Author's response to reviews

Title: The relation between body mass index and musculoskeletal symptoms in the working population.

Authors:

Laura Viester (l.viester@vumc.nl)
Evert ALM Verhagen (e.verhagen@vumc.nl)
Karen M Oude Hengel (karen.oudehengel@tno.nl)
Lando LJ Koppes (lando.koppes@tno.nl)
Allard J van der Beek (a.vanderbeek@vumc.nl)
Paulien M Bongers (paulien.bongers@tno.nl)

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Author's response to reviews: see over
Dear Editor,

In response to the editorial request we provide a point-by-point description of the changes made:

REVIEWER 1

We would like to thank the reviewer for the encouraging words and constructive feedback, which helped to improve our manuscript. Overall, in the revised version of our manuscript potential confounders have been presented in all tables (full models) and checking for interaction has been described more clearly in the paper. A point-by-point reply to the reviewer’s remarks and description of the changes made are provided below.

Major Compulsory Revisions

1. In this study, confounders were not well controlled. Only age and gender-adjusted models were reported. The outcomes of the study are common and sample size is large. Most of the important confounders, such as physical and psychosocial factors were not controlled for. Some existing confounders were included in the models only as dichotomized variables, such as smoking, physical activity. The sample size is large enough to control for many confounders. It is not justified ignoring those factors that change the crude effect size less than 10%.

We concur with the reviewer, and analyses have been adjusted accordingly. Initially, only confounders that affected the crude effect sizes > 10% were presented in the final model in the revised tables (table 2 & 3), additional full model effect sizes have been presented. Measured workbad factors were added as potential confounders: using force, working in awkward positions, repetitive motions, and use of vibrating tools. Only information on current smoking is available. Physical activity (PA) was measured as days a week physically active for 30 minutes or more of at least moderate intensity. PA was dichotomized to meeting the public health guidelines (yes/no). Potential psychosocial confounders, for instance stress, anxiety or depression disorders were not measured. This has been added to the discussion on limitations of the current study:
"In the analysis the association was controlled for several potential confounding factors, however some potential psychosocial confounders, for instance stress, anxiety or depression disorders, were not measured, and consequently could not be controlled for."

2. The rate of overweight/obesity, exposure to physical load factors, and occurrence of musculoskeletal symptoms differ in men and women. The effects of obesity on musculoskeletal symptoms may also differ in men and women. No gender-specific analysis was performed in this study. If findings were similar for men and women, then only gender combined results would be reported.

In the methods section, effect modification was defined as a significant interaction term (p<0.05) between physical workload and BMI. However, the results on Table 3 show that stratified analysis was used to assess effect modification, but not including the product term of physical workload x BMI in the model. How p-value was estimated for interaction using stratified analysis?

Stratified analyses were not used to assess or determine effect modification. First possible interaction for potential effect modifiers was checked by adding interaction terms to the model. This was performed for age, gender, and workload. Only if interaction was found (interaction term p-value < 0.05), stratified analyses were performed and presented. This is the usual and proper way to deal with interaction in epidemiology. This probably not described adequately in the methods section. Therefore, (section analysis, 2nd paragraph):

"The analyses were stratified for physical workload (high/low) if the associations between BMI and musculoskeletal symptoms differed between employees with high or low physical workload. Effect modification was defined as a significant interaction term (p<0.05) between physical workload and BMI" has been replaced by:

"Effect modification was defined as a significant interaction term (p<0.05) between potential effect modifiers (age, gender, physical workload) and BMI. Analyses were presented stratified for age, gender, or physical workload if the associations between BMI and musculoskeletal symptoms differed based on significant interaction terms."

As described, first gender interaction in the association between BMI and MSD was checked. Interaction terms all had p-values > 0.05. Therefore we conclude that findings are similar for men and women, and no gender stratified analysis was performed.
3. Why an interaction between physical workload and BMI was explored using a cross-sectional design, not using a cohort design?

Although cohort samples are preferred over cross-sectional data in studying relations (causally), due to limited statistical power in the cohort sample, interaction was studied in the cross-sectional data. We did not find significant interaction for workload in the baseline cohort data.

