

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Dose-response relationship of physical activity and mortality in people with noncommunicable diseases. Study protocol for a systematic review and meta-analysis of cohort studies

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028653
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2018
Complete List of Authors:	Geidl, Wolfgang; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Schlesinger, Sabrina; German Diabetes Center Düsseldorf (DZZ) Mino, Eriselda; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Miranda, Lorena; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Ryan, Anna; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Bartsch, Katja; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Janz, Lukas; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Pfeifer, Klaus; Friedrich-Alexander Universität Erlangen-Nürnberg, Department of Sport Science and Sport
Keywords:	Physical activity, Systematic review, Meta-analysis, Mortality, Noncommunicable diseases, Exercise

SCHOLARONE™  
Manuscripts

1  
2  
3 1 **Title page**  
4  
5 2

6 3 **Dose-response relationship of physical activity and mortality in people with noncommunicable**  
7 4 **diseases. Study protocol for a systematic review and meta-analysis of cohort studies**  
8  
9 5

10  
11 6 **Corresponding author:** Dr. Wolfgang Geidl, Department of Sport Science and Sport (DSS),  
12 7 Friedrich-Alexander University Erlangen-Nürnberg (FAU), Gebbertstraße 123b, 91058  
13 8 Erlangen (Germany); Tel.: +49-9131 85-25457, Fax. +49-9131 85-28198, E-mail address:  
14 9 wolfgang.geidl@fau.de  
15  
16  
17  
18  
19  
20

21 11 Wolfgang Geidl<sup>1</sup>, Sabrina Schlesinger<sup>2</sup>, Eriselda Mino<sup>1</sup>, Lorena Miranda<sup>1</sup>, Anna Ryan<sup>1</sup>, Katja  
22 12 Bartsch<sup>1</sup>, Lukas Janz<sup>1</sup>, Klaus Pfeifer<sup>1</sup>  
23  
24  
25

26 14 <sup>1</sup> Department of Sport Science and Sport, Division Exercise and Health, Friedrich-Alexander  
27 15 University Erlangen-Nürnberg (FAU), Erlangen, Germany  
28  
29

30 16 <sup>2</sup> German Diabetes Center Düsseldorf (DZZ), Düsseldorf, Germany  
31  
32  
33

34 18 **Keywords:** Exercise, Noncommunicable diseases, Mortality, Systematic review, Meta-  
35 19 analysis  
36  
37  
38  
39  
40

41 22 Word count: 3554  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 30 **ABSTRACT**

### 31 **Introduction**

32 This study protocol aims to outline our planned systematic review and dose-response meta-  
33 analysis on post-diagnosis physical activity and mortality in people with non-communicable  
34 diseases (NCD).

### 35 **Methods and analysis**

36 This document is built on the Preferred Reporting Items for Systematic Reviews and Meta-  
37 analysis for Protocols (PRISMA-P). A systematic literature search will be conducted in  
38 PubMed, Scopus, and Web of Science by two researchers to identify prospective observational  
39 studies investigating post-diagnosis physical activity or activity related energy expenditure with  
40 mortality in individuals with NCD. Target population will be defined as adults ( $\geq 18$  years) with  
41 one of the following NCDs: low back pain, type 2 diabetes mellitus, osteoarthritis, depressive  
42 disorder, chronic obstructive pulmonary disease, breast cancer, lung cancer, stroke, and  
43 ischemic heart diseases. We will focus on all-cause mortality as primary outcome, and  
44 investigate indications-specific mortality as secondary outcomes. For each identified study, we  
45 will conduct graphical dose-response analyses of mortality as a function of activity-related  
46 energy consumption. If more than two studies for one disease are available, we will perform  
47 linear and non-linear dose-response meta-analyses for this disease, by using random effects  
48 models. We will investigate heterogeneity across studies and publication bias. To assess the  
49 risk of bias and quality of the included studies, we will use the Cochrane risk of bias tool  
50 ROBINS-I.

### 51 **Ethics and dissemination**

52 As the systematic review is based on published studies, ethical considerations are not required.  
53 The systematic review and meta-analysis will be published in a peer-reviewed journal.

54  
55 International Prospective Register for Systematic Reviews (PROSPERO) registration number:  
56 CRD42018103357

57

58

59

## 60 **Strengths and limitations of this study**

- 61 • Our systematic review will be conducted and reported in accordance with the reporting  
62 guidance provided in the PRISMA-P statement and the Meta-analysis Of Observational  
63 Studies in Epidemiology (MOOSE) reporting guidelines
- 64 • The scope of our systematic search is wide-reaching, including nine NCDs and three  
65 large search engines
- 66 • Use of the novel Cochrane tool “Risk Of Bias In Non-randomised Studies - of  
67 Interventions” (ROBINS-I)
- 68 • Observational cohort studies will not provide a conclusive answer on causality between  
69 physical activity and mortality

## 71 **INTRODUCTION**

72 The World Health Organization (WHO) recommends at least 150 minutes of moderate-intensity  
73 physical activity per week to enhance health and reduce mortality.[1] For additional benefits,  
74 adults should increase their moderate-intensity physical activity to 300 minutes weekly. These  
75 recommendations apply to both healthy adults and adults with a noncommunicable disease  
76 (NCD), e.g. ischemic heart disease, cancer, or chronic pulmonary disease. However, if one  
77 considers the scientific evidence for physical activity and mortality on which the  
78 recommendations are based, a very large difference becomes apparent between healthy  
79 populations and those with a pre-existing NCD.

80 The data for healthy adults is comprehensive and unambiguous. Several large cohort studies  
81 consistently have demonstrated an inverse relationship between physical activity and  
82 mortality.[2] Arem et al.[3] pooled data from six cohort studies including 661,137 persons.  
83 Compared to individuals reporting no leisure-time physical activity, premature death decreased  
84 with increasing physical activity levels: 7.5 Metabolic Equivalent Tasks (METs) h/wk HR=0.80  
85 (95% CI 0.78–0.82), 7.5-15 METs h/wk HR=0.69, (0.67–0.70), and 15-22.5 METs h/wk  
86 HR=0.63 (0.62–0.65). These findings are consistent with the meta-analysis from Samitz et  
87 al.[4] including 80 studies with a total of 1.338.143 persons: compared to the lowest activity  
88 group), risk of premature death was remarkably reduced in the highest activity group HR=0.65  
89 [(95% CI) 0.60–0.71]; furthermore, each 1-h increment per week of moderate-intensity activity  
90 resulted in a lowered risk ratio (RR) of 0.96 (95% CI 0.93–0.98).

91 Accordingly, the updated new physical activity guidelines from the US includes a clear dose-  
92 response relationship between volume of physical activity and mortality rates for healthy adults

1  
2  
3 93 (see Figure 1).[5] The shape of the dose-response curve is not linear but regressive. This means  
4 94 the greatest differences in mortality rates occur between inactive and minimally active  
5 95 individuals. There is no lower threshold. Benefits start with any amount of physical activity.  
6  
7 96 Following the minimal recommendations, physical activity is equivalent to an energy  
8 97 expenditure of 8.25 MET-hours per week; at this level of physical activity about 70% of the  
9 98 benefits in mortality rates are reached.[6] With higher volumes of physical activity, the dose-  
10 99 response curve flattens out. However, 4-5 times this dose is also associated with further risk  
11  
12  
13  
14  
15 100 reductions and no adverse effects.  
16  
17

18 101  
19  
20 102 Figure 1. Relationship of moderate-to-vigorous physical activity to all-cause mortality

21  
22 103 << Insert Figure 1 around here >>  
23  
24 104

25  
26 105 For individuals with NCDs, the scientific data on dose-response-relations of physical activity  
27 106 and mortality is considerably weaker. For cancer, the meta-analysis from Li et al.[7] suggests  
28 107 that post-diagnosis physical activity levels may result in similar mortality risk reductions.  
29 108 Moore et al.[8] pooled data from six cohort studies with 654,827 individuals and adjusted their  
30 109 analysis for several confounders including pre-existing NCD. In contrast, they conclude that  
31 110 longevity effects of physical activity vary by pre-existing NCD. The current evidence from the  
32 111 US Physical Activity Guidelines Advisory Committee[6] reported a general relationship  
33 112 between higher post-diagnosis physical activity and lower mortality rates in five NCDs (breast  
34 113 or colorectal or prostate cancer, cardiovascular condition of hypertension, and type 2 diabetes).  
35 114 However, this report could not demonstrate dose-response relationships due to limited  
36 115 information. Overall, it is unclear whether mortality rates in individuals with NCD are affected  
37 116 in the same way as in healthy individuals. The dose-response relation between physical activity  
38 117 and mortality for NCDs is not well defined at present.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

50 118  
51  
52 119 **Objectives**

53  
54 120 This study protocol aims to describe our planned systematic review and dose-response meta-  
55 121 analysis on physical activity and mortality in people with NCDs. The planned study aims to  
56 122 define the dose-response relationship between post-diagnosis physical activity and mortality  
57 123 rates for nine NCD with a high burden of disease globally,[9] and specifically for  
58  
59 124 Germany[10]: low back pain (LBP), type 2 diabetes mellitus, osteoarthritis, depressive  
60

1  
2  
3 125 disorder, chronic obstructive pulmonary disease (COPD), breast cancer, lung cancer, stroke,  
4 and ischemic heart diseases.  
5 126  
6  
7 127  
8

## 9 128 **METHODS**

10  
11 129 This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-  
12 analysis for Protocols (PRISMA-P, Supplementary File 1).[11] Our systematic review will be  
13 130 conducted and reported in accordance with the reporting guidance provided in the PRISMA-P  
14 131 statement and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)  
15 132 reporting guidelines.[12, 13] Additionally, the Methodological Expectations of Cochrane  
16 133 Intervention Reviews (MECIR) and The Cochrane Handbook of Systematic Reviews in  
17 134 Interventions will be consulted to ensure for methodological quality.[14, 15]

18  
19 135 In view of the recommendations that endorse the pre-registration of systematic reviews, our  
20 136 protocol was registered within the International Prospective Register of Systematic Reviews  
21 137 (PROSPERO) on 5 September 2018 (registration number: CRD42018103375; available  
22 138 online at [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=103357](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=103357)).  
23 139  
24 140

### 25 141 **Eligibility criteria**

26 142 This study will include only research published in English language with no time restriction  
27 143 for the year of publication. We will include studies that investig [16, 12]ated the association  
28 144 between post-diagnosis physical activity levels with mortality among individuals with NCDs,  
29 145 and reported effect estimates (including hazard ratios, relative risks, odds ratios, or absolute  
30 146 mortality rates). Post-diagnosis physical activity will be defined as any form of physical  
31 147 activity, such as leisure-time, occupational, transport related, exercise as well as physical  
32 148 activity-related energy expenditure measured after diagnosis. Physical activity can be  
33 149 measured both using subjective methods (e.g. questionnaire) or objective methods (e.g.  
34 150 accelerometry); physical activity-related energy expenditure could be measured with any kind  
35 151 of objective methods (e.g. doubly labelled water).

36  
37 152 Studies will be excluded if they: (1) clearly deal with another topic; (2) include only the total  
38 153 population without information for subgroups with a NCD at baseline; (3) focus on  
39 154 prevention, i.e. when they include individuals at risk for developing one of the nine diseases;  
40 155 (4) report insufficient data to calculate dose-response relations (less than three different  
41 156 physical activity levels in MET hours per week); (5) are duplicate studies that are based on a  
42 157 data set that has already been taken into account.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 158 *Participants:* Participants  $\geq$  18 years with at least one of the following nine NCD at baseline:  
4  
5 159 osteoarthritis, low back pain, depressive disorder, ischemic heart disease, type 2 diabetes  
6  
7 160 mellitus, stroke, chronic obstructive pulmonary disease (COPD), lung cancer, and breast  
8  
9 161 cancer. The disease can either be confirmed by a physician or can be determined by self-  
10  
11 162 report. Studies which focused on children, adolescents, and pregnant women will be excluded,  
12  
13 163 as well as animal and cell culture studies.

14 164 *Outcomes:* Studies that assessed all-cause mortality as primary endpoint or any indication-  
15  
16 165 specific mortality as primary or secondary endpoint.

17 166 *Study design:* Prospective observational studies (including cohort, nested case-control, case-  
18  
19 167 cohort studies and follow-up studies of randomized controlled studies) published in a peer-  
20  
21 168 reviewed journal will be included. We will exclude cross-sectional, case only or case-control  
22  
23 169 studies, conference abstracts, comments, letters and reviews.

24 170

### 25 171 **Information sources**

26 172 Two researchers will search the following electronic databases: PubMed, Scopus and Web of  
27  
28 173 Science with all years covered. The reference list from the systematic reviews and meta-  
29  
30 174 analysis found will be hand searched for further hits.

31 175

### 32 176 **Search strategy**

33  
34 177 The search strategy was developed with the support of a specialist from the University  
35  
36 178 Library. The search is structured according to three main categories of the Population,  
37  
38 179 Intervention, Comparison, Outcome (PICO) concept: population/ problem (one of the nine  
39  
40 180 NCD), intervention (physical activity), and outcome (mortality); control as the fourth  
41  
42 181 category of PICO does not play a role in cohort studies we sought.[17] We defined search  
43  
44 182 terms for the three PICO categories including keywords and related synonyms, abbreviations,  
45  
46 183 spelling variations and controlled vocabulary, each separated by Boolean operator OR. Search  
47  
48 184 terms for the three PICO categories were combined with Boolean operator AND. The search  
49  
50 185 is restricted to the search fields Title and Abstract. We will conduct independent searches for  
51  
52 186 the nine NCD under consideration. The search is adapted to the special features of the three  
53  
54 187 databases, e.g. the use of Medical Subject Headings (MeSH) terms in PubMed. It should be  
55  
56 188 noted that the search is not filtered for observational studies, as reference lists of systematic  
57  
58 189 reviews and meta-analysis are eligible for additional hands on searching. The concrete search  
59  
60 190 terms used as well as their exemplary linking in the NCD COPD can be found in the  
191  
192 Supplementary File 2.



192

## 193 **Data Management**

194 The search results will be imported to the reference management and knowledge organization  
195 software Citavi Version 5 (Swiss Academic Software, Wädenswil, Switzerland). We will use  
196 separate project folders for each of the nine diseases, organised hierarchically in categories  
197 based on the inclusion and exclusion filters.

198

## 199 **Selection of eligible studies**

200 First, one person will screen each article's title and abstract against the eligibility criteria to  
201 identify relevant studies. Then, a second person will perform the same screening task to  
202 ensure that no studies were overlooked or incorrectly included. This procedure will have a  
203 positive effect on the accuracy and reliability of the screening process.[18] Moreover,  
204 increasing the number of contributors in this critical point of a systematic review enables a  
205 better timeliness and efficiency of the process.[19] If the screening process of title and  
206 abstract does not lead to a clear result, the article will be retrieved for full-text screening.

207

## 208 **Data extraction**

209 Data of the full texts will be extracted by two reviewers independently using an excel table  
210 (Supplementary File 3). This table has been pilot-tested with a small number of eligible  
211 articles from four reviewers (AR, EM, LM, WG). The following discussion ensured mutual  
212 understanding of the variables, standardisation of the data mask and a uniform data extraction  
213 system. Results of the double data extraction are checked for consistency. Disagreement will  
214 be discussed within three reviewers. Multiple publications with the same or very similar  
215 contents from one dataset are only considered once; duplicates with smaller sample size and  
216 lower follow-up duration will be excluded.

217

## 218 **Data items**

219 The information sought to extract includes basic details such as first author, year of  
220 publication, the study name, design, country where research was undertaken, age and sex, and  
221 mean follow-up time. Additionally, we will retrieve data on the total sample, total all-cause  
222 death cases, the number of participants in each physical activity category, death cases per the  
223 corresponding category, diagnosis and mortality data ascertainment, exposure to physical  
224 activity (for example, MET-h/week, minutes per day), and corresponding categories. Finally,

1  
2  
3 225 risk ratios with their 95% confidence intervals will be extracted from fully adjusted models  
4  
5 226 for every PA exposure category, as well as for dose-response data when available.  
6  
7 227

## 8 228 **Outcomes**

9  
10 229 The primary outcome of this review will be all-cause mortality, defined as the number of  
11  
12 230 deaths over the entire period of follow up regardless of the underlying cause of death. As  
13  
14 231 previously discussed, overall mortality is among the main investigated types of death  
15  
16 232 attributable to the lack of physical activity in persons affected by NCDs. The relationship  
17  
18 233 between physical activity and longevity is complex[20], and during a certain timeframe death  
19  
20 234 can be caused or affected by multiple factors. Hence, disease-specific standardised death rates  
21  
22 235 can leave out many cases that can blur the identification of a possible causal relation. If all-  
23  
24 236 cause mortality rates are not reported, disease-specific mortality rates will be considered.  
25  
26 237 Therefore, the secondary outcomes include indication-specific mortality, such as breast cancer  
27  
28 238 mortality for breast cancer cohorts.  
29  
30 239

## 31 240 **Risk of bias assessment**

32 241 Assessment of biases across included studies is very important, as the results can affect the  
33  
34 242 variability among single studies and consequently, the meta-analysis.[21] We will use the  
35  
36 243 Cochrane tool for assessing the “Risk Of Bias In Non-randomised Studies - of Interventions”  
37  
38 244 (ROBINS-I).[22] This tool pays particular attention to internal validity of a study by  
39  
40 245 comparing it to a hypothetical RCT. External validity of the study is not considered in this  
41  
42 246 tool and all generalizability, applicability or any ethical issues will not affect our judgements.  
43  
44 247 ROBINS-I is a seven domain-based approach of assessing risk of bias. The confounding  
45  
46 248 factors and selection bias have always been a matter of importance in observational study  
47  
48 249 designs, and both of them constitute two essential domains of ROBINS-I.[23, 23] Additional  
49  
50 250 domains include classification of interventions; deviations from intended interventions;  
51  
52 251 missing data; measurement of outcomes; and selection of the reported results.[24] The  
53  
54 252 systematic appraisal with ROBINS-I is conducted in three phases:  
55  
56 253 Phase (1): Protocol stage focuses on general forethoughts to be considered before appraising  
57  
58 254 single studies. Phase one deals with specifying the review question, identifying relevant  
59  
60 255 confounding domains to the included studies, and note possible co-interventions (exposures)  
256 that have an impact on study outcomes. Phase (2): The second stage is concerned with  
257 hypothesizing a randomised controlled trial and an elaboration of the stage two components  
258 (confounders and co-interventions) for each single study. Phase (3): This last stage is

1  
2  
3 259 concerned with the actual appraisal in the seven domains that expose the study to the risk of  
4  
5 260 bias. This instrument contains five options to answer the signalling questions (SQ): yes,  
6  
7 261 probably yes, no, probably not, and no information. In the same manner, the domain specific  
8  
9 262 judgments are based on five categories: low, moderate, serious, critical risk and no  
10  
11 263 information.

