BMJ -
Decision on
Manuscript
ID
BMJ-2019-
048737

Body: 14-Mar-2019

Dear Dr. Ekelund

Manuscript ID BMJ-2019-048737 entitled "Dose-response associations between accelerometry measured physical activity and sedentary time with all-cause mortality: a systematic review and harmonised meta-analysis"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Rafael Perera (statistician), Wim Weber, Jose Merino, John Fletcher, Daoxin Yin, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
There are some issues which will make it difficult to make a substantial impact. First is that there is a likelihood of reverse causality even when taking their secondary analysis excluding deaths after the first year. Other studies have excluded the first two years as a way of minimising this potential for bias.
The other critical issue is the use of quartiles to define levels of exposure. This is difficult as translating the different exposure levels to something tangible is not straightforward. These quartiles were study specific and hence might strongly depend on the distribution of each of these variables (both range and shape). For this, it would be critical to determine how comparable they are. The levels of heterogeneity observed could be a symptom of this issue.
With regards to identifying all studies, this is probably not true and the focus on including only those in English or Scandinavian already creates a bias (as well as the inclusion of two extra databases).
Some of these issues could be solved. Not sure all of them could.

- Most editors were in favour given the importance of the topic but one editor felt this was better suited for a more specialised journal and wondered about lack of novelty and how do these results better "inform public health recommendations".

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
BMJ -2019-048737

Thank you for the opportunity to review this excellent paper.

The authors address an important and impactful question for physical activity and public health – that is, what is the association between accelerometer-measured physical activity and sedentary behavior and mortality. The literature to date has been unable to address this question because device-based assessments of physical activity in prospective cohort studies were unavailable. This manuscript provides a harmonized meta-analysis combining aggregate data from 8 cohort studies of over 36,000 older adults (average age 63) of which about 70% were women.

The findings are quite impressive showing a stronger association between physical activity and sedentary behavior and mortality than previously observed with self-report methods. In addition, the authors propose daily thresholds at which mortality risk increases for total physical activity (300 counts per minute) and sedentary behavior (9.5 hours/day). In addition to the reported dose-response associations, these data are quite important for public health as they provide health-related thresholds for consideration in public health guidelines.

Below are major and minor suggestions for the authors to consider:

Major

1. Thresholds/cutpoints

a. How were these determined for total PA and sedentary behavior? Suggest the description be more explicit as this is an important finding. Were the thresholds simply the point at which the most risk reduction was achieved for total PA and the point of highest risk for sedentary? Is there a way to put a confidence interval around these thresholds?

b. With regard to the 300 CPM threshold for total PA – it would be very helpful if the authors will translate this for the reader. What does this mean for prescribing total PA for population health? What will public health professionals be able to say about this number? More specifically, is this an average per day?

c. In the conclusion of the abstract and the paper, the authors did not mention the thresholds proposed for total PA and for sedentary behavior. I'm curious as to why these data were not mentioned.

2. Validity of the intensity categories

a. The Discussion does a nice job pointing out the challenges of using current accelerometer intensity cutpoints for older adults and for women. Since this issue is pervasive in physical activity research, particularly among these demographic groups, could you suggest calibration studies of devices for relative intensity?

3. 10-minute bouts

a. Perhaps I missed it, were 10-minute bouts a criterion for all data? Are you able to analyze without the 10-minute bout rule? In the most recent Physical Activity Guidelines for Americans, the 10-minute bout criterion was removed. It would be important, for total PA, to know the data included bouts of less than 10 minutes.

4. Quality score

a. Were there different findings by quality score?

5. BMI

a. Did you test for interaction with BMI?

6. Public health efforts to improve physical activity

a. Completely understand this is a research paper, but it will have significant impact for physical activity and public health. For the broader public health audience, mentioning efforts such as WHO's recent Global Action Plan on Physical Activity 2018–2030: More Active People for a Healthier World (https://www.who.int/ncds/prevention/physical-activity/global-action-plan-2018-2030/en/) and the recent US initiative (Active People, Healthy Nation, https://www.cdc.gov/physicalactivity/activepeoplehealthynation/index.html) may help inform BMJ readers about population-based strategies to improve physical activity.

