Author’s response to reviews

Title: Associations between pressure pain threshold in the neck and postural control in patients with dizziness or neck pain – a cross sectional study

Authors:
Mari Kalland Knapstad (mariknap@hotmail.com)
Frederik Goplen (Frederik@goplen.no)
Tove Ask (tove.ask@helse-bergen.no)
Jan Skouen (jan.skouen@helse-bergen.no)
Stein Helge Nordahl (mail@shgn.no)

Version: 1 Date: 09 Aug 2019

Author’s response to reviews:

Changes in the manuscript is marked with "red".

BMSD-D-19-00714
Associations between pressure pain threshold in the neck and postural control in patients with dizziness or neck pain – a cross sectional study
Mari Kalland Knapstad; Frederik Kragerud Goplen; Tove Ask; Jan Sture Skouen; Stein Helge Glad Nordahl
BMC Musculoskeletal Disorders
Reviewers answer
Reviewer #1
Thank you for the opportunity to review the manuscript by Knapstad and colleagues a second time. The study investigated neck tenderness in 239 patients with dizziness and 129 with neck pain. The aim of the study was to evaluate whether neck tenderness was independently associated with postural instability. The relationship was analysed with linear regression. The manuscript has been improved but there are still several major concerns about the manuscript. The aim was to examine if neck tenderness was independently associated with neck tenderness. In my opinion the study lack variables to analyze this and cannot give any answer to the aim. In linear regression, the b-values indicate the individual contribution of each predictor to the model. In this study, the b-value reported are very small – therefore the variable(s) used in the model cannot predict dizziness. This is also seen in the R2 values. In linear/multiple regression there is not common to use effect size as an explanation for R2. Instead, the R2 value accounts for how much variation in dizziness that have been explained in your models. In Table 2 and Table 3 – only 4 to 8 % of the variation could be explained by neck tenderness (PPT) meaning that more than 90% of variation have not been explained in the study. And the models were not improved by including age, sex and general pain meaning that other variables will be
much more important. Again – I highly recommend the authors to discuss the analyses and the interpretation of the results with a statistician. Moreover – both the aim, result and discussion need to be rewritten.’

Response:
Thank you for these comments. To clarify, we did not aim to predict dizziness in this paper, only postural sway. The aim has now hopefully been satisfying clarified.

Balance is a multifactorial construct with a myriad of potential causes. Neck pain has been considered as one of the factors. We did not aim to build a regression model that would explain most of the variance, only if PPT had some explanatory contribution. The aim of this paper was to examine if PPT in the neck was associated with sway area. PPT was the only predictor of interest, the other variables were considered as adjusting variables.

Regarding effect, we mean the effect of PPT on sway, which we agree is small, as expected in an unselected group of dizzy patients. Dizziness is a multifactorial symptom, and we do not suggest that neck tenderness explains postural instability in a majority of dizzy patients. A minority of the patients could possibly have cervicogenic dizziness, however this is a theoretical disorder that to date lacks definite diagnostic criteria. We have revised the use of the term “effect” throughout the paper, not to confuse it with standardized effect sizes.

We have consulted with a statistician, who suggested the use of linear regression in order to examine the association between the two main variables while adjusting for covariates. R2 shows that PPT explains some of the variance in postural sway. R2 is thus interesting to report, but it was not the PPT explanatory power that was the main interest, but if there was an association at all between PPT and sway. The association turned out to be statistically significant, but we agree that further studies are necessary to determine the clinical significance.

Regarding remarks about p-values on descriptive statistic and normative values. This paper did not aim to examine between-group differences, but merely to examine the association between sway and PPT in two different populations. We think comparisons other than these would confuse the reader without adding information of value.

Reviewer #1
There is still lacking references and explanation for how pressure pain threshold (PPT) could measure mechanoreceptors in the deep cervical muscles or how the more superficial neck muscles with decreased PPT could affect postural sway.

Response:
This is not something we claim. As mentioned in the Discussion, PPT cannot directly measure altered proprioception of the neck, but the theory is that pain in the neck region influences the afferent input, and previous studies have supported this. The pressure pain threshold (PPT) reflect pain sensitivity and is a common method for quantifying tenderness [1, 2]. The reason we chose this method is that it might be a more objective technique than self-reported pain [3]. We see the reviewer’s point on measuring pain in the deep segmental muscle, however; we do not claim that PPT measure any muscles selectively. Pressure is applied to several defined points and may affect a number of both deep and superficial neck structures. PPT correlates well with other measures of pain and previous studies have indicated that patients with self-reported neck pain have impaired balance, and these findings are usually explained by the known connections between the proprioceptive, visual and vestibular systems.
Reviewer #1

Abstract: The purpose of the study – pressure pain threshold in the neck is independently associated - cannot be answered with the included variables as seen in the analyse results. The results must be rewritten concluding this and that only a small association have been found and 90% of the variations have not been explained. See further comments.
Response:
This has been revised. Please see comment above (ln 27 – 49) regarding R2 in this paper.

