**Author's response to reviews**

**Title:** Hard physical work combined with heavy smoking or overweight may result in so-called Modic changes

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**Version:** 2  **Date:** 3 September 2007

**Author's response to reviews:**

Response to the reviewers’ reports.

Thanks to the reviewers for their prompt and thorough reviews. We have made a number of changes in response to your comments and, where this was not possible, we have explained why in the text below. Our response has been written in cursive, below each of the reviewers’ comments. Changes to the text in the manuscript have been highlighted in yellow.

Reviewer: Massimo Mariconda

**General:**
The article deals with an interesting topic and the question posed is well defined by the authors. Indeed, associations of the so-called Modic changes in vertebral endplates with clinical symptoms are controversial and also the causal factors of these changes have not been fully clarified so far. Nevertheless, several flaws concerning both methods and results are recognisable in the study.

**Major Compulsory Revisions:**

1. **Methods (outcome variables).** Would it not have made sense to also conduct an analysis correlating the pain with the MRI abnormalities? This would have completed the triangle of abnormalities vs. work factors, LBP vs work factors, abnormalities vs. LBP. The interrelationships and clinical relevance is difficult to interpret unless you can also show that the abnormalities per se are associated with more pain.

Reply: It was not the purpose of this study to investigate whether there was an association between smoking/overweight/hard physical work and pain reporting in people with VIP. The purpose of this study was to investigate two pathological conditions, DD and VIP. We believe this to be clearly stated in the “Assumptions to be tested” section (last para on p. 5). The rationale for this study has been extensively explained in the Introduction, because there is a strong link between VIP and LBP, it would be relevant to study, specifically, VIP. This is analogous to
studies of other image-defined conditions, such as disc degeneration, osteoporosis or fractures.

2. Methods (Explanatory variables. Table 2). What counted as a ¿hard physical work¿? You should give qualitative (i.e. self-perception of a heavy workload, manual handling of materials, awkward postures, static sitting or standing work posture, and occupational driving exposure) and quantitative data (time spent at work) on the workload of the subjects. Also, the lifetime work exposure and psychosocial distress at work should be considered in the analysis.

Reply: It is correct that a state-of-the-art study of hard physical work would need a detailed study and classification of postures, exposures, duration etc. As this study is performed on an already existing data base, we did not have the possibility to design the study in relation to the particular objectives of this study. However, in order not to disappoint any readers in our use of this rather ¿blunt¿ definition of hard physical work, the words ¿self-reported¿ has been included in the title as well as in the text on validity and in Table 1. In addition, the text already discusses weaknesses of the study, emphasizing that any imprecise measures are more likely to result in underestimated associations than overestimated associations.

3. Methods (Data analysis). Your multivariate analysis should be adjusted for confounding factors that can modify the relationships between explanatory and outcome variables (i.e. family predisposition, educational level, practice of sports, lifetime work exposure, psychosocial work-related risk factors etc.). Models of multivariate regression analysis would be more fit for this purpose.

Response: As the purpose of the study is to investigate the associations between three particular explanatory variables in relation to four specific outcome variables, it is not relevant to add all sorts of potential confounders and modifiers, as is usually done in studies on low back pain, in which no particular hypothesis is tested apart from trying to find out if something is related to something. However, we want to apologies for the poor description of our analytical method. We must have assumed that the method used was self-explanatory, as we defined the subclassification of our variables in the text. However, in the amended version, on p.6, ¿Data analysis¿ last para, first line, the method is now clearly described as ¿a multi variable logistic regression¿.

4. Methods (page 7, line 9). You did not give data on the duration of smoking habit, previous tobacco use and time elapsed from the suspension of smoking. The duration of smoking habit can be of interest for its detrimental effects on bone (reduced BMP and microfractures) and other organs (nicotine-induced vasoconstriction). Please provide data on the duration of smoking habit, rather than just saying that it was possible for most smokers.

Response: As is clearly stated in the Introduction and Methods section, these data are secondary. It was therefore not possible to collect detail smoke data. This study must obviously be considered a preliminary investigation, and as such quite promising, which should incite others to continue, but then using more detailed physical exposure and smoke data. If our ¿blunt¿ definitions produced
the results that we find here, more detailed data might refine the results. In other
words, our summary definitions are unlikely to result in overestimated
associations. Further, our statement that it is likely that the duration of smoking is
similar in all participants is highly relevant. Most people in Denmark start smoking
in their late teens, and all participants were aged 40 at the time of the study and
the Danish society is fairly homogeneous, so it is quite likely that most fit this
model.

