BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028653
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2018
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Keywords:	Physical activity, Systematic review, Meta-analysis, Mortality, Noncommunicable diseases, Exercise

Title page

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

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Keywords: Exercise, Noncommunicable diseases, Mortality, Systematic review, Meta-analysis

Word count: 3554

ABSTRACT

Introduction

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

Methods and analysis

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

Ethics and dissemination

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

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

Strengths and limitations of this study

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

INTRODUCTION

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

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

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

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

Figure 1. Relationship of moderate-to-vigorous physical activity to all-cause mortality

<< Insert Figure 1 around here >>

For individuals with NCDs, the scientific data on dose-response-relations of physical activity and mortality is considerably weaker. For cancer, the meta-analysis from Li et al.[7] suggests that post-diagnosis physical activity levels may result in similar mortality risk reductions. Moore et al.[8] pooled data from six cohort studies with 654,827 individuals and adjusted their analysis for several confounders including pre-existing NCD. In contrast, they conclude that longevity effects of physical activity vary by pre-existing NCD. The current evidence from the US Physical Activity Guidelines Advisory Committee[6] reported a general relationship between higher post-diagnosis physical activity and lower mortality rates in five NCDs (breast or colorectal or prostate cancer, cardiovascular condition of hypertension, and type 2 diabetes). However, this report could not demonstrate dose-response relationships due to limited information. Overall, it is unclear whether mortality rates in individuals with NCD are affected in the same way as in healthy individuals. The dose-response relation between physical activity and mortality for NCDs is not well defined at present.

Objectives

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

disorder, chronic obstructive pulmonary disease (COPD), breast cancer, lung cancer, stroke, and ischemic heart diseases.

METHODS

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

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

Eligibility criteria

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

Studies will be excluded if they: (1) clearly deal with another topic; (2) include only the total population without information for subgroups with a NCD at baseline; (3) focus on prevention, i.e. when they include individuals at risk for developing one of the nine diseases; (4) report insufficient data to calculate dose-response relations (less than three different physical activity levels in MET hours per week); (5) are duplicate studies that are based on a data set that has already been taken into account.

Participants: Participants ≥ 18 years with at least one of the following nine NCD at baseline: osteoarthritis, low back pain, depressive disorder, ischemic heart disease, type 2 diabetes mellitus, stroke, chronic obstructive pulmonary disease (COPD), lung cancer, and breast cancer. The disease can either be confirmed by a physician or can be determined by self-report. Studies which focused on children, adolescents, and pregnant women will be excluded, as well as animal and cell culture studies.

Outcomes: Studies that assessed all-cause mortality as primary endpoint or any indication-specific mortality as primary or secondary endpoint.

Study design: Prospective observational studies (including cohort, nested case-control, case-cohort studies and follow-up studies of randomized controlled studies) published in a peer-reviewed journal will be included. We will exclude cross-sectional, case only or case-control studies, conference abstracts, comments, letters and reviews.

Information sources

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

Search strategy

The search strategy was developed with the support of a specialist from the University Library. The search is structured according to three main categories of the Population, Intervention, Comparison, Outcome (PICO) concept: population/ problem (one of the nine NCD), intervention (physical activity), and outcome (mortality); control as the fourth category of PICO does not play a role in cohort studies we sought.[17] We defined search terms for the three PICO categories including keywords and related synonyms, abbreviations, spelling variations and controlled vocabulary, each separated by Boolean operator OR. Search terms for the three PICO categories were combined with Boolean operator AND. The search is restricted to the search fields Title and Abstract. We will conduct independent searches for the nine NCD under consideration. The search is adapted to the special features of the three databases, e.g. the use of Medical Subject Headings (MeSH) terms in PubMed. It should be noted that the search is not filtered for observational studies, as reference lists of systematic reviews and meta-analysis are eligible for additional hands on searching. The concrete search terms used as well as their exemplary linking in the NCD COPD can be found in the Supplementary File 2.

Data Management

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

Selection of eligible studies

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

Data extraction

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

Data items

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

risk ratios with their 95% confidence intervals will be extracted from fully adjusted models for every PA exposure category, as well as for dose-response data when available.

