6 is now updated with CI.

B. Minor Essential Revisions

The term restrictive airway disease is used (page 7 methods) which may be confusing to readers since restrictive disease is often parenchymal. FEV1/FVC is more typically presented as a ratio without % predicted in assessing criteria for obstructive lung disease.

Comments from the authors: We tried not to use the term “airway disease” in relation to our data. We defined airways restriction (as measured by spirometry) as FVC and FEV1 less than 80% of predicted values and FEV1/FVC ≥0.7. Obstruction was defined according to the GOLD criteria, with the ratio of FEV1/FVC rather than %predicted, as described in the methods section.

Assessing measurements of thoracic kyphosis would be valuable.

Comments from the authors: Unfortunately, kyphosis was not measured in our study. This has been added to the discussion, page 10, for clarity.

Theoretical considerations in the assessment of associations would include location of the fracture and the effect of one or more fractures on thoracic deformity leading to impairment. In subjects with minimal or no changes in alignment or kyphosis one
would expect less impact on some aspects of pulmonary function than in subjects who have extensive kyphosis.

Comments from the authors: We have tried to address these considerations by analyzing number of fractures and fracture location, as in table 3 and 4 and the according text in the Results section. We have added the sentence “Women and men with 4 or more fractures had significantly lower FVC% predicted and FEV1% predicted than those without fracture.”, after checking post hoc analyses in ANCOVA.

It is troubling to include mild fractures in the analysis as moderate given a likely reduced effect on the outcome from a non-discrimination bias. Separate analyses of severe fractures and their associations would be useful to test this and excluding the small number of mild fractures from an analysis might also be informative. Information about what test for trend was used is of interest.

Comments from the authors: As there were very few mild fractures, coding mild fractures as moderate did not alter the results. We did some random analyses with mild fracture defined as no fracture, and the results were almost similar to the existing results, with only very minor differences. We are of course prepared to do all analyses all over again with mild fractures defined as no fracture if you prefer. We did separate analyses of severe fractures compared to no fracture, as shown in Table 5. Test for trend was performed using regression analysis.

Interesting findings:
Men and women have similar rates of fractures although women have lower bone density in the hip. The authors might discuss those findings and their implications.

Men show a distinct association of vertebral fractures to lung disease, women appear to show this in Table 6 with an association to severe lung disease.

Comments from the authors: We have added the following to the Discussion section: “When BMD is measured at the hip, it has been shown that relative risk of vertebral fractures increases 1.6 times per SD (35). In our study, men and women have similar rates of fractures, although women have lower BMD in the hip. This may indicate that fact that fracture risk is also affected by many other factors, such as other skeletal mechanisms (bone architecture and geometry)(36).”
Major compulsory revisions

**Design and subjects section, paragraph 2**
- “Of the 7,307 subjects ... e.e. a dual femur scan (n=3,854).” What did the authors mean by valid bone mineral density measurement? Did they measure bone mineral density twice?

**Comments from the authors:** We realize that “valid” may be confusing and has this term now been removed, and the paragraph has been altered somewhat to avoid misunderstandings about Tromsø 5 and 6. We simply mean that all subjects with BMD measurement in Tromsø 5 was invited to measure BMD in Tromsø 6.

- A flow diagram on the number of participants would be helpful.

**Comments from the authors:** A flow diagram has been added to the manuscript.

**Ascertainment of vertebral fracture, paragraph 1**
- The gold standard for diagnosing vertebral fracture is the Genant visual semi-quantitative method on X-rays of the vertebrae (Genant et al. J Bone Miner Res 1993; 8:1137-1148). However, the authors used vertebral fracture assessment on DXA images of the vertebrae, which usually are of poor quality. Has this method been validated? Do the authors have data on sensitivity and specificity?

**Comments from the authors:** In the Discussion, paragraph 6, we made some comments regarding the use of DXA images and the sensitivity and specificity as follows:

“Recent developments in DXA technology now allow population-based identification of prevalent vertebral fracture using DXA densitometers [2]. Although spine radiographs are generally considered to be the gold standard for the diagnosis of vertebral fractures [3, 4], the morphometric method used in our study is recognized to be easy and precise and with low radiation exposure [5-7]. The vertebral fracture assessment method has been used in many population settings, and its sensitivity and specificity are comparable to spinal radiographs in the ability to diagnose grade 2 and 3 vertebral fracture [2, 8]. Still, different methods may produce disparities.”

