PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between occupational physical activity and myocardial infarction – a prospective cohort study
AUTHORS	Johnsen, Anna; Alfredsson, Lars; Knutsson, Anders; Westerholm, Peter; Fransson, Eleonor

VERSION 1 - REVIEW

REVIEWER	Andreas Holtermann National Research Centre for the Working Environment, Copenhagen, Denmark
REVIEW RETURNED	05-Jun-2016

GENERAL COMMENTS	The paper ”the association between occupational physical activity and myocardial infarction – a prospective study” is investigating an important topic for occupational and public health. This is because a relatively high fraction of the work population has high occupational physical activity (OPA) and workers with OPA have an elevated incidence of CVD, but it remains unsettled if high OPA is an independent risk factor for development of CVD. This study fills some of our knowledge gap on this topic. As mentioned by the authors, the paper has several strengths, and some weaknesses, like the use of self-reported and categorical information of OPA. The manuscript is well written and clear. For the categorization of OPA, I would recommend to combine those lifting with those standing/walking much. This is because many workers may have a quite sedentary work, just requiring a few lifts per day (e.g. transportation of goods). Why did you only investigate the risk for myocardial infarction, and not IHD mortality? This would have led to more cases and probably reduced confidence intervals. The statistically analyses are generally sound. However, I think the “crude analyses” ought to be adjusted for age. Moreover, the adjustment for socioeconomic position based on occupation and education is problematic because of its very high correlation with OPA, and high risk for over-adjustment. I would like to see the results from a model without adjustment for socioeconomic position, but the other suggested confounders. Why do you adjust for the mediating factors? If interested in mediation, then I would recommend you to perform a proper mediation analysis. Table 3, the n in each category needs to be reported. The results should be interpreted with care because I expect some categories to have few participants.

	It is uncertain what is meant by the conclusion “this indicates that OPA alone is not sufficient to reduce the risk of myocardial infarction”, please rephrase

REVIEWER	Christina Bjørk Petersen National Institute of Public Health, University of Southern Denmark, Denmark
REVIEW RETURNED	19-Jun-2016

GENERAL COMMENTS	This is a well-written manuscript with sound study design and appropriate statistical methods that study the association between occupational physical activity and risk of myocardial infarction. I have some comments manily concering the exposure and the reporting of the results, that I hope will be useful to the authors. Main points: 1. I have concern about the classification of the occupational PA question responses. Participants were asked by three questions in the questionnaire: 1) Seated for more than half of their total working time (yes/no), 2) Lifting more than 5 kg for at least 2 h per day (yes/no) and lifting more than 20 or 30 kg at lest 5 times per day. This was categorized into three groups. 1) sedentary, no lifting 2)+PA work, no lifting 3) +PA/-PA ,+ lifting. While the beneficial effect of leisure time physical activity is well established, the evidence for the health effects of occupational physical activity is inconsistent. The inconsistency in these findings is most likely explained by the differences in the type of physical activity performed during working hours. Heavy lifting differs from aerobic activities and therefore, it is of interest also to study the group that are exposed to heavy lifting but not exposed to other physical activity at work. Even though, this is a minor group of people, the authors should include this category in the analysis separately from OPA 3 in main and subsequent analyses. 2. What was the validity of the diagnosis of myocardial infarction in national registers? The study has a very impressive response rate (82%) and as the follow-up information is based on register data, I expect that there is very little loss to follow-up, which is a great strength. I suggest, the authors include this information the manuscript. 3. Adjustments for confounding factors: The analyses were adjusted for a number of potential confounding factors incl. age. Why was age not used as the underlying time-scale in the cox regression analyses? The results presented in the abstract and also as in the result section are the unadjusted results. I suggest that the authors either also present the adjusted results as these show no associations. Otherwise, it should be clearly stated why the authors present the unadjusted results and conclude on the basis of these results. 4. The rationale of the study is that both occupational PA and leisure time PA is included in the recommendations on PA. It would be interesting to the combinations of being both active at work and in leisure time on the effect on MI. I suggest the authors include the joint effect analysis. 5. In the conclusions (and also first part of the discussion), it is stated that there is “no strong associations” – I suggest that the authors rephrase this. Either there is an association or there is not an association. Based on the findings, the conclusion should be that

