PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The dose–response relationship between physical activity and mortality in people with noncommunicable diseases: A study protocol for the systematic review and meta-analysis of cohort studies
AUTHORS	Geidl, Wolfgang; Schlesinger, Sabrina; Mino, Eriselda; Miranda, Lorena; Ryan, Anna; Bartsch, Katja; Janz, Lukas; Pfeifer, Klaus

VERSION 1 – REVIEW

REVIEWER	Kun Chen Zhejiang University school of public health
REVIEW RETURNED	25-Jan-2019

GENERAL COMMENTS	This study aimed at estimating dose-response relationship of physical activity and mortality in people with noncommunicable diseases. The goal is clear and the protocol is well designed.However, there is one question needed to be addressed. 1. The authors use a broad definition-patients with 'noncommunicable disease'- as their target population in this manuscript. Then why do they only include patients with low back pain, type 2 diabetes mellitus, osteoarthritis, depressive disorder… in this study, for there should be more and systematic classification of diseases for such a loose definition. Otherwise, they should reclassification them properly.

REVIEWER	Deborah Carvalho Malta Universidade Federal de Minas Gerais, Brazil
REVIEW RETURNED	03-Feb-2019

GENERAL COMMENTS	BMJ opinion PA protocol This is a study containing protocol aims to outline our planned systematic review and dose-response meta-analysis on post-diagnosis physical activity and mortality in people with non-communicable diseases (NCD). The study is planned properly and within the norms of the journal. Introduction - I suggest describing more clearly what would be the limit of current knowledge .... And how this study can contribute. Introduction Complete WHO recommendation on Physical Activity, 150 minutes or. 75 minutes of intense or vigorous activity (WHO) recommends at least 150 minutes of moderate-intensity Or complete - 75 minutes of intense activity

	World Health Organization. Global recommendations on physical activity for health. Geneva, Switzerland: World Health Organization, 2010 It is not clear - conduct graphical dose-response analyzes. I suggest explaining what it is about In Methods The nine diseases (NCD) NCDs: low back pain, type 2 diabetes mellitus, osteoarthritis, depressive disorder, chronic obstructive pulmonary disease, breast cancer, lung cancer, stroke, and ischemic heart diseases. To make clearer in the introduction and in methods the reason for the choice of these diseases, especially the choice of the mortality outcome, considering that low back pain (LBP) and osteoarthritis, effectively impact morbidity and non-mortality .... This is the weak point of the study. Reference 6 - inserts other diseases that were not included. You need to talk to these other diseases. There are evidences of PA influencing these diseases, because they were not included in the protocol. This point needs to be clearer. NCDs (breast or colorectal or prostate cancer, cardiovascular condition of hypertension, and type 2 diabetes). Definition - doubt - detailed the domains of practice of AP. However, the physical activity performed at home, cleaning, cleaning the house, will be considered? Post-diagnosis physical activity will be defined as any form of physical activity, such as leisure-time, occupational, transport related, exercise as well as physical activity-related energy expenditure measured after diagnosis. Physical activity can be measured both using subjective methods (e.g. questionnaire) or objective methods (e.g. accelerometry); physical activity-related energy expenditure could be measured with any kind of objective methods (eg doubly labeled water). In compliance with Etical ethical precepts International Prospective Register for Systematic Reviews (PROSPERO) registration number: CRD42018103357

REVIEWER	Tao Chen LSTM
REVIEW RETURNED	07-May-2019

GENERAL COMMENTS	This study was performed to exam the associate between the PA with mortality for NCD. Overall, it is well written and defined each component of PICOS. The major point is that the author collected several type of statistics but did not clarify how to combine these into one statistic. Another one is the reason of using so broad term NCDs, which actually refer to nine diseases.

REVIEWER	Dr Sonia Gran University of Nottingham UK
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	This protocol is very clearly written and sufficient detail have been provided. There are some places where clarity or justification is required: 1. If the objective is to focus on NCDs common in Germany should not both English and German language studies be included? 2. PEO (Population, Exposure, Outcome) should be used for observational studies rather than PICO. 3. What do the authors mean by 'prospective' studies? It is prospective in terms of data collection after starting the study? Or in relation to when the exposure and outcomes are measured? If it is the latter then case-control studies should not be included. 4. Could the authors use prospective literature searching using key papers and Google Scholar to be as comprehensive as possible? 5. There does not seem to be any mention of screening full texts. 6. Funnel plots can only be used if there are at least 10 studies.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

*1 (your comment 1) The authors use a broad definition-patients with ‘noncommunicable disease’- as their target population in this manuscript. Then why do they only include patients with low back pain, type 2 diabetes mellitus, osteoarthritis, depressive disorder… in this study, for there should be more and systematic classification of diseases for such a loose definition. Otherwise, they should reclassification them properly.
#1 (our revision 1) Thank you for the hint. We have explained the reasons for the selection of the nine NCDs in the introduction. In addition, we have specified the section objectives and defined that only nine relevant NCDs will be investigated. (page 4/ line 119-25; page 5/ line 137-8)