Minor Essential Revisions:

1. Title: You didn’t actually find any correlation between self-reported LBP and
hard physical work combined with other explanatory variables neither you
checked relationship between VIP and LBP. The word ‘painful’ should therefore
be avoided.

Response: On reflection, we agree that the word ‘painful’ should be used with
utmost care. Although it has been shown repeatedly that people with VIP are
much more likely to have LBP than others, also more likely than in people with
DD but without VIP, it is not sure that it is the VIP that hurts. VIP could be an
accessory finding to some changes in some other structure that is the real cause
of the pain. We have therefore changed the title to read: ‘Self-reported hard
physical work combined with heavy smoking or overweight may result in
so-called Modic changes’. A similar change has been made in the Abstract (first
sentence in the Background).

2. Abstract: In the results section you say there were no significant associations
between the single explanatory variables and pain or disc degeneration. In the
conclusions you state that the associations between VIP and hard physical work
and heavy smoking may have consequences on the prevention of LBP. Make
sure the two sections of the abstract give consistent figures.

Response: In the abstract section we clearly report two aspects: the single
variables and the combined variables. These are not to be confused. None of the
single variables was associated with the two pain variables or with DD but only
with VIP (heavy smoking, heavy work). Thereafter we report that the combination
variable of heavy work and smoking (plus heavy work and overweight) was more
strongly linked with VIP. The conclusions are completely in line with our results.

3. Results (page 8, line 33; table 5). You say hard physical work combined with
overweight was predictive of DD and VIP, with positive gradients going from
having neither factor to having both factors, but in Table 5 the combination of
these explanatory variables was not significantly associated to DD and there was
not positive gradient of odds ratios. Please decide which one is correct and make
sure the text and table give consistent figures.

Response: According to Table 5, in both the cases that you mention (DD and
VIP) there were positive gradients (1, 1.6, 1.7; and 1, 1.3, 2.9, respectively). In
other words, you must have misread the text. If you do, others may misread the
text in a similar manner. However, each step between the subgroups is not
significantly different from the previous. To avoid a lengthy explanatory text and
confusing discussion, the text has been changed to avoid this type of
misunderstandings, and the second part of the first sentence has been removed, emphasising only the strongest association (namely the OR of 2.9 for VIP in the combined category of both overweight and hard physical work.

4. Discussion (page 10, line 21) What did we find? You did not find significant associations between hard physical work combined with heavy smoking and self-reported LBP variables. Please change the text.
Response: The words and non-significant have been added to avoid confusion.

5. Discussion (page 11, line 5) You say the prevalence of VIP was higher with increasing loads, in relation to body weight or type of work but you did not find significant positive association between BMI and VIP. The heavy overweight was instead protective (see table 4). Please rephrase.
Response: No, we said Generally, the prevalence of VIP was higher, which is correct, as there was only one value out of line. That heavy overweight appears to be protective is an interesting finding that has been noted by others but the article is very long and difficult to read as it is, so we settled for the generally-statement to avoid having to break the flow of the discussion because of a secondary topic that was not the main topic of this work.

6. Discussion (page 11, line 17) and Conclusions. The reference no. 62 concluded that there is evidence for a dose-response relation between physical workload and LBP. You didn't actually find any correlation between LBP and hard physical work neither you carried out an analysis correlating the LBP with the MRI abnormalities. These sections should therefore be rephrased.
Response: Quite correct. We have removed the offending statement and as stated before, we have already previously reported on the link between VIP and LBP (ref. 48).

7. Conclusions. You need to clearly state that, whilst a higher degree of physical exposure was associated with VIP, it was not associated with the self-reported LBP in the current study. If you had looked at the relationship between the MRI changes and LBP you could have shed some light on this.
Response: Agree, and we have changed the offending statement.

8. References. Relevant references on the relationship between occupational variables and MRI changes of the lumbar spine have not been included in the list.
Response: It was not the pre hoc purpose of this study to investigate various occupational variables and MRI changes/LBP. We believed that smoking/overweight might be simply moderated by hard physical work but to our surprise found that it was the other way round. To change the concept now would be dishonest and, further, it would render the article even more cumbersome and difficult to read.

Discretionary Revisions:
1. Introduction: (smoking or overweight paragraph, page 3; line 24): Please provide bibliographic data to support your sentence sciatic pain can be considered a proxy measure for disc degeneration.
Response: We have added the word “probably” in combination with the word “considered”, leaving readers free to have other opinions on this matter.

