

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A cross sectional study of diet, physical activity, television viewing and sleep duration in 233,110 adults from the UK Biobank; the behavioural phenotype of cardiovascular disease and Type 2 diabetes.
AUTHORS	Cassidy, Sophie; Chau, Josephine; Catt, Michael; Bauman, Adrian; Trenell, Michael

VERSION 1 - REVIEW

REVIEWER	Mette Aadahl Research Centre for Prevention and Health, The Capital Region of Denmark, Glostrup, Denmark. Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen
REVIEW RETURNED	08-Oct-2015

GENERAL COMMENTS	<p>This paper report cross-sectional findings on self-reported diet, physical activity, TV-viewing time, and duration of sleep - separately and as cluster of the non-diet behaviours - across four groups of 1."no disease", 2.CVD, 3.Type 2 diabetes and 4.CVD+type 2 diabetes in a large UK biobank cohort of approximately (502,664) 240,000 men and women between 37 and 63 years of age. Data were analysed by logistic regression adjusting for gender, age, BMI (Objectively measured), Townsend Deprivation Index ethnicity, alcohol, smoking and meeting fruit/vegetable guidelines. The study finds that low physical activity, high TV-viewing time and sub-optimal sleep duration (<7 hours or >8 hours) are characteristics of CVD and type 2 diabetes and are likely to cluster.</p> <p>Generally the paper is well written, data collection methods and analytical approach appear sound, results are well presented and discussed, with a strong emphasis clinical and public health implications.</p> <p>I have a few rather minor comments and suggestions that I would like the authors to consider.</p> <ol style="list-style-type: none">1. Title: TV-viewing time would be a more correct term, rather than sedentary behavior, as the self-report question specifically ask about TV-viewing (- although can be considered as a marker of sedentary behaviour!). Likewise, I suggest the authors specify that sleep is in fact "sleep duration". Preferably, specify this in the title as well as throughout the manuscript (TV-viewing and Sleep duration both).2. Methods (P.6, line 48-) Please include a short description of collection of "Health status"/diagnosis information that was entered and verified by a UK Biobank nurse, during the verbal interview. Did the nurse classify diseases based on self-report disease-status or ??? -and is the nurse the clinician whose opinion is referred to p.6 line57??? Please clarify.
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	<p>P.8 line 14: Was no question asked on major changes in physical activity in the last five years? (similar to the question on change in diet). If yes, how were th responses?</p> <p>P.9, line 23-: The terms "poor sleep" and "good sleep" to me signal sleep quality rather than sleep duration. I suggest adding the "duration", as mentioned earlier.</p> <p>Results: P.12, bottom - "BMI and cardio-metabolic disease are strongly linked, yet the odds of being obese in the "Type 2+CVD" groues were less (OR_2.77 etc...)" Please specify where this result comes from.</p> <p>Discussion: I suggest the authors touch upon the low response rate and the relatively high number of missing values - and the possible implications for findings (if any!).</p>
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REVIEWER	<p>Bethany Barone Gibbs University of Pittsburgh, USA</p> <p>I have accepted grant funding to my institution from the National Institutes of Health (USA) and the HumanScale company.</p>
REVIEW RETURNED	01-Dec-2015

GENERAL COMMENTS	<p>This is a well written paper in a large, established cohort. The angle which describes the clustering poor lifestyle habits that need to be addressed in these diseased populations is well received and of import to public health. A few revisions could improve the the clarity and rigor of the paper:</p> <p>MAJOR COMMENTS</p> <p>1) Based on figure 1, 203,700 persons were excluded from the analysis due to 'other diseases'. I was unable to find a description of the diseases that were excluded here or a rationale for doing so. (I was looking for this information specifically in the population and study design or the disease categories sections of methods). It would also be nice to describe the excluded population (at least their sleep/tv/physical activity habits of interest) perhaps in the supplement.</p> <p>2) Referring to television viewing time as sitting time is incorrect and misleading. The authors note the limitation of tv as a surrogate for sitting time in the limitations section and use the weak rationale that it is commonly done and self-reported TV time has high reliability. There are numerous studies now that demonstrate the poor correlation between TV and total sitting time. There is also ample evidence the TV time is associated with worse dietary intake and other unhealthy behaviors, which would not be controlled for and thus could create residual confounding in the current analysis. For this latter reason, TV time is more consistently related to adverse disease outcomes vs. total sitting time and this is one of the main reasons that the media is over-interpreting the level of evidence that reducing sedentary behavior will have health benefits. Thus, please revise the title and manuscript to correctly say 'television time' rather than 'sitting time' - television time is well established to be a negative health behavior and thus your results would still have translation importance. Drawing parallels between sitting time and television viewing time (one of many sitting behaviors) would be more appropriate only in the discussion, though scientific literature of the detriment of television viewing rather than total sedentary behavior (as is currently in the discussion) would be more appropriate.</p>
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	<p>MINOR COMMENT</p> <p>3) A few places in the manuscript, the authors use phrases like 'as cardio-metabolic disease worsens'. This is misleading because it implies longitudinal, within-individual changes. Rather, rephrasing these to something like 'across increasing categories of cardio-metabolic disease' would be more correct.</p>
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REVIEWER	Dr Tom Yates University of Leicester, UK
REVIEW RETURNED	14-Dec-2015