Minor (Please note these comments were in Table format prior to posting on BMJ site:))

Page	Line	Comment
6	35	Change "Expert' to "Advisory".
7	6	Suggest to describe the intensities examined.
13	44	"Crucial" – is this the most accurate word here? Consider using important or vital or something else.
Throughout		Prefer to NOT use the qualifier "objective" when referring to PA measured with a device. Devices are not always the most objective methodology to address physical activity research questions.
14	34	Change "times" to "time"
15	12	Insert "intensity" after "moderate"
Table 2 and throughout		Suggest to use either "total" or "overall" throughout for consistency.
Forest plots		Spell out study names. Readers may not be familiar with the acronyms. Define "% weight" in footnote.
Supplementary Table 4 and throughout		Define "bouted" in footnote.
Funnel plots		Consider describing how to interpret the plots as these are a somewhat uncommon presentation of data.

Additional Questions:
Please enter your name: Janet Fulton

Job Title: Chief, Physical Activity and Health Branch

Institution: US Centers for Disease Control and Prevention (CDC)

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
General comments
While the study design used in this manuscript was appropriate, results of this manuscript add little new knowledge to the literature. First, the dose-response association between accelerometer-measured moderate-intensity physical activity and all-cause mortality found in this review (Figure 3e) was very similar with the association found in NHANES 2003-2006 participants alone (Figure 1A in Lee, 2016). Similarly, the dose-response association between accelerometer-measured sedentary behaviors and all-cause mortality found in this review (Figure 3f) was very similar with the association found in NHANES 2003-2006 participants alone (Figure 1C in Lee, 2016). Second, besides categorizing the time spent on physical activity and sedentary behaviors by quartiles as the exposure variable, the crude time spent as continuous variables should also be tested, so that the results could be translated quantitatively into effect size.

Reference
Lee PH (2016) Examining Non-Linear Associations between Accelerometer-Measured Physical Activity, Sedentary Behavior, and All-Cause Mortality Using Segmented Cox Regression. Front Physiol https://doi.org/10.3389/fphys.2016.00272

Specific comments

Page 4, lines 15. No need to specify the search update. Same for page 7, line 23.
Page 4, lines 19-24. Were there any requirements on the quality of the studies to be included? Same for page 8, lines 33-35.
Page 4, lines 33-35. Did you mean that you used Cox proportional hazards regression to re-analyze the data, or the included studies used Cox proportional hazards regression to analyze the data?
Page 4, line 43. "Did not participate". Did you mean that individual level participant data were not available?
Page 7, lines 27-34. Why not "accelerometry"?
Page 7, line 55 – page 8, line 3. Did you mean that only studies that placed the accelerometers at hip were included? In order to justify the exclusion of these three studies, the authors should provide evidence showing the lack of association of movement count data between accelerometers worn at different parts of the body.
Page 9, lines 3-19. These cutoffs were for ActiGraph accelerometer only.
Page 9, lines 42-44. I don't understand the rationale behind the categorization of exposure data into quartiles. It made the interpretation of the results difficult and the conclusion could not be translated quantitatively into effect size nor recommendations (e.g., one additional hour per day of sedentary behavior was associated with an elevated hazard of mortality of XXX).
Page 11, line 36. How were these two studies (26, 35) identified?

Table 1. It maybe clearer to use "number of deaths" instead of "number of cases". "Covariates" should be replaced by "Confounders".
Table 2. The unit for PA (min/d) was meaningless here as the volume of PA was categorized by quartiles.

Additional Questions:
Please enter your name: Paul Lee

Job Title: Assistant Professor

Institution: Hong Kong Polytechnic University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Recommendation:

Comments:
General comments:
Thank you for the opportunity to review this article. This manuscript is very well-written. The study is a well-coordinated collaborative project which enabled the harmonized analyses using objective measures of physical activity and sedentary time with large sample size. Since the current guidelines are informed primarily by studies using self-repot physical activity data, this paper provides crucial data for the advancement of public health recommendations.

Major comments:
-Did the authors set any inclusion/exclusion criteria for the participants in each study? Two studies (WAT2D and FHS) did not include chronic disease conditions as a covariate (Table 1). To minimize the risk of reverse causality, it would be better to perform a sensitivity analysis with Model C excluding the two studies and show the robustness of the current results. Also when comparing the magnitude of the association with those of self-report studies, it is of note that these studies either excluded participants with pre-existing CVD (Ref 39: Lear et al., 2017) or adjusted for history of cancer and heart disease (Ref 46: Arem et al., 2015); thus Model C would be a fair comparator?