Reviewer #1

Background:
The background have been improved and page 3-4 gives an explanation of the mechanism for proprioception including also that neck pain may influence proprioception.
The authors need to explain why they think that PPT (pressure on superficial neck muscles) relate to postural control. Are the superficial muscles important to measure? Or can PPT also investigate the deep structure? Why have you not include the patients self-rated pain intensity?
Response:
The argument for using PPT has been added to the background p.4, line 89-94. PPT is used to say something about the sensitivity for pain in the neck. If PPT can directly measure certain structures in the neck is not certain, however, we theorize that the higher sensitivity/lower tolerance for pain in the neck, the higher likelihood for altered afferent precision. In regards of self-reported neck pain we wanted to investigate PPT in dizzy patients regardless if they stated neck pain or not. In addition PPT reflects both self-reported pain but is perhaps a more objective measure. Please see out first comment as well.

Reviewer #1

Page 4 line 83: “The relationship has previously been mostly studied in patients with neck pain; however, it is not established whether the degree of neck pain is associated with the degree of postural control.” Is that a second aim of the study? Have you investigate that in your study?
Response:
The association between the degree of PPT and degree of sway is what we examine with linear regression as both are continuous variables. In this paper, we have used PPT as a measure of pain and sway as measure of postural control.

Reviewer #1

Page 4 line 89 “In this study we aim to examine whether neck tenderness, or the threshold for pain, is an independent predictor of postural instability in patients with dizziness and in patients with neck pain, controlling for age, sex, and generalised pain.
Please change the aim in the abstract so it is the same as in the background.
Response:
Apologies for this. This has now been changed to match the abstract, p. 4-5, line 95-96.

Reviewer #1

Is there two different test, both neck tenderness or the threshold for pain?
Response:
We acknowledge that these term has been used interchangeably and seems confusing. We mean that a high/low PPT reflects low/high tenderness. We have changed this throughout the manuscript to PPT, and that it is a measure for pain sensitivity.
Reviewer #1
Page 4 line 91: “In addition, since previous studies have found that patients with chronic pain conditions tend to have reduced balance [20-22], The references are studies where the patients could have reduced postural control due to age, and/or altered function in gluteus muscles and fibromyalgia. Why are these references selected to state that generalized pain are an important variable in this study? It seems likely that postural control in ref (20-22) are related to other mechanism than generalized pain?? The population are very different.
Response:
Thank you for this input. The references has been changes. Patients with fibromyalgia have previously been found to have altered balance. In addition, patients with neck pain, rarely have isolated but more of spread pain pattern. Thus, to adjust for pain in other parts of the body is relevant to examine if the PPT in the neck is independently associated with sway ADJUSTED for generalized pain, p. 4, ln 96-99.
Reviewer #1
Page 4 line 93: … it would be interesting to examine whether neck tenderness is independently associated with reduced postural control.
Delete the word independent. The results are weak and could not establish this.
Response:
This has now been deleted.

Method
Reviewer #1
Page 5, Design and setting: Include a flow chart of recruitment.
Response:
A flow chart has now been added, p. 6.

Reviewer #1
Participants: Give the eligibility criteria, and the sources and methods of selection of participants. In the previous manuscript “The first center was an earnose-throat (ENT) clinic that receives approximately 1200 referrals yearly from general practitioners and specialists concerning dizziness of suspected vestibular origin. The second center was an outpatient spine clinic that admits approximately 1400 patients”. Explain how the patients were selected and included in the study. How many denied to participate? Why was the groups not equal regarding participants, fewer in the neck pain group? Did the group differs in other background variables? Explain inclusion and exclusion criteria clearly. For example – could patients have other disease for example stroke, hip- or knee pain or other disease that may have impact on postural control. If this data were not collected, please include as limitation in Discussion.
Response:
As mentioned in the previous response, there were various reasons; Only local, secondary referrals were included at the ENT clinic. Unfortunately, we did not record all participants who were not invited (e.g. vestibular schwannomas, divers, stroke patients or tertiary referrals). This has been added in as a limitation under Discussion p. 17, ln 347-348. We, of course, registered the ones being excluded after starting the assessment.
Only the patients with neck pain at the spine clinic were included, and patients with other referral reasons were naturally not eligible.

