Author's response to reviews

Title: Are the determinants of vertebral endplate changes and severe disc degeneration in the lumbar spine the same? A magnetic resonance imaging study in middle-aged male workers

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

Please find enclosed our revised manuscript "Determinants of vertebral endplate changes: a magnetic resonance imaging study in middle-aged male workers". The title has been changed into "Are the determinants of vertebral endplate changes and severe disc degeneration in the lumbar spine the same? A magnetic resonance imaging study in middle-aged male workers".

We thank the reviewers for valuable comments. We have now revised our manuscript as requested: the detailed responses can be found below. The revisions have been underlined in the text.

We hope that the manuscript now fulfils your criteria of an article to be published in BMC Musculoskeletal Disorders.

Yours sincerely,

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Author's response to reviews

Reviewer #1: Michele Battié
Reviewer's report:
General

The study purpose is clearly stated and limited related knowledge exists. The authors’ aim to identify factors associated with the presence of Modic changes and examine whether the same factors are associated with Modic changes and severe disc degeneration (including collapse of the disc space). There is current interest in endplate or Modic changes as findings that may be relevant to back pain and, with the exception of age and previous reports of associations with body weight and male gender, little is known about what factors influence their presence.

The current study is an extension of an earlier report on the association of Modic changes and low back pain or sciatica in the same study sample. The prevalence of Modic changes (Types 1, 2, and 3) for the study sample was reported in the earlier publication, but probably warrants some repeating in the present study. A main finding of the earlier study was that Modic changes at the L5-S1 level, where findings were most prevalent, were significantly associated with pain, but an association with pain was not apparent when looking at lumbar levels L1-2 through L4-5. Thus, the authors concentrated further on L5-S1 when looking at determinants of Modic changes in the current study.

The methods seem sufficiently detailed to allow replication. There can be criticisms about the accuracy of some of the self-reported history data, such as lifetime leisure activity, in particular, but this is a limitation of all studies interested in such long-term activity exposures. Also, despite the limitations of the activity measure, which could be expected to dilute associations, the variable was associated with Modic changes.

We do agree with the inaccuracy of lifetime self-reported estimate (as discussed in the Discussion section).

There is always a possibility of confounding in such studies by some unmeasured or unknown confounding factors, but the authors state that age was controlled in all association analyses and multivariable analyses allowed for control of several other possible confounders.

That is correct.

Generally, the paper is clearly written and adds to the accumulating findings on factors associated with Modic changes and, if the findings are replicated, raises questions about the presumed association between Modic changes and disc degeneration and implied differences in determinants of Type I and Type II changes.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Table 3 provides the odds ratios with 95% confident intervals for associations between the independent variables and various categories of Modic changes.
The category of Type I changes was not included because none of the independent variables was statistically significantly related. However, because of the importance the authors have given to type I changes and the conclusion drawn regarding differences in determinants of type I and II changes, it would be helpful to see the ORs and CIs for type I added to the table. Exclusively type I changes constitute the smallest Modic change category and face power issues, but similarities and differences in direction and degree of association as compared to other findings would be informative.

Associations of type I changes have been now added to Table 3 (and of combined type I and type II have been excluded). As the determinants of type I changes were not significant in the univariate analyses, type I changes are not included in the multivariate analyses.

Also, there appears to be a mistake in the notations following Tables 3 and 4. Should the superscript “3,4” preceding “Subjects with both Modic I and II changes (n=23) or Modic I change (n=33) are excluded” be deleted? 3 and 4 are already used earlier in the notation to represent something else.

The footnotes in tables 3 and 4 have been clarified.

Also, following superscript “b” should read ‘severe disc degeneration’ in both tables.

The superscript "b" of the original paper included "severe disc degeneration" in both tables. The superscript “a” now refers to “severe disc degeneration” in Table 4.

