

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

TITLE (PROVISIONAL)	Occupational and leisure time physical activity: risk of all cause mortality and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study
AUTHORS	Andreas Holtermann, Jacob Louis Marott, Finn Gyntelberg, Karen Søgaard, Poul Suadicani, Ole Steen Mortensen, Eva Prescott and Peter Schnohr

VERSION 1 - REVIEW

REVIEWER	Maria Hagströmer, Associate Professor Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Sweden. I have no competing interest
REVIEW RETURNED	27/11/2011

GENERAL COMMENTS	<p>This paper is interesting and timely as regular physical activity is widely believed to provide a variety of health benefits, which include a reduction in the risk of premature mortality, as well as the risk of developing cardiovascular disease, diabetes, high blood pressure and obesity. As scientific evidence continues to accumulate, the results of recent studies have led to the suggestion that the health benefits of physical activity might differ between the different domains of physical activity, for example occupational and leisure time physical activity.</p> <p>In general the paper is well-written, includes a large study sample, a long follow-up period, based on sound theory and has followed the STROBE checklist. There are a few inconsistencies and methodological issues that need to be considered. See specific comments below.</p> <ol style="list-style-type: none">1. Introduction, line 33: The authors use the word gender. I wonder if they have considered using "sex" instead (Which is done in one place in the manuscript, see page 7, line 31). Sex means the biological differences and gender describes the characteristics that a society or culture delineates as masculine or feminine.2. Page 6, line 11-12: Please be more transparent how this is done. I.e. write the total sum of scores for example after the word summarizing and include a reference for the categories. I.e. why is not 2 low to 7-8 high?3. Page 6, line 32: The fact that the highest category of leisure time physical activity was merged to the one below can have affected the analysis, which is not discussed.4. Page 9, line 12: I seem to be a word missing. Several significant differences "for what" was found?5. Page 9, line 31: Please change the word increasing physical activity to higher as it is between the groups and not over time.6. Page 10, line 16-28. Why is leisure time physical activity used as a covariate when the data is stratified by the same variable?7. Page 13, line 6 and 9: Maybe self-reported is a better word than
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	<p>self-assessed, as the participants does not do the assessment, they report and the researchers assess their level based upon this.</p> <p>8. Discussion: Maybe these findings can lead to a recommendation or at least a discussion about measurement of physical activity including all domains. Total physical activity might attenuate the effect.</p> <p>9. Abstract: Please either use an abbreviation (OPA) throughout the abstract/manuscript or spell it out on all places.</p> <p>10. Abstract line 30: perhaps?</p> <p>11. Tables: In general OK information, but I hope the format will be more easy to read in a printed version, i.e without lines all over and consistent between tables.</p>
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REVIEWER	<p>Esteve Fernández Associate Professor Catalan Institute of Oncology - University of Barcelona Spain.</p> <p>No competing interests.</p>
REVIEW RETURNED	28/12/2011

REPORTING & ETHICS	<p>The authors have published a paper based on the same cohort and addressing the same objective but limiting the analyses to males (the outcome was ischemic heart disease instead of myocardial infarction+all-cause mortality). The reference, actually provided by the authors in the Introduction is:</p> <p>Holtermann A, Mortensen OS, Burr H, Søgaard K, Gyntelberg F, Suadicani P. Physical work demands and physical fitness in low social classes-- 30-year ischemic heart disease and all-cause mortality in the copenhagen male study. J Occup Environ Med. 2011 Nov;53(11):1221-7.</p> <p>This paper included only men of low social class (n=2707) and the results were almost identical (from the abstract): "multiple-adjusted Cox proportional hazard ratios showed an almost threefold increased risk of IHD mortality among men with high physical work demands and low physical fitness, but not among men with a high physical fitness.</p> <p>While the present paper extends the research to men and women, it is intriguing why the authors are publishing almost the same. I've not been able to download the fullpaper, but it will be necessary to check whether the Discussion (and other parts of the manuscript) are similar and redundant.</p>
GENERAL COMMENTS	<p>Major comment</p> <p>The authors have published a paper based on the same cohort and addressing the same objective but limiting the analyses to males (the outcome was ischemic heart disease instead of myocardial infarction+all-cause mortality). The authors should clarify and justify what the present paper adds to their previous one, in view that the main results are similar to those of the previous paper, and no relationship in women was apparent).</p> <p>Introduction</p> <p>1. It is not clear the reasonong included in lines 21-26, page 4. It is a circular argument.</p>

