Author's response to reviews

Title: Vitamin D levels appear to be normal in Danish patients attending secondary care for low back pain and a weak positive correlation between serum level Vitamin D and Modic changes was demonstrated: A cross-sectional cohort study of consecutive patients with non-specific low back pain

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Title: Vitamin D levels appear to be normal in Danish patients attending secondary care for low back pain and elevated in patients with Modic changes: A cross-sectional cohort study of consecutive patients with non-specific low back pain

Dear editor and reviewers,

First of all, we thank you all for your thorough review and very useful comments on the manuscript, which we believe have significantly improved its quality and logic. In the text below, we have addressed each of the reviewers’ concerns and in the uploaded manuscript, all changes can be followed with tracked changes.

Response to reviewer Dr Stewart Leavitt

1) An important premise of this study is that serum levels of 25(OH)D at 50 nmol/L (20 ng/mL) represent a normal and adequate value of vitamin D within the Danish study population. Since a majority of subjects with pain fall within this range, it is presumed that vitamin D does not influence the pain conditions. However, this needs further qualification and discussion....

We have made reference to large population-based studies in Denmark that reference the general population and we found no other reference for changing the standards for normality. We have addressed this further in the discussion and provided more references for this.

a) The authors only briefly reference a single paper, by Misekilde et al. (Ugeskr Laeger 2005), as the source of their definition accepting 50 nmol/L as the threshold of adequacy within the general population; however, this paper is available only in Danish and is inaccessible to most readers for review and verification.

The National Food Institute at The Technical University of Denmark conducted a thorough analysis in 2010 [1]. It is unfortunately in Danish, but it is based on international peer-reviewed papers. The aim of the investigation was to consider all new evidence concerning Vitamin D in regard to recommendations for Vitamin D intake and in regard to prevention of several diseases, including thresholds for the general population. The report on the outcomes of this investigation is available (in Danish) at http://www.dfvf.dk/Default.aspx?ID=8596&M=News&PID=0&NewsID=2012. In the report, concentrations below 50 nmol/L are considered to be a Vitamin D deficiency and concentrations above 50 nmol/L are considered normal. We have added the report as a reference instead of Mosekilde et al 2005 [2] in the section “Definition of Vitamin D deficiency”. We have also added a paper by Lips (2004) to support our definition [3]. Furthermore, we have made reference to a more recent study by Heidari et al who used thresholds of 50 nmol/L (or > 20 ng/mL) [4].

This, of course, does not signify, that concentrations above 50 nmol/L are the threshold for adequacy. Nor does it exclude that some people actually may need to have higher levels in order to stay well.

i) In much of the research on vitamin D and pain, 75 nmol/L (30 ng/mL) is considered the threshold point between insufficiency and adequacy, and persons with pain have often been found to have 25(OH)D levels below this threshold.

We compared our results with the results of Haroon et al (2011) [5], who used a similar threshold for adequacy 53 nmol/L. We think a comparison with an Irish study is relevant considering latitudes. In the submitted paper, this part was left out due to the fact that only 8 of 231 patients in general rheumatology clinics had non-specific backache. We have added this part again because of its relevance. We have also made reference to studies by Lotfi et al and AL FS et al[6, 7]. These studies used thresholds of 100 nmol/L (40 ng/mL) and 22.5 nmol/L. And Heidari et al used 50 nmol/L (<20 ng/mL) as the threshold for inadequacy. In regard to back pain, we do not think that 75 nmol/L is a standard threshold to distinguish between insufficiency and adequacy in back pain studies.

ii) Some guidance (eg, U.S. IOM Report, 2010) has suggested that 50 nmol/L (20 ng/mL) is minimally adequate to maintain bone health in healthy persons; however, this value has been debated as being too low by experts in the field and it particularly may not be relevant.
for persons with musculoskeletal pain conditions.

Good point and we are aware of the ongoing debate concerning sufficient levels of Vitamin D and also the debate about the possibility of an upper threshold. The design of our study does not make it possible to draw conclusions regarding thresholds.

b) The authors note (p. 11) that vitamin D levels of LBP patients in their study reflect those of the “healthier segment” of the general population in Denmark. At the same time, however, those levels in LBP subjects are consistent with inadequacies of vitamin D found in other research.