	there is “no association”. Minor points: 1. The frequency of cases (MI) are presented in Table 1. I suggest these are moved to Table 2. 2. There are no symbols for the footnotes in the Tables. I suggest that symbols are added to the table to indicate what the footnote refers to. 3. In Table 3, the authors should add the age-intervals to the categories (eg. 19-44 years, 45-54 years and 55-70 years). 4. In the discussion, it is suggested that the explanation of why more people in OPA 1 are physically active in leisure time is due to fatigue among people who are physically active at work. However, it may also be due to socioeconomic differences and thereby socioeconomic differences in health behaviour.

REVIEWER	Els Clays Ghent University, Belgium
REVIEW RETURNED	24-Jun-2016

GENERAL COMMENTS	This paper deals with a relevant topic for BMJ Open readers. The manuscript is well written and reports on valuable data that were retrieved from a well conducted study. My main concern however relates to the classification of occupational physical activity that was used in the paper. A three level definition was developed based on 3 separate items asking about sitting and lifting. I doubt whether this can be considered a valid classification. Combining items on lifting with sitting into a general measure of OPA is highly questionable. OPA level 2 (standing or walking) was not retrieved in a direct way from the sitting item. The sitting question was quite a-specific in terms of the dose (is more than half of working hours documented as meaningful cut-off?) and is documented in literature as an independent risk factor while the authors provide no convincing argument to treat it as reference category here. The authors report that their categorization of OPA was similar to the one used in the Copenhagen City Heart Study, but I do not completely agree on this. The measure used in the CCH study is based on a single item that asks participants to choose their matching level of OPA, with detailed descriptions containing sitting, standing, walking, lifting. This measure – unlike the one used in the present study – can be seen as an assessment of the level physical exertion on one’s job. The items in the WOLF study seem more suitable to study the effects of lifting loads, which has been shown a relevant risk factor for CVD. Another important limitation relates to the measure of leisure time physical activity, which is quite generic and a-specific, as no evaluation of the intensity of PA is included. Is any information regarding validity and reliability of this item available? A minor suggestion about the data presented in Table 1: add significance testing results for comparing characteristics between OPA levels.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Reviewers' Comments to Author:
For the categorization of OPA, I would recommend to combine those lifting with those

standing/walking much. This is because many workers may have a quite sedentary work, just requiring a few lifts per day (e.g. transportation of goods).

Respond from the author:
Thank you for this comment on the categorization of OPA. According to also the other reviewers' comments on this issue, we have now provided supplementary analyses where four categories of OPA were constructed, where the group with sedentary jobs in combination with lifting/carrying was treated as a separate category. We also added a supplementary analysis where OPA was combined with leisure-time physical activity.

Reviewers' Comments to Author:
Why did you only investigate the risk for myocardial infarction, and not IHD mortality? This would have led to more cases and probably reduced confidence intervals.

Respond from the author:
We agree that IHD mortality probable would have led to more cases, but in this study we wanted to stick to one diagnosis and therefore chose to use myocardial infarction, both fatal and nonfatal cases. One sentence is added in the discussion (page 16) about this: "In this study only cases of myocardial infarction were used, extension to other diagnosis of ischemic heart diseases would probably have led to more cases and higher power. However, we wanted to use the specific and well-defined outcome of myocardial infarction in this analysis."

Reviewers' Comments to Author:
The statistically analyses are generally sound. However, I think the "crude analyses" ought to be adjusted for age. Moreover, the adjustment for socioeconomic position based on occupation and education is problematic because of its very high correlation with OPA, and high risk for over-adjustment. I would like to see the results from a model without adjustment for socioeconomic position, but the other suggested confounders.

Respond from the author:
We agree about this and have now changed the crude analysis to model 1 including adjustment for age.