GENERAL COMMENTS	<p>This article provides a valuable and novel overview of the biobank database and the link between non-dietary lifestyle factors, type 2 diabetes and cardiovascular disease. Overall it is well written and adds to the current evidence-based</p> <p>I have the below comments which I hope the authors will find useful</p> <p>I have some concerns around the methods that the authors used to analyse the physical activity data. The authors mention that the questionnaire is based on IPAQ. However, there are some key differences. IPAQ asks about number of days on which activities are carried out for 10 minutes or more and then the average time the activity was carried out on those days. This allows for a simple frequency x duration calculation to get total volume. However, Biobank does not allow for this as the questions about duration are NOT linked to frequency. The frequency question asks “In a typical week, on how many days did you do 10 minutes or more of.....”. the frequency question asks “How many minutes did you usually spend doing XX on a typical day?” The guidance for this states “If the time you usually spend doing XX on EACH day of the week varies a lot, give an average of the time you spend doing moderate physical activity”. This does not allow for the frequency x duration calculation they these variables are not explicitly linked. For example, this wording allows for durations below 10 minutes. Someone might undertake an average of 7 minutes of vigorous intensity per day (7 days/week), but only do more than 10 minutes once a week. The wording of the questionnaire does not allow this possibility for be distinguished from other combinations.</p> <p>Given the above it may be safer to look at the frequency and duration variables separately for each intensity domain – much of the analysis reported should also be possible using the duration variables. Alternatively, the authors may want to consider the walking for pleasure, exercise and sports questions where frequency is linked to duration.</p> <p>The number not meeting the PA guidelines may also need some revision. Walking is normally considered moderate intensity (the pace has to be very slow to get below the 3-MET threshold). Current guidelines require 150 minutes per week (22 mins per day) for moderate or 75 minutes per week (11 mins per day). The number not achieving this level through walking, moderate or vigorous activity is almost certainly lower than the 43% reported (over 69% seem to achieve this level through walking alone).</p> <p>Please add the number with high physical activity and low sedentary behaviour and healthy sleep time to Table 2.</p>
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	<p>More detail around how other diseases were handled would be welcome. For example, in the CVD category, were non-diabetes comorbidities included. For example were those with CVD and cancer included or excluded. If they were included how were comorbidities handled in the analysis. If they were excluded, did this limit generalizability or otherwise dilute results.</p> <p>In the discussion on physical activity the authors discuss the importance of vigorous physical activity. It would be helpful to include an additional table that replicates Table 3, but reports ORs for the physical activity variables (i.e OR for low vigorous activity across the different disease states after adjustment for the same variables in Table 3 plus moderate physical activity and walking activity). This would allow for a quantitative assessment of the importance of vigorous intensity physical activity in relation to moderate physical activity and walking.</p> <p>For the discussion on sitting, it would helpful to note lack of evidence from RCTs as a step needed before guidance/policies can be changed</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Mette Aadahl

Institution and Country: Research Centre for Prevention and Health, The Capital Region of Denmark, Glostrup, Denmark; Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen

Comment: Generally the paper is well written, data collection methods and analytical approach appear sound, results are well presented and discussed, with a strong emphasis clinical and public health implications. I have a few rather minor comments and suggestions that I would like the authors to consider.