Outcomes

The primary outcome of this review will be all-cause mortality, defined as the number of deaths over the entire period of follow up regardless of the underlying cause of death. As previously discussed, overall mortality is among the main investigated types of death attributable to the lack of physical activity in persons affected by NCDs. The relationship between physical activity and longevity is complex[20], and during a certain timeframe death can be caused or affected by multiple factors. Hence, disease-specific standardised death rates can leave out many cases that can blur the identification of a possible causal relation. If all-cause mortality rates are not reported, disease-specific mortality rates will be considered. Therefore, the secondary outcomes include indication-specific mortality, such as breast cancer mortality for breast cancer cohorts.

Risk of bias assessment

Assessment of biases across included studies is very important, as the results can affect the variability among single studies and consequently, the meta-analysis.[21] We will use the Cochrane tool for assessing the "Risk Of Bias In Non-randomised Studies - of Interventions" (ROBINS-I).[22] This tool pays particular attention to internal validity of a study by comparing it to a hypothetical RCT. External validity of the study is not considered in this tool and all generalizability, applicability or any ethical issues will not affect our judgements. ROBINS-I is a seven domain-based approach of assessing risk of bias. The confounding factors and selection bias have always been a matter of importance in observational study designs, and both of them constitute two essential domains of ROBINS-I.[23, 23] Additional domains include classification of interventions; deviations from intended interventions; missing data; measurement of outcomes; and selection of the reported results.[24] The systematic appraisal with ROBINS-I is conducted in three phases:

Phase (1): Protocol stage focuses on general forethoughts to be considered before appraising single studies. Phase one deals with specifying the review question, identifying relevant confounding domains to the included studies, and note possible co-interventions (exposures) that have an impact on study outcomes. Phase (2): The second stage is concerned with hypothesizing a randomised controlled trial and an elaboration of the stage two components (confounders and co-interventions) for each single study. Phase (3): This last stage is

concerned with the actual appraisal in the seven domains that expose the study to the risk of bias. This instrument contains five options to answer the signalling questions (SQ): yes, probably yes, no, probably not, and no information. In the same manner, the domain specific judgments are based on five categories: low, moderate, serious, critical risk and no information.

The single studies will be rated independently by two reviewers, and any disagreement will be first noted and then followed by a discussion and a consultation with a third group member. The final assessment will result in a table including all the single studies along with their domain-specific and overall judgment conclusions.

Meta-biases assessment

We are aware of the implication of meta-biases (e.g., sampling, selection, and data extraction bias) for the internal validity of this study.[25] To minimise meta-biases, the entire process will follow the suggestions from the above guidelines. Retrieval bias will be minimised with a comprehensive and representative search strategy. Publication bias will be assessed via funnel plots.[26] In order to minimise selection bias (inclusion criteria and selector bias), inclusion criteria were selected on the basis of a comprehensive discussion. Furthermore, we employ double-check screening method against a clearly defined and specific criteria for eligibility. To address extractor biases, we will use a double-check data extraction approach, which has been proven to improve the extraction process.[27, 28] This review is limited to peer-reviewed published literature. A supplementary search for unpublished studies and literature does not take place. Thus, this review is to a certain extent susceptible to the grey literature bias.[29]

Data synthesis

For each identified study, we will conduct graphical dose-response analyses of mortality as a function of activity-related energy consumption. The data on the dose of physical activity will all be converted into a single unit, i.e. MET-h/week. Only studies that investigate the exposure to at least three different levels of physical activity will be included in the dose-response analysis. If the physical activity categories are defined without signing a specific value for the energy expenditure (e.g., only the three categories light physical activity, moderate physical activity, and vigorous physical activity) we will assume the corresponding absolute intensities to be 1,5- 3.0 METs for low, 3-6 METs for moderate, and ≥ 6 METs for high physical activity respectively .[30, 31] When studies report the duration of different

physical activities (e.g., 30 minutes of walking, running, or cycling), we will calculate the energy expenditure based on the compendium of physical activities.[30]

Summary risk ratios (RR) with 95% confidence interval (CI) will be calculated when two or more studies on the same exposure and outcome are available. We will apply random effects meta-analysis as described by DerSimonian and Laird.[32] If a study reported on separate risk estimates for subgroups (e.g. men and women), we will pool the data using a fixed effect model and include the combined estimate in the overall meta-analysis.

