

RESPONSE TO THE EVALUATION COMMITTEE AND REVIEWERS – BMJ 2019-048737

We thank the evaluation committee, the statistical editor and the reviewers for their constructive comments. Two major issues identified by the reviewers were; 1) the issue of reverse causality and; 2) stratification of exposure data by quartiles at study level.

We have performed a number of additional analyses to address these concerns. In short, the results are materially unchanged when excluding deaths within the first two years (Please see revised Supplementary table 6). We also conducted sensitivity analyses restricted to the four studies where total physical activity were similar, and thus homogeneous across quartiles, and the results were materially unchanged (Please see Table 1 at bottom of this document).

We believe the comments from the reviewers and the revisions made following these comments substantially improved the quality of our manuscript. We have highlighted all edits in the revision of our manuscript in red font and provide a point-by-point response to the editors' and reviewers' comments below.

COMMENT	RESPONSE	EDITS IN MANUSCRIPT
STATISTICAL EDITOR		
<p>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.</p> <p>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.</p> <p>With regards to identifying all studies, this is probably not true and the focus on including only those in English or Scandinavian</p>	<p>We agree reverse causality is a serious issue for all observational research. We have therefore reanalysed individual study data excluding deaths during the two first years of follow up and updated our sensitivity analysis (Supplementary Table 6). The results are materially unchanged for all physical activity variables and somewhat attenuated for the association between sedentary time and mortality.</p> <p>We consider the continuous dose-response curves presented in Figure 3 can effectively be translated into meaningful levels of physical activity intensity in minutes per day for maximal risk reduction. These curves are based on the absolute activity-level measured (using the quartile median) and thus incorporates information from all cohorts into a single continuous model irrespective of the cohort-</p>	<p>Manuscript edited (Supplementary data)</p>

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.

specific activity levels. What is crucial is that these data-points are based on the same accelerometer cut-points and thus, within the limitations of sample heterogeneity (age, sex) and accelerometry in general, reflect comparable activity patterns.

To address the statistical reviewers' concern regarding expressing exposures categorised by quartiles at study level, we grouped studies with similar mean total physical activity (CPM) and performed sensitivity analyses for associations between total activity, light intensity, moderate-to-vigorous intensity and sedentary time and mortality. In these four cohorts (WAT2D, NHANES, ABC and NNPAS1), of which three (NHANES, ABC, NNPAS1) are nationally representative population-based studies, the patterns of associations and point estimates in each of the quartiles are similar compared with the analyses including all studies for physical activity exposure variables and slightly attenuated for sedentary time suggesting our primary analyses are robust (see attached Table 1 at the bottom of this document). This also suggest the dose-response associations are robust despite the categorization by quartiles at study level. However, we acknowledge these four cohorts only account for about 25% to 40% of the weighting in our original analyses and some heterogeneity persist.

Restricting the literature search to English and Scandinavian language may introduce bias. However, it is unlikely any major study with large sample size examining associations between device-based measures of physical activity by

	<p>accelerometry and mortality would be published in a non-English language journal. Finally, we performed sensitivity analyses excluding the two studies from which the data haven't previously been published and the results were materially unchanged (please see supplementary material in our original manuscript).</p>	
EDITORS		
<p>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”.</p>	<p>We appreciate that most editors have a favourable opinion about our manuscript.</p> <p>The harmonized approach is a novel and unique study design for meta-analyses of exposure data that differ in definition and analytical procedures between studies. Exposure data from all studies were reanalysed and aligned which is impossible in a conventional meta-analysis where exposures (e.g. time in different intensity levels) are analysed and defined differently between studies. We further consider our results novel given the magnitude of the observed associations between total physical activity and intensity specific physical activity with mortality. Further, the observed estimates for maximal risk reductions, especially for light intensity physical activity, are novel and will likely inform public health recommendations as indicated in the US Physical Activity Guidelines advisory committee report (see Reference #1 in manuscript)</p>	
REVIEWER 1		
<p>Thank you for the opportunity to review this excellent paper.</p> <p>The authors address an important and impactful question for physical activity and public health – that is, what is the</p>	<p>We thank the reviewer for considering the results reported in our manuscript important for public health</p>	