-To further advance understanding and examine the "flip side" of PA-sedentary coin, a combined analysis examining a joint association of physical activity and sedentary time with mortality would give additional value to this paper (cf. Ekelund et al., 2016 Lancet).

Minor comments:
-In Methods, Page 9, the cutpoints for accelerometer data were originally developed and validated in younger adults (refs 13, 24, and 25), although older individuals constitute the majority of participants in the current analysis. It might be possible that the cutpoints affected the low numbers of participants undertaking bouted MVPA and VPA. Could you comment on the potential influence of the cutpoint selection on the results?

-In Supplementary Table 2, please add the range (min & max) of age in each study.

Additional Questions:
Please enter your name: Masamitsu Kamada

Job Title: Assistant Professor

Institution: The University of Tokyo

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Recommendation:

Comments:
This manuscript presents a systematic review and a harmonised meta-analysis of the effect of accelerometer-measured physical activity and sedentariness on all-cause mortality. The topic is very important as current guidelines are often based on self-reported activity which is known to be biased in several ways. As sensor-based studies are often limited in sample size and age range, it is reasonable and necessary to combine results from several studies.

The review and analysis are well-conducted and presented in general. However, I have two major concerns and comments:

(1) Maybe I got it wrong, but it seems that the quartiles have been constructed on the single cohort level. This means the quartile ranges are different from study to study? If this is the case, the authors have to explain, why they used this approach and why it is appropriate to analyse the different cohorts together, even when the quartiles of each cohort represent different ranges.

(2) Due to the limited studies available the sample is highly selected, indicated by the age distribution and the corresponding high proportion of women. This have been discussed. However, as this might highly limit the generalisation of the results, this have to be clearly stated at every stage, including the conclusions (e.g. abstract and conclusion).

Further the authors only focus on one method to estimate physical activity (epochs, count based). This should be mentioned (are there no other studies analysing PA and mortality with other methods?) and discussed as there are also methodological issues, important for the interpretation of the results (e.g. cpm-MET calibration).

As this is a systematic review, it is unclear to me, how the two additional (unpublished) studies have been selected? It seems to be a bit arbitrary to me. E.g. did the authors contacted all registered studies with unpublished data?

Specific comments

Page 3, line 16: from the previous sentence it cannot directly derived that underestimation of PA is likely.

Page 3, line 35: „steep" is imprecise, better give a number.

ABSTRACT
Page 4, line 47: age and sex distribution suggest that the studies are highly selected. This limits the conclusion and should clearly be stated even in the abstract conclusions.
Page 4, line 48: for survival time the median is usually appropriate.

INTRODUCTION

Page 6, line 54: „...this study was to conduct..."

METHODS
Page 7, line 34: how did you select the sensors namely added to the search? Some sensors are missing e.g. activPAL, axivity, physilog,...

Page 8, line 58 and page 9, line 3: is the wear-time of the studies comparable? If counts per wear-time is calculated there is a strong assumption that the distribution of counts across wear-time is comparable between studies. This have to be discussed.

Page 10, line 48: although the exclusion of early deaths have been widely used before, there are concerns about this method (please see: https://academic.oup.com/aje/article/146/8/672/71967). This should be discussed.

RESULTS
Page 11, line 41: see comment above. There should be more details about the age distribution of the studies. Is the mean value appropriate here?

Page 11, line 43: see comment above regarding the mean follow-up time.

DISCUSSION
Page 13, line 44: regarding the selective sample the conclusions have to be drawn carefully (e.g. for public health recommendations). Reverse causation might still be possible.

Page 14, line 3: „steep" is too imprecise.

Page 14, line 38: how was „more steeply" defined?

Page 17, line 46: Regarding the limitations, the conclusion should be drawn more carefully. Currently, the statement is very general.

FIGURES
Page 24, line 39: Explain why the two studies are only included in Figure 3e.

Table 1: as the age distribution seems to be very different and age is an important factor for PA, this information should be included in Table 1.

Supplementary Table 1: information about wear-time would be interesting as well.

Supplementary Table 5: explain how the reference was defined.