- Although the number of subjects with mild deformities is small, subjects with mild deformities should be moved to the group with subjects without vertebral fractures.
Comments from the authors: We did some random analyses with mild fracture defined as no fracture, and the results were almost similar to the existing results, with only very minor differences. We are of course prepared to do all analyses all over again with mild fractures defined as no fracture if you prefer.

Statistical analyses section, paragraph 3

- Did the authors check the assumptions of multiple regression (e.g. multicollinearity)?

Comments from the authors: We did test for multicollinearity between independent variables, but did not find high correlation between any of the covariates. As one could expect, both women and men showed highest correlation between height and weight (0.3-0.5, P<0.001) and between lung disease (CLD) and use of corticosteroids (0.5-0.6, P<0.001). Tolerance was high (>0.6). This information has been added to the methods section.

- Why did the authors correct for all these variables?

Comments from the authors: The choice of variables in the model is based on previous findings suggesting that these variables may act as confounders.

Minor essential revisions

Abstract, methods section:
- In this study, 2177 subjects were included. How many of them were male, and how many of them were female?

Comments from the authors: This information has now been added to the abstract.

- What did the authors mean by multiple adjusted FVC, FEV1 and FEV1/ FVC?

Comments from the authors: By multiple adjusted, we mean that a model with several variables were used to analyze the associations. We have, however, removed “multiple” as this may be confusing.

Discussion section, paragraph 3
- The authors stated “We used height measures ... this has most likely had minor impact on the results”. Please refer to previous data or remove this sentence.

Comments from the authors: We realize that this sentence was confusing and we have now changed the sentence and removed some parts.
Assessment of covariates section
- Did all the subjects respond?

Comments from the authors: We apologize for some confusing and missing information regarding covariates. For the % predicted model, we included only subjects who responded to all covariates (i.e. age, height, weight, smoking), as described in the Assessment of covariates section. However, for the multiple adjusted model, we further excluded subjects who did not respond to the variables in the model (i.e. BMD, physical inactivity, hormones).

The Methods/Design and subjects section is now updated with this information as follows: “For the multiple adjusted model, we further excluded subjects with missing values for hip BMD (n=475), physical inactivity (n=631), and/or hormone drugs (n=128 women), leaving 665 men and 800 women for inclusion in the adjusted model.”

Statistical analyses section, paragraph 1
- How did the authors define obstructive and restrictive ventilatory impairment?

Comments from the authors: Obstructive and restrictive impairment was defined as described in the Statistical analyses section: “Airways restriction was defined as FVC and FEV1 less than 80% of predicted values and FEV1/FVC ≥0.7. Obstruction was defined as FEV1/FVC <0.7, with mild obstruction defined as FEV1% predicted ≥80%, moderate obstruction as FEV1% predicted <80% and ≥50%, and severe obstruction defined as FEV1% predicted <50%.” This information has been moved to the second paragraph in Statistical analyses.

Results section, paragraph 1
- Please check the number of women included (1241 women in the results section and 1240 women in Table 1).

Comments from the authors: The correct number is 1240, this has now been corrected.

- Table 6. FEV1 % predicted and FEV1/FVC % predicted are already corrected for age, sex and height. Why did the authors correct for age, sex, height and lung disease in this multiple regression model?

Comments from the authors: We chose to include an adjusted model, although we agree that this could be seen as redundant, as the rates we analyze are based on %predicted values. We are prepared to remove the adjustments if that is preferable.
Discretionary revisions

Background section:
- Vertebral fractures are, in addition to kyphosis, height loss and chronic pain, related to a high annual number of incidental vertebral fractures (Lindsay R et al. JAMA 2001; 285:320-323). This information should be included in the background section.

Comments from the authors: This information has now been added to the background section.

Discussion section, paragraph 5
- Did the authors assess the kyphotic angle?

Comments from the authors: Unfortunately, kyphosis was not measured in our study. This has been added to the discussion, page 10, for clarity.