Author's response to reviews

Title: Population attributable fraction of type 2 diabetes due to physical inactivity in adults: a systematic review

Authors:

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Version: 3 Date: 8 February 2014

Author's response to reviews:

February 7, 2014

Dear Editor,

We are pleased to re-submit our manuscript, “Population attributable fraction of type 2 diabetes due to physical inactivity in adults: a systematic review” for consideration in BMC Public Health.

First, we thank all three reviewers for their detailed and insightful comments which we feel have greatly improved the clarity and quality of our manuscript. We have been diligent in incorporating the reviewers’ comments. These suggestions are addressed in the ‘Response to Reviewers’. The revisions are also highlighted using the ‘Track Changes’ function in Microsoft Word. We also attached a version of the manuscript with ‘Track Changes’ accepted.

We do hope the detailed response to reviewers is helpful in your evaluation of this revised manuscript and we look forward to clarifying further as needed.

Sincerely,

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Reviewer's report

Title: Population attributable fraction of type 2 diabetes due to physical inactivity in adults: a systematic review

Version: 2 Date: 24 December 2013

Reviewer: Edward Archer

Reviewer's report:
Review: Population attributable fraction of type 2 diabetes due to physical inactivity in adults: a systematic review

This systematic review sought to provide a best estimate of the population attributable fraction (PAF) for type 2 diabetes mellitus attributable to physical inactivity and the absence of sport participation.

Major Compulsory Revisions:
1. This review is a potentially important addition to the literature but suffers from a number of resolvable issues.
   a. The paper needs a major re-write with a competent editor. The research questions are clearly posed but the paper’s structure inhibits a clear understanding of how the study addressed each portion.
   i. The overall structure and organization of the paper (at times) appears confused and redundant.

Response: Thank you for the opportunity to revise the structure and clarify the message of our paper. The paper has now been restructured and edited.

Action: Please see the track changes highlighted in our manuscript.

ii. The paper should be re-organized to provide 1) a review of the variation that exists in PAF across the extant literature and 2) an analysis of the potential explanations for the demonstrated variation. At this point, neither point is entirely clear.

Response: We have modified our manuscript as suggested.

Action: Please see our revised discussion on pages 11-17.

iii. Writing & Grammar
   1. There are numerous grammatical and typographical errors throughout.

Response: The manuscript has now been extensively edited and proofread.

2. Poor proofreading:
   a. E.g., In the abstract, the sentence in line 35-36 is duplicated in lines 36-37.

Response: We have corrected this mistake.

Action: On page 2, it now reads: “In the US, PAFs for absence of playing sport ranged from 13% (95% CI: 3, 22) in men and 29% (95% CI: 17, 41) in women. In Finland, PAFs for absence of exercise ranged from 3% (95% CI: -11, 16) in men to 7% (95% CI: -9, 20) in women.”

   i. Line 59: the word “activity” is missing after leisure-time.
Response: We have corrected this mistake.

**Action:** On page 3, it now reads: “absence of leisure-time activity”

ii. Line 267: “There was no clear pattern emerged.”

Response: We have corrected this mistake.

**Action:** On page 14, it now reads: “A clear trend for the mean differences was not present. However, self-report measures were 44% (range: -78% to 500%) higher than those measured directly by accelerometers. This suggests there is a trend of self-report measures over reporting physical activity leading to an under-estimation of both physical inactivity and subsequent PAF estimates.”

iii. Line 139: “Was clear definition provided…”

Response: We have edited this sentence.

**Action:** On page 7, it now reads: “Was a clear definition provided for the exposure (physical inactivity)?”

3. Poor sentence structure:
   a. Beginning a paragraph with a conclusion without support.

Response: We have edited the entire manuscript to improve the paragraph structure and references provided throughout the manuscript.

**Action:** Please see track changes in the revised manuscript.

i. E.g., Line 232: “This is the first reason…” To state that “this” is the reason before giving the reader any indication of what “this” refers to is troublesome and indicative of poor logical structure.

Response: We agree with the reviewer and have re-written this paragraph.