4. Using a variable with 6 categories will provide better estimates than splitting the sample.

1. Normal BMI and no exposure to physical loads
2. Normal BMI and exposure to a physical load
3. Overweight and no exposure to physical loads
4. Overweight and exposure to a physical load
5. Obesity and no exposure to physical loads
6. Obesity and exposure to a physical load

We have struggled with presenting the data in a clear and straightforward manner and appreciate the reviewers help in this. Presenting the relation according to the proposed 6 categories has the advantage that there is a single reference category (as opposed to 2 reference categories). Resulting odds ratios can, therefore, be directly compared between all categories, and this would theoretically provide better estimates as a result of gain of power. From the resulting odds ratios can be read directly (in the original table this could be indirectly concluded) that high workload has a stronger effect on symptoms than BMI. This is indeed important additional information that also increases the possibility to compare these effect sizes between studies. Therefore, we have included this model in appendix I. However, since the research question was to explore if the association between BMI and musculoskeletal symptoms was different for high versus low workload, and stratifying the analysis based on the interaction found, it is possible to statistically test the significance of the association within groups. Furthermore, estimates in the original table 3 in the article were almost identical to those in the model with 6 categories.

5. In this study, the response was weighed for gender, age, sector, ethnic origin, level of urbanization, geographical region and level of education. However, weights
were not taken into account in the analysis, and survey data analysis was not used.

Survey data were used for the first research aim (cross-sectional analysis was performed with weighted cases), for the second research aim cohort data analysis was performed without weighting, because of selective loss to follow-up. This information has been added to the methods section (p 5&6).

6. Only two physical load factors were assessed. There was no information on other physical load factors such as working with hands above shoulder level, kneeling, squatting, using a vibrating tool, repetitive hand motions, work demanding keyboard use, and long periods sitting or standing.

Thank you for this comment. In the questionnaire also questions on using vibrating tools, and repetitive motions were included. These factors have been added to the model as potential confounders (see revision 1) and as descriptive variables in table 1.

For the evaluation of interaction the two physical load factors (using force and working in awkward positions) were selected because these factors reflect occupational differences (tested in cross-tables) in the study population relevant to our research question. Including for example repetitive motions (including mouse use) could also influence the association between BMI and upper extremity symptoms (carpal tunnel syndrome related to overweight) however does not reflect the same type of workload under study. For example office workers would have low physical workload in the first definition, but possibly high in the second definition. The formulation of the hypothesis in the introduction was adjusted to better describe the definition of workload.

7. Force and working in awkward positions were aggregated in a single variable. This is OK only for subgroup analysis. The combined variable does not control for possible joint effect of these two physical factors. Moreover, it is unclear whether exposure to force and working in awkward positions indicates current exposure, or ever exposure.

We agree that combining the factors does not control for joint effects. Therefore the combined variable was only used in exploring effect modification. The workload questions reflect current exposure ('currently’ has been added to the methods section). In the discussion (section methodological strengths/limitations, 2nd paragraph) we commented on this; workers with symptoms might have already changed to work with lower exposures (ever exposure would give additional information to better estimate the association).
8. Was the sample representative of the Dutch workforce? The response rate was extremely low. The possible effects of selection bias on the observed associations were not well discussed.

We do not know whether selective response influenced our findings, but we expect to have marginalized these effects by weighting the cross-sectional data. In the cohort data these weights (distribution of respondents on the weight-factors) stay within acceptable ranges, the respondents do not differ on this distribution compared to the total Dutch employed population.

In the Netherlands, response to surveys is usually relatively low, and the response of about 32% in was considered to be satisfactory given the heterogeneous population and relatively voluminous questionnaire. Second, bias may have occurred as a result of selective loss to follow-up.

Regarding the second aim, using the longitudinal data, persons lost to follow-up were younger and less often highly educated than those who responded to the follow-up questionnaire. However, no difference was found for the dependent variables BMI and musculoskeletal symptoms between those lost to follow-up and respondents. Hence, we are confident that selective loss to follow-up did not affect the essence of our findings. This was described briefly in the methods section and in the revised manuscript additionally has been added to the discussion (paragraph: methodological strengths and limitations).

9. Weight and height were not measured. They were based on self-reports. Were the associations of BMI with musculoskeletal symptoms underestimated or overestimated?

It is known from literature that self-reported weight leads to underestimation of actual weight. This is a systematic underestimation (the same proportional for all BMI categories) it would not have an effect on the estimated association. However it is possible that mostly those with higher BMI (or absolute larger differences with actual weight) underreport their weight. Misclassification in categories BMI would then hypothetically lead to underestimation of the association. This has been added to the manuscript (p.11 section discussion; paragraph: methodological strengths and limitations).