This is true and as we argue in our discussion, this is due to different thresholds for normality/deficiency. We argue that the levels in the LBP subjects, who participated in our study, reflect the levels of the general population in Denmark. It is difficult to compare cross-sectional studies from different parts of the world, not only in the matter of thresholds. We have added a section in our discussion on the matter.

At the moment there are only sparse published data on serum levels of 25(OH)D in the general Danish population. Glerup et al (2000) reported levels of 47.1 +/- 4.6 in a control group of Danish women [8]. Brot et al (2001) reported Vitamin D status in healthy middle-aged women in Denmark and found a mean serum 25(OH)D of 53.5 nmol/L in a group of 280 women regularly exposed to sun and not using vitamin supplements [9].

We have added the two references to the discussion, the section concerning our results reflecting normal population.

c) At the least, the authors should include a discussion of why the “normal and adequate” 25(OH)D level (50 nmol/L) within the Danish population might be lower than that reported in most other research — with supportive evidence of that contention.

We find the discussion of adequate thresholds interesting. The aim of our study though was not to investigate healthy Danish subjects and compare their levels of 25(OH)D to levels in healthy subjects in other subjects. A discussion of the “normal and adequate” 25(OH)D level within the Danish population lies beyond this paper. We do believe that the levels of 25(OH)D in the Danish population reflect that found by others such as Hagenau et al from 2009 who found that the mean 25(OH)D level was 54 nmol/l (95% CI: 52-57 nmol/l [10].

i) Is there something about the Danish population in particular that allows them to thrive at 25(OH)D levels that are considered insufficient in other world populations?

We do not feel competent to explain whether the Danish population has a special ability to thrive at different 25(OH)D levels than other populations in the world.

ii) Does this mean that what may be adequate vitamin D for most healthy persons within the Danish population may be inadequate and deleterious for a segment of the population that develops musculoskeletal disorders?

We do not think our research can answer that question, we can only speculate and discuss—and yes, it is possible.

iii) Or, does this satisfactorily demonstrate that factors apart from vitamin D levels must be considered?

In regard to LBP, it is well known that LBP is a multifactorial problem. Please note the section in our discussion page 14. Using the usual values for normality – these patients do not seem to have Vitamin D deficiency.

2) MODIC CHANGES...

a) The assessment of Modic changes is a unique and novel aspect of this study, and a more extensive explanation of these abnormalities and the reasons why they were selected for inclusion in data collection could be of benefit to readers. Also, please define Modic Type 1 vs Type 2 changes.

We have added the definitions by Modic in the introduction. Note first section in background.

b) It seems unclear in the presentation whether Modic changes have been found in previous research to play an important role in musculoskeletal pain conditions. Please explain.

We have elaborated a little more on page 4 with the conclusions of a systematic review from 2008 (Jensen et al) who found a significantly higher prevalence of Modic changes in populations with non-specific LBP in contrast to non-clinical populations [11].

3) DISCUSSION SECTION: Presentation of study limitations...
a) The authors should indicate that the nonrandom, cross-sectional design of the study poses strong limitations for projecting cause-effect relationships (or lack thereof) and the external validity of the results.

b) Was the study sample truly sufficient to explore significance the various factors considered? (Despite having conducted a pre-study power analysis.)
We believe so, of course a larger study sample would have provided narrower confidence intervals.

c) The lack of a healthy-subject control group drawn from the same population for comparison makes it difficult to confirm that 50 nmol/L 25(OH)D is an appropriate threshold for denoting vitamin D adequacy in the study population.
We believe that the extensive studies by Brot el al, Glerup et al and The Technical University of Denmark’s National Food Institute (most data unpublished though), and supported by Hagenau et al give us good reason to believe that the values of the general population and its variance are known for Danish people.
However, we agree that these values and the variance may hide sub-groups of people (those with musculoskeletal pain) who have generally lower values, thereby lowering the mean values for the population. This has been addressed further in the discussion

d) Since patients were not provided vitamin D supplementation, it cannot be assumed that raising 25(OH)D levels would not have been helpful in ameliorating their pain conditions to any extent.
Thanks. The study was not designed to address this, and we do not speculate in that. We have removed our comment in the conclusion regarding “no sub-group, who would benefit from treatment with Vitamin D”.
The design of this study cannot lead to that conclusion.