12 264 The single studies will be rated independently by two reviewers, and any disagreement will be  
13  
14 265 first noted and then followed by a discussion and a consultation with a third group member.

15 266 The final assessment will result in a table including all the single studies along with their  
16  
17 267 domain-specific and overall judgment conclusions.

18  
19 268

### 20 269 **Meta-biases assessment**

21  
22 270 We are aware of the implication of meta-biases (e.g., sampling, selection, and data extraction  
23  
24 271 bias) for the internal validity of this study.[25] To minimise meta-biases, the entire process  
25  
26 272 will follow the suggestions from the above guidelines. Retrieval bias will be minimised with a  
27  
28 273 comprehensive and representative search strategy. Publication bias will be assessed via funnel  
29  
30 274 plots.[26] In order to minimise selection bias (inclusion criteria and selector bias), inclusion  
31  
32 275 criteria were selected on the basis of a comprehensive discussion. Furthermore, we employ  
33  
34 276 double-check screening method against a clearly defined and specific criteria for eligibility.  
35  
36 277 To address extractor biases, we will use a double-check data extraction approach, which has  
37  
38 278 been proven to improve the extraction process.[27, 28] This review is limited to peer-  
39  
40 279 reviewed published literature. A supplementary search for unpublished studies and literature  
41  
42 280 does not take place. Thus, this review is to a certain extent susceptible to the grey literature  
43  
44 281 bias.[29]

45 282

### 46 283 **Data synthesis**

47 284 For each identified study, we will conduct graphical dose-response analyses of mortality as a  
48  
49 285 function of activity-related energy consumption. The data on the dose of physical activity will  
50  
51 286 all be converted into a single unit, i.e. MET-h/week. Only studies that investigate the  
52  
53 287 exposure to at least three different levels of physical activity will be included in the dose-  
54  
55 288 response analysis. If the physical activity categories are defined without signing a specific  
56  
57 289 value for the energy expenditure (e.g., only the three categories light physical activity,  
58  
59 290 moderate physical activity, and vigorous physical activity) we will assume the corresponding  
60  
291 absolute intensities to be 1,5- 3.0 METs for low, 3-6 METs for moderate, and  $\geq 6$  METs for  
292 high physical activity respectively .[30, 31] When studies report the duration of different

1  
2  
3 293 physical activities (e.g., 30 minutes of walking, running, or cycling), we will calculate the  
4  
5 294 energy expenditure based on the compendium of physical activities.[30]  
6  
7 295 Summary risk ratios (RR) with 95% confidence interval (CI) will be calculated when two or  
8  
9 296 more studies on the same exposure and outcome are available. We will apply random effects  
10  
11 297 meta-analysis as described by DerSimonian and Laird.[32] If a study reported on separate risk  
12  
13 298 estimates for subgroups (e.g. men and women), we will pool the data using a fixed effect  
14  
15 299 model and include the combined estimate in the overall meta-analysis.  
16  
17 300 Linear dose-response meta-analyses will be conducted by using the method as described by  
18  
19 301 Greenland and Longnecker.[33] In addition, we will investigate the shape of the association  
20  
21 302 by conducting non-linear dose-response meta-analysis as described by Orsini et al.[34]. For  
22  
23 303 this method the following data for at least three exposure categories are required: 1) the  
24  
25 304 quantified exposure value (MET-h/weeks), 2) the effect estimate with the corresponding 95 %  
26  
27 305 CI, and 3) the number of cases and person-years. If the information on the distribution of  
28  
29 306 cases, person years or non-cases is missing, data will be estimated as described  
30  
31 307 previously.[35, 36] The mean amount of exposure between two endpoints for each physical  
32  
33 308 activity category will be calculated. [2] When the lowest or highest category is open-ended  
34  
35 309 (example < 3), we will multiply the value by 1,25. [4]  
36  
37 310 Heterogeneity will be described by calculating tau<sup>2</sup> to assess the between-study variance and  
38  
39 311 I<sup>2</sup> statistic to investigate the variability of the observed effects in the meta-analyses.[37]  
40  
41 312 Possible sources of heterogeneity across studies will explored by conducting subgroup  
42  
43 313 analyses and meta-regression by accounting for e.g. sex, age, geographic location of the  
44  
45 314 studies, follow-up time, assessment of physical activity, risk of bias of the studies. Small  
46  
47 315 studies effect such as publication bias will be investigated by visual inspections of the funnel  
48  
49 316 plots and by applying Egger's test, whereas a p-value <0.1 indicates potential publication  
50  
51 317 bias.[38] Data analyses will be performed using the statistical software Stata (Version 15,  
52  
53 318 StataCorp, College Station, TX, USA). All tests will be two-sided with statistical significance  
54  
55 319 defined as p<0.05.  
56  
57 320

### 51 321 **Patient and public involvement**

53 322 As the systematic review will be based on published studies, patient or public involvement is  
54  
55 323 not applicable.  
56  
57 324

## 325 **CONCLUSION**

326 This study protocol provides a detailed description of the planned methodological approach  
327 for a systematic review and meta-analysis aimed to define the dose-response relationship  
328 between physical activity and mortality for nine relevant NCDs: type 2 diabetes mellitus,  
329 stroke, ischemic heart diseases, osteoarthritis, low back pain, COPD, depressive disorder,  
330 lung and breast cancer. For healthy individuals, current scientific work strongly questions the  
331 concept of a minimum dose of physical activity for lifetime extension. Our results might be  
332 helpful to inform updates on physical activity recommendations e.g. the national physical  
333 activity guidelines from the US or from Germany for individuals with NCD.[39, 6, 5] In  
334 particular, the planned dose-response analyses may help to specify the recommended amount  
335 of physical activity and define a minimum, optimum and maximum dose of physical activity  
336 for individuals with NCDs.

337

## 338 **Limitations**

339 Some potential sources of limitation are to be expected. Firstly, prospective observational  
340 cohort studies fail to provide conclusive evidence of a causal relationship between physical  
341 activity and mortality.[20, 40–42] Consequently, our review of cohort studies will also not  
342 provide a conclusive answer as to whether the reported relationships between physical activity  
343 and mortality are actually causal or only correlative. According to Hill et al.[43], however,  
344 confidence in a causal relationship increases when (1) a clear dose-response curve, (2) a  
345 strong association or a high effect size and (3) consistency of results in different studies are  
346 given. All these three factors will be examined in our systematic review. Thus, this work can  
347 contribute to estimating how likely a causal influence of physical activity on mortality rates  
348 is. Secondly, we will only include studies published in English. Studies published in other  
349 languages and grey, unpublished literature will not be included. Thirdly, the wide range of  
350 tools available to measure physical activity in terms of their psychometric properties and the  
351 domains that they assess may present another challenge. This variability in measurement  
352 instruments might introduce difficulties in generating one single energy metric unit of  
353 physical activity, thus questioning the inclusion of all the eligible studies in the dose-response  
354 analysis. On the other hand, we will consider any form of physical activity by representing it  
355 in associated energy consumption units; and we will not consider potential differences  
356 between e.g. different intensities (light vs. moderate vs. vigorous) or between physical activity  
357 in different contexts (e.g. leisure time pa vs. work-related pa). Fourthly, this study will only

1  
2  
3 358 consider activity behaviour and not sedentary behaviour even if there is a clear interaction  
4  
5 359 between physical activity and sitting with regard to mortality in healthy individuals.[44]  
6  
7 360

8 361 **List of abbreviations**

9  
10 362 **NCDs:** Noncommunicable Diseases

11  
12 363 **WHO:** World Health Organization

13  
14  
15 364 **PRISMA-P:** Preferred Reporting Items for Systematic Reviews and Meta-analysis for  
16 365 Protocols

17  
18  
19 366 **PICO:** Population, Intervention, Control, Outcome

20  
21 367 **MOOSE:** Meta-analysis Of Observational Studies in Epidemiology

22  
23 368 **MECIR:** Methodological Expectations of Cochrane Intervention Reviews

24  
25  
26 369 **COPD:** Chronic Obstructive Pulmonary Disease

27  
28 370 **LBP:** Low Back Pain

29  
30 371 **METs:** Metabolic Equivalent Tasks

31  
32 372 **SQ:** Signalling Question

33  
34 373 **RoB:** Risk of Bias

35  
36 374

37  
38  
39 375 **References**

40  
41 376 1 World Health Organization. Global recommendations on physical activity for health.  
42  
43 377 Geneva, Switzerland: World Health Organization 2010.

44  
45  
46 378 2 Warburton D, Bredin S. Health benefits of physical activity: a systematic review of  
47  
48 379 current systematic reviews. *Curr Opin Cardiol* 2017;32(5):541–56.  
49  
50 380 doi:10.1097/HCO.0000000000000437.

51  
52  
53 381 3 Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a  
54  
55 382 detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*  
56  
57 383 2015;175(6):959–67. doi:10.1001/jamainternmed.2015.0533.  
58  
59  
60

- 1  
2  
3 384 4 Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality:  
4  
5 385 systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol*  
6  
7 386 2011;40(5):1382–400. doi:10.1093/ije/dyr112.  
8  
9  
10 387 5 U.S. Department of Health and Human Services. Physical activity guidelines for  
11  
12 388 americans, 2nd edition. Washington, DC: U.S.: Department of Health and Human  
13  
14 389 Services 2018.  
15  
16  
17 390 6 2018 Physical Activity Advisory Committee. 2018 Physical activity guidelines advisory  
18  
19 391 committee scientific report. Washington, DC: U.S.: Department of Health and Human  
20  
21 392 Services 2018.  
22  
23  
24 393 7 Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer  
25  
26 394 mortality: findings from 71 prospective cohort studies. *Br J Sports Med* 2016;50(6):339–  
27  
28 395 45. doi:10.1136/bjsports-2015-094927.  
29  
30  
31 396 8 Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to  
32  
33 397 vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*  
34  
35 398 2012;9(11):e1001335. doi:10.1371/journal.pmed.1001335.  
36  
37  
38 399 9 Murray C, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291  
39  
40 400 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global  
41  
42 401 Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197–223. doi:10.1016/S0140-  
43  
44 402 6736(12)61689-4.  
45  
46  
47 403 10 Plass D, Vos T, Hornberg C, et al. Trends in disease burden in Germany: results,  
48  
49 404 implications and limitations of the Global Burden of Disease study. *Dtsch Arztebl Int*  
50  
51 405 2014;111(38):629–38. doi:10.3238/arztebl.2014.0629.  
52  
53  
54 406 11 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review  
55  
56 407 and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.  
57  
58 408 doi:10.1186/2046-4053-4-1.  
59  
60

- 1  
2  
3 409 12 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews  
4  
5 410 and meta-analyses: the PRISMA statement. *BMJ* 2009;339:10.1136/bmj.b2535.  
6  
7 411 doi:10.1371/journal.pmed.1000097.  
8  
9  
10 412 13 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in  
11  
12 413 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in  
13  
14 414 Epidemiology (MOOSE) group. *JAMA* 2000;283(15):2008–12.  
15  
16  
17 415 14 Higgins JPT, Lasserson T, Chandler J, et al. Methodological expectations of cochrane  
18  
19 416 intervention reviews. London: Cochrane 2016.  
20  
21 417 15 Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions  
22  
23 418 cochrane book series: The Cochrane Collaboration 2011.  
24  
25  
26 419 16 Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: a key  
27  
28 420 to evidence-based decisions. *ACP J Club* 1995;123(3):A12-3.  
29  
30  
31 421 17 Schardt C, Adams MB, Owens T, et al. Utilization of the PICO framework to improve  
32  
33 422 searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.  
34  
35 423 doi:10.1186/1472-6947-7-16.  
36  
37  
38 424 18 Edwards P, Clarke M, DiGiuseppi C, et al. Identification of randomized controlled trials  
39  
40 425 in systematic reviews: accuracy and reliability of screening records. *Stat Med*  
41  
42 426 2002;21(11):1635–40. doi:10.1002/sim.1190.  
43  
44  
45 427 19 Ng L, Pitt V, Huckvale K, et al. Title and abstract screening and evaluation in systematic  
46  
47 428 reviews (TASER): a pilot randomised controlled trial of title and abstract screening by  
48  
49 429 medical students. *Syst Rev* 2014;3:121. doi:10.1186/2046-4053-3-121.  
50  
51  
52 430 20 Kujala UM. Is physical activity a cause of longevity? It is not as straightforward as some  
53  
54 431 would believe. A critical analysis. *Br J Sports Med* 2018;52(14):914–18.  
55  
56 432 doi:10.1136/bjsports-2017-098639.  
57  
58  
59  
60



- 1  
2  
3 433 21 Higgins JP, Ramsay C, Reeves BC, et al. Issues relating to study design and risk of bias  
4  
5 434 when including non-randomized studies in systematic reviews on the effects of  
6  
7 435 interventions. *Res Synth Methods* 2013;4(1):12–25. doi:10.1002/jrsm.1056.  
8  
9  
10 436 22 Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in  
11  
12 437 non-randomised studies of interventions. *BMJ*;355:i4919. doi:10.1136/bmj.i4919.  
13  
14 438 23 Garcia-Doval I, van Zuuren EJ, Bath-Hextall F, et al. Systematic reviews: let's keep  
15  
16 439 them trustworthy. *Br J Dermatol* 2017;177(4):888–89. doi:10.1111/bjd.15826.  
17  
18  
19 440 24 Sterne JA, Higgins JPT, Elbers RG, et al. Risk Of Bias In Non-randomized Studies of  
20  
21 441 Interventions (ROBINS-I): detailed guidance, updated 20 October 2016. 2016. Available  
22  
23 442 at: <http://www.riskofbias.info>.  
24  
25  
26 443 25 Felson DT. Bias in meta-analytic research. *J Clin Epidemiol* 1992;45(8):885–92.  
27  
28 444 doi:10.1016/0895-4356(92)90072-U.  
29  
30  
31 445 26 Sterne JA, Harbord RM. Funnel plots in meta-analysis. *Stata J* 2004;4(2):127–41.  
32  
33 446 27 Mathes T, Klafen P, Pieper D. Frequency of data extraction errors and methods to  
34  
35 447 increase data extraction quality: a methodological review. *BMC Med Res Methodol*  
36  
37 448 2017;17(1):152. doi:10.1186/s12874-017-0431-4.  
38  
39  
40 449 28 Buscemi N, Hartling L, Vandermeer B, et al. Single data extraction generated more  
41  
42 450 errors than double data extraction in systematic reviews. *J Clin Epidemiol*  
43  
44 451 2006;59(7):697–703. doi:10.1016/j.jclinepi.2005.11.010.  
45  
46  
47 452 29 Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings:  
48  
49 453 an updated review of related biases. *Health Technol Assess* 2010;14(8):iii, ix-xi, 1-193.  
50  
51 454 doi:10.3310/hta14080.  
52  
53  
54 455 30 Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of physical  
55  
56 456 activities: a second update of codes and MET values. *Med Sci Sports Exerc*  
57  
58 457 2011;43(8):1575–81. doi:10.1249/MSS.0b013e31821ece12.  
59  
60

- 1  
2  
3 458 31 Haskell WL, Lee I, Pate RR, et al. Physical activity and public health: updated  
4  
5 459 recommendation for adults from the American College of Sports Medicine and the  
6  
7 460 American Heart Association. *Med Sci Sports Exerc* 2007;39(8):1423–34.  
8  
9 doi:10.1249/mss.0b013e3180616b27.  
10 461  
11  
12 462 32 DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*  
13  
14 463 2015;45(Pt A):139–45. doi:10.1016/j.cct.2015.09.002.  
15  
16  
17 464 33 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-  
18  
19 465 response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135(11):1301–  
20  
21 466 09.  
22  
23  
24 467 34 Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose-response  
25  
26 468 relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*  
27  
28 469 2012;175(1):66–73. doi:10.1093/aje/kwr265.  
29  
30  
31 470 35 Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative  
32  
33 471 variables in epidemiologic studies in a consistent form. *Am J Epidemiol*  
34  
35 472 1996;144(6):610–21.  
36  
37  
38 473 36 Aune D, Greenwood DC, Chan DSM, et al. Body mass index, abdominal fatness and  
39  
40 474 pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis  
41  
42 475 of prospective studies. *Ann Oncol* 2012;23(4):843–52. doi:10.1093/annonc/mdr398.  
43  
44  
45 476 37 Borenstein M, Higgins JPT, Hedges LV, et al. Basics of meta-analysis:  $I^2$  is not an  
46  
47 477 absolute measure of heterogeneity. *Res Synth Methods* 2017;8(1):5–18.  
48  
49 478 doi:10.1002/jrsm.1230.  
50  
51  
52 479 38 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a  
53  
54 480 simple, graphical test. *BMJ* 1997;315(7109):629–634.  
55  
56  
57 481 39 Rütten A, Pfeifer K, eds. National recommendations for physical activity and physical  
58  
59 482 activity promotion. Erlangen: FAU University Press 2016.  
60

- 1  
2  
3 483 40 Shiroma EJ, Lee I. Can we proceed with physical activity recommendations if (almost)  
4  
5 484 no clinical trial data exist on mortality? *Br J Sports Med* 2018;52(14):888–89.  
6  
7 485 doi:10.1136/bjsports-2018-099185.  
8  
9  
10 486 41 Wade KH, Richmond RC, Davey Smith G. Physical activity and longevity: how to move  
11  
12 487 closer to causal inference. *Br J Sports Med* 2018;52(14):890–91. doi:10.1136/bjsports-  
13  
14 488 2017-098995.  
15  
16  
17 489 42 O'Donovan G, Blazevich AJ, Boreham C, et al. The ABC of Physical Activity for  
18  
19 490 Health: a consensus statement from the British Association of Sport and Exercise  
20  
21 491 Sciences. *J Sports Sci* 2010;28(6):573–91. doi:10.1080/02640411003671212.  
22  
23  
24 492 43 Hill AB. The environment and disease: association or causation? *Proc R Soc Med*  
25  
26 493 1965;58:295–300.  
27  
28  
29 494 44 Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or  
30  
31 495 even eliminate, the detrimental association of sitting time with mortality? A harmonised  
32  
33 496 meta-analysis of data from more than 1 million men and women. *The Lancet*  
34  
35 497 2016;388(10051):1302–10. doi:10.1016/S0140-6736(16)30370-1.  
36  
37  
38 498  
39  
40 499  
41  
42 500  
43  
44 501  
45  
46  
47 502  
48  
49 503  
50  
51 504  
52  
53  
54 505  
55  
56 506  
57  
58  
59  
60

1  
2  
3 507 **Footnotes**

4  
5 508 **Author's contributions**

6 509 WG had the initial idea for this review he is the guarantor. WG, EM, SS, LM and AR  
7  
8 510 designed the study, including the development of the selection criteria, the risk of bias  
9  
10 511 assessment strategy, the search strategy, and data extraction strategy. KB and LL will check  
11  
12 512 up on the process of the screening. AR, EM and LM will retrieve the data from the studies  
13  
14 513 qualified for inclusion. SS will conduct the meta-analysis. EM, WG, and SS prepared the draft  
15  
16 514 of this study protocol. All authors provided substantial contribution to drafting the paper and  
17  
18 515 revising it critically for important intellectual content. All authors have read and approved the  
19  
20 516 final manuscript.