<p>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.</p> <p>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.</p>		
<p>Major</p> <p>1. Thresholds/cutpoints</p> <p>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?</p> <p>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</p>	<p>1a. The thresholds for all exposure variables were determined from the dose-response association analyses presented in Figure 2 and supplementary Table 5 as the point where the largest risk reductions were achieved. The 95% CIs are presented in Supplementary Table 5.</p> <p>1b. We agree this translation would be important. However, CPM is an arbitrary output from accelerometry and translating CPM into any meaningful number of physical activity energy expenditure would require a large free-living calibration study using doubly labelled water as the criterion. We are not aware of any such study. Therefore, and to facilitate interpretation of our results, we also present data on the risk reductions associated with time</p>	<p>No changes made</p>

<p>about this number? More specifically, is this an average per day?</p> <p>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.</p>	<p>spent in light, low light, high light, moderate and vigorous intensity and sedentary time including 95% CI in supplementary table 5. Finally, we discuss the total physical activity levels in relation to nationally representative samples from Norway, Sweden and US.</p> <p>1c. The primary aim of the manuscript was to determine the dose-response associations between total physical activity and intensity specific physical activity with mortality. The conclusion is expressed to address this aim.</p>	
<p>2. Validity of the intensity categories</p> <p>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?</p>	<p>We appreciate the reviewers comment about discussing the definition of intensity in absolute and relative terms. We are not aware of any calibration studies using relative intensity (i.e. % maximal cardio-respiratory fitness) as the criterion and agree such studies are needed. We have therefore edited the discussion and included a sentence suggesting that future studies aimed at identifying intensity thresholds based on relative intensity, especially in elderly are warranted. We have also amended the revised version of our manuscript including a discussion about intensity thresholds.</p>	<p>Manuscript edited</p>
<p>10-minute bouts</p> <p>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.</p>	<p>We analysed data for MVPA (min/d) irrespective of the accumulation pattern and for MVPA accumulated in 10-minute bouts. However, since very few individuals had any MVPA accumulated in 10-min bouts we only included total MVPA time in Tables and Figures. This is described in the results section (Page 12) and in Supplementary Table 4.</p>	<p>No changes made</p>
<p>Quality score</p> <p>Were there different findings by quality score?</p>	<p>We did not analyse the results by quality scores due to the homogeneity in these scores (range 8 to 9).</p>	<p>No changes made</p>

<p>BMI</p> <p>Did you test for interaction with BMI?</p>	<p>This is an interesting point. As the specific aim of this manuscript was to assess the dose-response associations between sedentary time, physical activity and mortality we consider it more appropriate to adjust for BMI as a confounder. However, we plan to examine the combined and stratified associations between physical activity and BMI in subsequent analyses.</p>	<p>No changes made</p>												
<p>Public health efforts to improve physical activity</p> <p>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.</p>	<p>We agree these strategies are important to underscore the importance of physical activity for public health and have amended the manuscript including references to these action plans.</p>	<p>Manuscript edited</p>												
<p>Minor (Please note these comments were in Table format prior to posting on BMJ site:))</p> <table border="0"> <thead> <tr> <th>Page</th> <th>Line</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td>6</td> <td>35</td> <td>Change "Expert" to "Advisory".</td> </tr> <tr> <td>7</td> <td>6</td> <td>Suggest to describe the intensities examined.</td> </tr> <tr> <td>13</td> <td>44</td> <td>"Crucial" – is this the most accurate word here? Consider using important or vital or something else.</td> </tr> </tbody> </table>	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.	<ol style="list-style-type: none"> 1. We have changed "Expert" to "Advisory" 2. We have included the specific intensity levels on page 7 3. We have changed 'crucial' to 'important' 4. Thanks for pointing this out. We have changed 'objective' to accelerometer in the figure legend (Fig 2) but think we have consistently avoided using 'objective' throughout the rest of the manuscript. 5. We have changed 'times' to 'time' 	<p>The manuscript is edited according to the minor issues raised by the reviewer highlighted in red font in the revised version of the manuscript (Comments 1 to 10).</p>
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<p>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.</p> <p>14 34 Change “times” to “time”</p> <p>15 12 Insert “intensity” after “moderate”</p> <p>Table 2 and throughout Suggest to use either “total” or “overall” throughout for consistency.</p> <p>Forest plots Spell out study names. Readers may not be familiar with the acronyms. Define “% weight” in footnote.</p> <p>Supplementary Table 4 and throughout Define “bouted” in footnote.</p> <p>Funnel plots Consider describing how to interpret the plots as these are a somewhat uncommon presentation of data.</p>	<ol style="list-style-type: none"> 6. We have inserted intensity after moderate on page 15. 7. Thanks for pointing this out. We have changed ‘overall’ to ‘total’ throughout the revised version of the manuscript. 8. We have provided the study names in the Figure legend to Figure 2. 9. We have defined %weight in the figure legend 10. We have defined ‘bouted’ in Supplementary Table 4 11. We believe Funnel plots with Egger’s test are the most commonly used way to analyse potential publication bias. A random scattered plot is an indication of lack of bias and tested by the Eggers test. 	
<p>REVIEWER 2</p>		
<p>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</p>	<p>While we acknowledge the important work by the reviewer (Lee 2016), we also respectfully disagree with the statement that these results add little new knowledge. First, we examined dose-response associations between total physical activity and different intensities, including light intensity, ‘low light’ and ‘high light’ intensity with mortality and observed strong associations between all exposures and mortality. Second, meta-analysing results from eight studies in a harmonised manner provide more robust evidence of the dose-response associations compared with data from a single study and with more confidence in the estimated</p>	<p>No changes made</p>