**Action:** On pages 12 & 13, it now reads: “A review of the variation that exists in PAF across the existent literature

The PAF estimates for T2DM that is attributable to physical inactivity varied widely from 3%-39% across studies (Janssen & Laksoonen). As determined from the performance on our quality assessment, the best quality data in this systematic review suggest that the PAF of T2DM due to physical inactivity in the USA for a non sport participant (never engaged in strenuous sports) ranged from 13% (95% CI: 3, 22) in men and 29% (95% CI: 17, 41) in women. In Finland, the PAF of T2DM due to physical inactivity for the occasional exerciser (# 30 min/day, subset of leisure-time activity domain) ranged from 3% (95% CI: -11, 16) to 7% (95% CI: -9, 20). The PAF estimates for T2DM attributable to physical inactivity varied widely. Specifically, further variation is notable across study design, countries and sex. Such divergence may be explained by the distinct inconsistency in quality across studies. Below we elaborate on how two
categories relating to study methodology and statistical analysis contribute to the observed variation in PAF estimates.

Analysis of the potential explanations for the demonstrated variation in PAF
There are two main issues details below that explain the wide variation we observe in the PAF estimates for T2DM attributable to physical inactivity: heterogeneous study methodology (i.e., study design, exposure and outcome measurement) and statistical methodology.

I. Methodology
Choice of study design
The choice of study design is a key factor that may explain substantial variation in PAF estimate. More recently, methodological advances demonstrate that prospective cohort studies are preferable for PAF estimation because the calculations rely on censored time to event data.[43, 44] Historically, there is a large body of literature estimating PAF from case-control and cross sectional data.[24] For example, only two of the eight studies included in this systematic review reported three prospective cohort studies that were designed to estimate PAF as a primary outcome measure. As such, we observed wide variation in PAF estimates due to fundamental differences in study design. Second, PAF is based on multiple assumptions. One of these assumptions is that PAF assumes that risk factors precede and be causally related to the outcome. This assumption requires a longitudinal study design – a prospective cohort study. Ignoring such assumptions can lead to inaccurate estimations and hence incorrect interpretation of PAF estimates. Lastly, length of followup is another critical factor in accurately valuing PAF. In this systematic review, the follow up period ranged from 5 to 20 years overall and from 7 to 12 years in the three prospective cohort studies. Importantly, short follow up times tend to overestimate PAF and longer followup times generally underestimate PAF.[21]"

b. Second sentence on lines 232-233 is nonsensical.
Response: We have rewritten this paragraph.
Action: Please see response to 3ai above.

4. Lines 62-67: This paragraph should be rewritten to emphasize what is known and why the present work is needed.
Response: We have re-written and edited the introduction.
Action: Please refer to the revised introduction on pages 3 & 4.

b. There are numerous statements that are suggestive of the importance of this work but the presentation detracts and obscures its value. (E.g., “Further this study provides an initial step toward developing criteria to report and evaluate PAFs in the future.”)
Response: We have re-written and edited the discussed to emphasize the importance of this work.

Action: Please refer to the revised discussion on pages 12 to 18.

1. The criteria for developing a consensus based on the present data need to be clearly and explicitly articulated. At present, they are not.

Response: We agree that this statement was not properly articulated. We have revised the concluding paragraph to more appropriately represent the findings of our paper. Upon reflection, we felt a consensus statement was too strong a conclusion for this paper.

Action: On page 19, it now reads: “PAF is a valuable statistic in ascertaining burden of a disease due to a specific risk factor from a public health perspective only when it is accurately calculated using an appropriate study design (i.e., a prospective cohort study). Future studies estimating PAF could reduce the wide variability we currently observe in PAF data by using valid and reliable methods to measures physical inactivity and by using consistent ‘best practice’ methodology for reporting PAF.[21, 54] Such improvements in study design methodology and consistent cutting edge methodology will facilitate appropriate and well-informed public health decision making choices.”

2. Concerns that need to be addressed
   a. Defend the “Quality assessment questions”:
      i. How was the validity of the seven questions ascertained?

Response: The validity of the quality assessment questions was not ascertained. Because our systematic review consisted of both prospective cohort studies and reviews, there was not a single relevant quality assessment questionnaire that was suitable such as the STROBE. Therefore, we developed a seven item quality assessment form was based on relevant questions from the STROBE and well as modified versions of Drummond et al. quality assessment checklist for economic evaluations. These modified questions were reviewed by an expert in the field (Dr. Goldsmith) and were modified so that they could be applied across all included studies and study designs. We have revised our methods section accordingly.