21 517 **Funding statement**

22 518 This research received no specific grant from any funding agency in the public, commercial or  
23  
24 519 not-for-profit sectors.

25 520 **Competing interests**

26  
27 521 The authors declare no conflict of interests.

28  
29 522 **Provenance and peer review**

30  
31 523 Not commissioned; externally peer reviewed.

32  
33 524 **Data sharing statement**

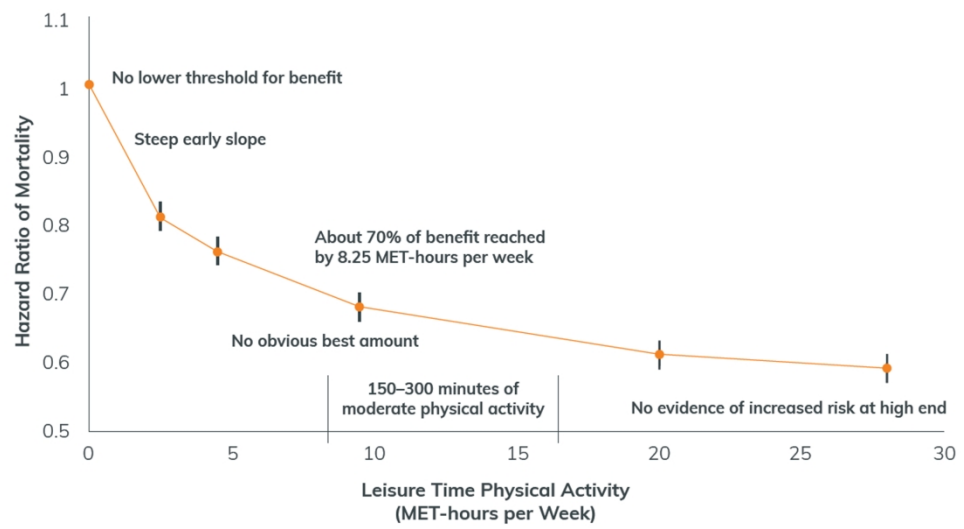
34 525 There are no additional data available despite the online supplementary files.

35  
36 526

37  
38 527 **Figures**

39 528 *Legend for Figure 1:* Reprinted with permission from: U.S. Department of Health and Human  
40  
41 529 Services. Physical Activity Guidelines for Americans, 2nd edition. Washington, DC: U.S.  
42  
43 530 Department of Health and Human Services; 2018.[5]  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Reprinted with permission from: U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd edition. Washington, DC: U.S. Department of Health and Human Services; 2018.[5]

338x190mm (300 x 300 DPI)

## Supplementary File 1: Completed PRISMA-P 2015 Checklist

### PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\*

Section and topic	Item No	Checklist item	(Page No.#)
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6 and Additional file

## Supplementary File 1: Completed PRISMA-P 2015 Checklist

			2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

## Supplementary File 2: Literature search strategy

### Dose-response relationship of physical activity and mortality in people with noncommunicable diseases. Study protocol for a systematic review and meta-analysis of cohort studies

Search strategy according to PICO framework:

#### Population

##### Indication specific keywords

##### *Breast cancer*

- #1 “breast neoplasm” [MeSH Terms]
- #2 “breast tumor”
- #3 “breast carcinoma”
- #4 “human mammary neoplasm”
- #5 “breast cancer”
- #6 “mammary cancer”
- #7 “breast malignant neoplasm”
- #8 “breast malignant tumor”
- #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

##### *Type 2 diabetes mellitus*

- #10 “diabetes mellitus, type 2” [MeSH Terms]
- #11 “noninsulin dependent diabetes mellitus”
- #12 “ketosis resistant diabetes mellitus”
- #13 “stable diabetes mellitus”
- #14 “type 2 diabetes mellitus”
- #15 “NIDDM”
- #16 “maturity onset diabetes mellitus”
- #17 “slow onset diabetes mellitus”
- #18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

##### *Chronic Obstructive Pulmonary Disease*

- #19 “COPD” [MeSH Terms]
- #20 “pulmonary disease, chronic obstructive” [MeSH Terms]
- #21 “COAD”
- #22 “chronic obstructive airway disease”
- #23 “chronic obstructive lung disease”
- #24 “chronic airflow obstruction”
- #25 #19 OR #20 OR #21 OR #22 OR #23 OR #24

##### *Ischemic heart disease*

- #26 “myocardial ischemia” [MeSH Terms]
- #27 “coronary artery disease” [MeSH Terms]
- #28 “myocardial infarction” [MeSH Terms]
- #29 “myocardial ischemia”
- #30 “coronary artery disease”



- 1  
2  
3 #31 “myocardial infarction”  
4 #32 #26 OR #27 OR #28 OR #29 OR #30 OR #31  
5

6  
7 ***Major depressive disorder***

- 8 #33 “depression” [MeSH Terms]  
9 #34 “depressive disorder, major” [MeSH Terms]  
10 #35 “depressive disorder”  
11 #36 “depressive symptoms”  
12 #37 “emotional depression”  
13 #38 #33 OR #34 OR #35 OR #36 OR #37  
14  
15

16  
17 ***Low back pain***

- 18 #39 “low back pain” [MeSH Terms]  
19 #40 “lumbago”  
20 #41 “low backache”  
21 #42 #39 OR #40 OR #41  
22  
23

24  
25 ***Stroke***

- 26 #43 “stroke” [MeSH Terms]  
27 #44 “cerebrovascular accident”  
28 #45 “CVA”  
29 #46 “apoplexy”  
30 #47 “brain vascular accident”  
31 #48 #43 OR #44 OR #45 OR #46 OR #47  
32  
33

34  
35 ***Osteoarthritis***

- 36 #49 “osteoarthritis” [MeSH Terms]  
37 #50 “osteoarthrosis”  
38 #51 “osteoarthritides”  
39 #52 “arthritis degenerative”  
40 #53 #49 OR #50 OR #51 OR #52  
41  
42

43  
44 ***Lung cancer***

- 45 #54 “lung neoplasm” [MeSH Terms]  
46 #55 “pulmonary neoplasm”  
47 #56 “lung cancer”  
48 #57 “pulmonary cancer”  
49 #58 #54 OR #55 OR #56 OR #57  
50  
51

52 **Intervention (Exposure)**

- 53 #59 “human activities” [MeSH Terms]  
54 #60 “motor activities” [MeSH Terms]  
55 #61 “leisure activities” [MeSH Terms]  
56 #62 “exercises” [MeSH Terms]  
57 #63 “running” [MeSH Terms]  
58 #64 “walking” [MeSH Terms]  
59 #65 “bicycling” [MeSH Terms]  
60

- 1  
2  
3 #66 “gardening” [MeSH Terms]  
4 #67 “sports” [MeSH Terms]  
5 #68 “activities of daily living” [MeSH Terms]  
6 #69 “human activity”  
7 #70 “motor activity”  
8 #71 “leisure activity”  
9 #72 “exercise”  
10 #73 “sport”  
11 #74 “physical activity”  
12 #74 “physical activities”  
13 #75 “nonexercise activity”  
14 #76 “nonexercise activities”  
15 #77 “energy expenditure”  
16 #78 “caloric expenditure”  
17 #79 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR  
18 #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78  
19  
20  
21  
22

### Comparator

None.

### Outcome

- 23  
24  
25  
26  
27  
28 #79 “mortality” [MeSH Terms]  
29 #80 “death”  
30 #81 “survival”  
31 #82 “life expectancy”  
32 #83 “years of life lost”  
33 #84 #79 OR #80 OR #81 OR #82 OR #83  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Years covered by search:** All years, no time restriction.

**Language:** English

**Study design filter:** No restriction.

#### PubMed search example for the Chronic Obstructive Coronary Disease:

**1#** (("COPD" OR "pulmonary disease, chronic obstructive"[MeSH Terms]) OR ("COPD"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR "COAD"[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract] OR "chronic obstructive lung disease"[Title/Abstract] OR "chronic airflow obstruction"[Title/Abstract]))

**2#** (("human activities" OR "motor activities" OR "leisure activities" OR "exercises" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sports" OR "activities of daily living"[MeSH Terms]) OR ("human activities"[Title/Abstract] OR "human activity"[Title/Abstract] OR "motor activity"[Title/Abstract] OR "motor activities"[Title/Abstract] OR "leisure activities"[Title/Abstract] OR "leisure activity"[Title/Abstract] OR "exercise"[Title/Abstract] OR "exercises"[Title/Abstract] OR "running"[Title/Abstract] OR "walking"[Title/Abstract] OR "bicycling"[Title/Abstract] OR "gardening"[Title/Abstract] OR "sports"[Title/Abstract] OR "sport"[Title/Abstract] OR "activities of daily living"[Title/Abstract] OR "physical activity"[Title/Abstract] OR "physical activities"[Title/Abstract] OR "nonexercise activity"[Title/Abstract] OR "nonexercise activities"[Title/Abstract] OR "energy expenditure"[Title/Abstract] OR "caloric expenditure"[Title/Abstract]))

**3#** (("mortality" [Title/Abstract] OR "death" [Title/Abstract] OR "survival" [Title/Abstract] OR "life expectancy" [Title/Abstract] OR "years of life lost"[Title/Abstract]) OR "mortality"[MeSH Terms])

**1# AND 2# AND 3#**

#### Scopus search example for the Chronic Obstructive Coronary Disease:

**1#** (TITLE-ABS ( "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure"))

**2#** (TITLE-ABS ( "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost"))

**3#** (TITLE-ABS ( "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction"))

**1# AND 2# AND 3#**

**Web of Science search example for the Chronic Obstructive Coronary Disease:**

**1#** "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction" **TOPIC**

**2#** "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction" **TITLE**

**3#** "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure" **TOPIC**

**4#** "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure" **TITLE**

**5#** "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost" **TOPIC**

**6#** "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost" **TITLE**

**1# OR 2# AND 3# OR 4# AND 5# OR 6#**

## Data extraction form

### No. Data items

- 1 Study id
- 2 Result number
- 3 First author
- 4 Year
- 5 Country
- 6 Sex
- 7 Age
- 8 Study design
- 9 Name of study
- 10 Follow\_up
- 11 N\_participants
- 12 Diagnosis/Breast Cancer verification
- 13 Mortality\_data\_ascertainment
- 14 N\_cases
- 15 PA assessment
- 16 Domain of PA
- 17 Exposure
- 18 Case\_per\_cat
- 19 Noncases\_per\_cat
- 20 Exposure\_cat
- 21 Risk ratio
- 22 RR\_lower confidence interval
- 23 RR\_upper confidence interval
- 24 Exposure\_dose
- 25 RR dose
- 26 RR\_dose\_lower confidence interval
- 27 RR\_dose\_upper confidence interval
- 28 RR\_other model
- 29 Quality\_score

# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028653.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Jul-2019
Complete List of Authors:	Geidl, Wolfgang; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Schlesinger, Sabrina; German Diabetes Center Düsseldorf (DZZ) Mino, Eriselda; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Miranda, Lorena; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Ryan, Anna; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Bartsch, Katja; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Janz, Lukas; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Pfeifer, Klaus; Friedrich-Alexander Universität Erlangen-Nürnberg, Department of Sport Science and Sport
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Global health, Public health, Sports and exercise medicine
Keywords:	Physical activity, Systematic review, Meta-analysis, Mortality, Noncommunicable diseases, Exercise

SCHOLARONE™  
Manuscripts

1  
2  
3 1 **Title page**  
4  
5 2

6  
7 3 **The dose–response relationship between physical activity and mortality in people with**  
8  
9 4 **noncommunicable diseases: A study protocol for the systematic review and meta-analysis of**  
10  
11 5 **cohort studies**  
12 6

13  
14 7 **Corresponding author:** Dr. Wolfgang Geidl, Department of Sport Science and Sport (DSS),  
15 8 Friedrich-Alexander University Erlangen-Nürnberg (FAU), Gebbertstraße 123b, 91058  
16 9 Erlangen (Germany); Tel.: +49-9131 85-25457, Fax. +49-9131 85-28198, E-mail address:  
17 10 wolfgang.geidl@fau.de  
18  
19  
20  
21  
22

23 12 Wolfgang Geidl<sup>1</sup>, Sabrina Schlesinger<sup>2</sup>, Eriselda Mino<sup>1</sup>, Lorena Miranda<sup>1</sup>, Anna Ryan<sup>1</sup>, Katja  
24 13 Bartsch<sup>1</sup>, Lukas Janz<sup>1</sup>, Klaus Pfeifer<sup>1</sup>  
25  
26  
27 14

28 15 <sup>1</sup> Department of Sport Science and Sport, Division Exercise and Health, Friedrich-Alexander  
29 16 University Erlangen-Nürnberg (FAU), Erlangen, Germany  
30  
31

32 17 <sup>2</sup> German Diabetes Center Düsseldorf (DZZ), Düsseldorf, Germany  
33  
34 18

35 19 **Keywords:** Exercise, Noncommunicable diseases, Mortality, Systematic review, Meta-  
36 20 analysis  
37  
38  
39 21  
40  
41 22  
42  
43 23

44 24 Word count: 3767  
45  
46 25  
47 26  
48  
49 27  
50  
51 28  
52  
53 29  
54  
55 30  
56  
57 31  
58  
59 32  
60 33

## 34 **ABSTRACT**

### 35 **Introduction**

36 This study protocol outlines our planned systematic review and dose–response meta-analysis  
37 of post-diagnosis physical activity and mortality in people with noncommunicable diseases  
38 (NCDs).

### 39 **Methods and analysis**

40 This study is based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis  
41 for Protocols (PRISMA-P). A systematic literature search will be conducted in various  
42 databases – namely, PubMed, Scopus and Web of Science – by two researchers in order to  
43 identify prospective observational studies that investigate post-diagnosis physical activity or  
44 activity-related energy expenditure and mortality in individuals with NCDs. The target  
45 population is adults ( $\geq 18$  years of age) with one of the following nine NCDs: low back pain,  
46 type 2 diabetes mellitus, osteoarthritis, depressive disorder, chronic obstructive pulmonary  
47 disease, breast cancer, lung cancer, stroke or ischemic heart disease. We will focus on all-cause  
48 mortality as the primary outcome and investigate indication-specific mortality as the secondary  
49 outcome. For each study identified as a result of the literature search, we will conduct graphical  
50 dose–response analyses of mortality as a function of activity-related energy consumption. If  
51 more than two studies are available for one disease, we will perform linear and non-linear dose–  
52 response meta-analyses for said disease using random effects models. We will investigate the  
53 heterogeneity of the studies and publication bias. To assess the risk of bias and the quality of  
54 the included studies, we will use the Risk Of Bias In Non-randomised Studies - of Interventions  
55 (ROBINS-I) tool, which is a Cochrane tool.

### 56 **Ethics and dissemination**

57 This systematic review will be conducted in compliance with ethical precepts. As the systematic  
58 review is based on published studies, approval from an ethics committee is not required. The  
59 systematic review and meta-analysis will be published in a peer-reviewed journal.

60 This study is registered in the International Prospective Register for Systematic Reviews  
61 (PROSPERO) registration number: CRD42018103357

### 62 **Strengths and limitations**

- 63 • Our systematic review will be conducted and reported in accordance with the reporting  
64 guidelines provided in the PRISMA-P statement and the reporting guidelines of the  
65 Meta-analysis Of Observational Studies in Epidemiology (MOOSE).



- 66 • The scope of our systematic search is wide-reaching, as it includes nine NCDs and three  
67 extensive medical databases.
- 68 • The study uses the novel ROBINS-I tool.
- 69 • However, the observational cohort studies do not provide a conclusive answer regarding  
70 the causality between physical activity and mortality.