e) FAIR BALANCE: I would recommend that, in the interest of fair balance, a “sensitivity analysis” be conducted and discussed to examine how the results and data interpretation might change if a more traditional 75 nmol/L threshold is used to demarcate 25(OH)D insufficiency vs adequacy in persons with musculoskeletal pain conditions.
As stated in the beginning, we believe the threshold to be right and what is widely accepted worldwide. However we did re-analyse the data with the suggested 75nmol/l and none of the associations changed significantly statistically or became statistically significant. Modic changes stayed significant though in the same direction.

f) The observations that vitamin D level was uncorrelated with LBP or leg pain level, or number of pain sites, is of interest and are well-illustrated in Figure 3. This would suggest that there is not a linear relationship of decreasing 25(OH)D and pain disorder severity or extent.
ii) However, it is still evident in the graphic depictions that, if a 75 nmol/L threshold is used, the vast majority of patients would fall below that level.
We are aware that a threshold of 75 nmol/L would categorise a larger percentage of our patients into Vitamin D deficient (precisely 71%).
ii) This suggests that vitamin D inadequacy may influence the development of a musculoskeletal pain condition, but not directly the severity of pain or the extent of the condition.
We believe that current evidence supports that Vitamin D deficiency may influence the development of a musculoskeletal pain condition (eg. Glerup et al). We cannot in our study conclude, that Vitamin D inadequacy is a main reason for the participants’ non-specific LBP.

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g) Still it must be acknowledged that not ALL persons with insufficient/deficient vitamin D develop pain conditions, and why some persons are prone to this while others are not has not been determined by available research evidence. (Modic changes might have been a novel way to help explain this, but the present study does not appear to provide answers in this regard.)
In regard to Modic changes, we agree that the results do not provide answers but it can contribute to new hypotheses.

h) The paradoxical findings for Modic changes — increasing at higher vitamin D levels — might be of some importance, if this finding can be assumed to be valid and not due to random effects or sample-specific artifact. In Figure 3 it appears that differences between categories (eg, 0, 1, 2, 1 and 2) may not be statistically significant and the Odds Ratio for this association (0.30) represents a small and possibly clinically unimportant effect size. Further discussion of this is needed.
We always have to take into account random effects and sample specific artefacts. There is no statistically significant difference between the categories of Modic changes. A summarised odds ratio of 0.3 with confidence intervals not even close to 1 we consider to be rather important – a more than three fold reduced risk. In the area of LBP OR above 2 and below 0.5 are rare for biological factors.

i) The relationship of BMI and 25(OH)D level appears to be a small effect size that may be of little consequence that is not elaborated in this study.

With the method of sample size we used, we had acceptable variance comparable to other studies.

4) CONCLUSIONS...

a) The statement, “…most of the Danish people with non-specific LBP do not have a vitamin D deficiency…” goes beyond the scope of the evidence, considering the limitations of the study and the particular definition of deficiency used here.

We carefully used the word "indicate" in the beginning of the sentence. However, the point is well taken and we have included our discussed limitations in the conclusion and rephrased it to read: The results of this study indicated that a group of Danish people with non-specific LBP did not have Vitamin D deficiency.

b) The statement, “Therefore, they do not constitute a specific sub-group of patients who could be treated with vitamin D,” which also implies that such patients would not benefit, is not confirmed by this study and is conjectural — especially, since effects of such supplementation were not examined.

This is a good comment, we have removed that part.

Minor Essential Revisions

The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

5) In Table 2, pain scores for LBP and Leg pain range from 0.0 upward. Why would someone scoring 0.0 be included in the study?

We looked further into the one person scoring 0 for LBP. At inclusion, the participant reported pain on the left side in transition between the lower lumbar spine and sacrum, but in the questionnaire he has not scored his back pain, only leg pain, which is the reason for the scoring 0.0. Not all patients reported leg pain.