Action: On pages 7 & 8, it now reads: “Because our systematic review consisted of both prospective cohort studies and reviews a published quality assessment checklist suitable for this study was not available. Therefore, we developed a seven item quality assessment form. This form was created after reviewing potentially relevant checklists such as the STROBE.[8, 9] From these examples, we created and modified questions relevant to assessing the quality of the PAF estimates included in this systematic review. The questions were structured so that they could be applied across all included studies and study designs (Table 3). All quality assessment questions were reviewed by an expert in the field. This quality assessment was not validated. We used dichotomized answers (+: yes, -:
no) for the quality assessment questions to create a score out of 7. Two authors (JCD, HAT) independently evaluated each study and any discrepancies were discussed and reviewed by a third author (KMK). Below, we outline each of the ‘yes’ criteria included in the quality assessment.”

b. Explain the impact of the attenuation from questionnaire (i.e., self-report) vs. objective measures. What does this mean for the body of literature?

i. Ditto for T2DM.
Response: We have amended our manuscript as suggested.

Action: On pages 14 & 15, it now reads: “In a systematic review, Prince[35] reported low-to-moderate correlations between self-report and direct measures of physical inactivity that ranged from -0.71 to 0.96. A clear trend for the mean differences was not present. However, self-report measures were 44% (range: -78% to 500%) higher than those measured directly by accelerometers. This suggests there is a trend of self-report measures over reporting physical activity leading to an under-estimation of both physical inactivity and subsequent PAF estimates.”

On page 15, it now reads: “Self-reported T2DM is also subject to measurement bias. For instance, the accuracy of self-reported T2DM is good (kappa = 0.78) and of moderate sensitivity (73%).[46, 47] However, T2DM can remain asymptomatic for at least 4 to 7 years before a clinical diagnosis is made.[48]. As a result, T2DM may be undiagnosed in up to 50% of cases.[49, 50] This underestimation of the incidence of T2DM leads to an underestimate of RR and PAF. Therefore, objective measurement of T2DM is desirable for accurate PAF estimates.”

c. Improve upon the explanation of the impact of the different operational definitions of inactivity on PAF and the necessity of the distinctions.
Response: We have modified this section in our discussion accordingly.

Action:

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Not suitable for publication unless extensively edited
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.

Reviewer 2 report
Title: Population attributable fraction of type 2 diabetes due to physical inactivity
Khan et al are trying to qualitatively synthesize the evidence from a limited number of studies which are completely heterogeneous in the design and data synthesis. PAF for physical inactivity varies widely and a major part of the manuscript is trying to explain the diversity of PAF estimate. Unfortunately there is not a clear meaningful conclusion on the relation of physical inactivity and DM2.

Response: Thank you for the opportunity to clarify our findings. We highlight that a qualitative synthesis of the evidence was the only form of synthesis we deemed appropriate for these data given the sample and study methodology heterogeneity. We use these methodological challenges in this systematic review to highlight research priorities moving forward. We have re-written and extensively edited our manuscript to provide a clear message of the findings.

Action: On page 11, it now reads: The PAF estimates for DM-2 attributable to physical inactivity varied widely ranging from 3%-39% across studies (Janssen & Laksoonen).

On page 7, it now reads: “Due to study design, sample and analytic heterogeneity, a meta-analysis of these data to determine PAF for DM-2 was not conducted.”

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I have no competing interests in relation to the specific paper. I have given talks, attended conferences, received consulting fees, and participated in clinical trials sponsored by industry (Novartis, Sanofi, AstraZeneca/BMS, MSD, Vianex, Boehringer Ing, Plus Pharmaceutical).

Reviewer's report

Title: Population attributable fraction of type 2 diabetes due to physical inactivity in adults: a systematic review

Version: 2
Date: 7 January 2014

Reviewer: Abiodun Oluyomi

Reviewer's report:

REVIEWER'S REPORT
Overall, this manuscript addresses contemporarily important issues. However, the manuscript may require a significant amount of revisions. Please review the following points. A copy of the manuscript with comments is also attached.

(A) Discretionary Revisions

Response: We thank the reviewer for this detailed and thorough review of our manuscript and for the specific comments that were appended. We have been diligent in making the suggested revisions and we thank the reviewer for improving the quality and clarity of this manuscript. Please see our track changes in the revised manuscript where we have addressed each comment by the reviewer. We look forward to clarifying further as needed.

(B) Minor Essential Revisions

1. Are the discussion and conclusions well balanced and adequately supported by the data?
   The discussion and conclusion sections are generally supported by the reported data, but there is room for improvements.

Response: The discussion and conclusions have now been edited and clarified.

Action: Please refer to the track changes in the discussion on pages 12-18.