Linear dose-response meta-analyses will be conducted by using the method as described by Greenland and Longnecker.[33] In addition, we will investigate the shape of the association by conducting non-linear dose-response meta-analysis as described by Orsini et al.[34]. For this method the following data for at least three exposure categories are required: 1) the quantified exposure value (MET-h/weeks), 2) the effect estimate with the corresponding 95 % CI, and 3) the number of cases and person-years. If the information on the distribution of cases, person years or non-cases is missing, data will be estimated as described previously.[35, 36] The mean amount of exposure between two endpoints for each physical activity category will be calculated. [2] When the lowest or highest category is open-ended (example < 3), we will multiply the value by 1,25. [4]

Heterogeneity will be described by calculating tau^2 to assess the between-study variance and I^2 statistic to investigate the variability of the observed effects in the meta-analyses.[37]

Possible sources of heterogeneity across studies will explored by conducting subgroup analyses and meta-regression by accounting for e.g. sex, age, geographic location of the studies, follow-up time, assessment of physical activity, risk of bias of the studies. Small studies effect such as publication bias will be investigated by visual inspections of the funnel plots and by applying Egger's test, whereas a p-value <0.1 indicates potential publication bias.[38] Data analyses will be performed using the statistical software Stata (Version 15, StataCorp, College Station, TX, USA). All tests will be two-sided with statistical significance defined as $p<0.05$.

Patient and public involvement

As the systematic review will be based on published studies, patient or public involvement is not applicable.

CONCLUSION

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

Limitations

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

consider activity behaviour and not sedentary behaviour even if there is a clear interaction between physical activity and sitting with regard to mortality in healthy individuals.[44]

List of abbreviations

NCDs: Noncommunicable Diseases

WHO: World Health Organization

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols

PICO: Population, Intervention, Control, Outcome

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

MECIR: Methodological Expectations of Cochrane Intervention Reviews

COPD: Chronic Obstructive Pulmonary Disease

LBP: Low Back Pain

METs: Metabolic Equivalent Tasks

SQ: Signalling Question

RoB: Risk of Bias

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Footnotes

Author's contributions

WG had the initial idea for this review he is the guarantor. WG, EM, SS, LM and AR designed the study, including the development of the selection criteria, the risk of bias assessment strategy, the search strategy, and data extraction strategy. KB and LL will check up on the process of the screening. 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 of this study protocol. All authors provided substantial contribution to drafting the paper and revising it critically for important intellectual content. All authors have read and approved the final manuscript.

Funding statement

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

Competing interests

The authors declare no conflict of interests.

Provenance and peer review

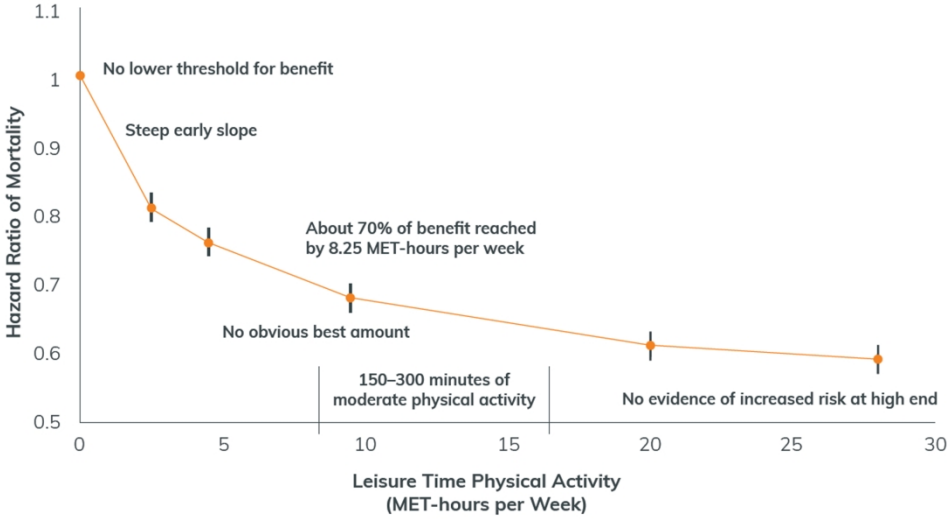
Not commissioned; externally peer reviewed.