We also agree about the correlation between socioeconomic position and OPA, model 5 therefore only includes adjustment for age, sex and other confounders. One sentence in the result (page 10) now refers to this. "It might be argued that socioeconomic status should not be adjusted for since it may lead to over-adjustment, model 5 is therefore without adjustment for socioeconomic status."

Reviewers' Comments to Author:
Why do you adjust for the mediating factors? If interested in mediation, then I would recommend you to perform a proper mediation analysis.

Respond from the author:
We agree about this and have decided not to include the model adjusted for mediating factors. As a consequence of this, the text about mediating factors in the method (page 6) has been removed.

Reviewers' Comments to Author:
Table 3, the n in each category needs to be reported. The results should be interpreted with care because I expect some categories to have few participants.

Respond from the author:
We have now added the n in table 3, we agree that the results from the stratified analyses needs to

be interpreted with caution, due to the few participants in some of the analyzed subgroups, this is also mentioned in the discussion (page 15-16).

Reviewers' Comments to Author:
It is uncertain what is meant by the conclusion “this indicates that OPA alone is not sufficient to reduce the risk of myocardial infarction”, please rephrase

Respond from the author:
This sentence is now changed, “Based on the results from this study, occupational physical activity in general does not seem to be enough for reducing the risk of myocardial infarction.”

Reviewer 2
Reviewers' Comments to Author:
Main points:
1. I have concern about the classification of the occupational PA question responses. Participants were asked by three questions in the questionnaire: 1) Seated for more than half of their total working time (yes/no), 2) Lifting more than 5 kg for at least 2 h per day (yes/no) and lifting more than 20 or 30 kg at lest 5 times per day. This was categorized into three groups. 1) sedentary, no lifting 2)+PA work, no lifting 3) +PA/-PA ,+ lifting. While the beneficial effect of leisure time physical activity is well established, the evidence for the health effects of occupational physical activity is inconsistent. The inconsistency in these findings is most likely explained by the differences in the type of physical activity performed during working hours. Heavy lifting differs from aerobic activities and therefore, it is of interest also to study the group that are exposed to heavy lifting but not exposed to other physical activity at work. Even though, this is a minor group of people, the authors should include this category in the analysis separately from OPA 3 in main and subsequent analyses.

Respond from the author:
Thank you for this comment on the categorization of OPA. We have now provided supplementary analyses where four categories of OPA were constructed, where the group with sedentary jobs in combination with lifting/carrying was treated as a separate category (supplementary table 1 and 2). This categorization results in few people in OPA 4 (n=349) and also few cases of myocardial infarction (n=7). We have added one sentence about this in the result (page 8): “An alternative categorization of occupational physical activity is presented in supplementary tables 1 and 2, where the group with sedentary jobs in combination with lifting/carrying was treated as a separate category.”

2. What was the validity of the diagnosis of myocardial infarction in national registers? The study has a very impressive response rate (82%) and as the follow-up information is based on register data, I expect that there is very little loss to follow-up, which is a great strength. I suggest, the authors include this information the manuscript.

Respond from the author:
We have added information of the validity of the data of myocardial infarction in the discussion on page 16:
“Data on myocardial infarction was obtained from the National Patient Register and the Cause of Death Register in Sweden. The proportion of cases of myocardial infarction identified by the registers has been found to be between 77 and 91.5 percent, which implies high validity and little loss of follow-up for this data.”

3. Adjustments for confounding factors: The analyses were adjusted for a number of potential confounding factors incl. age. Why was age not used as the underlying time-scale in the cox regression analyses?

Respond from the author:
We agree with the reviewer that using age as the underlying time-scale would have been an alternative way of specifying the models. However, we chose to include age as a continuous covariate in the models, which we think gives good adjustment for age without losing too much precision since only one extra parameter were added to the model. (In this way we could also evaluate the association between age and myocardial infarction, although this was not reported in the manuscript.)

Reviewers' Comments to Author:
The results presented in the abstract and also as in the result section are the unadjusted results. I suggest that the authors either also present the adjusted results as these show no associations. Otherwise, it should be clearly stated why the authors present the unadjusted results and conclude on the basis of these results.