<p>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.</p>	<p>effect sizes. Third, the results reported, particularly the results from the dose-response associations (i.e. Figure 3 and Supplementary Table 5) can effectively be translated quantitatively into amount of time (min/d) needed to maximally reduce the risk of death. Fourth, the associations between physical activity intensities with mortality are non-linear across a wide range of activity. Thus, an analysis of the associations between continuous exposure data with mortality appears less appropriate and such results should be interpreted cautiously as the effect is highly dependent on the reference levels of the exposure variables.</p>	
<p>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.</p>	<ol style="list-style-type: none"> 1. We have edited the date for the search in the revised manuscript. 2. Inclusion criteria are described on Page 7. We evaluated the quality of the studies who fulfilled the inclusion criteria. 3. Included studies used Cox regression to analyse the study specific data. We have rephrased this sentence in the abstract for clarity. 4. 1 study did not wish to participate in the meta-analyses 5. We consider the search terms used would capture "accelerometry" 6. We included a reference (#17) in our original manuscript showing the difference in acceleration from monitors placed at different body sites. 7. We have provided the cut-offs for both Actigraph and Actical in the original version of our manuscript and provided references for these cut-offs. 	<p>Manuscript edited</p> <p>Manuscript edited</p> <p>Manuscript edited</p> <p>No changes made</p> <p>No changes made</p> <p>No changes made</p> <p>No changes made</p>

<p>using objective measures of physical activity and sedentary time with large sample size. Since the current guidelines are informed primarily by studies using self-report physical activity data, this paper provides crucial data for the advancement of public health recommendations.</p>		
<p>-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?</p>	<p>We agree reverse causality is an issue in all observational research. We have reanalysed all individual study level data excluding those who deceased within the first two years of follow up in additional sensitivity analyses (See updated Supplementary Table 6). The results were materially unchanged except for sedentary time which was slightly attenuated.</p> <p>We also performed sensitivity analyses as suggested by the reviewer (Model C excluding WAT2D and FHS) and the results were materially unchanged suggesting robustness to this type of confounding (see Table 2 at the end of this document). Thus, we consider our primary model (Model B) accurately reflect the dose-response associations between accelerometry measured sedentary time and different intensities with mortality.</p>	<p>Manuscript edited (Supplementary data)</p>
<p>-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).</p>	<p>We agree this is an interesting question. However, our primary aim was to examine the dose-response associations between physical activity, intensities of physical activity, and sedentary time with mortality and consider these analyses outside the scope of the present manuscript. We aim to pursue this question in a separate analysis.</p>	<p>No changes made</p>
<p>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</p>	<p>Unfortunately, there are no consensus about the most optimal cut points to use in large and heterogeneous samples as in the current study. Available cut points derived</p>	<p>Manuscript edited</p>