Data sharing statement

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

Figures

Legend for Figure 1: 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]



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.#)
ADMINISTRATIVE INFORMATION			
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	
INTRODUCTION			
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
METHODS			
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 τ)	
	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"

#31 “myocardial infarction”
#32 #26 OR #27 OR #28 OR #29 OR #30 OR #31

Major depressive disorder

#33 “depression” [MeSH Terms]
#34 “depressive disorder, major” [MeSH Terms]
#35 “depressive disorder”
#36 “depressive symptoms”
#37 “emotional depression”
#38 #33 OR #34 OR #35 OR #36 OR #37

Low back pain

#39 “low back pain” [MeSH Terms]
#40 “lumbago”
#41 “low backache”
#42 #39 OR #40 OR #41

Stroke

#43 “stroke” [MeSH Terms]
#44 “cerebrovascular accident”
#45 “CVA”
#46 “apoplexy”
#47 “brain vascular accident”
#48 #43 OR #44 OR #45 OR #46 OR #47

Osteoarthritis

#49 “osteoarthritis” " [MeSH Terms]
#50 “osteoarthrosis”
#51 “osteoarthritides”
#52 “arthritis degenerative”
#53 #49 OR #50 OR #51 OR #52

Lung cancer

#54 “lung neoplasm” [MeSH Terms]
#55 “pulmonary neoplasm”
#56 “lung cancer”
#57 “pulmonary cancer”
#58 #54 OR #55 OR #56 OR #57

Intervention (Exposure)

#59 “human activities” [MeSH Terms]
#60 “motor activities” [MeSH Terms]
#61 “leisure activities” [MeSH Terms]
#62 “exercises” [MeSH Terms]
#63 “running” [MeSH Terms]
#64 “walking” [MeSH Terms]
#65 “bicycling” [MeSH Terms]

#66 “gardening” [MeSH Terms]
#67 “sports” [MeSH Terms]
#68 “activities of daily living” [MeSH Terms]
#69 “human activity”
#70 “motor activity”
#71 “leisure activity”
#72 “exercise”
#73 “sport”
#74 “physical activity
#74 “physical activities
#75 “nonexercise activity”
#76 “nonexercise activities”
#77 “energy expenditure”
#78 “caloric expenditure”
#79 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78

Comparator

None.

Outcome

#79 “mortality” [MeSH Terms]
#80 “death”
#81 “survival”
#82 “life expectancy”
#83 “years of life lost”
#84 #79 OR #80 OR #81 OR #82 OR #83

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

Scpous 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:	*BMJ Open*
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-Universitat Erlangen-Nurnberg, Department of Sport Science and Sport Schlesinger, Sabrina; German Diabetes Center Düsseldorf (DZZ) Mino, Eriselda; Friedrich-Alexander-Universitat Erlangen-Nurnberg, Department of Sport Science and Sport Miranda, Lorena; Friedrich-Alexander-Universitat Erlangen-Nurnberg, Department of Sport Science and Sport Ryan, Anna; Friedrich-Alexander-Universitat Erlangen-Nurnberg, Department of Sport Science and Sport Bartsch, Katja; Friedrich-Alexander-Universitat Erlangen-Nurnberg, Department of Sport Science and Sport Janz, Lukas; Friedrich-Alexander-Universitat Erlangen-Nurnberg, Department of Sport Science and Sport Pfeifer, Klaus; Friedrich-Alexander Universität Erlangen-Nürnberg, Department of Sport Science and Sport
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Global health, Public health, Sports and exercise medicine
Keywords:	Physical activity, Systematic review, Meta-analysis, Mortality, Noncommunicable diseases, Exercise