## 72 INTRODUCTION

73 The World Health Organization (WHO) recommends at least 150 minutes of moderate-intensity  
74 physical activity or 75 minutes of vigorous-intensity physical activity per week to enhance  
75 health and reduce mortality.[1] For additional benefits, adults should increase their moderate-  
76 intensity physical activity to 300 minutes or engage in 150 minutes of vigorous-intensity  
77 physical activity per week. These recommendations apply to both healthy adults and adults with  
78 noncommunicable diseases (NCDs) (e.g. ischemic heart disease, breast cancer, chronic  
79 pulmonary disease). However, if one considers the scientific evidence for physical activity and  
80 mortality on which the recommendations are based, an extensive disparity becomes apparent  
81 between healthy populations and those with a pre-existing NCD.

82 The data for healthy adults are comprehensive and unambiguous. Numerous large cohort  
83 studies have consistently demonstrated an inverse relationship between physical activity and  
84 mortality.[2] Arem et al.[3] pooled data from six cohort studies of 661,137 persons. Compared  
85 to individuals who reported having no leisure-time physical activity, premature death decreased  
86 with increased physical activity levels: 7.5 metabolic equivalent tasks (MET) h/wk (Hazard  
87 Ratio (HR) = 0.80; 95% confidence interval (CI); 0.78–0.82); 7.5–15 MET h/wk (HR = 0.69;  
88 0.67–0.70); and 15–22.5 MET h/wk (HR = 0.63; 0.62–0.65). These findings are consistent with  
89 the meta-analysis conducted by Samitz et al.[4] This analysis comprised 80 studies with a total  
90 of 1,338,143 persons. Compared to the lowest activity group, the risk of premature death was  
91 remarkably reduced in the highest activity group (HR = 0.65; 95% CI; 0.60–0.71). Furthermore,  
92 each one-hour increment of moderate-intensity activity per week resulted in a lowered risk ratio  
93 (RR) of 0.96 (95% CI; 0.93–0.98).

94 Accordingly, the updated physical activity guidelines from the US Department of Health and  
95 Human Services[5] include a clear dose–response relationship between the volume of physical  
96 activity and the mortality rates of healthy adults. The shape of the dose–response curve is not  
97 linear but regressive, thus meaning that the greatest difference in mortality rates occurs among  
98 inactive and minimally active individuals. It is clear that benefits can be gained with any amount

1  
2  
3 99 of physical activity. For healthy individuals, current scientific research is sceptical of a  
4  
5 100 minimum dose of physical activity to ensure lifetime extension. Following the minimum  
6  
7 101 recommendations, physical activity is equivalent to energy expenditure of 8.25 MET hours per  
8  
9 102 week. At this level of physical activity, about 70% of the benefits in relation to mortality rates  
10  
11 103 are reached.[6] Higher volumes of physical activity mean that the dose–response curve flattens  
12  
13 104 out. However, roughly five times this dose is also associated with more risk reductions and no  
14  
15 105 adverse effects.

15 106 For individuals with distinct NCDs, the scientific data on the dose–response relationship  
16  
17 107 between physical activity and mortality are considerably weaker. For cancer, the meta-analysis  
18  
19 108 by Li et al.[7] suggests that post-diagnosis physical activity levels may result in similar risk  
20  
21 109 reductions in mortality. Moore et al.[8] pooled data from six cohort studies that comprised  
22  
23 110 654,827 individuals and adjusted their analysis for several confounders, including pre-existing  
24  
25 111 NCDs. In contrast to Li et al.,[7] they conclude that the longevity effects of physical activity  
26  
27 112 vary according to the pre-existing NCD. The current evidence from the US Physical Activity  
28  
29 113 Guidelines Advisory Committee[6] reports a general relationship between higher post-  
30  
31 114 diagnosis physical activity and lower mortality rates in five NCDs (breast cancer, colorectal  
32  
33 115 cancer, prostate cancer, cardiovascular condition of hypertension and type 2 diabetes).  
34  
35 116 However, this report did not demonstrate the dose–response relationships due to the limited  
36  
37 117 information it had regarding the NCDs that were worked on. In addition, the report does not  
38  
39 118 include all NCDs with high levels of morbidity and mortality in Western countries. In Germany,  
40  
41 119 the following NCDs are in the top 10 NCDs with the highest burden of disease: ischemic heart  
42  
43 120 disease, low back pain, lung cancer, breast cancer, stroke, chronic obstructive pulmonary  
44  
45 121 disease (COPD), major depressive disorder and diabetes.[9] The high disease burden of these  
46  
47 122 NCDs refers to the loss of life due to premature death and years spent living with a disability  
48  
49 123 as a result of the disease. For some NCDs, such as low back pain or major depressive disorder,  
50  
51 124 the high burden is mainly caused by a loss of healthy years. However, the data from Plass et  
52  
53 125 al.[9] also show at least a small influence on mortality rates. Overall, it is unclear whether  
54  
55 126 physical activity positively affects mortality rates in individuals with NCDs in the same way  
56  
57 127 that physical activity affects the mortality rates of healthy individuals. Thus, it is clear that the  
58  
59 128 dose–response relationship between physical activity and mortality in adults with an NCD is  
60  
129 not well defined at present.

130

## 131 **Objectives**

132 This study protocol aims to describe the planned systematic review and dose–response meta-  
133 analysis of physical activity and mortality in adults with NCDs. The planned study aims to  
134 define the dose–response relationship between post-diagnosis physical activity and mortality  
135 rates for nine NCDs with a high global burden of disease,[10] especially in Germany.[9] The  
136 nine NCDs are: low back pain, type 2 diabetes mellitus, osteoarthritis, depressive disorder,  
137 COPD, breast cancer, lung cancer, stroke and ischemic heart disease. Our results may inform  
138 updates on national physical activity recommendations for individuals with NCDs.[5, 6] The  
139 planned dose–response analyses may help specify the recommended amount of physical  
140 activity and define a minimum, optimum and maximum dose of physical activity for  
141 individuals with NCD.

## 143 **METHODS**

144 This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-  
145 analysis for Protocols (PRISMA-P, Supplementary File 1).[11] Our systematic review will be  
146 conducted and reported in accordance with the reporting guidelines provided in the PRISMA  
147 statement and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)  
148 reporting guidelines.[12,13] Additionally, the *Methodological Expectations of Cochrane*  
149 *Intervention Reviews* and the *Cochrane Handbook of Systematic Reviews in Interventions* will  
150 be consulted to ensure methodological quality.[14, 15]

151 In view of the recommendations that endorse the pre-registration of systematic reviews, our  
152 protocol was registered with the International Prospective Register of Systematic Reviews  
153 (PROSPERO) on September 5, 2018 (registration number: CRD42018103375; available  
154 online at [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=103357](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=103357)).

## 156 **Eligibility criteria**

157 This study will only include research published in the English language. There are no time  
158 restrictions in relation to the year of publication. We will include studies that investigate the  
159 association between post-diagnosis physical activity levels and mortality among adults with  
160 NCD and report on the effect estimates, including the hazard ratios, relative risks, odds ratios  
161 or absolute mortality rates.[16,12] For this study, post-diagnosis physical activity will be  
162 defined as any form of physical activity, such as leisure-time, occupational, transport-related,  
163 exercise and any physical activity-related energy expenditure measured after diagnosis.

1  
2  
3 164 Physical activity can be measured using subjective methods (e.g. questionnaires) or objective  
4  
5 165 methods (e.g. accelerometry). Physical activity-related energy expenditure can be measured  
6  
7 166 using any kind of objective method (e.g. doubly labelled water).

8  
9 167 Studies will be excluded if they: (1) clearly deal with another topic; (2) include only the total  
10  
11 168 population without information for subgroups with NCDs at the baseline; (3) focus on  
12  
13 169 prevention only (i.e. when they include individuals at risk of developing one of the nine  
14  
15 170 diseases); (4) report insufficient data (i.e. less than three different physical activity levels in  
16  
17 171 MET hours per week) to calculate the dose–response relationship; (5) are duplicate studies  
18  
19 172 that are based on a data set that has already been taken into account.

20  
21 173 Participants: The participants for the study will be comprised of those who are  $\geq 18$  years of  
22  
23 174 age with at least one of the following nine NCDs at the baseline: osteoarthritis, low back pain,  
24  
25 175 depressive disorder, ischemic heart disease, type 2 diabetes mellitus, stroke, COPD, lung  
26  
27 176 cancer or breast cancer. The disease can either be confirmed by a physician or determined by  
28  
29 177 self-reporting. Studies that have children, adolescents and pregnant women as the participants  
30  
31 178 will be excluded, as will studies that focus on animal and cell cultures.

32  
33 179 Outcomes: The outcomes will be studies that assessed all-cause mortality as the primary  
34  
35 180 endpoint or any indication-specific mortality as the primary or secondary endpoint.

36  
37 181 Study design: Prospective observational studies, including cohort, nested case-control, case-  
38  
39 182 cohort studies and follow-up studies of randomised controlled studies published in a peer-  
40  
41 183 reviewed journal will be included. We will exclude cross-sectional, case only or case-control  
42  
43 184 studies, conference abstracts, comments, letters and reviews.

44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### 185 186 **Information sources**

187 Two researchers will search the following electronic databases: PubMed, Scopus and Web of  
188  
189 Science. All years will be covered. The reference list from the systematic reviews and meta-  
190  
191 analyses will be manually searched to locate further results.

### 192 193 **Search strategy**

194 The search strategy was developed with the support of a specialist from the University  
195  
196 Library. The search is structured according to three main categories of the Population,  
197  
198 Intervention, Comparison, Outcome (PICO) concept. The population is one of the nine NCDs;  
199  
200 the intervention is the physical activity; the outcome is mortality; and control, as the fourth  
201  
202 category of PICO, does not play a role in the cohort studies we sought out.[17] We defined  
203  
204 the search terms for the three PICO categories; these terms included keywords and related

1  
2  
3 198 synonyms, abbreviations, spelling variations and controlled vocabulary, each separated by  
4  
5 199 Boolean operator OR. The search terms for the three PICO categories will be combined with  
6  
7 200 Boolean operator AND. The search will be restricted to the search fields of the title and the  
8  
9 201 abstract. Independent searches will be conducted for the nine NCDs under consideration. The  
10  
11 202 search is adapted to the special features of the three databases (e.g. the use of medical subject  
12  
13 203 heading terms in PubMed). It should be noted that the search is not filtered for observational  
14  
15 204 studies, as reference lists of systematic reviews and meta-analyses are eligible for additional  
16  
17 205 manual searching. The concrete search terms used can be found in Supplementary File 2.  
18

206

### 207 **Data management**

208 The search results will be imported to the reference management and knowledge organisation  
21  
22 209 software, Citavi Version 5 (Swiss Academic Software, Wädenswil, Switzerland). We will use  
23  
24 210 separate project folders for each of the nine NCDs. These folders will be organised  
25  
26 211 hierarchically in categories, based on the various inclusion and exclusion filters.  
27

212

### 213 **Selection of eligible studies**

214 First, one researcher will screen each article's title and abstract against the eligibility criteria  
22  
23 215 to identify all relevant studies. Then, a second researcher will perform the same screening task  
24  
25 216 to ensure that no studies were overlooked or incorrectly included. This procedure will have a  
26  
27 217 positive effect on the accuracy and reliability of the screening process.[18] Moreover,  
28  
29 218 increasing the number of contributors in this critical point of the systematic review enables  
30  
31 219 the improved timeliness and efficiency of the process.[19] If the screening process of the title  
32  
33 220 and abstract does not lead to a clear result, the article will be retrieved for full-text screening.  
34  
35 221

221

### 222 **Data extraction**

223 Data of the full texts will be independently extracted by two reviewers using an Excel table  
24  
25 224 (Supplementary File 3). This table has been pilot-tested with a number of eligible articles  
26  
27 225 from four reviewers (AR, EM, LM, WG). The ensuing discussion secured a mutual  
28  
29 226 understanding of the variables, the standardisation of the Excel data mask and a uniform  
30  
31 227 system of data extraction. The results of the double data extraction will be checked for  
32  
33 228 consistency. Any disagreements will be openly discussed by the three reviewers. Multiple  
34  
35 229 publications with the same or very similar content will only be considered once; duplicates  
36  
37 230 with smaller sample sizes and shorter follow-up durations will be excluded.  
38  
39 231

231

## 232 **Data items**

233 The information for extraction includes basic details such as the first author, year of  
234 publication, study name, design, country where research was undertaken, age and sex of  
235 participants and mean follow-up time. Additionally, we will retrieve data regarding the total  
236 sample, total all-cause death cases, the number of participants in each physical activity  
237 category, death cases per the corresponding category, diagnosis and mortality data  
238 ascertainment, exposure to physical activity (e.g. MET h/week, m/day) and any corresponding  
239 categories. Finally, RR with 95% CIs will be extracted from fully adjusted models for every  
240 physical activity exposure category, as well as for dose-response data, when available.

## 242 **Outcomes**

243 The primary outcome of this review will be all-cause mortality, defined as the number of  
244 deaths over the entire period of follow-up, regardless of the underlying cause of death. As  
245 previously discussed, overall mortality is one of the main investigated types of death  
246 attributable to a lack of physical activity in persons affected by NCD. The relationship  
247 between physical activity and longevity is complex,[20] and during a certain timeframe, death  
248 can be caused or affected by multiple factors. Hence, disease-specific standardised death rates  
249 can exclude many cases that can blur the identification of a possible causal relation. If all-  
250 cause mortality rates are not reported, disease-specific mortality rates will be considered.  
251 Thus, the secondary outcomes include indication-specific mortalities such as breast cancer  
252 mortality.

## 254 **Risk of bias assessment**

255 Assessment of bias across the included studies is very important, as the results can affect the  
256 variability among single studies and consequently, the meta-analysis.[21] We will use the  
257 Cochrane ROBINS-I for assessing bias.[22] This tool pays particular attention to the internal  
258 validity of a study by comparing it to a hypothetical randomised controlled trial (RCT). The  
259 external validity of the study is not considered in this tool, and any generalisability,  
260 applicability or ethical issues will not affect our judgement.  
261 ROBINS-I is a domain-based method of assessing the risk of bias. Seven domains are  
262 included in total. Confounding factors and selection bias have always been a matter of  
263 importance in observational study designs, and both of these elements constitute two essential  
264 domains of ROBINS-I.[23] The additional domains of ROBINS-I include the classification of  
265 interventions, deviations from intended interventions, missing data, measurement of outcomes

1  
2  
3 266 and selection of the reported results.[24] Through ROBINS-I, systematic appraisal is  
4  
5 267 conducted in three phases:  
6  
7 268 Phase 1: The protocol stage focuses on any general forethoughts to be considered prior to  
8  
9 269 appraising each study. This stage specifies the review question, identifies the relevant  
10  
11 270 confounding domains for the included studies and notes possible co-interventions (exposures)  
12  
13 271 that have an impact on study outcomes.  
14  
15 272 Phase 2: The second stage is concerned with hypothesising a RCT and elaborating on the  
16  
17 273 confounders and co-interventions for each study.  
18  
19 274 Phase 3: The final stage focuses on the actual appraisal in the seven domains that expose the  
20  
21 275 study to the risk of bias. This instrument contains five options to answer the signalling  
22  
23 276 questions – namely, yes, probably yes, no, probably not and no information. In the same  
24  
25 277 manner, the domain-specific judgments are based on five categories – namely, low, moderate,  
26  
27 278 serious, critical risk and no information.  
28  
29 279 Each study will be independently rated by two reviewers, and any disagreement will be first  
30  
31 280 noted and then followed by a discussion and consultation with a third group member. The  
32  
33 281 final assessment will result in a table that includes all of the studies along with the domain-  
34  
35 282 specific and overall conclusions reached by the reviewers.  
36  
37 283

### 284 **Meta-biases assessment**

36 285 We are aware of the implication of meta-biases (e.g. sampling, selection and data extraction  
37  
38 286 bias) for the internal validity of this study.[25] To minimise meta-biases, the entire process  
39  
40 287 will follow the suggestions of the above guidelines. Retrieval bias will be minimised with a  
41  
42 288 comprehensive and representative search strategy. If the number of included studies permits  
43  
44 289 this, publication bias will be assessed via funnel plots.[26] To minimise selection bias,  
45  
46 290 inclusion criteria were selected on the basis of a comprehensive discussion. Furthermore, we  
47  
48 291 will employ a double-check screening method against a clearly defined and specific criterion  
49  
50 292 for eligibility. To address extractor biases, we will use a double-check approach of data  
51  
52 293 extraction, which has been proven to improve the extraction process.[27,28] This review is  
53  
54 294 limited to peer-reviewed published literature. A supplementary search for unpublished studies  
55  
56 295 and literature will not occur, thus meaning that, to a certain extent, this review is susceptible  
57  
58 296 to grey literature bias.[29]  
59  
60 297

## 298 **Synthesis of results**

299 First, following the methodological approach of Warburton and Bredin,[2] for each identified  
300 study, we will conduct graphical dose–response analyses of mortality as a function of activity-  
301 related energy consumption. The data regarding the dose of physical activity will be  
302 converted into a single unit (i.e. MET h/week). Only studies that investigate exposure to at  
303 least three different levels of physical activity will be included in the dose–response analysis.  
304 If the physical activity categories are defined without assigning a specific value for energy  
305 expenditure, we will assume the corresponding absolute intensities to be 1.5–3.0 MET for a  
306 low level of physical activity; 3–6 MET for moderate physical activity; and  $\geq 6$  MET for a  
307 high level of physical activity.[30, 31] When studies report the duration of different physical  
308 activities (e.g. 30 minutes of walking, running or cycling), we will calculate the energy  
309 expenditure based on the compendium of physical activities.[30]

310 Second, for each of the nine NCDs, summary RRs with 95% CIs will be calculated when two  
311 or more studies of the same exposure and outcome are available. We will apply random  
312 effects meta-analysis, as described by DerSimonian and Laird.[32] If a study reports on  
313 separate risk estimates for subgroups (e.g. men and women), we will pool the data using a  
314 fixed effect model and include the combined estimate in the overall meta-analysis.