	<p>Methods</p> <p>2. Please clarify how was assigned the scores for occupational physical activity.</p> <p>3. Please include here or in discussion whether there's room for missclassification of alcohol consumption. What does "daily intake" mean? Are consumers of, ie, one drink/day classified similarly to those declaring 10 drinks/day?</p> <p>4. Did the authors check the assumption of proportionality of the risks over time to apply Cox's regression?</p> <p>Results</p> <p>5. In tables with HR, please provide the number of person-years instead of total number of participants</p> <p>6. HR from fully-adjusted models are similar to HR from age-adjusted models. Thus, I should recommend to simplify the tables by including only the fully-adjusted estimates.</p> <p>7. Please, include a test for trend to support the statements about the "dose-response" trend.</p> <p>Discussion</p> <p>8. Please include in addition to the limitations already discussed their potential effect on the results (how biased would be the HR estimates and in which direction?)</p>
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REVIEWER	Christine Autenrieth Institute of Epidemiology II Helmholtz Zentrum München - German Research Center for Environmental Health Germany
REVIEW RETURNED	02/01/2012

THE STUDY	<p>This is an interesting study assessing how leisure time physical activity (PA) modifies the association between occupational PA and risk of all-cause mortality as well as myocardial infarction. The text is well organized and nicely read.</p> <p>Comments:</p> <p>1) Please provide more information about covariables, e.g., how was hypertension and household income levels defined?</p> <p>2) Please provide references for the standard procedures of the assessment of covariables.</p> <p>3) The large age range (25-66) might be a problem, since PA was measured at different ages. Authors should discuss that PA patterns may vary between age groups.</p> <p>4) Leisure time PA was only measured at baseline. This should be discussed in more detail in the limitation section since leisure time PA patterns may vary considerably during an individual's life course.</p>
RESULTS & CONCLUSIONS	<p>Comments:</p> <p>1) In the tables, adjustment is made for cholesterol, however, it is not listed as a confounder in the method section.</p> <p>2) Associations described in this study should be cautiously interpreted. The conclusion that men with high occupational PA should be more physically active during leisure time is not clearly supported by the presented results. Among men with high occupational PA, no hazard ratios between low and high leisure time</p>

	PA is reported. 3) Why did the authors choose to perform a separate analysis with participants having a low educational level instead of including education as a confounding variable?
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VERSION 1 – AUTHOR RESPONSE

Dear Managing Editor, BMJ Open, Richard Sands

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. In accordance to your requests, we have included the study design type in the title, modified the abstract in accordance with the new guidelines, and included in the contribution section that all authors have approved the final version of the manuscript.

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 Maria Hagströmer

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

General comment:

This paper is interesting and timely as regular physical activity is widely believed to provide a variety of health benefits, which include a reduction in the risk of premature mortality, as well as the risk of developing cardiovascular disease, diabetes, high blood pressure and obesity. As scientific evidence continues to accumulate, the results of recent studies have led to the suggestion that the health benefits of physical activity might differ between the different domains of physical activity, for example occupational and leisure time physical activity.

In general the paper is well-written, includes a large study sample, a long follow-up period, based on sound theory and has followed the STROBE checklist. There are a few inconsistencies and methodological issues that need to be considered. See specific comments below.

Response:

We are glad you find the potential differential health effects from physical activity at different settings of interest. Please see our response to your specific comments below.

Specific comment:

1. Introduction, line 33: The authors use the word gender. I wonder if they have considered using “sex” instead (Which is done in one place in the manuscript, see page 7, line 31). Sex means the biological differences and gender describes the characteristics that a society or culture delineates as masculine or feminine.

Response:

We have now used the term sex instead of gender throughout the manuscript

Specific comment:

2. Page 6, line 11-12: Please be more transparent how this is done. I.e. write the total sum of scores for example after the word summarizing and include a reference for the categories. I.e. why is not 2 low to 7-8 high?

Response:

We have now followed your suggestion, making it more transparent. The categorization was chosen for making a comparable categorization as previous studies on the exact same question, but only including a single round and not two rounds as in this study (e.g. reference nr 1). The reference is

now given in the text.

Specific comment:

3. Page 6, line 32: The fact that the highest category of leisure time physical activity was merged to the one below can have affected the analysis, which is not discussed.

Response:

Because of the very few participants responding in the highest category of leisure time physical activity, merging of the responses to the second highest category could only have a minor impact on the risk estimates from the second highest category alone. This is now discussed in the strength and limitation section.

Specific comment:

4. Page 9, line 12: I seem to be a word missing. Several significant differences “for what” was found?

Response:

Thank you. This is now corrected.