2. Introduction (page 4, line 1): I suggest to delete the word “Nevertheless”.
Response: Done.

3. Intro (page 4, line 44): Please provide data regarding the high frequency of heavy smokers among people in the lower social classes.
Response: Done.

4. Methods (page 7, line 23). Please give the Kappa values for the test-re-test reliability data, rather than just saying there was satisfactory intra- and inter-examiner agreement.
Response: Done.

Reviewer: Elizabeth Dean

General:
Review of Ms. Titled “Hard Physical Work Combined with Heavy Smoking or Overweight May Result in Painful Vertebrae”

General assessment.
Adequacy of the question: This study outlines an interesting and important question particularly in light of the prevalence of lifestyle conditions and their enormous social and economic burdens. There are questions I have however, related to the Methods including the analyses, that need to be addressed before I can complete a thorough review of the Results and validity of the conclusions. Overall, the work may have merit but ascertain this, the Ms. needs to be tightened.

Adequacy of the Methods: Some elaboration of the description of these is needed as outlined in specific comments below.

Soundness of the Data: Adequate description of the primary data set which is shown as Table 1 which is helpful.

Adequacy of the standards of the Ms.
Adequate.

Adequacy of the discussion and conclusion
Adequate.

Adequacy of the Title and Abstract.
The following title may be more explanatory: ¿Associations among Physical Work, Smoking and Being Overweight in Relation to Painful Vertebral Bodies in a Cohort of 40 Year Old Danes¿

However, do we know for sure that the pain experienced is from the vertebral bodies or from secondarily affected soft tissue (e.g., well innervated structures such as the periosteum and muscle). I am a bit fuzzy on my anatomy of bone. This needs to be clear to ensure that the term ¿painful vertebral bodies¿ is defensible.

Response: We have struggled with this title, in the past and now, and have changed it to read ¿Self-reported physical work combined with heavy smoking or overweight may result in so-called Modic changes¿. Your suggestion includes the word ¿associations¿ but the title needs to emphasize that this is about the combination of variables.

The Abstract may need editing to correspond with suggested edits.

Response: Some changes have been made to the abstract, which are shown as highlights,

Acceptability of the writing.

I suggest that the investigators use the words ¿it¿, ¿this¿, and ¿there¿ more sparingly, by rewiring sentences with these constructions to minimize ambiguity and improve clarity.

Response: We have gone through the manuscript with a fine comb to make sure that no such ambiguities exist anymore.

SPECIFIC COMMENTS

Introduction

Re ¿What is the cause of ¿lower social class!¿

Is a discussion of ¿social class¿ really relevant? Rather than engage in discussion about ¿class¿, which some might consider a dubious distinction these days, would it not suffice to discuss the relationship of hard physical work to low back pain irrespective of ¿class¿. I am not necessarily suggesting ruling this out, but for me, more justification is needed to make this a ¿class¿ issue. If the investigators choose to retain ¿class¿ as a factor, then a definition of ¿class¿ and in particular ¿low social class¿ is needed. Further, if ¿class¿ is deemed to be central to this work, given it is highlighted at the beginning of the Introduction, why does this not appear in the title?

Response: The concept of social class is by no means a dead one, as witnessed by the information in our reference 1. According to the contemporary literature, most people would have no problems with the concept of social class is defined in relation to work, education, and income, and its importance in health and disease is well accepted. The purpose of this study was to investigate if smoking/overweight might be modified by hard physical work, and as all these three variables are commonly encountered in the lower social classes, the statement on social class was one way of entering the subject. Another author,
for example you, might have wanted to do this in another way. However, unless the present introduction is truly erroneous or unsuitable, we are of the opinion that the intellectual approach is the property of the authors, so to speak. We would therefore greatly appreciate if we could be free from re-writing the whole Introduction text. Also, we do not think that it is relevant to include more text on social class, definitions, consequences etc. as this is merely a brief passage in the introduction.

Re Hard physical work?
What is meant by this exactly? This point arises in the Ms. that the perception/experience of work as hard for example, can reflect the conditioning level of the person responding. Do the investigators have any knowledge of the physical conditioning levels of the respondents?
Response: True. We have discussed this aspect in one of the answers to the other reviewer and we are now using the term self-reported hard physical work (in addition to our text in the validity section).