315 Third, indication-specific linear dose-response meta-analyses will be conducted using the  
316 method described by Greenland and Longnecker.[33] In addition, we will investigate the  
317 shape of the association by conducting non-linear dose-response meta-analysis, as described  
318 by Orsini et al.[34]. For this method, the following data for at least three exposure categories  
319 are required: 1) the quantified exposure value (MET h/weeks); 2) the effect estimate with the  
320 corresponding 95% CI; and the number of cases and person-years. If the information  
321 regarding the distribution of cases, person-years or non-cases is missing, data will be  
322 estimated as previously described.[35, 36] The mean amount of exposure between two  
323 endpoints for each physical activity category will be calculated.[2] When the lowest or  
324 highest category is open-ended (e.g.  $< 3$ ), we will multiply the value by 1.25.[4]

325 Heterogeneity will be described by calculating  $\text{Tau}^2$  to assess the between-study variance and  
326 calculating the  $I^2$  statistic to investigate the variability of the observed effects in the meta-  
327 analyses.[37] Possible sources of heterogeneity across the studies will be explored by  
328 conducting subgroup analyses and meta-regressions by accounting for various factors (e.g.  
329 sex, age, geographic location of the studies, follow-up time, assessment of physical activity,  
330 risk of bias of the studies). The small-studies effect (e.g. publication bias) will be investigated  
331 by conducting visual inspections of the funnel plots and applying Egger's test, at which  $p <$



1  
2  
3 332 0.1 indicates potential publication bias.[38] Data analyses will be performed using the  
4  
5 333 statistical software Stata (Version 15, StataCorp, College Station, TX, USA). All tests will be  
6  
7 334 two-sided, with statistical significance defined as  $p < 0.05$ .

8 335

### 10 336 **Patient and public involvement**

11  
12 337 As the systematic review will be based on published studies, patient or public involvement is  
13  
14 338 not applicable.

15 339

### 17 340 **Limitations**

18  
19 341 Some potential limitations are to be expected. First, prospective observational cohort studies  
20  
21 342 fail to provide conclusive evidence of a causal relationship between physical activity and  
22  
23 343 mortality.[20, 39-41] Consequently, our review of cohort studies does not provide a  
24  
25 344 conclusive answer as to whether the reported relationships between physical activity and  
26  
27 345 mortality are actually causal or only correlative. According to Hill et al.,[42] however,  
28  
29 346 confidence in a causal relationship increases when (1) a clear dose-response curve, (2) a  
30  
31 347 strong association or a high effect size and (3) consistency of results in different studies are  
32  
33 348 given. These three factors will be examined in our systematic review. Thus, this work can  
34  
35 349 contribute to estimations of the likelihood of the causal influence of physical activity on  
36  
37 350 mortality rates. Second, we will only include studies published in English. Studies published  
38  
39 351 in other languages and grey, unpublished literature will not be included. Third, the wide range  
40  
41 352 of tools available to measure physical activity in terms of their psychometric properties and  
42  
43 353 the domains that they assess may present another challenge. This variability in measurement  
44  
45 354 instruments may present difficulties in generating one single energy metric unit of physical  
46  
47 355 activity, thus questioning the inclusion of all the eligible studies in the dose-response analysis.  
48  
49 356 However, we will consider any form of physical activity by representing it in associated  
50  
51 357 energy consumption units, and we will not consider potential differences between different  
52  
53 358 intensities (i.e. light vs. moderate vs. vigorous) or between physical activity in different  
54  
55 359 contexts (e.g. leisure time physical activity vs. occupational physical activity). Fourth, this  
56  
57 360 study will only consider activity behaviour, not sedentary behaviour, even if there is a clear  
58  
59 361 interaction between physical activity and sedentary behaviour with regard to mortality in  
60  
61 362 healthy individuals.[43]

56 363

### 58 364 **List of abbreviations**

59  
60 365 **NCD:** Noncommunicable Disease

1  
2  
3 366 **WHO:** World Health Organization  
4

5 367 **PRISMA-P:** Preferred Reporting Items for Systematic Reviews and Meta-analysis for  
6  
7 368 Protocols  
8

9 369 **PICO:** Population, Intervention, Control, Outcome  
10

11 370 **MOOSE:** Meta-analysis Of Observational Studies in Epidemiology  
12

13 371 **COPD:** Chronic Obstructive Pulmonary Disease  
14

15 372 **LBP:** Low Back Pain  
16

17 373 **MET:** Metabolic Equivalent Tasks  
18

19 374 **SQ:** Signalling Question  
20

21 375 **RoB:** Risk of Bias  
22

23 376  
24

25 377 **References**  
26

27 378 1 World Health Organization. Global recommendations on physical activity for health.  
28  
29 379 Geneva, Switzerland: World Health Organization 2010.  
30

31 380 2 Warburton D, Bredin S. Health benefits of physical activity: a systematic review of  
32  
33 381 current systematic reviews. *Curr Opin Cardiol* 2017;32(5):541–56.  
34  
35 382 doi:10.1097/HCO.0000000000000437.  
36  
37

38 383 3 Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a  
39  
40 384 detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*  
41  
42 385 2015;175(6):959–67. doi:10.1001/jamainternmed.2015.0533.  
43  
44

45 386 4 Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality:  
46  
47 387 systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol*  
48  
49 388 2011;40(5):1382–400. doi:10.1093/ije/dyr112.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 389 5 U.S. Department of Health and Human Services. Physical activity guidelines for  
4  
5 390 americans, 2nd edition. Washington, DC: U.S.: Department of Health and Human  
6  
7 391 Services 2018.  
8  
9  
10 392 6 2018 Physical Activity Advisory Committee. 2018 Physical activity guidelines advisory  
11  
12 393 committee scientific report. Washington, DC: U.S.: Department of Health and Human  
13  
14 394 Services 2018.  
15  
16  
17 395 7 Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer  
18  
19 396 mortality: findings from 71 prospective cohort studies. *Br J Sports Med* 2016;50(6):339–  
20  
21 397 45. doi:10.1136/bjsports-2015-094927.  
22  
23  
24 398 8 Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to  
25  
26 399 vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*  
27  
28 400 2012;9(11):e1001335. doi:10.1371/journal.pmed.1001335.  
29  
30  
31 401 9 Plass D, Vos T, Hornberg C, et al. Trends in disease burden in Germany: results,  
32  
33 402 implications and limitations of the Global Burden of Disease study. *Dtsch Arztebl Int*  
34  
35 403 2014;111(38):629–38. doi:10.3238/arztebl.2014.0629.  
36  
37  
38 404 10 Murray C, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291  
39  
40 405 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global  
41  
42 406 Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197–223. doi:10.1016/S0140-  
43  
44 407 6736(12)61689-4.  
45  
46  
47 408 11 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review  
48  
49 409 and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.  
50  
51 410 doi:10.1186/2046-4053-4-1.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 411 12 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews  
4  
5 412 and meta-analyses: the PRISMA statement. *BMJ* 2009;339:10.1136/bmj.b2535.  
6  
7 413 doi:10.1371/journal.pmed.1000097.  
8  
9  
10 414 13 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in  
11  
12 415 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in  
13  
14 416 Epidemiology (MOOSE) group. *JAMA* 2000;283(15):2008–12.  
15  
16  
17 417 14 Higgins JPT, Lasserson T, Chandler J, et al. Methodological expectations of cochrane  
18  
19 418 intervention reviews. London: Cochrane 2016.  
20  
21  
22 419 15 Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions  
23  
24 420 cochrane book series: The Cochrane Collaboration 2011.  
25  
26  
27 421 16 Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: a key  
28  
29 422 to evidence-based decisions. *ACP J Club* 1995;123(3):A12-3.  
30  
31  
32 423 17 Schardt C, Adams MB, Owens T, et al. Utilization of the PICO framework to improve  
33  
34 424 searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.  
35  
36 425 doi:10.1186/1472-6947-7-16.  
37  
38  
39 426 18 Edwards P, Clarke M, DiGiuseppi C, et al. Identification of randomized controlled trials  
40  
41 427 in systematic reviews: accuracy and reliability of screening records. *Stat Med*  
42  
43 428 2002;21(11):1635–40. doi:10.1002/sim.1190.  
44  
45  
46 429 19 Ng L, Pitt V, Huckvale K, et al. Title and abstract screening and evaluation in systematic  
47  
48 430 reviews (TASER): a pilot randomised controlled trial of title and abstract screening by  
49  
50 431 medical students. *Syst Rev* 2014;3:121. doi:10.1186/2046-4053-3-121.  
51  
52  
53 432 20 Kujala UM. Is physical activity a cause of longevity? It is not as straightforward as some  
54  
55 433 would believe. A critical analysis. *Br J Sports Med* 2018;52(14):914–18.  
56  
57 434 doi:10.1136/bjsports-2017-098639.  
58  
59  
60

- 1  
2  
3 435 21 Higgins JP, Ramsay C, Reeves BC, et al. Issues relating to study design and risk of bias  
4  
5 436 when including non-randomized studies in systematic reviews on the effects of  
6  
7 437 interventions. *Res Synth Methods* 2013;4(1):12–25. doi:10.1002/jrsm.1056.  
9  
10 438 22 Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in  
11  
12 439 non-randomised studies of interventions. *BMJ*;355:i4919. doi:10.1136/bmj.i4919.  
14  
15 440 23 Garcia-Doval I, van Zuuren EJ, Bath-Hextall F, et al. Systematic reviews: let's keep  
16  
17 441 them trustworthy. *Br J Dermatol* 2017;177(4):888–89. doi:10.1111/bjd.15826.  
19  
20 442 24 Sterne JA, Higgins JPT, Elbers RG, et al. Risk Of Bias In Non-randomized Studies of  
21  
22 443 Interventions (ROBINS-I): detailed guidance, updated 20 October 2016. 2016. Available  
23  
24 444 at: <http://www.riskofbias.info>.  
26  
27 445 25 Felson DT. Bias in meta-analytic research. *J Clin Epidemiol* 1992;45(8):885–92.  
28  
29 446 doi:10.1016/0895-4356(92)90072-U.  
31  
32 447 26 Sterne JA, Harbord RM. Funnel plots in meta-analysis. *Stata J* 2004;4(2):127–41.  
33  
34 448 27 Mathes T, Klaben P, Pieper D. Frequency of data extraction errors and methods to  
35  
36 449 increase data extraction quality: a methodological review. *BMC Med Res Methodol*  
37  
38 450 2017;17(1):152. doi:10.1186/s12874-017-0431-4.  
39  
40 451 28 Buscemi N, Hartling L, Vandermeer B, et al. Single data extraction generated more  
41  
42 452 errors than double data extraction in systematic reviews. *J Clin Epidemiol*  
43  
44 453 2006;59(7):697–703. doi:10.1016/j.jclinepi.2005.11.010.  
45  
46 454 29 Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings:  
47  
48 455 an updated review of related biases. *Health Technol Assess* 2010;14(8):iii, ix-xi, 1-193.  
49  
50 456 doi:10.3310/hta14080.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 457 30 Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of physical  
4  
5 458 activities: a second update of codes and MET values. *Med Sci Sports Exerc*  
6  
7 459 2011;43(8):1575–81. doi:10.1249/MSS.0b013e31821ece12.  
8  
9  
10 460 31 Haskell WL, Lee I, Pate RR, et al. Physical activity and public health: updated  
11  
12 461 recommendation for adults from the American College of Sports Medicine and the  
13  
14 462 American Heart Association. *Med Sci Sports Exerc* 2007;39(8):1423–34.  
15  
16 463 doi:10.1249/mss.0b013e3180616b27.  
17  
18  
19  
20 464 32 DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*  
21  
22 465 2015;45(Pt A):139–45. doi:10.1016/j.cct.2015.09.002.  
23  
24  
25 466 33 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-  
26  
27 467 response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135(11):1301–  
28  
29 468 09.  
30  
31  
32  
33 469 34 Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose-response  
34  
35 470 relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*  
36  
37 471 2012;175(1):66–73. doi:10.1093/aje/kwr265.  
38  
39  
40 472 35 Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative  
41  
42 473 variables in epidemiologic studies in a consistent form. *Am J Epidemiol*  
43  
44 474 1996;144(6):610–21.  
45  
46  
47 475 36 Aune D, Greenwood DC, Chan DSM, et al. Body mass index, abdominal fatness and  
48  
49 476 pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis  
50  
51 477 of prospective studies. *Ann Oncol* 2012;23(4):843–52. doi:10.1093/annonc/mdr398.  
52  
53  
54  
55 478 37 Borenstein M, Higgins JPT, Hedges LV, et al. Basics of meta-analysis:  $I^2$  is not an  
56  
57 479 absolute measure of heterogeneity. *Res Synth Methods* 2017;8(1):5–18.  
58  
59 480 doi:10.1002/jrsm.1230.  
60

- 1  
2  
3 481 38 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a  
4  
5 482 simple, graphical test. *BMJ* 1997;315(7109):629–634.  
6  
7  
8 483 39 Shiroma EJ, Lee I. Can we proceed with physical activity recommendations if (almost)  
9  
10 484 no clinical trial data exist on mortality? *Br J Sports Med* 2018;52(14):888–89.  
11  
12 485 doi:10.1136/bjsports-2018-099185.  
13  
14  
15 486 40 Wade KH, Richmond RC, Davey Smith G. Physical activity and longevity: how to move  
16  
17 487 closer to causal inference. *Br J Sports Med* 2018;52(14):890–91. doi:10.1136/bjsports-  
18  
19 488 2017-098995.  
20  
21  
22  
23 489 41 O'Donovan G, Blazeovich AJ, Boreham C, et al. The ABC of Physical Activity for  
24  
25 490 Health: a consensus statement from the British Association of Sport and Exercise  
26  
27 491 Sciences. *J Sports Sci* 2010;28(6):573–91. doi:10.1080/02640411003671212.  
28  
29  
30 492 42 Hill AB. The environment and disease: association or causation? *Proc R Soc Med*  
31  
32 493 1965;58:295–300.  
33  
34  
35 494 43 Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or  
36  
37 495 even eliminate, the detrimental association of sitting time with mortality? A harmonised  
38  
39 496 meta-analysis of data from more than 1 million men and women. *The Lancet*  
40  
41 497 2016;388(10051):1302–10. doi:10.1016/S0140-6736(16)30370-1.  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

#### Footnotes

#### Author's contributions

WG had the initial idea for this review; he is the guarantor of the study. WG, EM, SS, LM, AR and KP designed the study, including the development of the selection criteria, the risk of bias assessment strategy, the search strategy and the data extraction strategy. KB and LJ will monitor the screening process. AR, EM and LM will retrieve the data from the studies qualified for inclusion. SS will conduct the meta-analysis. EM, WG and SS prepared the draft

1  
2  
3 506 of this study protocol. All authors contributed substantially to the drafting of the paper and its  
4  
5 507 revisions. All authors have read and approved the final manuscript.  
6  
7 508

#### 8 509 **Funding statement**

10 510 This research received no specific grant from any funding agency in the public, commercial or  
11  
12 511 not-for-profit sectors.  
13  
14 512

#### 15 513 **Competing interests**

16  
17 514 The authors declare no conflict of interests.  
18  
19 515

#### 20 516 **Provenance and peer review**

22 517 This research was not commissioned and was externally peer reviewed.  
23  
24 518

#### 25 519 **Data sharing statement**

27 520 Data (including the extracted contents from the searched articles) are available upon  
28  
29 521 reasonable request from Dr. Wolfgang Geidl; mail: wolfgang.geidl@fau.de  
30  
31 522  
32  
33 523  
34 524  
35  
36 525  
37  
38 526  
39  
40 527  
41  
42 528  
43 529  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## Supplementary File 1: Completed PRISMA-P 2015 Checklist

### PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\*

Section and topic	Item No	Checklist item	(Page No.#)
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6 and Additional file

## Supplementary File 1: Completed PRISMA-P 2015 Checklist

			2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

## Supplementary File 2: Literature search strategy

### Dose-response relationship of physical activity and mortality in people with noncommunicable diseases. Study protocol for a systematic review and meta-analysis of cohort studies

Search strategy according to PICO framework:

#### Population

##### Indication specific keywords

###### *Breast cancer*

- #1 “breast neoplasm” [MeSH Terms]
- #2 “breast tumor”
- #3 “breast carcinoma”
- #4 “human mammary neoplasm”
- #5 “breast cancer”
- #6 “mammary cancer”
- #7 “breast malignant neoplasm”
- #8 “breast malignant tumor”
- #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

###### *Type 2 diabetes mellitus*

- #10 “diabetes mellitus, type 2” [MeSH Terms]
- #11 “noninsulin dependent diabetes mellitus”
- #12 “ketosis resistant diabetes mellitus”
- #13 “stable diabetes mellitus”
- #14 “type 2 diabetes mellitus”
- #15 “NIDDM”
- #16 “maturity onset diabetes mellitus”
- #17 “slow onset diabetes mellitus”
- #18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

###### *Chronic Obstructive Pulmonary Disease*

- #19 “COPD” [MeSH Terms]
- #20 “pulmonary disease, chronic obstructive” [MeSH Terms]
- #21 “COAD”
- #22 “chronic obstructive airway disease”
- #23 “chronic obstructive lung disease”
- #24 “chronic airflow obstruction”
- #25 #19 OR #20 OR #21 OR #22 OR #23 OR #24

###### *Ischemic heart disease*

- #26 “myocardial ischemia” [MeSH Terms]
- #27 “coronary artery disease” [MeSH Terms]
- #28 “myocardial infarction” [MeSH Terms]
- #29 “myocardial ischemia”
- #30 “coronary artery disease”

- 1  
2  
3 #31 “myocardial infarction”  
4 #32 #26 OR #27 OR #28 OR #29 OR #30 OR #31  
5