Specific comment:

5. Page 9, line 31: Please change the word increasing physical activity to higher as it is between the groups and not over time.

Response:

Done

Specific comment:

6. Page 10, line 16-28. Why is leisure time physical activity used as a covariate when the data is stratified by the same variable?

Response:

Thank you for finding this mistake. Leisure time physical activity is now deleted as a covariate

Specific comment:

7. Page 13, line 6 and 9: Maybe self-reported is a better word than self-assessed, as the participants does not do the assessment, they report and the researchers assess their level based upon this.

Response:

Your recommendation is followed.

Specific comment:

8. Discussion: Maybe these findings can lead to a recommendation or at least a discussion about measurement of physical activity including all domains. Total physical activity might attenuate the effect.

Response:

We agree, and have inserted a short discussion about this in the discussion section.

Specific comment:

9. Abstract: Please either use an abbreviation (OPA) throughout the abstract/manuscript or spell it out on all places.

Response:

It is now spelled out on all places

Specific comment:

10. Abstract line 30: perhaps?

Response:

It is now deleted

Specific comment:

11. Tables: In general OK information, but I hope the format will be more easy to read in a printed version, i.e without lines all over and consistent between tables.

Response:

We also hope so

Ad reviewer Esteve Fernández

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

General comment:

The authors have published a paper based on the same cohort and addressing the same objective but limiting the analyses to males (the outcome was ischemic heart disease instead of myocardial infarction+all-cause mortality). The reference, actually provided by the authors in the Introduction is: Holtermann A, Mortensen OS, Burr H, Søgaard K, Gyntelberg F, Suadicani P.

Physical work demands and physical fitness in low social classes--30-year ischemic heart disease and all-cause mortality in the copenhagen male study.

J Occup Environ Med. 2011 Nov;53(11):1221-7.

This paper included only men of low social class (n=2707) and the results were almost identical (from the abstract): "multiple-adjusted Cox proportional hazard ratios showed an almost threefold increased risk of IHD mortality among men with high physical work demands and low physical fitness, but not among men with a high physical fitness.

While the present paper extends the research to men and women, it is intriguing why the authors are publishing almost the same. I've not been able to download the fullpaper, but it will be necessary to check whether the Discussion (and other parts of the manuscript) are similar and redundant.

Major comment

The authors have published a paper based on the same cohort and addressing the same objective but limiting the analyses to males (the outcome was ischemic heart disease instead of myocardial infarction+all-cause mortality). The authors should clarify and justify what the present paper adds to their previous one, in view that the main results are similar to those of the previous paper, and no relationship in women was apparent).

Response:

We are glad you are aware of our previous papers conducted on the "Copenhagen Male Study", which is a completely different cohort than the cohort this manuscript is based on, called the "Copenhagen City Heart Study". The main aspects added in this study in respect to our previous studies on the other cohort are: 1) risk estimates from occupational physical activity for cardiovascular outcomes among both females and males, 2) investigate if the findings on the males in one cohort can be replicated in another cohort, 3) use information on occupational physical activity from two rounds which may be particularly important with this long follow-up time, 4) investigate the risk for cardiovascular outcomes from high occupational physical activity among persons with different levels of leisure time physical activity (previously only investigated among persons with different levels of physical fitness)

Specific comment:

Introduction

1. It is not clear the reasoning included in lines 21-26, page 4. It is a circular argument.

Response:

We see the needs for rephrasing. The paragraph is now modified to make the argumentation logical.

Specific comment:

Methods

2. Please clarify how was assigned the scores for occupational physical activity.

Response:

This is now clarified with the following changes in the text:

To reduce risk of misclassification, the main predictor variable was based on combined information from assessment in 1976-78 and 1981-83, summarizing the total sum of scores. Then, the scores were categorized into: "low" = score 2-3, "moderate" = score 4-5, and "high" = score 6-8.

Specific comment:

3. Please include here or in discussion whether there's room for missclassification of alcohol consumption. What does "daily intake" mean? Are consumers of, ie, one drink/day classified similarly to those declaring 10 drinks/day?

Response:

Drinking was based on self-report: Never/almost never, monthly, weekly, and daily. These answers include beer, wine, and alcohol consumption. Daily drinking includes all subjects that drink at least 1 drink/day. This crude measure of alcohol may cause some misclassification of alcohol consumption. This is now described as a methodological limitation in the discussion section.

Specific comment:

4. Did the authors check the assumption of proportionality of the risks over time to apply Cox's regression?

Response:

Yes, the deviation from the proportional hazards assumption was evaluated by Schoenfeld residuals, and by inspection of log-log plots. No significant deviations were found.

