

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Risk factors for ischaemic heart disease mortality among men with different occupational physical demands. A 30-year prospective cohort study
<b>AUTHORS</b>	Andreas Holtermann, Ole Steen Mortensen, Karen Sogaard, Finn Gyntelberg and Poul Suadicani

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Alex Burdorf, Erasmus MC
<b>REVIEW RETURNED</b>	05/10/2011

<b>THE STUDY</b>	Overall, a nice paper with some suggestions for improvements.
<b>RESULTS &amp; CONCLUSIONS</b>	Although, I think the authors should consider an analysis with an interaction term. But..this is my preference, but may be not of the authors.
<b>GENERAL COMMENTS</b>	<p>Remarks</p> <ol style="list-style-type: none"><li>1. The interesting observation that physical load and physical activity/fitness seem to interact to some extent was reported earlier, e.g. Russo OEM 2006 and a related commentary with other references. I think the authors could draw attention to the observation that PA (preventive factor) is something else than physical load (risk factor), and the current work present some explanation for this.</li><li>2. The physical work demands are not defined in the methods with sufficient details, please present more information</li><li>3. The Cox regression presents HR, which may be interpreted as a proxy for RR, but the results should be presented as HR, since that is the measure of association in the analysis.</li><li>4. The authors should consider a formal analysis of interaction, which could be presented in a single table, instead of the current stratification. The slight disadvantage with the current approach is that adjustment is done for the same variable but with another distribution, since essentially we have 3 different populations with different size, which may complicate the picture of relevant (i.e. not only significant) variables.</li><li>5. The statement that "Surprisingly, among men with moderate physical work demands, but not among others, those who reported exposure to regular psychological work pressure" may be partly due</li></ol>

	<p>to the suggestion in remark 4.</p> <p>6. In the discussion the authors could pay attention to the distribution of men with good physical fitness cq PA over the 3 levels of physical work demands. This gives some input into the interesting results that physically demanding jobs will certainly not lead to physically healthy persons.</p> <p>7. Is there any information on change of job during the -70s and -80s, since it may very well be that a single measure in 1970 will be a good proxy for the next 20 years and, thus, the statement on misclassification on exposure could be substantiated.</p>
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<b>REVIEWER</b>	<p>Marco M Ferrario          Centro Studi EPIMED - Epidemiologia e Medicina Preventiva          Università degli studi dell'Insubria          Varese, Italy</p> <p>No conflicts in interest</p>
<b>REVIEW RETURNED</b>	15/10/2011

<b>THE STUDY</b>	<p>The study question is not clear. Please explain it better.          Physical fitness. Add "maximum" to "The load chosen..". In addition: are you sure of the three step levels? Are not too high?          Alcohol consumption in the weekends not given. Why?          Why lipid measurements are not included. Which might be the effect(s) of not having them.          Blood pressure: only one measurement? This should be discussed based on the Results showing a strong effect of BP levels, both of systolic diastolic BP.</p>
<b>RESULTS &amp; CONCLUSIONS</b>	<p>I suggest to include in Table 1 in addition to the listed independent variables physical work demand, which is the stratifying variable for the following tables. I do not think it is meaningful to add models adjusting also for the independent variables.          Not clear why social class is added to the last model only, in all tables.          The worker healthy effect bias may play some role? Please add some considerations in Discussion.          Conclusions are too general, please be more specific.</p>

### VERSION 1 – AUTHOR RESPONSE

Thank you for the clear and constructive comments from the reviewers to our paper. We have revised the paper taking into account all suggestions to the extent possible. Moreover, we have modified the abstract in accordance with the new guidelines.

How we addressed the points made by the reviewers appears below. The changes performed in the manuscript are marked with MS Word "track changes".

Ad reviewer Alex Burdorf.

We would like to thank you for the positive and constructive comments, improving our paper.

Comment:

- Overall, a nice paper with some suggestions for improvements.
- I think the authors should consider an analysis with an interaction term. But..this is my preference, but may be not of the authors.

Response:

In previous papers from the Copenhagen male Study, which are referred to in the present paper, using the same baseline, cohort, and duration of follow-up, we addressed the interaction of occupational physical activity and leisure time physical activity as a predictor of IHD and all-cause mortality, and also the interaction of occupational physical activity and physical fitness (VO<sub>2</sub>max). As described, the purpose of the present paper was to address in a much broader sense if established and potential risk factors for IHD mortality might differ between groups with different occupational physical work demands since, due to the load on the cardiovascular system induced by these demands, this may have influenced their vulnerability to risk factors. In the context of the present paper, interaction analyses would thus be either post hoc or superfluous, so we prefer to maintain the analysis strategy we have already applied.