Specific points:

Comment 1: Title: TV-viewing time would be a more correct term, rather than sedentary behavior, as the self-report question specifically ask about TV-viewing (- although can be considered as a marker of sedentary behaviour!). Likewise, I suggest the authors specify that sleep is in fact "sleep duration". Preferably, specify this in the title as well as throughout the manuscript (TV-viewing and Sleep duration both).

Response 1: Thank you for this suggestion, we have changed the title to include television viewing and sleep duration, and have updated the text throughout the manuscript.

Comment 2: Methods (P.6, line 48) Please include a short description of collection of "Health status"/diagnosis information that was entered and verified by a UK Biobank nurse, during the verbal interview. Did the nurse classify diseases based on self-report disease-status or ????? -and is the nurse the clinician whose opinion is referred to p.6 line57??? Please clarify.

Response 2: During the verbal interview the UK Biobank nurse was able to ask participants further details about any disease condition they self-reported during the touchscreen questionnaire. From this information they were able to enter and verify disease diagnosis. No medical records were used for this. This has been made clearer on P6,L21-23. The clinician opinion for the diseases to include in the CVD group, refers to Professor Adrian Bauman who is an author on this manuscript, this has been made

clearer on P7,L2.

Comment 3: P.8 line 14: Was no question asked on major changes in physical activity in the last five years? (Similar to the question on change in diet). If yes, how were the responses?

Response 3: We agree this would have been interesting however this question was not asked within the UK Biobank questionnaire.

Comment 4: P.9, line 23:- The terms "poor sleep" and "good sleep" to me signal sleep quality rather than sleep duration. I suggest adding the "duration", as mentioned earlier.

Response 4: Thank you for this suggestion; we have added 'duration' into the sleep variables throughout the manuscript, making "good sleep duration" and "poor sleep duration".

Comment 5: Results: P.12, bottom - "BMI and cardio-metabolic disease are strongly linked, yet the odds of being obese in the "Type 2+CVD" groups were less (OR_2.77 etc...)" Please specify where this result comes from.

Response 5: Thank you for highlighting this. The logistic regression model estimates all of the coefficients for all of the predictors included in the model. When looking at the odds of reporting an 'unhealthy phenotype' in each disease category we included predictor variables such as BMI. As BMI was a predictor variable included in the model, it calculated that the odds of being obese (OR 2.77) were lower than the odds of reporting an 'unhealthy phenotype' (3.29) in those with Type 2 diabetes + CVD. However, we do feel that this may confuse the reader and does not need to be included in the results; therefore we have excluded this information.

Comment 6: Discussion: I suggest the authors touch upon the low response rate and the relatively high number of missing values - and the possible implications for findings (if any!).

Response 6: Thank you for this suggestion, we have included these factors in the limitations (P14,L20-22).

Reviewer: 2

Reviewer Name: Bethany Barone Gibbs

Institution and Country: University of Pittsburgh, USA

Please state any competing interests or state 'None declared': I have accepted grant funding to my institution from the National Institutes of Health (USA) and the HumanScale company.

Comment: This is a well written paper in a large, established cohort. The angle which describes the clustering poor lifestyle habits that need to be addressed in these diseased populations is well received and of import to public health. A few revisions could improve the clarity and rigor of the paper:

Specific comments:

Comment 1: Based on figure 1, 203,700 persons were excluded from the analysis due to 'other diseases'. I was unable to find a description of the diseases that were excluded here or a rationale for doing so. (I was looking for this information specifically in the population and study design or the disease categories sections of methods). It would also be nice to describe the excluded population (at least their sleep/tv/physical activity habits of interest) perhaps in the supplement.

Response 1: Thank you for highlighting this important point. The 203,700 excluded participants included those who reported any disease other than CVD or diabetes. There was a wide variety of other diseases including respiratory, gastrointestinal, renal, neurology, musculoskeletal, haematology, gynaecology, immunological and infectious. This has been made clearer on P7,L10-14. In supplement 2 we have included a summary table of

some key demographics and lifestyle behaviours of the excluded group who had information on physical activity, sitting and sleep.