6  
7 ***Major depressive disorder***

- 8 #33 “depression” [MeSH Terms]  
9 #34 “depressive disorder, major” [MeSH Terms]  
10 #35 “depressive disorder”  
11 #36 “depressive symptoms”  
12 #37 “emotional depression”  
13 #38 #33 OR #34 OR #35 OR #36 OR #37  
14  
15

16  
17 ***Low back pain***

- 18 #39 “low back pain” [MeSH Terms]  
19 #40 “lumbago”  
20 #41 “low backache”  
21 #42 #39 OR #40 OR #41  
22  
23

24  
25 ***Stroke***

- 26 #43 “stroke” [MeSH Terms]  
27 #44 “cerebrovascular accident”  
28 #45 “CVA”  
29 #46 “apoplexy”  
30 #47 “brain vascular accident”  
31 #48 #43 OR #44 OR #45 OR #46 OR #47  
32  
33

34  
35 ***Osteoarthritis***

- 36 #49 “osteoarthritis” [MeSH Terms]  
37 #50 “osteoarthrosis”  
38 #51 “osteoarthritides”  
39 #52 “arthritis degenerative”  
40 #53 #49 OR #50 OR #51 OR #52  
41  
42

43  
44 ***Lung cancer***

- 45 #54 “lung neoplasm” [MeSH Terms]  
46 #55 “pulmonary neoplasm”  
47 #56 “lung cancer”  
48 #57 “pulmonary cancer”  
49 #58 #54 OR #55 OR #56 OR #57  
50  
51

52 **Intervention (Exposure)**

- 53 #59 “human activities” [MeSH Terms]  
54 #60 “motor activities” [MeSH Terms]  
55 #61 “leisure activities” [MeSH Terms]  
56 #62 “exercises” [MeSH Terms]  
57 #63 “running” [MeSH Terms]  
58 #64 “walking” [MeSH Terms]  
59 #65 “bicycling” [MeSH Terms]  
60

- 1  
2  
3 #66 “gardening” [MeSH Terms]  
4 #67 “sports” [MeSH Terms]  
5 #68 “activities of daily living” [MeSH Terms]  
6 #69 “human activity”  
7 #70 “motor activity”  
8 #71 “leisure activity”  
9 #72 “exercise”  
10 #73 “sport”  
11 #74 “physical activity”  
12 #74 “physical activities”  
13 #75 “nonexercise activity”  
14 #76 “nonexercise activities”  
15 #77 “energy expenditure”  
16 #78 “caloric expenditure”  
17 #79 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR  
18 #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78  
19  
20  
21

22  
23 **Comparator**

24 None.

25  
26 **Outcome**

- 27  
28 #79 “mortality” [MeSH Terms]  
29 #80 “death”  
30 #81 “survival”  
31 #82 “life expectancy”  
32 #83 “years of life lost”  
33 #84 #79 OR #80 OR #81 OR #82 OR #83  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Years covered by search:** All years, no time restriction.

**Language:** English

**Study design filter:** No restriction.

#### PubMed search example for the Chronic Obstructive Coronary Disease:

**1#** (("COPD" OR "pulmonary disease, chronic obstructive"[MeSH Terms]) OR ("COPD"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR "COAD"[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract] OR "chronic obstructive lung disease"[Title/Abstract] OR "chronic airflow obstruction"[Title/Abstract]))

**2#** (("human activities" OR "motor activities" OR "leisure activities" OR "exercises" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sports" OR "activities of daily living"[MeSH Terms]) OR ("human activities"[Title/Abstract] OR "human activity"[Title/Abstract] OR "motor activity"[Title/Abstract] OR "motor activities"[Title/Abstract] OR "leisure activities"[Title/Abstract] OR "leisure activity"[Title/Abstract] OR "exercise"[Title/Abstract] OR "exercises"[Title/Abstract] OR "running"[Title/Abstract] OR "walking"[Title/Abstract] OR "bicycling"[Title/Abstract] OR "gardening"[Title/Abstract] OR "sports"[Title/Abstract] OR "sport"[Title/Abstract] OR "activities of daily living"[Title/Abstract] OR "physical activity"[Title/Abstract] OR "physical activities"[Title/Abstract] OR "nonexercise activity"[Title/Abstract] OR "nonexercise activities"[Title/Abstract] OR "energy expenditure"[Title/Abstract] OR "caloric expenditure"[Title/Abstract]))

**3#** (("mortality" [Title/Abstract] OR "death" [Title/Abstract] OR "survival" [Title/Abstract] OR "life expectancy" [Title/Abstract] OR "years of life lost"[Title/Abstract]) OR "mortality"[MeSH Terms])

**1# AND 2# AND 3#**

#### Scopus search example for the Chronic Obstructive Coronary Disease:

**1#** (TITLE-ABS ( "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure"))

**2#** (TITLE-ABS ( "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost"))

**3#** (TITLE-ABS ( "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction"))

**1# AND 2# AND 3#**

**Web of Science search example for the Chronic Obstructive Coronary Disease:**

**1#** "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction" **TOPIC**

**2#** "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction" **TITLE**

**3#** "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure" **TOPIC**

**4#** "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure" **TITLE**

**5#** "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost" **TOPIC**

**6#** "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost" **TITLE**

**1# OR 2# AND 3# OR 4# AND 5# OR 6#**

# Data extraction form

## No. Data items

- 1 Study id
- 2 Result number
- 3 First author
- 4 Year
- 5 Country
- 6 Sex
- 7 Age
- 8 Study design
- 9 Name of study
- 10 Follow\_up
- 11 N\_participants
- 12 Diagnosis/Breast Cancer verification
- 13 Mortality\_data\_ascertainment
- 14 N\_cases
- 15 PA assessment
- 16 Domain of PA
- 17 Exposure
- 18 Case\_per\_cat
- 19 Noncases\_per\_cat
- 20 Exposure\_cat
- 21 Risk ratio
- 22 RR\_lower confidence interval
- 23 RR\_upper confidence interval
- 24 Exposure\_dose
- 25 RR dose
- 26 RR\_dose\_lower confidence interval
- 27 RR\_dose\_upper confidence interval
- 28 RR\_other model
- 29 Quality\_score



# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028653.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Aug-2019
Complete List of Authors:	Geidl, Wolfgang; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Schlesinger, Sabrina; German Diabetes Center Düsseldorf (DZZ) Mino, Eriselda; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Miranda, Lorena; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Ryan, Anna; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Bartsch, Katja; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Janz, Lukas; Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Sport Science and Sport Pfeifer, Klaus; Friedrich-Alexander Universität Erlangen-Nürnberg, Department of Sport Science and Sport
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Global health, Public health, Sports and exercise medicine
Keywords:	Physical activity, Systematic review, Meta-analysis, Mortality, Noncommunicable diseases, Exercise

SCHOLARONE™  
Manuscripts

1  
2  
3 1 **Title page**  
4  
5 2

6  
7 3 **The dose–response relationship between physical activity and mortality in people with**  
8  
9 4 **noncommunicable diseases: A study protocol for the systematic review and meta-analysis of**  
10  
11 5 **cohort studies**  
12 6

13  
14 7 **Corresponding author:** Dr. Wolfgang Geidl, Department of Sport Science and Sport (DSS),  
15 8 Friedrich-Alexander University Erlangen-Nürnberg (FAU), Gebbertstraße 123b, 91058  
16 9 Erlangen (Germany); Tel.: +49-9131 85-25457, Fax. +49-9131 85-28198, E-mail address:  
17 10 wolfgang.geidl@fau.de  
18  
19  
20  
21  
22

23 12 Wolfgang Geidl<sup>1</sup>, Sabrina Schlesinger<sup>2</sup>, Eriselda Mino<sup>1</sup>, Lorena Miranda<sup>1</sup>, Anna Ryan<sup>1</sup>, Katja  
24 13 Bartsch<sup>1</sup>, Lukas Janz<sup>1</sup>, Klaus Pfeifer<sup>1</sup>  
25  
26  
27 14

28 15 <sup>1</sup> Department of Sport Science and Sport, Division Exercise and Health, Friedrich-Alexander  
29 16 University Erlangen-Nürnberg (FAU), Erlangen, Germany  
30  
31

32 17 <sup>2</sup> German Diabetes Center Düsseldorf (DZZ), Düsseldorf, Germany  
33  
34  
35  
36 18

37 19 **Keywords:** Exercise, Noncommunicable diseases, Mortality, Systematic review, Meta-  
38 20 analysis  
39  
40  
41  
42  
43  
44 21  
45 22  
46 23  
47 24  
48 25  
49 26  
50 27  
51 28  
52 29  
53 30  
54 31  
55 32  
56 33  
57  
58  
59  
60

24 Word count: 3794

## 34 **ABSTRACT**

### 35 **Introduction**

36 This study protocol outlines our planned systematic review and dose–response meta-analysis  
37 of post-diagnosis physical activity and mortality in people with noncommunicable diseases  
38 (NCDs).

### 39 **Methods and analysis**

40 This study is based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis  
41 for Protocols (PRISMA-P). A systematic literature search will be conducted in various  
42 databases – namely, PubMed, Scopus and Web of Science – by two researchers in order to  
43 identify prospective observational studies that investigate post-diagnosis physical activity or  
44 activity-related energy expenditure and mortality in individuals with NCDs. The target  
45 population is adults ( $\geq 18$  years of age) with one of the following nine NCDs: low back pain,  
46 type 2 diabetes mellitus, osteoarthritis, depressive disorder, chronic obstructive pulmonary  
47 disease, breast cancer, lung cancer, stroke or ischemic heart disease. We will focus on all-cause  
48 mortality as the primary outcome and investigate indication-specific mortality as the secondary  
49 outcome. For each study identified as a result of the literature search, we will conduct graphical  
50 dose–response analyses of mortality as a function of activity-related energy consumption. If  
51 more than two studies are available for one disease, we will perform linear and non-linear dose–  
52 response meta-analyses for said disease using random effects models. We will investigate the  
53 heterogeneity of the studies and publication bias. To assess the risk of bias and the quality of  
54 the included studies, we will use the Risk Of Bias In Non-randomised Studies - of Interventions  
55 (ROBINS-I) tool, which is a Cochrane tool.

### 56 **Ethics and dissemination**

57 This systematic review will be conducted in compliance with ethical precepts. As the systematic  
58 review is based on published studies, approval from an ethics committee is not required. The  
59 systematic review and meta-analysis will be published in a peer-reviewed journal.

60 This study is registered in the International Prospective Register for Systematic Reviews  
61 (PROSPERO) registration number: CRD42018103357

### 62 **Strengths and limitations**

- 63 • Our systematic review will be conducted and reported in accordance with the reporting  
64 guidelines provided in the PRISMA-P statement and the reporting guidelines of the  
65 Meta-analysis Of Observational Studies in Epidemiology (MOOSE).

- 66 • The scope of our systematic search is wide-reaching, as it includes nine NCDs and three  
67 extensive medical databases.
- 68 • The study uses the novel ROBINS-I tool.
- 69 • However, the observational cohort studies do not provide a conclusive answer regarding  
70 the causality between physical activity and mortality.

## 72 INTRODUCTION

73 The World Health Organization (WHO) recommends at least 150 minutes of moderate-intensity  
74 physical activity or 75 minutes of vigorous-intensity physical activity per week to enhance  
75 health and reduce mortality.[1] For additional benefits, adults should increase their moderate-  
76 intensity physical activity to 300 minutes or engage in 150 minutes of vigorous-intensity  
77 physical activity per week. These recommendations apply to both healthy adults and adults with  
78 noncommunicable diseases (NCDs) (e.g. ischemic heart disease, breast cancer, chronic  
79 pulmonary disease). However, if one considers the scientific evidence for physical activity and  
80 mortality on which the recommendations are based, an extensive disparity becomes apparent  
81 between healthy populations and those with a pre-existing NCD.

82 The data for healthy adults are comprehensive and unambiguous. Numerous large cohort  
83 studies have consistently demonstrated an inverse relationship between physical activity and  
84 mortality.[2] Arem et al.[3] pooled data from six cohort studies of 661,137 persons. Compared  
85 to individuals who reported having no leisure-time physical activity, premature death decreased  
86 with increased physical activity levels: 7.5 metabolic equivalent tasks (MET) h/wk (Hazard  
87 Ratio (HR) = 0.80; 95% confidence interval (CI); 0.78–0.82); 7.5–15 MET h/wk (HR = 0.69;  
88 0.67–0.70); and 15–22.5 MET h/wk (HR = 0.63; 0.62–0.65). These findings are consistent with  
89 the meta-analysis conducted by Samitz et al.[4] This analysis comprised 80 studies with a total  
90 of 1,338,143 persons. Compared to the lowest activity group, the risk of premature death was  
91 remarkably reduced in the highest activity group (HR = 0.65; 95% CI; 0.60–0.71). Furthermore,  
92 each one-hour increment of moderate-intensity activity per week resulted in a lowered risk ratio  
93 (RR) of 0.96 (95% CI; 0.93–0.98).

94 Accordingly, the updated physical activity guidelines from the US Department of Health and  
95 Human Services[5] include a clear dose–response relationship between the volume of physical  
96 activity and the mortality rates of healthy adults. The shape of the dose–response curve is not  
97 linear but regressive, thus meaning that the greatest difference in mortality rates occurs among  
98 inactive and minimally active individuals. It is clear that benefits can be gained with any amount

1  
2  
3 99 of physical activity. For healthy individuals, current scientific research is sceptical of a  
4  
5 100 minimum dose of physical activity to ensure lifetime extension. Following the minimum  
6  
7 101 recommendations, physical activity is equivalent to energy expenditure of 8.25 MET hours per  
8  
9 102 week. At this level of physical activity, about 70% of the benefits in relation to mortality rates  
10  
11 103 are reached.[6] Higher volumes of physical activity mean that the dose–response curve flattens  
12  
13 104 out. However, roughly five times this dose is also associated with more risk reductions and no  
14  
15 105 adverse effects.

15 106 For individuals with distinct NCDs, the scientific data on the dose–response relationship  
16  
17 107 between physical activity and mortality are considerably weaker. For cancer, the meta-analysis  
18  
19 108 by Li et al.[7] suggests that post-diagnosis physical activity levels may result in similar risk  
20  
21 109 reductions in mortality. Moore et al.[8] pooled data from six cohort studies that comprised  
22  
23 110 654,827 individuals and adjusted their analysis for several confounders, including pre-existing  
24  
25 111 NCDs. In contrast to Li et al.,[7] they conclude that the longevity effects of physical activity  
26  
27 112 vary according to the pre-existing NCD. The current evidence from the US Physical Activity  
28  
29 113 Guidelines Advisory Committee[6] reports a general relationship between higher post-  
30  
31 114 diagnosis physical activity and lower mortality rates in five NCDs (breast cancer, colorectal  
32  
33 115 cancer, prostate cancer, cardiovascular condition of hypertension and type 2 diabetes).  
34  
35 116 However, this report did not demonstrate the dose–response relationships due to the limited  
36  
37 117 information it had regarding the NCDs that were worked on. In addition, the report does not  
38  
39 118 include all NCDs with high levels of morbidity and mortality in Western countries. In Germany,  
40  
41 119 the following NCDs are in the top 10 NCDs with the highest burden of disease: ischemic heart  
42  
43 120 disease, low back pain, lung cancer, breast cancer, stroke, chronic obstructive pulmonary  
44  
45 121 disease (COPD), major depressive disorder and diabetes.[9] The high disease burden of these  
46  
47 122 NCDs refers to the loss of life due to premature death and years spent living with a disability  
48  
49 123 as a result of the disease. For some NCDs, such as low back pain or major depressive disorder,  
50  
51 124 the high burden is mainly caused by a loss of healthy years. However, the data from Plass et  
52  
53 125 al.[9] also show at least a small influence on mortality rates. Overall, it is unclear whether  
54  
55 126 physical activity positively affects mortality rates in individuals with NCDs in the same way  
56  
57 127 that physical activity affects the mortality rates of healthy individuals. Thus, it is clear that the  
58  
59 128 dose–response relationship between physical activity and mortality in adults with an NCD is  
60  
129 not well defined at present.

130

## 131 **Objectives**

132 This study protocol aims to describe the planned systematic review and dose–response meta-  
133 analysis of physical activity and mortality in adults with NCDs. The planned study aims to  
134 define the dose–response relationship between post-diagnosis physical activity and mortality  
135 rates for nine NCDs with a high global burden of disease,[10] especially in Germany.[9] The  
136 nine NCDs are: low back pain, type 2 diabetes mellitus, osteoarthritis, depressive disorder,  
137 COPD, breast cancer, lung cancer, stroke and ischemic heart disease. Our results may inform  
138 updates on national physical activity recommendations for individuals with NCDs.[5, 6] The  
139 planned dose–response analyses may help specify the recommended amount of physical  
140 activity and define a minimum, optimum and maximum dose of physical activity for  
141 individuals with NCD.

## 143 **METHODS**

144 This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-  
145 analysis for Protocols (PRISMA-P, Supplementary File 1).[11] Our systematic review will be  
146 conducted and reported in accordance with the reporting guidelines provided in the PRISMA  
147 statement and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)  
148 reporting guidelines.[12,13] Additionally, the *Methodological Expectations of Cochrane*  
149 *Intervention Reviews* and the *Cochrane Handbook of Systematic Reviews in Interventions* will  
150 be consulted to ensure methodological quality.[14, 15]

151 In view of the recommendations that endorse the pre-registration of systematic reviews, our  
152 protocol was registered with the International Prospective Register of Systematic Reviews  
153 (PROSPERO) on September 5, 2018 (registration number: CRD42018103375; available  
154 online at [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=103357](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=103357)).

## 156 **Eligibility criteria**

157 This study will only include research published in the English language. There are no time  
158 restrictions in relation to the year of publication. We will include studies that investigate the  
159 association between post-diagnosis physical activity levels and mortality among adults with  
160 NCD and report on the effect estimates, including the hazard ratios, relative risks, odds ratios  
161 or absolute mortality rates.[16,12] For this study, post-diagnosis physical activity will be  
162 defined as any form of physical activity, such as leisure-time, occupational, transport-related,  
163 exercise and any physical activity-related energy expenditure measured after diagnosis.