Re Smoking or overweight?
I am aware of the literature that supports people of low income, low education, and engaged in unskilled employment, tend to have poorer health habits than others, e.g., they smoke more, exercise less, and tend to weigh more (generally poorer health outcomes). A grammatical point in this paper given that smoking and overweight are frequently paired, is that these words are not parallel. An appropriate alternative would be Being a smoker and being overweight. This needs to be checked throughout the Ms.
Response: This is a problem that we have already thought a great deal about. However, to use the correct grammatical terms makes the text very unwieldy, especially in tables and when the variables are used frequently. A look through the literature informed us that the solution we chose is frequently chosen by others. We have therefore selected to combine the verb (smoking), and the nouns (work and overweight), with the expectation that this combination will be considered an acceptable jargon.

Page 6. Data analysis.
More detail is needed regarding the calculation of the Odds Ratio and the association statistics, and these points need to be clearer in the tables.
Response: It is not customary, since quite some years now, to provide description of how to calculate odds ratios or references on how to do this, as it is available in all statistical text books and is part of the education program for most health professions. We have gone through the tables and note that odds ratios are used only in Table 5, in which it is clearly labelled as such.

Page 6. The section on Validity is important and well written as it addresses many key questions that come to mind in relation to this study based on secondary data analysis.
Response: Thank you.
In the tables, I would suggest describing what the bold face means in the legends below the tables, and specify again that p<0.05.

Response: Sorry, it has been corrected now (bold face) and we have removed the p-values instead to include odds ratios with their confidence intervals only, as they suffice to illustrate the results.

Major compulsory revisions: Address points above.
Response: Done

Minor essential revision: English grammar points mentioned above.
Response: Done

Discretionary Revisions: I would like the investigators to respond to two points in this category, however, if addressed satisfactorily, may not need to change the content.
Response: Done.

The issues related to the use of the term ‘social class’ and the issues of whether painful vertebral bodies is valid (bone pain vs. secondary soft tissue pain).
Response: Done.

CHANGES TO THE MANUSCRIPT

The title has been altered to include the words ‘so-called Modic changes’ instead of ‘painful vertebral bodies’

Abstract: The Background has been re-written to go with the change in the title. Also the word ‘self-reported’ has been added to the Objectives. The words logistic regression have been added to the Methods section.

In the Results, an extra sentence was injected, providing the odds ratio for the combination variable of heavy smoking and hard work.

Introduction, 3rd para, 1st sentence has been somewhat altered to accommodate the concept of verb and noun joined together (smoking and overweight)

6th para, 2nd sentence, the word ‘probably’ has been added in relation to sciatic pain being considered a proxy measure for disc degeneration. The following sentence has been re-arranged to avoid the word ‘this’.

On p.4, 5th para, 1st sentence, another re-write to avoid the word ‘this’.

At the bottom of p.4, ‘Could smoking and hard physical work’, 2nd sentence, a reference is provided for the statement that life-style is related to social class.

Methods, Data analysis, 3rd para, 1st sentence, the words ‘logistic regression’ have been added.
Under the heading of \textit{Validity}, we have added text on type of work in the 3rd sentence (\textit{and even so, people may change jobs and tasks may also vary over time. Nevertheless, this self-reported})

p.7, 6th line. We have added a text on dose-response and in the same para, last line, we have removed the word \textit{it} to write \textit{smoking}.

Same side, 2nd para from the bottom, we have added text intra- and interexaminer tests. (The reason why the percentage agreement is reported for VIP is that there were too few findings to make kappa analysis possible.)

Results, at the bottom of p.8, \textit{Summary of findings}. The word \textit{there} has been removed through a slight re-write of the sentence.

Discussion, subheading: \textit{What did we find} 2nd para, 3rd sentence, another re-write to avoid the word \textit{this}.

Same heading, last para, 2nd sentence, the words \textit{and non-significant} were added.

Conclusions, 1st para, 2nd sentence: the word \textit{there} has been removed, which necessitated a small re-write.

2nd para, an extra sentence has been added \textit{However, these combinations did not result in significant associations with any of the pain variables.}

Table 1, text has been added in relation to self-reported type of work.

Tables 4 and 5 have both had an explanatory text added in relation to significant findings written in bold.

\textbf{AUTHORS' COMMENTS}

We have done our best to accommodate the reviewers' comments, and hope that the end result will be considered acceptable.

Kind regards

Charlotte Leboeuf-Yde
(on behalf of the authors)