Discretionary Revisions (which the author can choose to ignore)
The title accurately portrays the primary purpose of the study and the abstract is clearly written. I would suggest, however, that the 3rd sentence of the “Results” paragraph be extended to clarify that ‘exposure to whole-body vibration besides age was the only significant determinant for disc degeneration at L5-S1.’ Also, the odds ratios would have more meaning if the unit change in the associated determinant were stated.

We have extended the abstract as suggested. We have added the unit changes after the significant results in the multivariate results (Results section).

In the 3rd and final paragraph of the “Background” section, the authors note a focus on the L5-S1 level “because the association of Modic changes with pain symptoms seems so prominent at L5-S1 level [24]”. The authors should state that they are referring to their previous findings in the same study sample.

The paragraph was modified according to the reviewer’s suggestion.

What next?: Accept after minor essential revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Reviewer #2: Charlotte Leboeuf-Yde

Reviewer’s report:

General
This is an interesting article on a hot topic. I think it could benefit from some changes, though.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Abstract. It would be helpful if all variables used in the analyses were listed in the methods section. Otherwise the reader cannot judge the value of the final results of the multivariate analyses.

   The variables have been added to the abstract.

2. You need to be more careful with your references. Perhaps you should check that you have quoted everything correctly. I had some of your references at hand and I do not always agree with you on your interpretation of their contents. Specifically:
   - Background, 1st para: Ref. 1 Modic 1988 (Imaging of degenerative disk disease...) does not contain original data and should therefore not be used as a reference of "facts". Ref. 2 is the one you should refer to, when using Modic as the source. Also de Roos (ref 3) is OK. Adding a narrative text as reference gives the reader the false impression that there is multiple underlying evidence.

   The paragraph was modified according to the reviewer’s suggestion.

   - In the Background, 2nd para you discuss risk factors. In your last sentence, I suggest that you place the relevant references after each statement, for the sentence to read: "In addition to age (19,20), weight (19) and male gender (19) have been shown to be associated with Modic changes." In other words, your ref. 1 should not be included because it is not a study of risk factors. In ref. 19, I found positive associations with age, males and weight. Ref. 20, which is the only of your three suggested references that can identify risk, as it had prospective data, did in fact fail to detect any factors associated with new Modic changes (notably age and physical work load did not turn out positive) but you had only 23 such subjects, so that might be an explanation and also, new Modic changes might be relevant at an earlier stage only. According to the cross-sectional data though, there was a positive association with age but not with physical workload. Therefore, you should not speak about "increased risk" but merely of association, and definitely not "associations with an increasing risk".

   The paragraph was modified according to the reviewer’s suggestion.

   - Background, third para, second sentence. You say that you choose to study the L5-S1 level because a previous study (ref 21) had shown the association between Modic changes and pain to be "so prominent at the L5-S1 level". According to the text in that article, in which number of episodes, VAS for pain last week and past 3 months were reported for L5-S1 and for all lumber levels, the odds ratios were not higher for L5-S1. However, as far as I remember, in most studies on the prevalence of Modic changes, these are most COMMON in the lowest disc, so perhaps that is what you should write instead?
It is true that Modic changes are located more likely at the two lowest levels. In our population, 80% of Modic changes were at these two levels. The reason for putting main focus on L5-S1 was because the association of pain episodes and LBP during the past week was significant only at this level. Text has been changed accordingly.

2b. And if you concentrate on L5-S1, why then do the analyses at all levels? Or...if you believe that L5-S1 is so important, why not analyze L5-S1 separately and those above as one group? All this overlapping of individuals seems a pity.

The main focus was on L5-S1 level (see above). Unfortunately, the statistical power was not sufficient to analyze the upper levels (L1 to L4) separately.

3. Materials and methods, image analysis. A very good description of this aspect, the only things I did not find was a statement as to whether the radiologists were blind also to the study subjects' clinical picture.

This has been added.

There was no intra-examiner reliability study for the disc degeneration study, I take it? Is there a reference on how easy it is to do this reliably?