Comment 2: Referring to television viewing time as sitting time is incorrect and misleading. The authors note the limitation of tv as a surrogate for sitting time in the limitations section and use the weak rationale that it is commonly done and self-reported TV time has high reliability. There are numerous studies now that demonstrate the poor correlation between TV and total sitting time. There is also ample evidence the TV time is associated with worse dietary intake and other unhealthy behaviors, which would not be controlled for and thus could create residual confounding in the current analysis. For this latter reason, TV time is more consistently related to adverse disease outcomes vs. total sitting time and this is one of the main reasons that the media is over-interpreting the level of evidence that reducing sedentary behavior will have health benefits. Thus, please revise the title and manuscript to correctly say 'television time' rather than 'sitting time' - television time is well established to be a negative health behavior and thus your results would still have translation importance. Drawing parallels between sitting time and television viewing time (one of many sitting behaviors) would be more appropriate only in the discussion, though scientific literature of the detriment of television viewing rather than total sedentary behavior (as is currently in the discussion) would be more appropriate.

Response 2: Thank you for highlighting this important point (also raised by Reviewer 1, Comment 1). As have adapted our terminology as described to Reviewer 1 and also emphasised the limitation of TV viewing as a surrogate for other sedentary behaviors (P15,L4-9 and P17,L1-5).

Comment 3: A few places in the manuscript, the authors use phrases like 'as cardio-metabolic disease worsens'. This is misleading because it implies longitudinal, within-individual changes. Rather, rephrasing these to something like 'across increasing categories of cardio-metabolic disease' would be more correct.

Response 3: We agree that this language is not as concise as we intended and have changed the wording to 'across worsening categories of cardio-metabolic disease' (P11, L6-7 + P17, L7-8 + P18, L5-6).

Reviewer: 3

Reviewer Name: Dr Tom Yates

Institution and Country: University of Leicester, UK

Please state any competing interests or state 'None declared': None

Comment: This article provides a valuable and novel overview of the biobank database and the link between non-dietary lifestyle factors, type 2 diabetes and cardiovascular disease. Overall it is well written and adds to the current evidence-based

Specific comments

Comment 1: I have some concerns around the methods that the authors used to analyse the physical activity data. The authors mention that the questionnaire is based on IPAQ. However, there are some key differences. IPAQ asks about number of days on which activities are carried out for 10 minutes or more and then the average time the activity was carried out on those days. This allows for a simple frequency x duration calculation to get total volume. However, Biobank does not allow for this as the questions about duration are NOT linked to frequency. The frequency question asks "In a typical week, on how many days did you do 10 minutes or more of.....". the frequency question asks "How many

minutes did you usually spend doing XX on a typical day?" The guidance for this states "If the time you usually spend doing XX on EACH day of the week varies a lot, give an average of the time you spend doing moderate physical activity". This does not allow for the frequency x duration calculation they these variables are not explicitly linked. For example, this wording allows for durations below 10 minutes. Someone might undertake an average of 7 minutes of vigorous intensity per day (7 days/week), but only do more than 10 minutes once a week. The wording of the questionnaire does not allow this possibility for be distinguished from other combinations. Given the above it may be safer to look at the frequency and duration variables separately for each intensity domain – much of the analysis reported should also be possible using the duration variables. Alternatively, the authors may want to consider the walking for pleasure, exercise and sports questions where frequency is linked to duration.

Response : We appreciate your concern and close investigation into our physical activity analysis. It is correct that the IPAQ questionnaire has been slightly adapted, indeed the UK Biobank protocol states that *'the questions on physical activity that have been included in the UK Biobank questionnaire were adapted, based upon piloting, from a validated survey instrument [craig 2003]'*. We have made this clearer on P7,L19. As suggested, we have performed the analysis for separate frequency and duration variables (**PLEASE SEE RESULTS AT THE END OF THIS DOCUMENT**) but it made no difference to the overall outcomes. Indeed the odds ratios for reporting low physical activity or the unhealthy phenotype remained exactly the same when using the duration variable only, compared to using frequency x duration. We have added these results into the online supplement 3, but feel that the minor differences in the IPAQ and UK Biobank questionnaire does not justify changing our analysis in the manuscript as explained below (Points 1 through 3). We reiterate however, that we have included the adapted analyses as a supplement to allow readers to view.