Response to Reviewer 2

*1 (your comment 1) Introduction - I suggest describing more clearly what would be the limit of current knowledge .... And how this study can contribute.
#1 (our revision 1) We have 1) made it clearer in the introduction that there is a discrepancy between the current minimum recommendations for physical activity and the underlying evidence, and 2) following the objectives section more clearly formulated what the benefits of our work in eliminating this discrepancy are. (page 4/ line 107-19; page 5/ line 138-42)

*2 Introduction. Complete WHO recommendation on Physical Activity, 150 minutes or. 75 minutes of intense or vigorous activity. (WHO) recommends at least 150 minutes of moderate-intensity Or complete - 75 minutes of intense activity World Health Organization. Global recommendations on physical activity for health. Geneva, Switzerland: World Health Organization, 2010
#2 We have completed the WHO recommendations for physical activity. The alternative "75 minutes of vigorous-intensity physical activity" instead of 150 minutes of moderate physical activity has been added to the text. (page 3/ line 75)

*3 It is not clear - conduct graphical dose-response analyzes. I suggest explaining what it is about.
#3 We have inserted the corresponding literature reference for the specific methodological procedure of the graphical dose-response analyses. (page 9/ line 300)

*4 In Methods. The nine diseases (NCD) NCDs: low back pain, type 2 diabetes mellitus, osteoarthritis, depressive disorder, chronic obstructive pulmonary disease, breast cancer, lung cancer, stroke, and ischemic heart diseases. To make clearer in the introduction and in methods the reason for the choice of these diseases, especially the choice of the mortality outcome, considering that low back pain (LBP) and osteoarthritis, effectively impact morbidity and non-mortality ....This is the weak point of the study.
#4 Thank you for the hint - this point was also noted by other reviewers. We have explained the reasons for the selection of the nine NCDs in the introduction. In addition, we have specified the section objectives and defined that only nine relevant NCDs will be investigated. (page 4/ line 119-30; page 5/ line 136-8)

*5 Reference 6 - inserts other diseases that were not included. You need to talk to these other diseases. There are evidences of PA influencing these diseases, because they were not included in the protocol. This point needs to be clearer. NCDs (breast or colorectal or prostate cancer, cardiovascular condition of hypertension, and type 2 diabetes).
#5 You are right: Exercise is treatment for plenty of NCDs. For example, Pedersen & Saltin (2015) worked out the health benefits of physical activity for 26 different NCDs. In the introduction, we have now clarified on what basis we selected the nine NCDs in our study. From our point of view, this makes an argumentation/enumeration of the countless diseases not taken into account superfluous. We have therefore decided, also for better readability, not to explicitly address the unprocessed NCDs. (page 4/ line 119-25)

*6 Definition - doubt - detailed the domains of practice of AP. However, the physical activity performed at home, cleaning, cleaning the house, will be considered?
#6 Our study actually considers all forms of physical activity. This includes all types of physical activities in the different domains mentioned. So yes, if, for example, a questionnaire (such as the IPAQ) is used to calculate the total activity that also measures household physical activity, we will include this study. (page 5-6/ line 163-7)

*7 In compliance with Etical ethical precepts International Prospective Register for Systematic Reviews (PROSPERO) registration number: CRD42018103357
#7 We overworked the section “Ethics and dissemination” and adopted the proposed wording. (page 2/ line 57)

Response to Reviewer 3

*1 (your comment 1) The major point is that the author collected several type of statistics but did not clarify how to combine these into one statistic.
#1 (our revision 1) The section synthesis of results describes the analysis/combination of results. To make our analysis strategy even clearer, we have optimised the description of the planned procedure in this section. In particular, it is clearer now how the individual indication-specific statistics are summarized.

*2 Another one is the reason of using so broad term NCDs, which actually refer to nine diseases.
#2 Thank you for the hint - this point was also noted by other reviewers. We have explained the reasons for the selection of the nine NCDs in the introduction. In addition, we have specified the section objectives and defined that only nine relevant NCDs will be investigated. (page 4/ line 119-25; page 5/ line 134-38)

Response to Reviewer 4

*1 (your comment 1) If the objective is to focus on NCDs common in Germany should not both English and German language studies be included?
#1 (our revision 1) We had briefly discussed this topic with the librarian during the development of the search strategy and came to the conclusion that German researchers also mostly publish in English. At that time, we were not aware of any German study that had been published in German. As a rule, German articles in the databases have an English title (and partly also an English abstract), and thus we did not come across any German-language study in our entire extensive research. This confirmed our decision to use English as our sole search language.

*2 PEO (Population, Exposure, Outcome) should be used for observational studies rather than PICO.
#2 Thank you for pointing that out. The PEO scheme also seems to fit well with our study. As to the best of our knowledge we found PEO in the literature mostly to be used in qualitative studies. Therefore we decided to us PICO in our study. Thus, we already referred to PICO when registering the study in the PROSPERO database. Therefore we would like to keep the reference to PICO in the study protocol.