Reviewer #1
Page 5, line 121. Patients with neck pain &gt; 3 months were included. Have the included neck pain patients also dizziness?
Response:
The patients were asked if they experienced dizziness the last 14 days and this was registered and is now included in table 1. However, doing a subgrouping of these patients would result in a loss of power in the regression analysis and we chose to group the patients according to their primary complaint and referral center.

Reviewer #1
Page 6, line 135 “This threshold has previously been found to predict shoulder neck pain”
Please include normal values for PPT. How much pressure are “abnormal”? In Table 1, are the mean value for PPT “normal” or high in the two study groups? Include in the method.
Page 7 line 160 Postural control. What is the normal value for postural sway area with eyes open and eyes closed? Please include this in the manuscript
Response:
There are no published normative values for the PPT in these exact cites, nor sway area for the platform used. Walton et al (2011) examined the PPT in healthy controls at the upper fibers of trapezius of 251.8 kPa [4]. However, we do not believe that this is a just comparison as it is a different site. Besides, we feel that the question of the PPT values were normal or abnormal is a question on the side of aim of this paper. Still, we acknowledge that to examine if the association was present in a healthy population would enhance the paper. The lack of a comparative normal population has now been included as limitation p. 17, ln 350-351.

Reviewer #1
Page 8, line 180 “…medical chart data as age, sex and symptom characteristic” Please include symptom characteristic in Table 1. For example, how many patients in the neck pain group had also dizziness?
Response:
This has now been added to Table 1.

Reviewer #1
Page 8, line 195 “The sample size was estimated based on recommendations by Green [28] for multiple regression…”
Are the variables age, sex and generalized pain included as independent variables in a multiple regression Model (Model 2 and Model 3)? Multiple regression allows you to determine the overall fit (variance explained) of the model and the relative contribution of each of the predictors to the total variance explained. The reviewer have understand that you want to explain how much of the variation in postural control that can be explained by the variables included in model 1 (and model 2 and 3) "as a whole". Not to show the "relative contribution" of each independent variable in explaining the variance. Is this correct?
Also, adjusted R² need to be reported that compares the descriptive power of regression models—two or more variables (model 2 and 3). Every predictor or independent variable, added to a model increases the R-squared value and never decreases it. A model that includes several predictors will return higher R² values and may seem to be a better fit. However, this result is due to it including more terms. The adjusted R-squared compensates for the addition of variables and only increases if the new predictor enhances the model above what would be obtained by probability. Conversely, it will decrease when a predictor improves the model less than what is predicted by chance.

Response:
We absolutely agree that multiple regression allows you to determine the overall fit of the model and the relative contribution of each of the predictors to the total variance explained. However, as mentioned in the beginning balance is a multifactorial construct with myriad of potential causes. Neck pain has been considered as one of the factors. We did not aim to build a regression model that would explain most of the variance, only if PPT had some explanatory contribution. The aim of this paper was to examine if PPT in the neck was associated with sway area. PPT was the only predictor of interest, the other variables were considered as adjusting variables, not independent predictors. R² in this case show, like the reviewer points out that there are many factors that are lacking in explaining the sway in these patients. However, we wanted to explore the possible relation of PPT in the neck and body sway. The b-values are small for the PPT, however, the analysis show a tendency of the PPT having an effect on sway in dizzy patients from the ENT-clinic. This has not previously been found. Seemingly, a change in PPT is associated with a change in sway.

After the advice of the statistician we have now changed the text in the Analysis section, p. 9, ln 194-210, and removed “multiple regression”.

Reviewer #1
Page 9, line 216 “Descriptive data are given in Table 1.”
Descriptive data typically also include the overall sample size, sample sizes in important subgroups (e.g., for each treatment or exposure group), and demographic or clinical characteristics such as the average age, the proportion of subjects of each sex, how many months/years with dizziness and/or neck pain, working, on sick-leave and so on. Please include important information of the study sample and p-value e.g between-group differences (neck pain and Dizziness group) in Table 1.

Response:
The symptom duration, and concurrent complaints has been added. Age and sex was written in the text, however we have now moved it into Table 1. We do not quite understand the reasons for adding p-values as these are descriptive variables and statistics test between-group differences were not the aim if this paper.