- 1) The reviewer states that the UK Biobank frequency and duration questions are not explicitly linked as *"The frequency question asks "In a typical week, on how many days did you do 10 minutes or more of.....". the duration question asks "How many minutes did you usually spend doing XX on a typical day?"* Although the frequency and duration variables are not explicitly linked in the UK Biobank questionnaire, they are likely to be cognitively linked in exactly the same way as the IPAQ, with the major difference being no minimum bout criterion. The minimum bout of 10 mins originally proposed by IPAQ in 1998 was consistent with the science at the time; this criterion is being challenged, as smaller amounts of activity may confer benefits, especially of high intensity; hence this difference may inflate the prevalence estimates slightly in the Biobank data, but are unlikely to have any influence on the correlates or associations, which is the central focus of this paper.
- 2) In relation to the duration question, the reviewer makes the point that *"The guidance for this states "If the time you usually spend doing XX on EACH day of the week varies a lot, give an average of the time you spend doing moderate physical activity".* A participant completing IPAQ does also cognitively average their time if it varied throughout the week, so there is no difference here.
- 3) Total mets min week has provided to researchers a well-defined single summative physical activity variable which is easily understood, and which has reasonable discriminant validity (and good categorisation into active and inactive groups) for very large samples or population surveillance, as here with the Biobank data; clearly this may be inappropriate for small intervention trial samples (Bauman 2009, Journal of physical activity and health 1:6). We feel that it is important to provide a continuity of units with other studies that have used IPAQ so have retained this analysis alongside the additional assessment.

Comment 2: The number not meeting the PA guidelines may also need some revision. Walking is normally considered moderate intensity (the pace has to be very slow to get below the 3-MET threshold). Current guidelines require 150 minutes per week (22 mins per day) for moderate or 75 minutes per week (11 mins per day). The number not achieving this level through walking, moderate or vigorous activity is almost certainly lower than the 43% reported (over 69% seem to achieve this level through walking alone).

Response 2: Thank you for this observation. We have now included those individuals who meet the 150min moderate recommendation through walking, and the results have been updated on Table 2.

Comment 3: Please add the number with high physical activity and low sedentary behaviour and healthy sleep time to Table 2.

Response 3: The proportion of adults reporting a 'HEALTHY phenotype' (high physical activity, low TV viewing and healthy sleep) have been added as well as the proportions reporting an 'UNHEALTHY phenotype' (low physical activity, high TV viewing and healthy sleep) on table 2.

Comment 4: More detail around how other diseases were handled would be welcome. For example, in the CVD category, were non-diabetes comorbidities included. For example were those with CVD and cancer included or excluded. If they were included how were comorbidities handled in the analysis. If they were excluded, did this limit generalizability or otherwise dilute results.

Response 4: Thank you for raising an important clarification. The only comorbidities that we excluded were those in the CVD group who reported diabetic complications including diabetic neuropathy, diabetic nephropathy and diabetic eye disease (added on P7,L3-4). This was to reduce the likelihood of having patients with diabetes in the CVD group. All other comorbidities were included in the 'CVD', 'Type 2 diabetes without CVD', and 'Type 2 diabetes + CVD' groups. This was because there was such a large number of comorbidities listed in the UK Biobank, therefore correcting for these would have led to overadjustment.

Comment 5: In the discussion on physical activity the authors discuss the importance of vigorous physical activity. It would be helpful to include an additional table that replicates Table 3, but reports ORs for the physical activity variables (i.e OR for low vigorous activity across the different disease states after adjustment for the same variables in Table 3 plus moderate physical activity and walking activity). This would allow for a quantitative assessment of the importance of vigorous intensity physical activity in relation to moderate physical activity and walking.

Response 5: Thank you for this suggestion, we have included an additional table (Table 3) comparing the odds for reporting low walking, moderate and vigorous intensity activity across the disease states. The results highlight the importance of vigorous activity, which has been described in the text (P12,L5-7).

Comment 6: For the discussion on sitting, it would helpful to note lack of evidence from RCTs as a step needed before guidance/policies can be changed

Response 6: We agree and have added this into the discussion on P20,L4-6.