Respond from the author:
The results presented in the abstract are adjusted for age, sex and socioeconomic status. We have added one sentence in the abstract, that “further adjustment did not alter the results”.

4. The rationale of the study is that both occupational PA and leisure time PA is included in the recommendations on PA. It would be interesting to the combinations of being both active at work and in leisure time on the effect on MI. I suggest the authors include the joint effect analysis.

Respond from the author:
Yes, we agree with the reviewer that this is an interesting analysis and we have now conducted a joint effect analysis. However, since this was not included in our primary aim of the study, we have added these results in supplementary table 3. We have added text about this analysis in the result (page 12): “A joint effect analysis between occupational physical activity and leisure time physical activity, and the association with myocardial infarction, was made as a supplementary analysis (supplementary table 3). The result showed a significant increased risk for myocardial infarction for people with a lot of standing and walking at work, and never or seldom were physical active during leisure time.”
The combination of being active both at work and at leisure time doesn´t seem to have any significant effect on the risk of myocardial infarction in this study.

5. In the conclusions (and also first part of the discussion), it is stated that there is “no strong associations” – I suggest that the authors rephrase this. Either there is an association or there is not an association. Based on the findings, the conclusion should be that there is “no association”.

Respond from the author:
We agree and this has now been changed.

Minor points:
1. The frequency of cases (MI) are presented in Table 1. I suggest these are moved to Table 2.

Respond from the author:
We have now added the cases of myocardial infarction in table 2.

2. There are no symbols for the footnotes in the Tables. I suggest that symbols are added to the table to indicate what the footnote refers to.

Respond from the author:
We have now added symbols for the footnotes.

3. In Table 3, the authors should add the age-intervals to the categories (eg. 19-44 years, 45-54 years and 55-70 years).

Respond from the author:
We agree about this and the age intervals are now added in table 3.

4. In the discussion, it is suggested that the explanation of why more people in OPA 1 are physically active in leisure time is due to fatigue among people who are physically active at work. However, it may also be due to socioeconomic differences and thereby socioeconomic differences in health behaviour.

Respond from the author:
This is true, we have added this in the discussion on page 15. “Other possible explanations may involve socioeconomic differences between the groups and thereby differences in health behavior.”

Reviewer 3
Reviewers' Comments to Author:
My main concern however relates to the classification of occupational physical activity that was used in the paper. A three level definition was developed based on 3 separate items asking about sitting and lifting. I doubt whether this can be considered a valid classification. Combining items on lifting with sitting into a general measure of OPA is highly questionable. OPA level 2 (standing or walking) was not retrieved in a direct way from the sitting item. The sitting question was quite a-specific in terms of the dose (is more than half of working hours documented as meaningful cut-off?) and is documented in literature as an independent risk factor while the authors provide no convincing argument to treat it as reference category here.

Respond from the author:
Thank you for this important comment. We agree with the reviewer that the questions on OPA were rather general, and that more specific questions on OPA would have been preferable. Regarding the categorization of OPA, we have now added supplementary analyses where we use four categories of OPA instead of three, where those with the combination of sitting a lot at work and lifting/carrying at work are treated as a separate category. We also discuss the limitations regarding the self-reported data of OPA in the discussion and have added a comment on the unspecific nature of the items (page 16).

Reviewers' Comments to Author:
The authors report that their categorization of OPA was similar to the one used in the Copenhagen City Heart Study, but I do not completely agree on this. The measure used in the CCH study is based on a single item that asks participants to choose their matching level of OPA, with detailed descriptions containing sitting, standing, walking, lifting. This measure – unlike the one used in the present study – can be seen as an assessment of the level physical exertion on one’s job. The items in the WOLF study seem more suitable to study the effects of lifting loads, which has been shown a relevant risk factor for CVD.

Respond from the author:
Thanks for the observation about the categorization. We have now changed the sentence about the similarity to the categorization in the Copenhagen City Heart Study (page 14): “Unlike the present study, they used a combination of baseline and follow up measures after five years in their categorization of occupational physical activity.”