The reliability of disc degeneration evaluation was not evaluated in this study. We have added a sentence (the first paragraph on p. 6), where we refer to the original study.

4. I have a serious problem with the division of Modic I and II into separate groups. If you consider II to be the continuation of I, they should be analyzed together. When, in the bivariate analysis you find that BMI and waist circumference are linked with type II but not the two combined, this might be a function of age (type II comes after type I, i.e. for many a function of age). This can be seen to be true in your multivariate analysis where BMI is significantly associated with both Modic II and Modic both types. When you state in your report that you found nothing for the Modic Is, this gives the reader a feeling that there is nothing interesting there, but it might simply be that they were too few for significant findings to occur. If you want to conduct your analyses in this way (and you should decide that but then at least tell us why you do it), and if you then want to account for the type Is, you must tell us if the estimates were similar to those found for type II, but that the low number prevented significance.

We have observed that the genetic background of Modic type II changes is stronger than for combined type I and II changes (unpublished observation). We believe that type II changes represent a more chronic entity, and at least some type I changes may represent a more reversible, "benign" phenotype, converting back to normal bone marrow instead of progressing to type II. This is the probable explanation for a stronger association for type II changes than for all Modic changes.

Secondly, the number of type I changes was comparatively low in the current population. Therefore, we may have missed significant associations between type I changes and investigated determinants because of the low statistical power.

5. Statistical analysis. You tell us what the reference group is in your modic analyses but you do not say anything about this in relation to the disc degeneration group.
The reference group in the analyses of severe disc degeneration (all those without severe disc degeneration) has been clarified in the Methods and in Tables 3 and 4. Furthermore, we have excluded the description of cross-tabulations in the comparisons of the two occupational groups as this is trivial in this context.

6. In a previous study, to which you refer (14), it was noted that people without degenerative disc findings on MRI resembled people with degenerative disc findings but WITHOUT Modic changes on a number of variables but that disc degeneration COMBINED with Modic changes did produce a large number of statistically significant associations. Therefore, I think that your study would benefit from another approach: 1. People without severe disc degeneration and without Modic changes should should make up one subgroup, 2. people with severe disc degeneration and without Modic changes should make up another subgroup, and 3. people with both severe disc degeneration and Modic changes should make up the third group. As it is now, you cannot really compare your two groups, those with Modic changes and those with severe disc degeneration, because they contain overlapping individuals. I suspect that you will augment your odds ratios, if you do it the other way round, as suggested.

We regard the paper of Kjaer et al (ref. 14) an excellent study. However, the statistical power of our study was not sufficient for this method.

7. In your result section you seem to forget that AGE was positively associated with Modic changes and degeneration and also in the discussion.

This is stated in the Results (beginning of the paragraphs describing the determinants of both imaging findings, i.e. Modic changes and severe disc degeneration) and part of one paragraph in the Discussion. We have, however, clarified in more details the existence of an association between age and the MRI changes both in the Results and in the Discussion.

8. Discussion, 1st para. "To the authors' knowledge, no population-based study has previously focused on the determinants of modic changes". You have one such study in your list of references, number 14, Per Kjær.

This excellent reference has been recognized in the beginning of the Discussion.

9. In the Discussion, second para, last sentence, you introduce for the first time the fact that you found most Modic changes at the levels of the two lowest discs. However, you have forgotten to tell us about that in the Result section, as far as I can see.

This has been added to the Results.

In fact, you seem to have forgotten to add references to some of your tables and figures, throughout the text.

To the authors' knowledge, all the tables and figures have been cited in the text.

10. Discussion, third para: Why mention waist circumference, when it vanished in the multivariate analyses analyses?
Waist circumference did not vanish in the multivariate analyses. Due to collinearity of BMI and waist circumference only one could be selected for the final multivariate analysis.

11. Discussion p.10 at the bottom of the page. You speak about smoking and degeneration and Modic changes and talk about a trend between smoking and Modic changes but not with disc degeneration and use a Finnish twin study (ref 5) to support these findings. However, you need to read that report again. They did not deal with Modic changes, as far as I remember and what did they conclude on smoking again? There were two such studies, in the first study they found something which they refuted in number two, if I remember it correctly.