Results
Reviewer #1
Page 11, line 219-227 The Results are a bit difficult to follow.
Line 219 “PPT is not a significant predictor…” – are this for both groups? Not for adjusted data (age, sex and generalized pain)?

Response:
This has now been revised p. 11, ln 244-245.
Line 222-227, The values in the results part are not included in Table 2 you refer to?  
Page 13, line 232-237. The values in the results part are not included in Table 3 you refer to?  
Response:  
Apologies for this. These values have been back transformed from the log transformation and we have stated that under Analysis p. 9, ln 208-209. The tables include the log-transformed values. (In the regression, sway data were log transformed and the independent (kPa) is in its original metrics. To interpret the amount of change in the original metric of the outcome, we have exponentiated the coefficient and confidence interval of the sway. To calculate the percentage change per unit change of PPT, we then subtract 1 from this number and multiply by 100. These values are the values from the back transformed coefficients (sway data were log transformed)).

Discussion  
The Discussion need to be rewritten due to my comments about results, statistics. The detailed can be revised again but here are the main comments.  
Reviewer #1  
Page 14, Line 243-250. Your results as shown in Table 2 and 3 have shown a very weak model(s) with only 6-8% variance explained. Was the effect robust? You need to deliberate your results more carefully and discuss the shortcoming of the results.

Response:  
We have now revised the section, p14, ln 267-274.

Reviewer #1  
Line 252  However, these studies did not analyse the quantitative relationship between the degree of neck pain and postural control…..  
Was this an aim of the present study?  
Response:  
Yes. Thus, the use of linear regression. However, we used PPT as it may be a more objective measure.

Reviewer #1  
Line 258  PPT cannot directly measure altered proprioception of the neck, but the theory is that pain in the neck region influences the afferent input, and previous studies have supported this [7, 31].  
Is PPT a test for pain in deeper muscle layers and other deep tissues? Have you any references or theory for that?  
Response  
See comment above after the reviewer’s initial comment above (ln 26-49).

Reviewer #1  
Line 261 “The observed relationship in dizzy patients might be due to an amplifying effect of increased neck pain in patients who already have a sensory deficit.”  
Increased neck pain may be a result of higher muscle tension when trying to “stabilize” dizziness, to make the “world be steady”? Why should it be a results of sensory deficit? Include other possible explanation for neck tenderness.

Response  
This section is revised, p 14, ln 285-289. We agree that dizziness might lead to increased muscle tension in the neck. However; we do not propose that neck pain should be the result of a sensory deficit. However, we think that damage to the neck muscles could cause both pain and sensory deficit due to damage of the proprioceptive muscle spindles. If the dizzy patient already has
some sensory deficits due to vestibular disorders e.g., the additional neck pain could be the reason for the observed relationship.

Reviewer #1
Line 269 “The Romberg ratio is considered to be an indication of visual dependency due to proprioceptive deficit [27], and we found that a reduction in the Romberg ratio was associated with an increase in PPT in both the upper and lower neck. Seemingly, patients with a higher PPT had a smaller ratio between the eyes closed and eyes open conditions.”
Line 273 “A possible interpretation of our findings is that a lower PPT in the neck is associated with less reliable cervical proprioceptive information and thus higher visual dependency, therefore causing larger differences between sway in the two conditions.”
In methods, page 8 line 172 have you wrote that higher ratio indicates greater visual dependency. It is not clear to the reviewer what you mean? Can you please clarify the interpreting of the results?
Response
This section has been revised. Hopefully it reads easier. If you stand more unsteady with eyes closed, compared to eyes open, it is an indication of possible proprioceptive deficit as the patient relies more on vision due to proprioceptive issues. P. 15, ln 294 - 304.

Reviewer #1
Line 279 “Posturography with eyes closed when standing on foam rubber is considered mostly to rely on vestibular function because vision is eliminated and proprioceptive feedback from the feet is unreliable [33]. In this condition, the brain might choose not to rely on proprioceptive information from the neck as well as from the feet. However, the finding of a relationship between sway area and PPT in the lower neck in this condition, after adjusting for age, sex, and generalised pain, might indicate that neck proprioception still contributes to postural.
Your models have a very weak explanation (R2) for PPT and the dependent variable dizziness. You need to be cautious with the interpreting and what you can draw for conclusions, please consider rewriting.
Response
Thank you for this comment. To clarify, the dependent variable is sway area, not dizziness. We have revised this section to be more cautious p. 15-16, In. 310-315. However, we feel that we have to discuss the possible explanations to our findings.