6) There probably should be some discussion that the Nordic Council of Ministers has appointed a working group to reassess and revise guidelines for vitamin D recommendations, and that many believe current guidance sets thresholds too low. See: [http://www.slv.se/en-gb/Startpage-NNR/](http://www.slv.se/en-gb/Startpage-NNR/)

We support an on-going adjustment of guidelines in regard to Vitamin D as well as in other areas, if new evidence supports an adjustment. In the preliminary report, we have not found adjustment in thresholds of 25(OH)D and it is not the aim of our paper whether current thresholds reflect sufficient levels of 25(OH)D.

7) A final proofing of the article is recommended.

A native English person has checked the manuscript.

8) CLARIFICATION OF REFERENCE CITATIONS...

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a) I would recommend that all reference citations be reviewed for completeness and consistency with the journal’s preferred style.

We have used the reference batch for EndNote delivered by the BMC and we believe references are in the correct style.

b) REFERENCE 7 -- recommended citation would be:


Thank you. We have changed the reference.

c) REFERENCE 23 -- “Dimension RaMC: Sample Size Calculator. In.;2012.” This reference is incomplete and needs to be checked.

Yes, something is missing—we have added that.

I hope that these observations and recommendations are received in the spirit of constructive criticism and are helpful.

We appreciate your thorough review and we have addressed all comments above and in most cases incorporated your suggestions in the manuscript.
Response to reviewer Henning Glerup

Reviewer's report:
The study is well designed. The first objective is to describe vitamin D level in Danish LBP patients. This objective is fulfilled by the study. Second objective is to investigate how the vitamin D levels are related to a number of parameters. And third to examine the associations between vitamin D deficiency and Modic changes, muscle weakness, paresthesia and widespread pain. There is a number of limitations in these two latter objectives: First of all only 11% (n=17) had moderate/severe vitamin D deficiency and only one patient had in fact severe deficiency. It is likely that the weak representation of vitamin D deficiency in the study group will hamper any signal on vitamin D deficiency related muscle pain or weakness in the larger study group. In my experience vitamin D deficiency related myopathy is primarily seen in vitamin D levels below 25 nmol/l. The strength of the study could possibly have been increased if the authors had included measurements of PTH, as secondary hyperparathyroidism indicate more severe vitamin D deficiency. The authors are, however, aware of this limitation in the study as indicated on page 12.

This is a very good point: We have changed the paragraph in which we discuss our findings in relation to myopathy-related symptoms.

The title of the paper are: “Vitamin D levels appear to be normal in Danish patients attending secondary care for LBP and elevated in patients with Modic changes: ….”

The first part of the title is in agreement with the study results. Vitamin D deficiency seems not to be an important part of the explanation of LBP in the Danish study group. However, the study cannot rule out the importance of vitamin D deficiency in LBP in other study groups with a higher frequency of severe vitamin D deficiency. This could be a likely explanation for the conflicting results when comparing to other studies.

Yes, you are right. Therefore, we have also mentioned this particular study population in the title.

The second part of the title is, however, not correct. The authors demonstrate a weak correlation between vitamin D levels and Modic changes, but none of the vitamin D levels has been found increased above normal levels.

Again, you are right, we have changed the title to “slightly higher”. We do not think the association is weak – see comments to reviewer above.

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Major compulsory revisions:
The title should be changed. A suggestion could be: “Vitamin D levels appear to be normal in Danish patients attending secondary care for LBP. A weak positive correlation between serum levels of vitamin D and Modic changes was demonstrated. ….”

Thanks, well phrased. We have tried to change the title accordingly

p. 13, second paragraph: “It is possible……. in inflammation. ” This paragraph is rather speculative, and should not be part of this paper. I do not know any data that could support the suggestion, that even high normal levels of 25-OH-vitamin D could result in a decreased ability to reduce inflammation”.

I suggest that the paragraph is simply deleted from the paper.

We are aware that this part is speculative in our attempt to develop new hypotheses. We have removed this paragraph.

Minor essential revisions:
p. 4, second paragraph, second line: “There is evidence.....” I suggest: “Previous studies suggest that Vitamin D may......”