Title page

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

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Keywords: Exercise, Noncommunicable diseases, Mortality, Systematic review, Meta-analysis

Word count: 3767

ABSTRACT

Introduction

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

Methods and analysis

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

Ethics and dissemination

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

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

Strengths and limitations

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

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

INTRODUCTION

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

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

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

of physical activity. For healthy individuals, current scientific research is sceptical of a minimum dose of physical activity to ensure lifetime extension. Following the minimum recommendations, physical activity is equivalent to energy expenditure of 8.25 MET hours per week. At this level of physical activity, about 70% of the benefits in relation to mortality rates are reached.[6] Higher volumes of physical activity mean that the dose–response curve flattens out. However, roughly five times this dose is also associated with more risk reductions and no adverse effects.

For individuals with distinct NCDs, the scientific data on the dose–response relationship between physical activity and mortality are considerably weaker. For cancer, the meta-analysis by Li et al.[7] suggests that post-diagnosis physical activity levels may result in similar risk reductions in mortality. Moore et al.[8] pooled data from six cohort studies that comprised 654,827 individuals and adjusted their analysis for several confounders, including pre-existing NCDs. In contrast to Li et al.,[7] they conclude that the longevity effects of physical activity vary according to the pre-existing NCD. The current evidence from the US Physical Activity Guidelines Advisory Committee[6] reports a general relationship between higher post-diagnosis physical activity and lower mortality rates in five NCDs (breast cancer, colorectal cancer, prostate cancer, cardiovascular condition of hypertension and type 2 diabetes). However, this report did not demonstrate the dose–response relationships due to the limited information it had regarding the NCDs that were worked on. In addition, the report does not include all NCDs with high levels of morbidity and mortality in Western countries. In Germany, the following NCDs are in the top 10 NCDs with the highest burden of disease: ischemic heart disease, low back pain, lung cancer, breast cancer, stroke, chronic obstructive pulmonary disease (COPD), major depressive disorder and diabetes.[9] The high disease burden of these NCDs refers to the loss of life due to premature death and years spent living with a disability as a result of the disease. For some NCDs, such as low back pain or major depressive disorder, the high burden is mainly caused by a loss of healthy years. However, the data from Plass et al.[9] also show at least a small influence on mortality rates. Overall, it is unclear whether physical activity positively affects mortality rates in individuals with NCDs in the same way that physical activity affects the mortality rates of healthy individuals. Thus, it is clear that the dose–response relationship between physical activity and mortality in adults with an NCD is not well defined at present.

Objectives

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

METHODS

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

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

Eligibility criteria

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

Physical activity can be measured using subjective methods (e.g. questionnaires) or objective methods (e.g. accelerometry). Physical activity-related energy expenditure can be measured using any kind of objective method (e.g. doubly labelled water).

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

Participants: The participants for the study will be comprised of those who are ≥ 18 years of age with at least one of the following nine NCDs at the baseline: osteoarthritis, low back pain, depressive disorder, ischemic heart disease, type 2 diabetes mellitus, stroke, COPD, lung cancer or breast cancer. The disease can either be confirmed by a physician or determined by self-reporting. Studies that have children, adolescents and pregnant women as the participants will be excluded, as will studies that focus on animal and cell cultures.

Outcomes: The outcomes will be studies that assessed all-cause mortality as the primary endpoint or any indication-specific mortality as the primary or secondary endpoint.

Study design: Prospective observational studies, including cohort, nested case-control, case-cohort studies and follow-up studies of randomised controlled studies published in a peer-reviewed journal will be included. We will exclude cross-sectional, case only or case-control studies, conference abstracts, comments, letters and reviews.