2. Are limitations of the work clearly stated?
   The only limitation listed is authors’ inability to conduct meta-analysis due to the heterogeneity of the studies that they reviewed. Authors may need to revisit this point – to highlight other avenues for limitations could have resulted from the use of other articles (as is the case in systematic reviews), or limitations that are inherent to the methodological approaches for the conduct of systematic reviews in general.

Response: We have expanded our limitations section to include issues inherent to the methodological approaches for systematic reviews and from article selection.

Action: On pages 16 & 17, it now reads: “Study heterogeneity was due in part to the inclusion criteria for this systematic review. Specifically, we included studies studies that estimated PAF or PAR using modeling on raw data from a prospective cohort design or (ii) that used published adjusted relative risk. Further, data from each study on physical inactivity were collected from different populations using different sampling and estimation methodologies. These above differences contribute to the wide variation in PAF T2DM attributable to physical inactivity.”

3. Is the writing acceptable?
Authors need to review and revise manuscript writing for grammar and style. Importantly, authors need to make sure that sentences/statements are complete and clear (throughout the paper). Also, thoughts/arguments/discussions need to flow better from one part of the paper to the next (in an orderly sequence).

Response: Thank you for the opportunity to revise our manuscript for clarity. We have edited the entire manuscript and improved the flow of the discussion.

Action: Please refer to track changes throughout the manuscript.

4. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Authors may need to improve on this in the background section and the discussion section.

Response: The introduction and discussion have now been rewritten.

Action: Please refer to track changes in the introduction and discussion sections.

5. Is the question posed by the authors well defined?
Authors described the manuscript as a systematic review. They also claim that, to their knowledge, no systematic review has ascertained the PAF of DM-2 attributable to physical inactivity, and, therefore the aim of the current manuscript is to (i) quantify the PAF of DM-2 attributable to physical inactivity and absence of sport participation or exercise for men and women.

Generally, the background/introduction section provides authors the opportunity to present the prevailing knowledge about their topic, establish the basis for their inquiries, and define, in clear statements and unambiguous terms, the objective of their paper.

The background section of this manuscript touched on some important issues that are relevant to the topic of interest. However, the introductory discussions presented are too scanty to support the premise that the objective of the paper is well defined. A more robust background section may be necessary.

Response: We have now modified our introduction section to include a detailed rationale of why this systematic review is needed based on what is currently known in the literature.

Action: Please refer to track changes in the introduction.

(C) Major Compulsory Revisions
1. Are the data sound?
It is not clear whether authors actually excluded studies with data from cross-sectional studies and case-control studies as they had stated in the study selection and eligibility section. (See manuscript: Rows 85-89 vs. Rows 237-238). Authors may need to clarify this issue throughout the paper.

Response: We did exclude studies with data from cross-sectional and case-control studies. However, some reviews were included because they based their RRadj source on data from prospective cohort studies and were therefore deemed eligible throughout the manuscript. We have clarified this point throughout the manuscript.

Action: On page 4, it now reads: “Of note, reviews were included if their RRadj estimates were based on prospective cohort studies.”

2. Do the title and abstract accurately convey what has been found? Authors reported in the Abstract section that: “… of all eight articles reporting PAFs ….” Meanwhile, in the body of the manuscript and tables, authors suggest that PAFs were calculated using previously reported data (e.g. table 2, with the phrase: “plugged into PAF crude formula.”). Somehow, it is not clear to the reader WHO did the plugging. Essentially, authors may need to reconcile the abstract content with the body of the manuscript, if indeed the current authors actually calculated the PAFs. Otherwise the manuscript needs to clarify these issues.

Response: Thank you for the opportunity to clarify. The authors did not calculate PAF directly. PAFs were calculated using the previously reported data. Of note, we only reconstructed 95% CIs when missing using a substitution method. In table-2, the reconstructed 95% CIs are labeled with an upper hyphenated small letter (a). We have clarified the tables and abstract accordingly.

Action: On page 2, it now reads: “We reconstructed 95% CIs for studies missing these data using a substitution method.”

On page 6, it now reads: “Of note, we estimated the confidence intervals (95% CI) for PAF using the substitution method when these data were not reported.[26] All calculations done by the authors are labeled with an ‘a’.”

In Table 2, it now reads: “a The authors used a substitution method described in the methods section to calculate the 95%CI for the domain specific PAF%.”

OTHER COMMENTS:
1. Are the methods appropriate and well described?
   Overall, the methods seem well defined.

2. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Authors reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards.
Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.