Your suggestion has been followed.

Minor comment:
Table 1. Weakness in legs. According to the table this parameter in measured by self-reporting from the patient. Using this method the vitamin D deficiency related muscle weakness will be underestimated, as patients more often will report general fatigue rather than muscle weakness. Ideally the muscle strength should have been measured by an objective method. However, in this setting I do not thing the method used will change the conclusions of the study.

We agree with you that it would also have been interesting to include clinical examination findings of muscle weakness. However, we refer to the general symptoms that have been related to Vitamin D deficiency in the literature. We have commented on the matter in our discussion.

Comments to reviewer Behzad Heidari
The authors of paper entitled "VitaminD levels appear to be normal in Danish patients attending secondary care.............. " intended to determine the relationship between vitamin D deficiency and simple back pain(BP) in a cross-sectional study.In addition several secondary aims including association between vitamin D and age,sex BMD,Modic changes ...were also assessed.They found a significant inverse relationship between vitamin D and Modic changes but not with BP, and the authors conluded that Modic changes were protective of low vitamin D

1- Simple BP should be defined.

We have now defined low back pain in the paper with reference to Dionne et al [12].

2-Modic changes also require to be defined.

Point well taken, see comment to first reviewer. We have elaborated the paragraph regarding Modic and added the definition by Modic [13].

3-Introduction section should be shorten.

We have revised the introduction but find it hard to shorten without missing important information. We have combined three major topics in the paper – LBP, Modic changes, Vitamin D deficiency, and their possible association. Therefore, the theoretical part appears to be long.

Methods
4-To determine the status of Vitamin D in BP it was required to include a control group without BP

There are design issues here. Determination of the prevalence of a condition in a specific population only requires that population.

5-Sample size does not seem to be adequate to detect a significant differences for several research questions of this study.

We believe that based on our sample calculations, which were based on previously reported levels of variance that if there were clear tendencies these would become apparent, even with this sample size.

6- Details of statistical analysis for relationship or comparisons have not been presented

We may have been unclear on some of the comparisons and we have revised the section on statistical analyses to read: Differences in distributions of descriptive data in the groups of Vitamin D deficiencies were cross-tabulated and tested using Fisher’s Exact Test. Correlations between Vitamin D levels and the variables of interest were visualised in scatter plots and further investigated using a Pearson correlation coefficient for continuous and normally distributed data.
and a Spearman correlation coefficient for categorical data and non-normally distributed data. Associations between low Vitamin D levels and clinical variables of interest were expressed as odds ratios with 95% CI obtained from logistic regression. For these analyses, outcome variable (reduced Vitamin D) and explanatory variables (Modic changes yes/no, muscle weakness, paresthesia, and widespread pain if number of pain sites was > 5) were dichotomised.

7-Discussion section requires to be revised. In regard to the direction of relationship between Modic changes and vitamin D - Based on data presented in Introduction, it is also possible that sufficient vitamin D may be protective of Modic changes.

Point well taken, this is a controversy that needs further investigation Minor compulsory revision

what is the difference between degenerative spondylolistesis- and spondylolystesis with spondylosis?

Spondylolisthesis is a movement of one vertebra over another. When it occurs due to age or disc degeneration, it is called Degenerative Spondylolisthesis. Spondylolysis is a condition in which there is a defect in a portion of the spine called the pars interarticularis, which can cause the movement of one vertebrae over another (spondylolisthesis). The last part is considered pathologic and therefore part of our exclusion criteria. We believe these conditions to be well known to people working in the area of LBP.

How the authors found variations of serum vitamin D variations over the investigation periods? Did they re pitted serum vitamin D assessment for two or three consecutive months?

Data were collected over a 3-month period and we simply reported the mean values for the levels for the people by month.

How the authors determined the relation between vitamin D and clinical symptoms. It is required to describe in Method section for example, whether patients with or without paresthesia were compared in regard to serum vitamin D?

See chapter on statistical analyses: cross-tabulation of values for clinical variables for the subgroups of people with severe/moderate deficiency, mild deficiency, and normal, including statistical testing, calculating correlation coefficients, and odds ratios for the dichotomised variables.