Information sources

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

Search strategy

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

synonyms, abbreviations, spelling variations and controlled vocabulary, each separated by Boolean operator OR. The search terms for the three PICO categories will be combined with Boolean operator AND. The search will be restricted to the search fields of the title and the abstract. Independent searches will be conducted for the nine NCDs under consideration. The search is adapted to the special features of the three databases (e.g. the use of medical subject heading terms in PubMed). It should be noted that the search is not filtered for observational studies, as reference lists of systematic reviews and meta-analyses are eligible for additional manual searching. The concrete search terms used can be found in Supplementary File 2.

Data management

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

Selection of eligible studies

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

Data extraction

Data of the full texts will be independently extracted by two reviewers using an Excel table (Supplementary File 3). This table has been pilot-tested with a number of eligible articles from four reviewers (AR, EM, LM, WG). The ensuing discussion secured a mutual understanding of the variables, the standardisation of the Excel data mask and a uniform system of data extraction. The results of the double data extraction will be checked for consistency. Any disagreements will be openly discussed by the three reviewers. Multiple publications with the same or very similar content will only be considered once; duplicates with smaller sample sizes and shorter follow-up durations will be excluded.

Data items

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

Outcomes

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

Risk of bias assessment

Assessment of bias across the included studies is very important, as the results can affect the variability among single studies and consequently, the meta-analysis.[21] We will use the Cochrane ROBINS-I for assessing bias.[22] This tool pays particular attention to the internal validity of a study by comparing it to a hypothetical randomised controlled trial (RCT). The external validity of the study is not considered in this tool, and any generalisability, applicability or ethical issues will not affect our judgement.

ROBINS-I is a domain-based method of assessing the risk of bias. Seven domains are included in total. Confounding factors and selection bias have always been a matter of importance in observational study designs, and both of these elements constitute two essential domains of ROBINS-I.[23] The additional domains of ROBINS-I include the classification of interventions, deviations from intended interventions, missing data, measurement of outcomes

and selection of the reported results.[24] Through ROBINS-I, systematic appraisal is conducted in three phases:

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

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

Phase 3: The final stage focuses on the actual appraisal in the seven domains that expose the study to the risk of bias. This instrument contains five options to answer the signalling questions – namely, yes, probably yes, no, probably not and no information. In the same manner, the domain-specific judgments are based on five categories – namely, low, moderate, serious, critical risk and no information.

Each study will be independently rated by two reviewers, and any disagreement will be first noted and then followed by a discussion and consultation with a third group member. The final assessment will result in a table that includes all of the studies along with the domain-specific and overall conclusions reached by the reviewers.

Meta-biases assessment

We are aware of the implication of meta-biases (e.g. sampling, selection and data extraction bias) for the internal validity of this study.[25] To minimise meta-biases, the entire process will follow the suggestions of the above guidelines. Retrieval bias will be minimised with a comprehensive and representative search strategy. If the number of included studies permits this, publication bias will be assessed via funnel plots.[26] To minimise selection bias, inclusion criteria were selected on the basis of a comprehensive discussion. Furthermore, we will employ a double-check screening method against a clearly defined and specific criterion for eligibility. To address extractor biases, we will use a double-check approach of data extraction, which has been proven to improve the extraction process.[27,28] This review is limited to peer-reviewed published literature. A supplementary search for unpublished studies and literature will not occur, thus meaning that, to a certain extent, this review is susceptible to grey literature bias.[29]

Synthesis of results

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

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

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

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

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

Patient and public involvement

As the systematic review will be based on published studies, patient or public involvement is not applicable.

Limitations

Some potential limitations are to be expected. First, prospective observational cohort studies fail to provide conclusive evidence of a causal relationship between physical activity and mortality.[20, 39-41] Consequently, our review of cohort studies does not provide a conclusive answer as to whether the reported relationships between physical activity and mortality are actually causal or only correlative. According to Hill et al.,[42] however, confidence in a causal relationship increases when (1) a clear dose-response curve, (2) a strong association or a high effect size and (3) consistency of results in different studies are given. These three factors will be examined in our systematic review. Thus, this work can contribute to estimations of the likelihood of the causal influence of physical activity on mortality rates. Second, we will only include studies published in English. Studies published in other languages and grey, unpublished literature will not be included. Third, the wide range of tools available to measure physical activity in terms of their psychometric properties and the domains that they assess may present another challenge. This variability in measurement instruments may present difficulties in generating one single energy metric unit of physical activity, thus questioning the inclusion of all the eligible studies in the dose-response analysis. However, we will consider any form of physical activity by representing it in associated energy consumption units, and we will not consider potential differences between different intensities (i.e. light vs. moderate vs. vigorous) or between physical activity in different contexts (e.g. leisure time physical activity vs. occupational physical activity). Fourth, this study will only consider activity behaviour, not sedentary behaviour, even if there is a clear interaction between physical activity and sedentary behaviour with regard to mortality in healthy individuals.[43]