<p>of participants in the current analysis. It might be possible that the cutpoints affected the low numbers of participants undertaking bouts of MVPA and VPA. Could you comment on the potential influence of the cutpoint selection on the results?</p>	<p>in samples of older individuals are lower (Evenson et al, Prev Med Reports 2015;2:750-56). However, cut points are highly influenced by the activities chosen for the specific calibration protocol. We chose to identify intensity based on a previous validation study only including locomotor activities (Freedson et al, MSSE 1998) where the association between acceleration and energy expenditure is linear within the range of intensities relevant for this study. We have edited the discussion commenting on this issue.</p>	
<p>-In Supplementary Table 2, please add the range (min & max) of age in each study.</p>	<p>We have amended the revised version of our manuscript stating that all individuals ≤ 40 years of age were excluded before analyses in those studies that originally included younger participants.</p>	<p>Manuscript edited</p>
<p>Reviewer 4</p>		
<p>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.</p>	<p>We thank the reviewer for considering our manuscript important.</p>	
<p>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.</p>	<p>The reviewer is correct we constructed the quartiles on cohort level. The best approach is to pool individual data from all cohorts and thereafter construct quartiles. However, this was not possible due to legal data sharing issues. As this issue is one of the key issues raised by several reviewers, we conducted sensitivity analyses including</p>	

	<p>cohorts with similar activity profiles and reanalysed the data (see response to statistical editor and Table 1 below). The results from these analyses showed that the association between sedentary time and mortality was attenuated whereas associations for all physical activity variables were materially unchanged and very similar to those when all 8 cohorts were analysed suggesting the results are robust. Finally, we included all data in one restricted cubic spline model to retrieve the continuous dose-response pattern based on the absolute PA-levels within each cohort.</p>	
<p>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).</p>	<p>We agree most of the cohorts are not representative and do not suggest these results should be generalised to younger cohorts. We have therefore amended the conclusion adding "in middle-aged and older individuals" and clarified all individuals ≤ 40 years of age were excluded prior to analyses.</p>	<p>Manuscript edited accordingly</p>
<p>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).</p>	<p>We compared our results to previous studies examining associations between physical activity energy expenditure assessed by the doubly labelled water method (Reference #40) and total activity assessed by a wrist worn device (Reference #41). We discussed potential limitations with our study including single-axis accelerometry and combining data from studies using two different brands of accelerometry in our original manuscript. Excluding the two studies that assessed physical activity using the Actical accelerometer did not change the results (see supplementary table 7 in the manuscript).</p>	<p>No changes made</p>
<p>As this is a systematic review, it is unclear to me, how the two additional (unpublished) studies have been selected? It seems</p>	<p>The two studies included that haven't published data on the associations between physical activity and mortality are</p>	<p>No changes made</p>

to be a bit arbitrary to me. E.g. did the authors contacted all registered studies with unpublished data?	studies in which consortia partners are principal investigators and have direct access to the data. Excluding these studies from the analyses did not affect the results (See Supplementary Table 7). We did not contact additional studies with unpublished data.	
Page 3, line 16: from the previous sentence it cannot directly derived that underestimation of PA is likely.	Thanks for pointing this out. We have edited this sentence in the revised version of the manuscript	Manuscript edited
Page 3, line 35: „steep“ is imprecise, better give a number.	Manuscript edited and “steep” is changed to “statistically significantly increased”	Manuscript edited
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.	The generalisability of our results is discussed in the manuscript. Conclusion edited as requested	Manuscript edited
Page 4, line 48: for survival time the median is usually appropriate.	We have provided median follow up time in abstract	Manuscript edited
Page 6, line 54: „...this study was to conduct...“	Thanks for spotting this error.	Manuscript edited
Page 7, line 34: how did you select the sensors namely added to the search? Some sensors are missing e.g. activPAL, axivity, physilog,...	The specific sensors included as search terms are the most frequently used sensors. If additional studies using other sensors are available these would be picked up by the other search terms.	No changes made
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.	First, we inclusion criteria included >10 hrs/d of wear time as indicated in the methods section of our manuscript. This effectively reduce the heterogeneity in wear time. Second, wear time information are included in the revised version of Supplementary table 1 and comparable between studies (range 843 to 910 min/d). The results from the sensitivity analysis presented in Supplementary Table 7 excluding the two studies (REGARDS and FHS) assessing physical activity using a different monitor (Actical which provides substantially lower total counts) were very similar to the	Manuscript edited