1  
2  
3 164 Physical activity can be measured using subjective methods (e.g. questionnaires) or objective  
4  
5 165 methods (e.g. accelerometry). Physical activity-related energy expenditure can be measured  
6  
7 166 using any kind of objective method (e.g. doubly labelled water).

8  
9 167 Studies will be excluded if they: (1) clearly deal with another topic; (2) include only the total  
10  
11 168 population without information for subgroups with NCDs at the baseline; (3) focus on  
12  
13 169 prevention only (i.e. when they include individuals at risk of developing one of the nine  
14  
15 170 diseases); (4) report insufficient data (i.e. less than three different physical activity levels in  
16  
17 171 MET hours per week) to calculate the dose–response relationship; (5) are duplicate studies  
18  
19 172 that are based on a data set that has already been taken into account.

20  
21 173 Participants: The participants for the study will be comprised of those who are  $\geq 18$  years of  
22  
23 174 age with at least one of the following nine NCDs at the baseline: osteoarthritis, low back pain,  
24  
25 175 depressive disorder, ischemic heart disease, type 2 diabetes mellitus, stroke, COPD, lung  
26  
27 176 cancer or breast cancer. The disease can either be confirmed by a physician or determined by  
28  
29 177 self-reporting. Studies that have children, adolescents and pregnant women as the participants  
30  
31 178 will be excluded, as will studies that focus on animal and cell cultures.

32  
33 179 Outcomes: The outcomes will be studies that assessed all-cause mortality as the primary  
34  
35 180 endpoint or any indication-specific mortality as the primary or secondary endpoint.

36  
37 181 Study design: Prospective observational studies, including cohort, nested case-control, case-  
38  
39 182 cohort studies and follow-up studies of randomised controlled studies published in a peer-  
40  
41 183 reviewed journal will be included. We will exclude cross-sectional, case only or case-control  
42  
43 184 studies, conference abstracts, comments, letters and reviews.

44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### 185 186 **Information sources**

187 Two researchers will search the following electronic databases: MEDLINE (PubMed),  
188 Scopus and the Web of Science Core Collection (Web of Science). All years will be covered.  
189 The reference list from the systematic reviews and meta-analyses will be manually searched  
190 to locate further results. Additionally, one researcher will use the Google Scholar forward  
191 citation search for all eligible articles identified via the database search.

192

### 193 **Search strategy**

194 The search strategy was developed with the support of a specialist from the University  
195 Library. The search is structured according to three main categories of the Population,  
196 Intervention, Comparison, Outcome (PICO) concept. The population is one of the nine NCDs;  
197 the intervention is the physical activity; the outcome is mortality; and control, as the fourth

1  
2  
3 198 category of PICO, does not play a role in the cohort studies we sought out.[17] We defined  
4  
5 199 the search terms for the three PICO categories; these terms included keywords and related  
6  
7 200 synonyms, abbreviations, spelling variations and controlled vocabulary, each separated by  
8  
9 201 Boolean operator OR. The search terms for the three PICO categories will be combined with  
10  
11 202 Boolean operator AND. The search will be restricted to the search fields of the title and the  
12  
13 203 abstract. Independent searches will be conducted for the nine NCDs under consideration. The  
14  
15 204 search is adapted to the special features of the three databases (e.g. the use of medical subject  
16  
17 205 heading terms in PubMed). It should be noted that the search is not filtered for observational  
18  
19 206 studies, as reference lists of systematic reviews and meta-analyses are eligible for additional  
20  
21 207 manual searching. The concrete search terms used can be found in Supplementary File 2.  
22  
23 208

### 209 **Data management**

24 210 The search results will be imported to the reference management and knowledge organisation  
25  
26 211 software, Citavi Version 5 (Swiss Academic Software, Wädenswil, Switzerland). We will use  
27  
28 212 separate project folders for each of the nine NCDs. These folders will be organised  
29  
30 213 hierarchically in categories, based on the various inclusion and exclusion filters.  
31  
32 214

### 32 215 **Selection of eligible studies**

34 216 First, one researcher will screen each article's title and abstract against the eligibility criteria  
35  
36 217 to identify all relevant studies. Then, a second researcher will perform the same screening task  
37  
38 218 to ensure that no studies were overlooked or incorrectly included. This procedure will have a  
39  
40 219 positive effect on the accuracy and reliability of the screening process.[18] Moreover,  
41  
42 220 increasing the number of contributors in this critical point of the systematic review enables  
43  
44 221 the improved timeliness and efficiency of the process.[19] If the screening process of the title  
45  
46 222 and abstract does not lead to a clear result, the article will be retrieved for full-text screening.  
47  
48 223

### 48 224 **Data extraction**

50 225 Data of the full texts will be independently extracted by two reviewers using an Excel table  
51  
52 226 (Supplementary File 3). This table has been pilot-tested with a number of eligible articles  
53  
54 227 from four reviewers (AR, EM, LM, WG). The ensuing discussion secured a mutual  
55  
56 228 understanding of the variables, the standardisation of the Excel data mask and a uniform  
57  
58 229 system of data extraction. The results of the double data extraction will be checked for  
59  
60 230 consistency. Any disagreements will be openly discussed by the three reviewers. Multiple



1  
2  
3 231 publications with the same or very similar content will only be considered once; duplicates  
4  
5 232 with smaller sample sizes and shorter follow-up durations will be excluded.  
6  
7 233

#### 8 234 **Data items**

9  
10 235 The information for extraction includes basic details such as the first author, year of  
11  
12 236 publication, study name, design, country where research was undertaken, age and sex of  
13  
14 237 participants and mean follow-up time. Additionally, we will retrieve data regarding the total  
15  
16 238 sample, total all-cause death cases, the number of participants in each physical activity  
17  
18 239 category, death cases per the corresponding category, diagnosis and mortality data  
19  
20 240 ascertainment, exposure to physical activity (e.g. MET h/week, m/day) and any corresponding  
21  
22 241 categories. Finally, RR with 95% CIs will be extracted from fully adjusted models for every  
23  
24 242 physical activity exposure category, as well as for dose-response data, when available.  
25  
26 243

#### 27 244 **Outcomes**

28  
29 245 The primary outcome of this review will be all-cause mortality, defined as the number of  
30  
31 246 deaths over the entire period of follow-up, regardless of the underlying cause of death. As  
32  
33 247 previously discussed, overall mortality is one of the main investigated types of death  
34  
35 248 attributable to a lack of physical activity in persons affected by NCD. The relationship  
36  
37 249 between physical activity and longevity is complex,[20] and during a certain timeframe, death  
38  
39 250 can be caused or affected by multiple factors. Hence, disease-specific standardised death rates  
40  
41 251 can exclude many cases that can blur the identification of a possible causal relation. If all-  
42  
43 252 cause mortality rates are not reported, disease-specific mortality rates will be considered.  
44  
45 253 Thus, the secondary outcomes include indication-specific mortalities such as breast cancer  
46  
47 254 mortality.  
48  
49 255

#### 50 256 **Risk of bias assessment**

51  
52 257 Assessment of bias across the included studies is very important, as the results can affect the  
53  
54 258 variability among single studies and consequently, the meta-analysis.[21] We will use the  
55  
56 259 Cochrane ROBINS-I for assessing bias.[22] This tool pays particular attention to the internal  
57  
58 260 validity of a study by comparing it to a hypothetical randomised controlled trial (RCT). The  
59  
60 261 external validity of the study is not considered in this tool, and any generalisability,  
262 applicability or ethical issues will not affect our judgement.  
263 ROBINS-I is a domain-based method of assessing the risk of bias. Seven domains are  
264 included in total. Confounding factors and selection bias have always been a matter of

1  
2  
3 265 importance in observational study designs, and both of these elements constitute two essential  
4  
5 266 domains of ROBINS-I.[23] The additional domains of ROBINS-I include the classification of  
6  
7 267 interventions, deviations from intended interventions, missing data, measurement of outcomes  
8  
9 268 and selection of the reported results.[24] Through ROBINS-I, systematic appraisal is  
10  
11 269 conducted in three phases:

12 270 Phase 1: The protocol stage focuses on any general forethoughts to be considered prior to  
13  
14 271 appraising each study. This stage specifies the review question, identifies the relevant  
15  
16 272 confounding domains for the included studies and notes possible co-interventions (exposures)  
17  
18 273 that have an impact on study outcomes.

19 274 Phase 2: The second stage is concerned with hypothesising a RCT and elaborating on the  
20  
21 275 confounders and co-interventions for each study.

22 276 Phase 3: The final stage focuses on the actual appraisal in the seven domains that expose the  
23  
24 277 study to the risk of bias. This instrument contains five options to answer the signalling  
25  
26 278 questions – namely, yes, probably yes, no, probably not and no information. In the same  
27  
28 279 manner, the domain-specific judgments are based on five categories – namely, low, moderate,  
29  
30 280 serious, critical risk and no information.

31 281 Each study will be independently rated by two reviewers, and any disagreement will be first  
32  
33 282 noted and then followed by a discussion and consultation with a third group member. The  
34  
35 283 final assessment will result in a table that includes all of the studies along with the domain-  
36  
37 284 specific and overall conclusions reached by the reviewers.  
38

### 39 286 **Meta-biases assessment**

40  
41 287 We are aware of the implication of meta-biases (e.g. sampling, selection and data extraction  
42  
43 288 bias) for the internal validity of this study.[25] To minimise meta-biases, the entire process  
44  
45 289 will follow the suggestions of the above guidelines. Retrieval bias will be minimised with a  
46  
47 290 comprehensive and representative search strategy. If the number of included studies permits  
48  
49 291 this, publication bias will be assessed via funnel plots.[26] To minimise selection bias,  
50  
51 292 inclusion criteria were selected on the basis of a comprehensive discussion. Furthermore, we  
52  
53 293 will employ a double-check screening method against a clearly defined and specific criterion  
54  
55 294 for eligibility. To address extractor biases, we will use a double-check approach of data  
56  
57 295 extraction, which has been proven to improve the extraction process.[27,28] This review is  
58  
59 296 limited to peer-reviewed published literature. A supplementary search for unpublished studies  
60  
297 and literature will not occur, thus meaning that, to a certain extent, this review is susceptible  
298  
to grey literature bias.[29]

299

## 300 **Synthesis of results**

301 First, following the methodological approach of Warburton and Bredin,[2] for each identified  
302 study, we will conduct graphical dose–response analyses of mortality as a function of activity-  
303 related energy consumption. The data regarding the dose of physical activity will be  
304 converted into a single unit (i.e. MET h/week). Only studies that investigate exposure to at  
305 least three different levels of physical activity will be included in the dose–response analysis.  
306 If the physical activity categories are defined without assigning a specific value for energy  
307 expenditure, we will assume the corresponding absolute intensities to be 1.5–3.0 MET for a  
308 low level of physical activity; 3–6 MET for moderate physical activity; and  $\geq 6$  MET for a  
309 high level of physical activity.[30, 31] When studies report the duration of different physical  
310 activities (e.g. 30 minutes of walking, running or cycling), we will calculate the energy  
311 expenditure based on the compendium of physical activities.[30]

312 Second, for each of the nine NCDs, summary RRs with 95% CIs will be calculated when two  
313 or more studies of the same exposure and outcome are available. We will apply random  
314 effects meta-analysis, as described by DerSimonian and Laird.[32] If a study reports on  
315 separate risk estimates for subgroups (e.g. men and women), we will pool the data using a  
316 fixed effect model and include the combined estimate in the overall meta-analysis.

317 Third, indication-specific linear dose-response meta-analyses will be conducted using the  
318 method described by Greenland and Longnecker.[33] In addition, we will investigate the  
319 shape of the association by conducting non-linear dose-response meta-analysis, as described  
320 by Orsini et al.[34]. For this method, the following data for at least three exposure categories  
321 are required: 1) the quantified exposure value (MET h/weeks); 2) the effect estimate with the  
322 corresponding 95% CI; and the number of cases and person-years. If the information  
323 regarding the distribution of cases, person-years or non-cases is missing, data will be  
324 estimated as previously described.[35, 36] The mean amount of exposure between two  
325 endpoints for each physical activity category will be calculated.[2] When the lowest or  
326 highest category is open-ended (e.g.  $< 3$ ), we will multiply the value by 1.25.[4]

327 Heterogeneity will be described by calculating  $\text{Tau}^2$  to assess the between-study variance and  
328 calculating the  $I^2$  statistic to investigate the variability of the observed effects in the meta-  
329 analyses.[37] Possible sources of heterogeneity across the studies will be explored by  
330 conducting subgroup analyses and meta-regressions by accounting for various factors (e.g.  
331 sex, age, geographic location of the studies, follow-up time, assessment of physical activity,  
332 risk of bias of the studies). The small-studies effect (e.g. publication bias) will be investigated

1  
2  
3 333 by conducting visual inspections of the funnel plots and applying Egger's test, at which  $p <$   
4 334 0.1 indicates potential publication bias.[38] Data analyses will be performed using the  
5 335 statistical software Stata (Version 15, StataCorp, College Station, TX, USA). All tests will be  
6  
7  
8 336 two-sided, with statistical significance defined as  $p < 0.05$ .  
9

10 337

### 11 338 **Patient and public involvement**

12 339 As the systematic review will be based on published studies, patient or public involvement is  
13  
14 340 not applicable.  
15

16 341

### 17 342 **Limitations**

18 343 Some potential limitations are to be expected. First, prospective observational cohort studies  
19 344 fail to provide conclusive evidence of a causal relationship between physical activity and  
20 345 mortality.[20, 39-41] Consequently, our review of cohort studies does not provide a  
21 346 conclusive answer as to whether the reported relationships between physical activity and  
22 347 mortality are actually causal or only correlative. According to Hill et al.,[42] however,  
23 348 confidence in a causal relationship increases when (1) a clear dose-response curve, (2) a  
24 349 strong association or a high effect size and (3) consistency of results in different studies are  
25 350 given. These three factors will be examined in our systematic review. Thus, this work can  
26 351 contribute to estimations of the likelihood of the causal influence of physical activity on  
27 352 mortality rates. Second, we will only include studies published in English. Studies published  
28 353 in other languages and grey, unpublished literature will not be included. Third, the wide range  
29 354 of tools available to measure physical activity in terms of their psychometric properties and  
30 355 the domains that they assess may present another challenge. This variability in measurement  
31 356 instruments may present difficulties in generating one single energy metric unit of physical  
32 357 activity, thus questioning the inclusion of all the eligible studies in the dose-response analysis.  
33 358 However, we will consider any form of physical activity by representing it in associated  
34 359 energy consumption units, and we will not consider potential differences between different  
35 360 intensities (i.e. light vs. moderate vs. vigorous) or between physical activity in different  
36 361 contexts (e.g. leisure time physical activity vs. occupational physical activity). Fourth, this  
37 362 study will only consider activity behaviour, not sedentary behaviour, even if there is a clear  
38 363 interaction between physical activity and sedentary behaviour with regard to mortality in  
39 364 healthy individuals.[43]  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 366 **List of abbreviations**

4  
5 367 **NCD:** Noncommunicable Disease

6  
7 368 **WHO:** World Health Organization

8  
9 369 **PRISMA-P:** Preferred Reporting Items for Systematic Reviews and Meta-analysis for  
10  
11 370 Protocols

12  
13 371 **PICO:** Population, Intervention, Control, Outcome

14  
15 372 **MOOSE:** Meta-analysis Of Observational Studies in Epidemiology

16  
17 373 **COPD:** Chronic Obstructive Pulmonary Disease

18  
19 374 **LBP:** Low Back Pain

20  
21 375 **MET:** Metabolic Equivalent Tasks

22  
23 376 **SQ:** Signalling Question

24  
25 377 **RoB:** Risk of Bias

26  
27 378

28  
29 379 **References**

30  
31 380 1 World Health Organization. Global recommendations on physical activity for health.  
32  
33 381 Geneva, Switzerland: World Health Organization 2010.

34  
35 382 2 Warburton D, Bredin S. Health benefits of physical activity: a systematic review of  
36  
37 383 current systematic reviews. *Curr Opin Cardiol* 2017;32(5):541–56.  
38  
39 384 doi:10.1097/HCO.0000000000000437.

40  
41 385 3 Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a  
42  
43 386 detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*  
44  
45 387 2015;175(6):959–67. doi:10.1001/jamainternmed.2015.0533.

46  
47 388 4 Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality:  
48  
49 389 systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol*  
50  
51 390 2011;40(5):1382–400. doi:10.1093/ije/dyr112.