Specific comment:

Results

5. In tables with HR, please provide the number of person-years instead of total number of participants

Response:

Person-years at risk are now included in table 3 and 4

Specific comment:

6. HR from fully-adjusted models are similar to HR from age-adjusted models. Thus, I should recommend to simplify the tables by including only the fully-adjusted estimates.

Response:

We see your point, but prefer to show both the crude (age-adjusted) and fully-adjusted estimates. This is both because of loss of information for not showing the modulations of the estimates from the two models, and because of the ability to compare the crude estimates among different studies (for later meta-analyses etc.)

Specific comment:

7. Please, include a test for trend to support the statements about the "dose-response" trend.

Response:

We tested for trend on the associations between physical activity and risk of all-cause mortality and myocardial infarction stratified by sex (table 3). We found a significant trend ($p=0.008$) for the association between occupational physical activity and all-cause mortality. None of the other tests for trend were significant.

We also tested for trends on the associations between the combined measure of occupational physical activity and risk of all-cause mortality and myocardial infarction stratified by leisure time physical activity among males and females (table 4). A significant trend for the association between occupational physical activity and all-cause mortality was found for males with low ($p=0.01$) and moderate ($p=0.01$) leisure time physical activity. The remaining tests for trend were insignificant. This

is now described in the manuscript.

Specific comment:

Discussion

8. Please include in addition to the limitations already discussed their potential effect on the results (how biased would be the HR estimates and in which direction?)

Response:

This is now done.

Ad reviewer Christine Autenrieth

General comment:

This is an interesting study assessing how leisure time physical activity (PA) modifies the association between occupational PA and risk of all-cause mortality as well as myocardial infarction. The text is well organized and nicely read.

Response:

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

Comment:

1) Please provide more information about covariables, e.g., how was hypertension and household income levels defined?

Response:

Hypertension was based on self-reported use of anti-hypertensive medicine. This is now specified in the method section.

Household income was self-reported, based on average per month within the last year. The categories for household income were:

Low: <7000 Danish crowns

Moderate: 7000-16000 Danish crowns

High: >16000 Danish crowns

However, because these details do not make so much sense with the average income today (this was in 1981-1983), we prefer not to report them. We specify in the method section that the household income was based on average per month within the last year.

Comment:

2) Please provide references for the standard procedures of the assessment of covariables.

Response:

Reference to a publication describing all covariates in detail is now given in the method section.

Appleyard M. The Copenhagen City Heart Study, Østerbrounderøgelsen. A book of tables with data from the first examination (1976–78) and a five year follow-up (1981–83). Scand J Soc Med 1984.

Comment:

3) The large age range (25-66) might be a problem, since PA was measured at different ages.

Authors should discuss that PA patterns may vary between age groups.

Response:

We agree that this may be a concern and ought to be discussed. However, because of the rather similar mean age between the different levels of occupational physical activity (table 1), we don't think this would make a significant influence on the results of the study. This is now discussed in the strengths and limitations section.

Comment:

4) Leisure time PA was only measured at baseline. This should be discussed in more detail in the limitation section since leisure time PA patterns may vary considerably during an individual's life

course.

Response:

We agree. This is now mentioned as a limitation.

Comment:

1) In the tables, adjustment is made for cholesterol, however, it is not listed as a confounder in the method section.

Response:

Thank you! Cholesterol is now included as a confounder in the method section

Comment:

2) Associations described in this study should be cautiously interpreted. The conclusion that men with high occupational PA should be more physically active during leisure time is not clearly supported by the presented results. Among men with high occupational PA, no hazard ratios between low and high leisure time PA is reported.

Response:

You are correct. This interpretation is now rephrased or deleted from the abstract, key messages.

Comment:

3) Why did the authors choose to perform a separate analysis with participants having a low educational level instead of including education as a confounding variable?

Response:

Education level (social class) could be a potential confounder in this study. However, occupational physical activity and educational level are very highly correlated. Adjusting for educational level is therefore likely to impose an over-adjustment of the risk estimates. For investigating the independent effects of occupational physical activity, it is necessary to investigate the risk estimates from occupational physical activity on stratified analysis on educational level.

VERSION 2 – REVIEW

REVIEWER	Maria Hagströmer Associate Professor, RPT Division of Physiotherapy Department of Neurobiology, Care Sciences and Society Karolinska Institutet
REVIEW RETURNED	17/01/2012

GENERAL COMMENTS	The manuscript has been revised to my complete satisfaction. I have no further comments.
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