	primary results presented in Table 2. Thus, it is unlikely substantial differences in wear time affect the main results.	
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.	Reverse causality is always an issue in observational research. We have amended our manuscript and provide sensitivity analyses where deaths during the first two years are excluded and the results are materially unchanged. Further, we have extended the discussion re the issue of reverse causality (See supplementary Table 6 and discussion in the revised version of our manuscript).	Manuscript edited
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?	We have included information that all individuals ≤ 40 years of age were excluded before analyses.	Manuscript edited
Page 11, line 43: see comment above regarding the mean follow-up time.	We provide median and mean follow up in the revised version of our manuscript.	Manuscript edited
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.	Please see comments above re reverse causation.	No changes made
Page 14, line 3: „steep“ is too imprecise.	Please see comment above re “steep” changed to “increased more rapidly based on the shape of the curve for the dose-response association.”	Manuscript edited
Page 14, line 38: how was „more steeply“ defined?	Please see response to the comment above “increased more rapidly based on the shape of the curve for the dose-response association.”	Manuscript edited
Page 17, line 46: Regarding the limitations, the conclusion should be drawn more carefully. Currently, the statement is very general.	We have rephrased the conclusion including “in middle-aged and older individuals”	Manuscript edited
Page 24, line 39: Explain why the two studies are only included in Figure 3e.	This is explained in the manuscript and is due to the discrepancy between activity monitors/cut-points for estimating CPM and all intensities except for MVPA	No changes made

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.	Information about mean age and SD are included in Supplementary Table 1. All cohorts restricted their analyses to those ≥ 40 years of age.	Manuscript edited
Supplementary Table 1: information about wear-time would be interesting as well.	Supplementary table 1 amended accordingly	Manuscript edited
Supplementary Table 5: explain how the reference was defined.	This information is given in our manuscript (Please see Page 10, L28-29) and now also included as footnote to Supplementary table 5	Manuscript edited
Reviewer 5		
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), bouts 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 bouts MVPA. This helps readers to make better decisions regarding modifying physical activity level.	We thank the reviewer for considering our manuscript of importance.	
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.	We thank the reviewer for these comments.	No changes made

<p>Methods are adequately described. Extensive sensitivity analyses were done to examine if the relationships held.</p> <p>Results are clearly stated.</p> <p>Interpretation and conclusions are warranted from the results presented. Strengths and limitations are described.</p>		
<p>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).</p>	<p>This information is now added to the methods section and to the Table heading in Supplementary Table 8.</p>	<p>Manuscript edited</p>
<p>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?</p> <p>Supplementary Table 3. Would it be helpful to include the range for the quartiles for each physical activity measure on top of the medians?</p>	<p>We have amended the footnote to Supplementary table 2 including this information.</p> <p>The coding system is specific for cohort studies and described in the reference http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf.</p> <p>We have included the range for the medians in Supplementary table 3.</p>	<p>Manuscript edited</p> <p>No changes made</p> <p>Manuscript edited</p>
<p>Supplementary Figure 1. Could you add details on how to interpret funnel plots?</p>	<p>Funnel plots are visually interpreted by symmetry vs. asymmetry and by the Eggers test for asymmetry. The individual study data points should be evenly distributed in the graph.</p>	<p>No changes made</p>
<p>Reviewer 6</p>		
<p>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</p>	<p>We thank the reviewer for considering our manuscript novel and of interest to clinicians and policy makers.</p>	

<p>accelerometry devices from 2 manufacturers (Actigraph and Actical).</p> <p>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.</p>		
<p>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.</p>	<p>We agree reverse causation is an issue in all observational research and this point was pointed out by several reviewers. We therefore reanalysed all data excluding the two studies in which data on prevalent diseases were unavailable and the results were materially unchanged (Please see table 2 at the end of this document).</p> <p>To further address the issue re reverse causation, we have updated our sensitivity analysis excluding deaths within the first two years and the results were materially unchanged (Please see updated Table 6 in supplementary materials).</p> <p>We also agree with the reviewer stratification by disease status would further address the issue of reverse causation. However, we are concerned about sample size and power in some of the included studies to conduct these analyses.</p>	

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.