List of abbreviations

NCD: Noncommunicable Disease

WHO: World Health Organization

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols

PICO: Population, Intervention, Control, Outcome

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

COPD: Chronic Obstructive Pulmonary Disease

LBP: Low Back Pain

MET: Metabolic Equivalent Tasks

SQ: Signalling Question

RoB: Risk of Bias

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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

of this study protocol. All authors contributed substantially to the drafting of the paper and its revisions. All authors have read and approved the final manuscript.

Funding statement

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

Competing interests

The authors declare no conflict of interests.

Provenance and peer review

This research was not commissioned and was externally peer reviewed.

Data sharing statement

Data (including the extracted contents from the searched articles) are available upon reasonable request from Dr. Wolfgang Geidl; mail: wolfgang.geidl@fau.de

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.#)
ADMINISTRATIVE INFORMATION			
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	
INTRODUCTION			
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
METHODS			
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 τ)	
	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"

#31 “myocardial infarction”
#32 #26 OR #27 OR #28 OR #29 OR #30 OR #31

Major depressive disorder

#33 “depression” [MeSH Terms]
#34 “depressive disorder, major” [MeSH Terms]
#35 “depressive disorder”
#36 “depressive symptoms”
#37 “emotional depression”
#38 #33 OR #34 OR #35 OR #36 OR #37

Low back pain

#39 “low back pain” [MeSH Terms]
#40 “lumbago”
#41 “low backache”
#42 #39 OR #40 OR #41

Stroke

#43 “stroke” [MeSH Terms]
#44 “cerebrovascular accident”
#45 “CVA”
#46 “apoplexy”
#47 “brain vascular accident”
#48 #43 OR #44 OR #45 OR #46 OR #47

Osteoarthritis

#49 “osteoarthritis” " [MeSH Terms]
#50 “osteoarthrosis”
#51 “osteoarthritides”
#52 “arthritis degenerative”
#53 #49 OR #50 OR #51 OR #52

Lung cancer

#54 “lung neoplasm” [MeSH Terms]
#55 “pulmonary neoplasm”
#56 “lung cancer”
#57 “pulmonary cancer”
#58 #54 OR #55 OR #56 OR #57

Intervention (Exposure)

#59 “human activities” [MeSH Terms]
#60 “motor activities” [MeSH Terms]
#61 “leisure activities” [MeSH Terms]
#62 “exercises” [MeSH Terms]
#63 “running” [MeSH Terms]
#64 “walking” [MeSH Terms]
#65 “bicycling” [MeSH Terms]

#66 “gardening” [MeSH Terms]
#67 “sports” [MeSH Terms]
#68 “activities of daily living” [MeSH Terms]
#69 “human activity”
#70 “motor activity”
#71 “leisure activity”
#72 “exercise”
#73 “sport”
#74 “physical activity
#74 “physical activities
#75 “nonexercise activity”
#76 “nonexercise activities”
#77 “energy expenditure”
#78 “caloric expenditure”
#79 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78

Comparator

None.