Additional Questions:
Please enter your name: Jochen Klenk

Job Title: Professor

Institution: Ulm University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Reviewer: 5

Recommendation:

Comments:

- This article is well-written examining the non-linear dose-response associations between objectively assessed total physical activity, different intensities of activity (light-intensity physical activity (low light-intensity physical activity, high light-intensity physical activity), moderate-to-vigorous intensity physical activity (MVPA), bouted MVPA) with all-cause mortality from 8 studies via harmonized meta-analysis.

- The article adds and supports the new physical activity recommendations for Americans (2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: US Department of Health and Human Services; 2018.) to limit sedentary time and also MVPA do not have to occur in 10 minutes bouts. Previously, there were no recommendations on sedentary time; and MVPA were recommended to be in bouted MVPA. This helps readers to make better decisions regarding modifying physical activity level.

- The research question is clearly defined and appropriately answered through the analyses.

- Participants are adequately described (Supplementary Table 1) for the 8 studies included in the analyses.

- Methods are adequately described. Extensive sensitivity analyses were done to examine if the relationships held.

- Results are clearly stated.

- Interpretation and conclusions are warranted from the results presented. Strengths and limitations are described.

- Questions/clarifications:

--- Figure 3a-3f. Could you add "Figure 3a-3f" to methods on page 11 along with Supplementary Table 8. Add that exposure reference was set as the median of the medians in the reference group for the splines (only listed in Figure description).

--- Supplementary Table 2. What does the * indicate? What does it mean if you have two letters (e.g. A* B) under comparability? Does the coding system for case-control

studies (http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf) also apply to the current study?

--- Supplementary Table 3. Would it be helpful to include the range for the quartiles for each physical activity measure on top of the medians?

--- Supplementary Figure 1. Could you add details on how to interpret funnel plots?

Additional Questions:
Please enter your name: Jungwha Lee

Job Title: Associate Professor

Institution: Northwestern University Feinberg School of Medicine

Reimbursement for attending a symposium?: No

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Reviewer: 6

Recommendation:

Comments:
The manuscript by Ekelund and colleagues describes a harmonised pooled analysis of physical activity and sedentary behaviour and risk for all cause mortality. Physical activity was measured in the included studies using waist-worn accelerometry devices from 2 manufacturers (Actigraph and Actical). The idea is novel, the paper is well written, and the statistical analyses are carefully planned, executed, and reported. Results are interpreted in a clear and straightforward way and the paper will be of interest to both clinicians and policy makers with an interest in physical activity. The main strength of the study is the harmonisation strategy for the accelerometry physical activity data. Minimising heterogeneity in the calculation of the exposure is itself a major step forward for the physical activity field, a field that has historically relied on the rather messy information questionnaires often provide.

My only major reservation with this paper has to do with the measures taken to reduce chances of reverse causation, i.e. the possibility that the effect sizes were not inflated by the inclusion of participants who both had lower physical activity/more sedentary behaviour and died early due to established sickness. I do not feel that all possibilities the available datasets offered were exhausted. Two cohorts did not even adjust for major prevalent disease at baseline (Murabito et al, 2015; Bakrania et al, 2017), which needs to be acknowledged in the discussion. The majority of cohorts had available information on history of established/diagnosed CVD (e.g. CHD, stroke) and cancer, conditions that can encourage or even impose less physical activity and more sedentary behaviour. Model 3 in these cohorts used such information for adjustments and results were broadly similar with Model 2 (which was adjusted for age, sex, BMI, and SES). This is not always an adequate measure against reverse causation; it is not uncommon that adjustment for major chronic disease/disease history in the multivariate model has minimal impact on the estimates, but stratification of the analyses by disease status produces very different results in each stratum. A sensitivity analysis excluding all participants with a history of major CVD and cancer would strengthen the paper by adding internal validity to these results and confidence to the study's key messages. For the same reason and considering the relatively short mean follow up (<7yrs), excluding the first year of follow up is reasonable. But another sensitivity analyses excluding fatal events in the first 2-3 years of events would also strengthen interpretation and offer reassurance that the larger than previous literature effects sizes this study reports are likely to be real.

Additional Questions:
Please enter your name: Emmanuel Stamatakis

Job Title: Professor, physical activity lifestyle,and population health

Institution: University of Sydney

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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