Results for Reviewer 3 (comment 1)

COMPARISON OF RESULTS FOR FREQ X DURATION, FREQUENCY ONLY, DURATION ONLY

1) FREQ X DURATION (the current manuscript analysis, Total Mets.min.week')

A-proportion attaining PA quartile in each disease group

	HEALTHY	CVD	T2D without CVD	T2D+CVD
Total Physical activity (MET.mins/wk)	103,993	113,469	4074	11,574
≤918 (Low physical activity)	25.0	30.5	35.4	40.1
>918-1902	25.0	24.2	22.5	22.2
>1902-3706	25.0	22.2	20.7	19.7
>3706-19278 (High physical activity)	25.0	23.2	21.3	18.0

B-Odds of reporting unhealthy behaviours

	Low physical activity	High sitting time [TV viewing]	Poor sleep	UNHEALTHY PHENOTYPE <i>Low Physical Activity + High Sitting + Poor Sleep</i>
No Disease	1.00	1.00	1.00	1.00
CVD	1.23 (1.20 to 1.25)	1.42 (1.39 to 1.45)	1.37 (1.34 to 1.39)	2.15 (2.03 to 2.28)
Type 2 diabetes without CVD	1.43 (1.34 to 1.53)	1.59 (1.49 to 1.69)	1.38 (1.30 to 1.47)	2.14 (1.85 to 2.48)
Type 2 diabetes + CVD	1.71 (1.64 to 1.78)	1.92 (1.85 to 1.99)	1.52 (1.46 to 1.58)	3.29 (3.02 to 3.58)

2) FREQUENCY ONLY (days/week)

A-proportion attaining PA quartile in each disease group

	HEALTHY	CVD	T2D without CVD	T2D+CVD
Total frequency physical activity (days)	103,993	113,469	4074	11,574
≤7 (Low physical activity)	25.4	30.6	33.9	38.9
>7-11	28.7	28.0	27.5	25.7
>11-14	21.5	21.0	20.1	19/6
>14 (High physical activity)	24.4	20.3	18.5	15.8

B-Odds of reporting unhealthy behaviour

	Low physical activity	High sitting time [TV viewing]	Poor sleep	Low Physical Activity + High Sitting + Poor Sleep
No Disease	1.00	1.00	1.00	1.00
CVD	1.23 (1.21 to 1.26)	1.42 (1.39 to 1.45)	1.37 (1.34 to 1.39)	2.11 (1.99-2.23)
Type 2 diabetes without CVD	1.34 (1.25 to 1.44)	1.59 (1.49 to 1.69)	1.38 (1.30 to 1.47)	2.11 (1.83-2.44)
Type 2 diabetes + CVD	1.63 (1.56 to 1.71)	1.92 (1.85 to 1.99)	1.52 (1.46 to 1.58)	3.07 (2.82-3.34)

3) DURATION ONLY (minutes)

A-proportion attaining PA quartile in each disease group

	HEALTHY	CVD	T2D without CVD	T2D+CVD
Total duration physical activity (mins)	103,993	113,469	4074	11,574

≤60 (Low physical activity)	27.8	34.1	39.5	44.7
>60-105	23.5	21.1	20.7	19.3
>105-180	26.4	23.4	20.2	19.7
>180 (High physical activity)	22.3	21.4	19.6	16.4

B-Odds of reporting unhealthy behaviour

	Low physical activity	High sitting time [TV viewing]	Poor sleep	Low Physical Activity + High Sitting + Poor Sleep
No Disease	1.00	1.00	1.00	1.00
CVD	1.23 (1.21 to 1.26)	1.42 (1.39 to 1.45)	1.37 (1.34 to 1.39)	2.12 (2.00 to 2.24)
Type 2 diabetes without CVD	1.43 (1.34 to 1.53)	1.59 (1.49 to 1.69)	1.38 (1.30 to 1.47)	2.13 (1.85 to 2.44)
Type 2 diabetes + CVD	1.72 (1.65 to 1.80)	1.92 (1.85 to 1.99)	1.52 (1.46 to 1.58)	3.29 (3.04 to 3.57)

VERSION 2 – REVIEW

REVIEWER	Mette Aadahl Research Centre for Prevention and Health, The Capital Region of Denmark & Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.
REVIEW RETURNED	29-Jan-2016

GENERAL COMMENTS	I believe the authors have responded adequately to all issues raised by the reviewers and that the manuscript has been well revised.
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REVIEWER	Bethany Barone Gibbs University of Pittsburgh, USA
REVIEW RETURNED	19-Jan-2016

GENERAL COMMENTS	The authors have done a good job at addressing my comments. I have none further.
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REVIEWER	Tom Yates University of Leicester
REVIEW RETURNED	27-Jan-2016

GENERAL COMMENTS	The authors should be congratulated on their thorough and informative response to the peer-review. I have no further concerns or comments
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