That is correct. Battié et al. (1991) and (1995) investigated the association between smoking and disc degeneration. The text has been clarified.

12. I do not quite understand your interpretation of your own data on p.11, last para. You say that the determinants of Modic changes and severe disc degeneration differ especially at L5-S1 level. Looking at Table 4 with the multivariate analyses, I note that age is positively associated with both Modic and degeneration, regardless if you report results for all levels or only at L5-S1. BMI is related to Modic regardless all levels of L5-S1 but not with severe disc degeneration, regardless where in the spine. Only vibration exposure comes out significant at L5-S1 only (for discs) but not for all level discs vs. not for all levels or L5-S1 in Modic changes.

The determinants investigated (all age-adjusted) do differ at L5-S1. We excluded age from this discussion because it is self-evident that age is a determinant of all degenerative phenomena.

13. In the discussion section, last para before conclusions, you say that the determinants of Modic type I and II are different. You did not study this aspect, so this text should be removed. I have discussed this aspect before in this text.

We have added the analyses of type I changes and therefore the statement in the Discussion has not been changed.

14. References. I believe that the "et al" procedure is inadmissible in this journal. All authors should be listed, is my experience.

The paragraph was modified according to the reviewer's suggestion.

15. Check if you have referred to all tables and figures in the text. I could not find a reference to Table 1 and I could only find Fig. 1.

They were both cited in the Methods section (Figure 1: p. 5, the last paragraph). Table 1 has now been removed to the beginning of the Results section.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. The title would benefit if the subject of disc degeneration was included. For example "Determinants of vertebral endplate changes and disc degeneration..."

The title has been changed as suggested.
2. Method. This comment comes too late, but how did you succeed in squeezing your study subjects into your à priori (don't forget the accent on the "a") alcohol consumption groups? They do not include all possibilities. For example, nobody was supposed to drink alcohol once a month or 4-11 times a month, nor was it possible to drink alcohol 5-6 times a week.

This has been clarified (see p. 4, paragraph 3 and Table 1).

3. Results. I suggest that you start your result section by a brief demographic description of your study sample including differences/no differences between the two study groups. You should not only describe your Modic findings but also your disc findings in this initial text.

We have now added a new paragraph in the beginning about the demographics of the study population. We have added the prevalence of disc degeneration in the same paragraph as the prevalence of Modic changes.

4. Determinant of Modic changes, p.8, 4th line. You write that the odds ratios "ranged from 1.42 to 1.48" but they did not range as there were only two values. In other words: "They were 1.42 and 1.48, respectively."

The paragraph was modified according to the reviewer’s suggestion.

5. Discussion, second para. You find a larger prevalence of Modic changes (56%) than that in a previous Danish study (22%). You suggest that this can be explained by a gender difference. Why? In the Danish study there was no significant overrepresentation of males with Modic changes. However, in the Danish study, all study subjects were 40 yrs. In yours, you had a more older subjects and a considerably larger number of people with Modic II, which is consistent with them being older. Is that not a better explanation?

We have added age as one explanation. Furthermore, we have discussed the genetic homogeneity of the Finnish population, which may be one further explanation.

6. You then proceed to discuss age (as I suggest above). However, your three references (1,19, 20) are suspect. Ref. 1 is a narrative text, and in ref 19 age was found to be linked with Modic changes but in ref. 20 age was not linked with new cases of Modic but only with present Modic changes...

We have excluded ref. 1 from this part of the text.

7. When you, in the discussion, p.12, second para, talk about the limitations of your study and the temporal relationship, I think that it is worth emphasising again that AGE is a true predictor for both disc degeneration and Modic changes.

We have added text about the effect of age.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published.

The manuscript was checked by a native English speaker but we do not protest if some linguistic revisions are still made in the editorial office.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.