10. Smoking and physical activity were included the models as dichotomized variables. Was information gathered regarding current, past smoking, or intensity and duration of physical activity?
Information was gathered on current smoking (yes/no). Information on past smoking is not available. Physical activity was assessed as days a week physically active for 30 minutes or more of at least moderate intensity, and consequently dichotomized (according to the public health guidelines). Therefore, we have no absolute information on intensity or duration in minutes a day/week, high/medium intensity. In the methods section has been added that information was gathered regarding current smoking.

11. In Table 1, only proportions were reported. Therefore, there is no need to repeat “%” in each row. In this table, for some characteristics column proportion and for some other characteristics row proportions were reported. It is difficult to compare the proportions across BMI categories.

Our apologies for the unclear table. All values now represent column proportions. Table 1. Adjusted: % has been removed from each row. In the legend of table 1 has been added: “variables are presented as proportions, with the exception of age (mean, SD).”

12. Patients having pain at one location are more likely to have musculoskeletal pain in another location. Was there an association between BMI and musculoskeletal pain only in those with multisite pain, but not in the subjects with pain in a single location only?

Thank you for this interesting remark and question. It would certainly be relevant to further look into this aspect of multisite symptoms in a different paper. We believe that this goes beyond the scope of the present study, and that it could be distracting from the main research question and message, as already several sub-questions were included in the present paper.

13. Was there an interaction between physical activity and obesity?

For all potential effect modifiers interaction was studied. No significant interaction for any of the body regions was found (in the lower extremity, closest to interaction; p-value = 0.106). In the revised document this has been more extensively described in the (methods/results) section.

14. In Table 2, unadjusted results would be replaced by age-and gender-adjusted results (OR age-adjusted results for gender-specific analysis), and age-and gender-
adjusted results (or age-adjusted results) replaced by full-model results (adjusted for all measured confounders).

Table 2 has been adjusted according to suggested modifications (in accordance with revision 1)

15. Table 3, full model needs to be reported, not age and gender adjusted.

Table 3 has been adjusted according to suggested modifications (in accordance with revision 1)

**Minor Essential Revisions**

1. In the Introduction on page 4, the second paragraph, the hypothesis on the joint effect of physical load and obesity is not well formulated. Physical load is also associated with shoulder, elbow, wrist, and back symptoms. Only OA is mentioned. If the hypothesis is that there is an interaction between obesity and physical load factor, why subgroup analysis was performed?

The formulation of the hypothesis in the introduction was adjusted to better describe the definition of workload in the manuscript. "Our hypothesis is that in workers with high physical workload, the association in weightbearing joints will be increased, through additional physical strain, since overweight and obese individuals experience greater loads on their joints than normal-weight individuals."

2. Were age and education included in the model as continuous or dichotomized variables?

Age was included in the model as continuous variable and education as categorical variable with 3 groups (low, intermediate, and high educational level). This information has been added in methods section, in the paragraph on potential confounders.

3. On page 7, last paragraph, please change "en" to "and" was associated with upper extremity symptoms

Our apologies, this has been adjusted accordingly.
4. How the lower confidence interval of OR = 1.05 can be 1.14 (CI: 1.14-1.98).

Adjusted value in the text = 1.51 (correct value from table 4).

5. What is the reason for reporting some texts in italics?

The text should not have appeared in italics in the pdf, this has been corrected.
REVIEWER 2

Discretionary Revisions

The authors have written an interesting paper investigating the link between BMI and musculoskeletal disorder. They have an important statistical sample and obtain interesting data. I would like the author include some information about an important musculoskeletal disorder as Fibromyalgia. BMI has been related with Fibromyalgia.

We thank the reviewer for positive words and the constructive remark. In the discussion we have now added Fibromyalgia in the section on possible mechanisms explaining the link between BMI and musculoskeletal disorders, in addition to, for example, osteoarthritis.

The comments were addressed in a revised manuscript. In response to the editor's request we have revised the manuscript to clarify that ethical approval was not required for this study.

Yours sincerely,

Drs. L. Viester

Department of Public and Occupational Health

VU University Medical Center

van der Boechorststraat 7

NL-1081 BT Amsterdam

T: +31 20 4441708

F: +31 20 4448387

Email: lviester@vumc.nl