Reviewers' Comments to Author:

Another important limitation relates to the measure of leisure time physical activity, which is quite generic and a-specific, as no evaluation of the intensity of PA is included. Is any information regarding validity and reliability of this item available?

Respond from the author:
We agree with the reviewer that the question of leisure time physical activity is quite generic and unspecific, which might lead to misclassification of leisure-time physical activity. However, based on this question, leisure time physical activity in WOLF has previously been shown to be associated with several cardiovascular risk factors in the expected direction (Fransson EIM, 2003). We have now added a comment regarding the unspecific assessment of leisure time physical activity as a limitation in the discussion (page 16): “These limitations regarding assessment of occupational physical activity, also largely applies to the assessment of leisure time physical activity in the WOLF study.”

Reviewers' Comments to Author:
A minor suggestion about the data presented in Table 1: add significance testing results for comparing characteristics between OPA levels.

Respond from the author:
We have added significance testing results in table 1.

VERSION 2 – REVIEW

REVIEWER	Andreas Holtermann National Research Centre for the Working Environment, Denmark
REVIEW RETURNED	18-Aug-2016

GENERAL COMMENTS	I thank the authors for their responses to my comments and for performing the requested additional analyses and modifications of the manuscript accordingly

REVIEWER	Christina Bjørk Petersen National Institute of Public Health, University of Southern Denmark
REVIEW RETURNED	31-Aug-2016

GENERAL COMMENTS	I believe you have sufficiently addressed all of my previous comments. I have only two further comments to add. 1) I still have some concern regarding the exposure variable - the authors claims to investigate occupational physical activity – however standing 50 % of the day is hardly considered physical activity (although it is not sedentary) while walking is physical activity. The exposure categories are more related to heavy lifting with or not with or without sedentary work. I suggest the authors specify what is meant by occupational physical activity in the overall aim and in the discussion. 2) Regarding the discussion on the outcome measure (MI) and choosing not to include ischemic heart disease (IHD), I believe that an argument of choosing to look at MI and not IHD could also be that MI is a more precise diagnosis of heart disease than IHD. So expecting a causal relationship we would expect a stronger association to MI than IHD. Often studies lack power to study MI and therefore study IHD. However, if would be interesting to see if the same pattern was present for IHD. If the authors has the possibility,

	they could run the sensitivity analysis for IHD and possibly also all-cause mortality and include a note on these finding.

REVIEWER	Els Clays Ghent University, Belgium
REVIEW RETURNED	25-Aug-2016

GENERAL COMMENTS	The authors responded well to all reviewers' comments and revised their manuscript accordingly.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2

1) I still have some concern regarding the exposure variable - the authors claims to investigate occupational physical activity – however standing 50 % of the day is hardly considered physical activity (although it is not sedentary) while walking is physical activity. The exposure categories are more related to heavy lifting with or not with or without sedentary work. I suggest the authors specify what is meant by occupational physical activity in the overall aim and in the discussion.

Our response:

Thank you for this comment. We have now added the following text in the aim and in the discussion, respectively.

Page 4: The aim of this study was to investigate if occupational physical activity in terms of standing/walking and lifting/carrying at work, is associated with the risk of myocardial infarction and if the association is modified by age, sex, socio-economic status and leisure time physical activity.

Page 15: For example, the predefined cut-off for sitting or standing more or less than 50 % of the working day was used in our study. This may not necessarily be the best way of defining being sedentary versus physically active at work.

2) Regarding the discussion on the outcome measure (MI) and choosing not to include ischemic heart disease (IHD), I believe that an argument of choosing to look at MI and not IHD could also be that MI is a more precise diagnosis of heart disease than IHD. So expecting a causal relationship we would expect a stronger association to MI than IHD. Often studies lack power to study MI and therefore study IHD. However, if would be interesting to see if the same pattern was present for IHD. If the authors has the possibility, they could run the sensitivity analysis for IHD and possibly also all-cause mortality and include a note on these finding.

Our response:

We agree that it would be interesting to add further outcomes in relation to occupational physical activity and we hope that we will have the possibility to do these analyses in a future study.