Table 1. Meta-analysis for the associations between total physical activity, different intensities of physical activity or sedentary time by quartiles and all-cause mortality. Analyses are restricted to 4 studies (ABC, NHANES, NNPAS and WAT2D) that were similar in total physical activity (CPM). To facilitate a direct comparison, data from our main analysis (Model B) including all eight studies are highlighted in red font.

	Model B Adjusted for sex, age, BMI, SES and wear time (except for CPM). MVPA and Sedentary are mutually adjusted.			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Total PA (CPM)	1 (Ref) (N=1945; 386)	0.45 (0.36; 0.56) (N=1944; 149) 0.48 (0.43; 0.54)	0.43 (0.20; 0.90) (N=1936; 91) 0.34 (0.26; 0.45)	0.29 (0.20; 0.41) (N=1925; 71) 0.27 (0.23; 0.32)
LPA (min/d)	1 (Ref) (N=1924; 371)	0.59 (0.47; 0.74) (N=1924; 168) 0.60 (0.54; 0.68)	0.45 (0.34; 0.59) (N=1939; 107) 0.44 (0.38; 0.51)	0.45 (0.32; 0.43) (N=1951; 82) 0.38 (0.28; 0.51)
MVPA (min/d)	1 (Ref) (N=1912; 417)	0.58 (0.42; 0.79) (N=1934; 142) 0.64 (0.55; 0.74)	0.52 (0.27; 1.07) (N=1959; 87) 0.55 (0.40; 0.74)	0.54 (0.33; 0.89) (N=1945; 82) 0.52 (0.43; 0.61)
Sedentary (min/d)	1 (Ref) (N=1944; 99)	0.99 (0.71; 1.40) (N=1940; 126) 1.28 (1.09; 1.51)	1.39 (1.00; 1.93) (N=1940; 188) 1.71 (1.36; 2.15)	2.03 (1.39; 2.97) (N=1926; 315) 2.63 (1.94; 3.56)

Table 2. Meta-analysis for the associations between total physical activity, different intensities of physical activity or sedentary time by quartiles and all-cause mortality according to Model C excluding participants from two studies (FHS and WAT2D) in which data on chronic diseases at baseline were unavailable.

	Model C Adjusted for sex, age, BMI, SES, wear time (except for CPM) and covariates included in Manuscript Table 1. MVPA and Sedentary are mutually adjusted.			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Total PA (CPM)	1 (Ref) (N=8271; 1126)	0.49 (0.44; 0.55) (N=8279; 465)	0.34 (0.25; 0.47) (N=8278; 250)	0.28 (0.23; 0.33) (N=8280; 205)
LPA (min/d)	1 (Ref) (N=8267; 1033)	0.61 (0.54; 0.69) (N=8285; 491)	0.44 (0.36; 0.54) (N=8267; 305)	0.37 (0.27; 0.52) (N=8289; 217)
Low LPA (min/d)	1 (Ref) (N=8258; 958)	0.64 (0.56; 0.74) (N=8290; 490)	0.49 (0.39; 0.61) (N=8287; 343)	0.42 (0.33; 0.53) (N=8273; 255)
High LPA	1 (Ref) (N=8256; 1108)	0.54 (0.47; 0.63) (N=8295; 456)	0.39 (0.32; 0.37) (N=8267; 263)	0.38 (0.23; 0.61) (N=8293; 219)
MVPA (min/d)	1 (Ref) (N=8200; 1081)	0.66 (0.58; 0.76) (N=8331; 451)	0.56 (0.39; 0.79) (N=8299; 287)	0.55 (0.42; 0.71) (N=8278; 227)
Sedentary (min/d)	1 (Ref) (N=8277; 306)	1.30 (1.10; 1.53) (N=8279; 398)	1.69 (1.34; 2.13) (N=8278; 532)	2.65 (2.02; 3.48) (N=8274; 810)