Reviewer #1
Line 295 “This might suggest that the upper neck is more related to generalised pain compared to lower neck pain.”
Please delete, you have not results to draw this conclusion.
Response
It was not meant as a conclusion, but a suggested explanation of our findings. Still, we have now deleted the section.

Reviewer #1
Line 299 “The effect size….”
Please rewritten and discuss the explained variance for postural control due to the included independent variables (predictors) in multiple regression.
Response
Please see the first comment about the aim of this study above (ln 27-49). Consulting our statistician, he advises to avoid using the word “multiple” and just use “linear regression”, as we used the other variables as adjusting variables, and not as several other predictors.

Reviewer #1
Line 300 “However, previous studies examining PPT in the neck areas found a minimal detectable change ranging from 69 to 113 kPa [34, 35].
Please include in the Method section the reliability and minimal detectable change for PPT test in patients with dizziness (35)
Response
We have now added the ICC and MDC values from a previous study, p. 7, ln 146-150.
Reviewer #1
Line 304 “In light of this, it is interesting to speculate whether the association found in this study, however small, might influence the patients’ symptoms and feeling of unsteadiness.”
Do you mean for neck pain of dizziness group? Were any of the patients (in neck pain group or dizziness group) examined for cervical dizziness? How can this conclusion be drawn from your results?
Response
To explain, we merely discuss the results and its possible explanations. It is just suggestions based on the observed association between PPT and sway in the results. It is not a conclusion. Cervicogenic dizziness is still a disputed entity, and as mentioned under limitations, this study only examined large symptom groups. It has now been revised to clarify. P. 16, ln 317-318.

Reviewer #1
Line 307. Previous studies have found that patients with dizziness disorders often report neck pain [18, 19], which might be due to increasing fear of head movement [37] and avoidance behaviour [38, 39]. Still, after adjusting for generalized pain, PPT was independently associated with sway area in the present study.

The reviewer is not clear how the authors mean? The neck muscle tension increase in dizziness and may cause the neck pain. Please explain.
Response
This section was implemented as a response to the reviewer’s previous comment “The reviewer do not agree with the conclusion and reported results in the discussion. Can the authors declare that PPT predicts postural sway? Or may increased postural sway (of different causes) increase muscle tenderness?”

The full section was “Over time, a decrease in postural control might in turn result in an increase in neck pain. Previous studies have found that patients with dizziness disorders often report neck pain [5, 6], which might be due to increasing fear of head movement [7] and avoidance behaviour [8, 9]. Still, after adjusting for generalized pain, PPT was independently associated with sway area in the present study” and was meant to discuss that it is a possibility that increased sway can cause a lower PPT. This has been moved up to p. 14, ln 285-287, and we have aimed to argue that both can influence each other.
Reviewer #1
Line 313 “First, the effect sizes found in this paper were relatively small, although there is no consensus on cut-off values for the way area, thus making an interpretation of the actual value difficult. “

R2 is a statistical measure that represents the proportion of the variance for a dependent variable that's explained by an independent variable or variables in a regression model. What do you mean with cut-off values? Discuss the explained variance of your models see previous comments. This part (313-335 and Conclusion) need to be rewritten. Moreover, adjuster R2 should be included that tells how well the model (s) generalizes.

Response
Apologies. We found some spelling errors. There is no agreement on cut-off values on “healthy” sway area, thus making the interpretation of the changed sway rate per unit increase of PPT difficult in terms of clinical relevance. This has now been revised, p. 16, ln 332-336.
We have not chosen to include the adjusted R2, as PPT was the only predictor we included and the other variables considered as adjustments variables.

Reviewer #1
Some question have not been answered from the previous review.
Neck tenderness
Difficult to understand where the pressure was examined – 9 points each side, include a figure that shows examined points?
Response:
Do to copy rights, we cannot include the illustration, however; we have clearly stated where the illustrations can be found, p. 7, ln 162.

Reviewer #1
Postural control
Could the Rhomberg ratio be affected of other disease or illness? Need to be interpreted in discussion.
Response
This is now been adressed in the discussion p. 15, ln 302-304.

Results
Table 1. To be able to understand the table please include normative values of postural sway or at least discuss in the Discussion the differences between the patients related to people without dizziness or neck pain.

Response
To our knowledge, there are no published comparable normative values on this exact platform or these sites for measuring PPT. Again, the aim was to examine association between sway and PPT.