Comment:

1. The interesting observation that physical load and physical activity/fitness seem to interact to some extent was reported earlier, e.g. Russo OEM 2006 and a related commentary with other references. I think the authors could draw attention to the observation that PA (preventive factor) is something else than physical load (risk factor), and the current work presents some explanation for this.

Response:

We agree. This aspect is now included in the discussion section.

Comment:

2. The physical work demands are not defined in the methods with sufficient details, please present more information

Response:

This is now explicitly described in the method section

Comment:

3. The Cox regression presents HR, which may be interpreted as a proxy for RR, but the results should be presented as HR, since that is the measure of association in the analysis.

Response:

We agree with the reviewer that HR is a measure of relative risk. This is already briefly addressed in the Statistical analysis section, and in presentation of the results in the tables we present these as HR.

Comment:

4. The authors should consider a formal analysis of interaction, which could be presented in a single table, instead of the current stratification. The slight disadvantage with the current approach is that adjustment is done for the same variable but with another distribution, since essentially we have 3 different populations with different size, which may complicate the picture of relevant (i.e. not only significant) variables.

Response:

Please see our previous response to your comment concerning choice of analysis strategy.

Comment:

5. The statement that "Surprisingly, among men with moderate physical work demands, but not among others, those who reported exposure to regular psychological work pressure" may be partly due to the suggestion in remark 4.

Response:

We find it unlikely that data manipulation would contribute to answer the observation and prefer to keep the expression used.

Comment:

6. In the discussion the authors could pay attention to the distribution of men with good physical fitness cq PA over the 3 levels of physical work demands. This gives some input into the interesting results that physically demanding jobs will certainly not lead to physically healthy persons.

Response:

This important aspect is now described in the discussion section.

Comment:

7. Is there any information on change of job during the -70s and -80s, since it may very well be that a single measure in 1970 will be a good proxy for the next 20 years and, thus, the statement on misclassification on exposure could be substantiated.

Response:

Information on job title was available only from the first baseline in the cohort, i.e. 1970-71.

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Ad reviewer Marco M Ferrario

We would like to thank you for the positive and constructive comments, improving the paper.

Comment:

The study question is not clear. Please explain it better.

Response:

We see your point. The study question and hypothesis are now clarified in the abstract and introduction sections.

Comment:

Physical fitness. Add "maximum" to "The load chosen..". In addition: are you sure of the three step levels? Are not too high?

Response:

"maximum" is now included in the sentence.

The three steps were applied in only a very few cases.

Comment:

Alcohol consumption in the weekends not given. Why?

Response:

Unfortunately, we don't have specific information about alcohol consumption during the weekends.

Comment:

Why lipid measurements are not included. Which might be the effect(s) of not having them.

Response:

Unfortunately, lipid measurements are not available at baseline. Lipids could therefore be a potential confounder/risk factor in this study. However, the direction of its effect is uncertain. This is now included as a methodological aspect in the discussion section.

Comment:

Blood pressure: only one measurement? This should be discussed base on the Results showing a strong effect of BP levels, both of systolic and diastolic BP.

Response:

We have added a brief statement in the results section addressing table 1 that despite the fact that blood pressure was measured only once, the predictive strength of systolic as well as diastolic was strong.

Comment:

I suggest to include in Table 1 in addition to the listed independent variables physical work demand, which is the stratifying variable for the following tables. I do not think it is meaningful to add models adjusting also for the independent variables.

Response:

The idea of the paper is to challenge the relative importance of a number of risk factors for IHD mortality among men with different occupational physical work demands. Thus, table 1 presents the role of these factors, when they "stand alone", i.e. are adjusted for age only, and in various other models taking into account factors associated with these single items. We believe that keeping the table as it is will uphold the flow of the presentation from a logical narrative point of view.

Comment:

Not clear why social class is added to the last model only, in all tables.

Response:

Social class is included in the last model only to explicitly show the independent results (after adjusting for the potential confounders) with and without adjustment for social class. This is chosen because social class may be considered an "over-adjustment", since social class is strongly associated with physical work demands.

Comment:

The worker healthy effect bias may play some role? Please add some considerations in Discussion.

Response:

Yes, the healthy worker effect may impose a significant bias of the result. This is now considered in the discussion section.

Comment:

Conclusions are too general, please be more specific.

Response:

We want to be careful with providing very specific conclusions. However, we have specified the conclusions in the abstract and discussion sections.