- 1  
2  
3 391 5 U.S. Department of Health and Human Services. Physical activity guidelines for  
4  
5 392 americans, 2nd edition. Washington, DC: U.S.: Department of Health and Human  
6  
7 393 Services 2018.  
8  
9  
10 394 6 2018 Physical Activity Advisory Committee. 2018 Physical activity guidelines advisory  
11  
12 395 committee scientific report. Washington, DC: U.S.: Department of Health and Human  
13  
14 396 Services 2018.  
15  
16  
17 397 7 Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer  
18  
19 398 mortality: findings from 71 prospective cohort studies. *Br J Sports Med* 2016;50(6):339–  
20  
21 399 45. doi:10.1136/bjsports-2015-094927.  
22  
23  
24 400 8 Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to  
25  
26 401 vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*  
27  
28 402 2012;9(11):e1001335. doi:10.1371/journal.pmed.1001335.  
29  
30  
31 403 9 Plass D, Vos T, Hornberg C, et al. Trends in disease burden in Germany: results,  
32  
33 404 implications and limitations of the Global Burden of Disease study. *Dtsch Arztebl Int*  
34  
35 405 2014;111(38):629–38. doi:10.3238/arztebl.2014.0629.  
36  
37  
38 406 10 Murray C, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291  
39  
40 407 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global  
41  
42 408 Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197–223. doi:10.1016/S0140-  
43  
44 409 6736(12)61689-4.  
45  
46  
47 410 11 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review  
48  
49 411 and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.  
50  
51 412 doi:10.1186/2046-4053-4-1.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 413 12 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews  
4  
5 414 and meta-analyses: the PRISMA statement. *BMJ* 2009;339:10.1136/bmj.b2535.  
6  
7 415 doi:10.1371/journal.pmed.1000097.  
8  
9  
10 416 13 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in  
11  
12 417 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in  
13  
14 418 Epidemiology (MOOSE) group. *JAMA* 2000;283(15):2008–12.  
15  
16  
17 419 14 Higgins JPT, Lasserson T, Chandler J, et al. Methodological expectations of cochrane  
18  
19 420 intervention reviews. London: Cochrane 2016.  
20  
21  
22 421 15 Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions  
23  
24 422 cochrane book series: The Cochrane Collaboration 2011.  
25  
26  
27 423 16 Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: a key  
28  
29 424 to evidence-based decisions. *ACP J Club* 1995;123(3):A12-3.  
30  
31  
32 425 17 Schardt C, Adams MB, Owens T, et al. Utilization of the PICO framework to improve  
33  
34 426 searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.  
35  
36 427 doi:10.1186/1472-6947-7-16.  
37  
38  
39 428 18 Edwards P, Clarke M, DiGiuseppi C, et al. Identification of randomized controlled trials  
40  
41 429 in systematic reviews: accuracy and reliability of screening records. *Stat Med*  
42  
43 430 2002;21(11):1635–40. doi:10.1002/sim.1190.  
44  
45  
46 431 19 Ng L, Pitt V, Huckvale K, et al. Title and abstract screening and evaluation in systematic  
47  
48 432 reviews (TASER): a pilot randomised controlled trial of title and abstract screening by  
49  
50 433 medical students. *Syst Rev* 2014;3:121. doi:10.1186/2046-4053-3-121.  
51  
52  
53 434 20 Kujala UM. Is physical activity a cause of longevity? It is not as straightforward as some  
54  
55 435 would believe. A critical analysis. *Br J Sports Med* 2018;52(14):914–18.  
56  
57 436 doi:10.1136/bjsports-2017-098639.  
58  
59  
60

- 1  
2  
3 437 21 Higgins JP, Ramsay C, Reeves BC, et al. Issues relating to study design and risk of bias  
4  
5 438 when including non-randomized studies in systematic reviews on the effects of  
6  
7 439 interventions. *Res Synth Methods* 2013;4(1):12–25. doi:10.1002/jrsm.1056.  
9  
10 440 22 Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in  
11  
12 441 non-randomised studies of interventions. *BMJ*;355:i4919. doi:10.1136/bmj.i4919.  
14  
15 442 23 Garcia-Doval I, van Zuuren EJ, Bath-Hextall F, et al. Systematic reviews: let's keep  
16  
17 443 them trustworthy. *Br J Dermatol* 2017;177(4):888–89. doi:10.1111/bjd.15826.  
19  
20 444 24 Sterne JA, Higgins JPT, Elbers RG, et al. Risk Of Bias In Non-randomized Studies of  
21  
22 445 Interventions (ROBINS-I): detailed guidance, updated 20 October 2016. 2016. Available  
23  
24 446 at: <http://www.riskofbias.info>.  
26  
27 447 25 Felson DT. Bias in meta-analytic research. *J Clin Epidemiol* 1992;45(8):885–92.  
28  
29 448 doi:10.1016/0895-4356(92)90072-U.  
31  
32 449 26 Sterne JA, Harbord RM. Funnel plots in meta-analysis. *Stata J* 2004;4(2):127–41.  
33  
34 450 27 Mathes T, Klaben P, Pieper D. Frequency of data extraction errors and methods to  
35  
36 451 increase data extraction quality: a methodological review. *BMC Med Res Methodol*  
37  
38 452 2017;17(1):152. doi:10.1186/s12874-017-0431-4.  
40  
41 453 28 Buscemi N, Hartling L, Vandermeer B, et al. Single data extraction generated more  
42  
43 454 errors than double data extraction in systematic reviews. *J Clin Epidemiol*  
44  
45 455 2006;59(7):697–703. doi:10.1016/j.jclinepi.2005.11.010.  
47  
48 456 29 Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings:  
49  
50 457 an updated review of related biases. *Health Technol Assess* 2010;14(8):iii, ix-xi, 1-193.  
51  
52 458 doi:10.3310/hta14080.  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 459 30 Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of physical  
4  
5 460 activities: a second update of codes and MET values. *Med Sci Sports Exerc*  
6  
7 461 2011;43(8):1575–81. doi:10.1249/MSS.0b013e31821ece12.
- 8  
9  
10 462 31 Haskell WL, Lee I, Pate RR, et al. Physical activity and public health: updated  
11  
12 463 recommendation for adults from the American College of Sports Medicine and the  
13  
14 464 American Heart Association. *Med Sci Sports Exerc* 2007;39(8):1423–34.  
15  
16 465 doi:10.1249/mss.0b013e3180616b27.
- 17  
18  
19  
20 466 32 DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*  
21  
22 467 2015;45(Pt A):139–45. doi:10.1016/j.cct.2015.09.002.
- 23  
24  
25 468 33 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-  
26  
27 469 response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135(11):1301–  
28  
29 470 09.
- 30  
31  
32  
33 471 34 Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose-response  
34  
35 472 relations: examples, an evaluation of approximations, and software. *Am J Epidemiol*  
36  
37 473 2012;175(1):66–73. doi:10.1093/aje/kwr265.
- 38  
39  
40 474 35 Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative  
41  
42 475 variables in epidemiologic studies in a consistent form. *Am J Epidemiol*  
43  
44 476 1996;144(6):610–21.
- 45  
46  
47 477 36 Aune D, Greenwood DC, Chan DSM, et al. Body mass index, abdominal fatness and  
48  
49 478 pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis  
50  
51 479 of prospective studies. *Ann Oncol* 2012;23(4):843–52. doi:10.1093/annonc/mdr398.
- 52  
53  
54  
55 480 37 Borenstein M, Higgins JPT, Hedges LV, et al. Basics of meta-analysis:  $I^2$  is not an  
56  
57 481 absolute measure of heterogeneity. *Res Synth Methods* 2017;8(1):5–18.  
58  
59 482 doi:10.1002/jrsm.1230.

- 1  
2  
3 483 38 Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a  
4  
5 484 simple, graphical test. *BMJ* 1997;315(7109):629–634.  
6  
7  
8 485 39 Shiroma EJ, Lee I. Can we proceed with physical activity recommendations if (almost)  
9  
10 486 no clinical trial data exist on mortality? *Br J Sports Med* 2018;52(14):888–89.  
11  
12 487 doi:10.1136/bjsports-2018-099185.  
13  
14  
15 488 40 Wade KH, Richmond RC, Davey Smith G. Physical activity and longevity: how to move  
16  
17 489 closer to causal inference. *Br J Sports Med* 2018;52(14):890–91. doi:10.1136/bjsports-  
18  
19 490 2017-098995.  
20  
21  
22  
23 491 41 O'Donovan G, Blazeovich AJ, Boreham C, et al. The ABC of Physical Activity for  
24  
25 492 Health: a consensus statement from the British Association of Sport and Exercise  
26  
27 493 Sciences. *J Sports Sci* 2010;28(6):573–91. doi:10.1080/02640411003671212.  
28  
29  
30 494 42 Hill AB. The environment and disease: association or causation? *Proc R Soc Med*  
31  
32 495 1965;58:295–300.  
33  
34  
35 496 43 Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or  
36  
37 497 even eliminate, the detrimental association of sitting time with mortality? A harmonised  
38  
39 498 meta-analysis of data from more than 1 million men and women. *The Lancet*  
40  
41 499 2016;388(10051):1302–10. doi:10.1016/S0140-6736(16)30370-1.  
42  
43  
44  
45 500

## 501 **Footnotes**

### 502 **Author's contributions**

503 WG had the initial idea for this review; he is the guarantor of the study. WG, EM, SS, LM,  
504 AR and KP designed the study, including the development of the selection criteria, the risk of  
505 bias assessment strategy, the search strategy and the data extraction strategy. KB and LJ will  
506 monitor the screening process. AR, EM and LM will retrieve the data from the studies  
507 qualified for inclusion. SS will conduct the meta-analysis. EM, WG and SS prepared the draft

1  
2  
3 508 of this study protocol. All authors contributed substantially to the drafting of the paper and its  
4  
5 509 revisions. All authors have read and approved the final manuscript.  
6  
7 510

8 511 **Funding statement**

9  
10 512 This research received no specific grant from any funding agency in the public, commercial or  
11  
12 513 not-for-profit sectors.  
13  
14 514

15 515 **Competing interests**

16  
17 516 The authors declare no conflict of interests.  
18  
19 517

20 518 **Provenance and peer review**

21  
22 519 This research was not commissioned and was externally peer reviewed.  
23  
24 520

25 521 **Data sharing statement**

26  
27 522 Data (including the extracted contents from the searched articles) are available upon  
28  
29 523 reasonable request from Dr. Wolfgang Geidl; mail: wolfgang.geidl@fau.de  
30  
31 524

32 525

33 526

34 527

35 528

36 529

37 530

38 531

39

40

41

42

43

44

45

46

47

48

49

50

51

52

## Supplementary File 1: Completed PRISMA-P 2015 Checklist

### PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\*

Section and topic	Item No	Checklist item	(Page No.#)
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6 and Additional file

## Supplementary File 1: Completed PRISMA-P 2015 Checklist

			2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

## Supplementary File 2: Literature search strategy

### Dose-response relationship of physical activity and mortality in people with noncommunicable diseases. Study protocol for a systematic review and meta-analysis of cohort studies

Search strategy according to PICO framework:

#### Population

##### Indication specific keywords

###### *Breast cancer*

- #1 “breast neoplasm” [MeSH Terms]
- #2 “breast tumor”
- #3 “breast carcinoma”
- #4 “human mammary neoplasm”
- #5 “breast cancer”
- #6 “mammary cancer”
- #7 “breast malignant neoplasm”
- #8 “breast malignant tumor”
- #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

###### *Type 2 diabetes mellitus*

- #10 “diabetes mellitus, type 2” [MeSH Terms]
- #11 “noninsulin dependent diabetes mellitus”
- #12 “ketosis resistant diabetes mellitus”
- #13 “stable diabetes mellitus”
- #14 “type 2 diabetes mellitus”
- #15 “NIDDM”
- #16 “maturity onset diabetes mellitus”
- #17 “slow onset diabetes mellitus”
- #18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

###### *Chronic Obstructive Pulmonary Disease*

- #19 “COPD” [MeSH Terms]
- #20 “pulmonary disease, chronic obstructive” [MeSH Terms]
- #21 “COAD”
- #22 “chronic obstructive airway disease”
- #23 “chronic obstructive lung disease”
- #24 “chronic airflow obstruction”
- #25 #19 OR #20 OR #21 OR #22 OR #23 OR #24

###### *Ischemic heart disease*

- #26 “myocardial ischemia” [MeSH Terms]
- #27 “coronary artery disease” [MeSH Terms]
- #28 “myocardial infarction” [MeSH Terms]
- #29 “myocardial ischemia”
- #30 “coronary artery disease”

- 1  
2  
3 #31 “myocardial infarction”  
4 #32 #26 OR #27 OR #28 OR #29 OR #30 OR #31  
5

6  
7 ***Major depressive disorder***

- 8 #33 “depression” [MeSH Terms]  
9 #34 “depressive disorder, major” [MeSH Terms]  
10 #35 “depressive disorder”  
11 #36 “depressive symptoms”  
12 #37 “emotional depression”  
13 #38 #33 OR #34 OR #35 OR #36 OR #37  
14  
15

16  
17 ***Low back pain***

- 18 #39 “low back pain” [MeSH Terms]  
19 #40 “lumbago”  
20 #41 “low backache”  
21 #42 #39 OR #40 OR #41  
22  
23

24  
25 ***Stroke***

- 26 #43 “stroke” [MeSH Terms]  
27 #44 “cerebrovascular accident”  
28 #45 “CVA”  
29 #46 “apoplexy”  
30 #47 “brain vascular accident”  
31 #48 #43 OR #44 OR #45 OR #46 OR #47  
32  
33

34  
35 ***Osteoarthritis***

- 36 #49 “osteoarthritis” [MeSH Terms]  
37 #50 “osteoarthrosis”  
38 #51 “osteoarthritides”  
39 #52 “arthritis degenerative”  
40 #53 #49 OR #50 OR #51 OR #52  
41  
42

43  
44 ***Lung cancer***

- 45 #54 “lung neoplasm” [MeSH Terms]  
46 #55 “pulmonary neoplasm”  
47 #56 “lung cancer”  
48 #57 “pulmonary cancer”  
49 #58 #54 OR #55 OR #56 OR #57  
50  
51

52 **Intervention (Exposure)**

- 53 #59 “human activities” [MeSH Terms]  
54 #60 “motor activities” [MeSH Terms]  
55 #61 “leisure activities” [MeSH Terms]  
56 #62 “exercises” [MeSH Terms]  
57 #63 “running” [MeSH Terms]  
58 #64 “walking” [MeSH Terms]  
59 #65 “bicycling” [MeSH Terms]  
60

- 1  
2  
3 #66 “gardening” [MeSH Terms]  
4 #67 “sports” [MeSH Terms]  
5 #68 “activities of daily living” [MeSH Terms]  
6 #69 “human activity”  
7 #70 “motor activity”  
8 #71 “leisure activity”  
9 #72 “exercise”  
10 #73 “sport”  
11 #74 “physical activity”  
12 #74 “physical activities”  
13 #75 “nonexercise activity”  
14 #76 “nonexercise activities”  
15 #77 “energy expenditure”  
16 #78 “caloric expenditure”  
17 #79 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR  
18 #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78  
19  
20  
21

22  
23 **Comparator**

24 None.

25  
26 **Outcome**

- 27  
28 #79 “mortality” [MeSH Terms]  
29 #80 “death”  
30 #81 “survival”  
31 #82 “life expectancy”  
32 #83 “years of life lost”  
33 #84 #79 OR #80 OR #81 OR #82 OR #83  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



**Years covered by search:** All years, no time restriction.

**Language:** English

**Study design filter:** No restriction.

#### PubMed search example for the Chronic Obstructive Coronary Disease:

**1#** (("COPD" OR "pulmonary disease, chronic obstructive"[MeSH Terms]) OR ("COPD"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR "COAD"[Title/Abstract] OR "chronic obstructive airway disease"[Title/Abstract] OR "chronic obstructive lung disease"[Title/Abstract] OR "chronic airflow obstruction"[Title/Abstract]))

**2#** (("human activities" OR "motor activities" OR "leisure activities" OR "exercises" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sports" OR "activities of daily living"[MeSH Terms]) OR ("human activities"[Title/Abstract] OR "human activity"[Title/Abstract] OR "motor activity"[Title/Abstract] OR "motor activities"[Title/Abstract] OR "leisure activities"[Title/Abstract] OR "leisure activity"[Title/Abstract] OR "exercise"[Title/Abstract] OR "exercises"[Title/Abstract] OR "running"[Title/Abstract] OR "walking"[Title/Abstract] OR "bicycling"[Title/Abstract] OR "gardening"[Title/Abstract] OR "sports"[Title/Abstract] OR "sport"[Title/Abstract] OR "activities of daily living"[Title/Abstract] OR "physical activity"[Title/Abstract] OR "physical activities"[Title/Abstract] OR "nonexercise activity"[Title/Abstract] OR "nonexercise activities"[Title/Abstract] OR "energy expenditure"[Title/Abstract] OR "caloric expenditure"[Title/Abstract]))

**3#** (("mortality" [Title/Abstract] OR "death" [Title/Abstract] OR "survival" [Title/Abstract] OR "life expectancy" [Title/Abstract] OR "years of life lost"[Title/Abstract]) OR "mortality"[MeSH Terms])

**1# AND 2# AND 3#**

#### Scopus search example for the Chronic Obstructive Coronary Disease:

**1#** (TITLE-ABS ( "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure"))

**2#** (TITLE-ABS ( "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost"))

**3#** (TITLE-ABS ( "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction"))

**1# AND 2# AND 3#**

**Web of Science search example for the Chronic Obstructive Coronary Disease:**

**1#** "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction" **TOPIC**

**2#** "COPD" OR "chronic obstructive pulmonary disease" OR "COAD" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "chronic airflow obstruction" **TITLE**

**3#** "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure" **TOPIC**

**4#** "human activit\*" OR "motor activit\*" OR "physical activit\*" OR "leisure activit\*" OR "exercise" OR "running" OR "walking" OR "bicycling" OR "gardening" OR "sport\*" OR "activit\* of daily living" OR "nonexercise activit\*" OR "energy expenditure" OR "caloric expenditure" **TITLE**

**5#** "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost" **TOPIC**

**6#** "mortality" OR "death" OR "survival" OR "life expectancy" OR "years of life lost" **TITLE**

**1# OR 2# AND 3# OR 4# AND 5# OR 6#**

# Data extraction form

## No. Data items

- 1 Study id
- 2 Result number
- 3 First author
- 4 Year
- 5 Country
- 6 Sex
- 7 Age
- 8 Study design
- 9 Name of study
- 10 Follow\_up
- 11 N\_participants
- 12 Diagnosis/Breast Cancer verification
- 13 Mortality\_data\_ascertainment
- 14 N\_cases
- 15 PA assessment
- 16 Domain of PA
- 17 Exposure
- 18 Case\_per\_cat
- 19 Noncases\_per\_cat
- 20 Exposure\_cat
- 21 Risk ratio
- 22 RR\_lower confidence interval
- 23 RR\_upper confidence interval
- 24 Exposure\_dose
- 25 RR dose
- 26 RR\_dose\_lower confidence interval
- 27 RR\_dose\_upper confidence interval
- 28 RR\_other model
- 29 Quality\_score