*3 What do the authors mean by 'prospective' studies? It is prospective in terms of data collection after starting the study? Or in relation to when the exposure and outcomes are measured? If it is the latter then case-control studies should not be included.
#3 Prospective means that the activity levels were not surveyed retrospectively but prospectively, i.e. after the start of the study. We agree that normal case control studies should not be included; this is also not the case in our study (see the phrase "we will exclude …case only or case control studies"). However, nested case control studies and case cohort studies must be distinguished from “normal” case control studies and should be included. (page 6/ line 184-5)

*4 Could the authors use prospective literature searching using key papers and Google Scholar to be as comprehensive as possible?
#4 Thank you for raising our attention to this. We will conduct our literature search in three different databases: PubMed, Scopus and Web of Science. The limitation of Google scholar includes the inadequate, less often updated, citation information (Falagas, FASEB J. 22, 338–342 (2008)). To ensure that our literature search is as comprehensive as possible, we will also check the reference lists from the systematic reviews and meta-analysis identified during the search for further potential articles.

*5 There does not seem to be any mention of screening full texts.
#5 If the title and abstract allow a clear decision on inclusion or exclusion of an article, full texts are only used for content analysis afterwards. A screening of the full texts will be applied if the title and abstract do not allow a clear decision (see last sentence in the section selection of eligible studies "If the screening process of title and abstract does not lead to a clear result, the article will be retrieved for full-text screening"). (page 7/ line 220-1)

*6 Funnel plots can only be used if there are at least 10 studies.
#6 We have included this application requirement in the section on Funnel plots (“If the number of included studies permits, publication bias will be assessed via funnel plots”). (page 9/ line 289-9)

VERSION 2 – REVIEW

REVIEWER	Tao Chen Liverpool School of Tropical Medicine
REVIEW RETURNED	17-Jul-2019

GENERAL COMMENTS	The article was improved a lot. Personally, it will be good to change the title from "....with noncommunicable diseases...." .into

	".....with nine noncommunicable diseases...." . Currently, the title is too broad with ambition.

REVIEWER	Dr Sonia Gran Centre of Evidence Based Dermatology University of Nottingham UK
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	I am happy with the responses apart from the one about prospective literature searching using Google Scholar: I would probably also search using citation searching on Google Scholar - i.e. select half a dozen of the "included studies" found from your search and for each of them search within citing articles " for key words. This would have a three-fold purpose - (i) it would indicate whether there is a particular database bias that means that the studies are underreported or overreported in the databases you have chosen, (ii) it would allow you to see how sensitive your database estimate is likely to be and (iii) it would reassure the reader that you have used complementary search strategies as well as conventional ones. Also, PubMed and Web of Science are interfaces not databases. Please can the databases used e.g. Medline be specified. It is advisable to have an information specialist as part of the author team for systematic reviews to ensure the literature search is conducted properly.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 3

*1 (your comment 1) Please leave your comments for the authors below The article was improved a lot. Personally, it will be good to change the title from "....with noncommunicable diseases...." .into ".....with nine noncommunicable diseases...." . Currently, the title is too broad with ambition.

#1 (our revision 1) Thank you for this hint. We discussed this proposal for changing the title with the team of authors. From our point of view, the proposed title is unfortunately misleading: "People with nine chronic diseases" can be understood as meaning that we have only included people diagnosed with nine chronic diseases. Therefore, we did not change the title. In order to not create false expectations, we have prominently highlighted the limitation to the nine chronic diseases examined in the Abstract (page 2, line 45), in the Strenghts and Limitations (page 3, line 66), and in the Objectives (page 5, line 135) of our manuscript.

Response to Reviewer 4

*1 (your comment 1) I would probably also search using citation searching on Google Scholar - i.e. select half a dozen of the "included studies" found from your search and for each of them search within citing articles " for key words. This would have a three-fold purpose - (i) it would indicate whether there is a particular database bias that means that the studies are underreported or overreported in the databases you have chosen, (ii) it would allow you to see how sensitive your database estimate is likely to be and (iii) it would reassure the reader that you have used complementary search strategies as well as conventional ones.

#1 (our revision 1) We have correspondingly expanded our search strategy. The paragraph Information sources includes now the following statement "Additionally, one researcher will use the Google Scholar forward citation search for all eligible articles identified via the database search." (page 6, line 190-191)

*2 Also, PubMed and Web of Science are interfaces not databases. Please can the databases used e.g. Medline be specified.

#2 We specified the used databases. "Two researchers will search the following electronic databases: MEDLINE (PubMed), Scopus and the Web of Science Core Collection (Web of Science)." (page 6, line 187-188)

*3 It is advisable to have an information specialist as part of the author team for systematic reviews to ensure the literature search is conducted properly.

#3 The search strategy was developed with the support of an information specialist from the University Library. This specialist gave his valuable advice on the search strategy we had developed. Nevertheless, he does not fulfill the criteria from the International Committee of Medical Journal Editors (ICMJE) on which authorship should be based http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Therefore, we did not change the list of authors.