Outcome

#79 “mortality” [MeSH Terms]
#80 “death”
#81 “survival”
#82 “life expectancy”
#83 “years of life lost”
#84 #79 OR #80 OR #81 OR #82 OR #83

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

Scpous 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:	*BMJ Open*
Manuscript ID	bmjopen-2018-028653.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Aug-2019
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Global health, Public health, Sports and exercise medicine
Keywords:	Physical activity, Systematic review, Meta-analysis, Mortality, Noncommunicable diseases, Exercise

Title page

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

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Keywords: Exercise, Noncommunicable diseases, Mortality, Systematic review, Meta-analysis

Word count: 3794

ABSTRACT

Introduction

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

Methods and analysis

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

Ethics and dissemination

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

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

Strengths and limitations

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

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

INTRODUCTION

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

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

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

of physical activity. For healthy individuals, current scientific research is sceptical of a minimum dose of physical activity to ensure lifetime extension. Following the minimum recommendations, physical activity is equivalent to energy expenditure of 8.25 MET hours per week. At this level of physical activity, about 70% of the benefits in relation to mortality rates are reached.[6] Higher volumes of physical activity mean that the dose–response curve flattens out. However, roughly five times this dose is also associated with more risk reductions and no adverse effects.

For individuals with distinct NCDs, the scientific data on the dose–response relationship between physical activity and mortality are considerably weaker. For cancer, the meta-analysis by Li et al.[7] suggests that post-diagnosis physical activity levels may result in similar risk reductions in mortality. Moore et al.[8] pooled data from six cohort studies that comprised 654,827 individuals and adjusted their analysis for several confounders, including pre-existing NCDs. In contrast to Li et al.,[7] they conclude that the longevity effects of physical activity vary according to the pre-existing NCD. The current evidence from the US Physical Activity Guidelines Advisory Committee[6] reports a general relationship between higher post-diagnosis physical activity and lower mortality rates in five NCDs (breast cancer, colorectal cancer, prostate cancer, cardiovascular condition of hypertension and type 2 diabetes). However, this report did not demonstrate the dose–response relationships due to the limited information it had regarding the NCDs that were worked on. In addition, the report does not include all NCDs with high levels of morbidity and mortality in Western countries. In Germany, the following NCDs are in the top 10 NCDs with the highest burden of disease: ischemic heart disease, low back pain, lung cancer, breast cancer, stroke, chronic obstructive pulmonary disease (COPD), major depressive disorder and diabetes.[9] The high disease burden of these NCDs refers to the loss of life due to premature death and years spent living with a disability as a result of the disease. For some NCDs, such as low back pain or major depressive disorder, the high burden is mainly caused by a loss of healthy years. However, the data from Plass et al.[9] also show at least a small influence on mortality rates. Overall, it is unclear whether physical activity positively affects mortality rates in individuals with NCDs in the same way that physical activity affects the mortality rates of healthy individuals. Thus, it is clear that the dose–response relationship between physical activity and mortality in adults with an NCD is not well defined at present.

Objectives

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

METHODS

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

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

Eligibility criteria

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

Physical activity can be measured using subjective methods (e.g. questionnaires) or objective methods (e.g. accelerometry). Physical activity-related energy expenditure can be measured using any kind of objective method (e.g. doubly labelled water).

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

Participants: The participants for the study will be comprised of those who are ≥ 18 years of age with at least one of the following nine NCDs at the baseline: osteoarthritis, low back pain, depressive disorder, ischemic heart disease, type 2 diabetes mellitus, stroke, COPD, lung cancer or breast cancer. The disease can either be confirmed by a physician or determined by self-reporting. Studies that have children, adolescents and pregnant women as the participants will be excluded, as will studies that focus on animal and cell cultures.

Outcomes: The outcomes will be studies that assessed all-cause mortality as the primary endpoint or any indication-specific mortality as the primary or secondary endpoint.

Study design: Prospective observational studies, including cohort, nested case-control, case-cohort studies and follow-up studies of randomised controlled studies published in a peer-reviewed journal will be included. We will exclude cross-sectional, case only or case-control studies, conference abstracts, comments, letters and reviews.

Information sources

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

Search strategy

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

category of PICO, does not play a role in the cohort studies we sought out.[17] We defined the search terms for the three PICO categories; these terms included keywords and related synonyms, abbreviations, spelling variations and controlled vocabulary, each separated by Boolean operator OR. The search terms for the three PICO categories will be combined with Boolean operator AND. The search will be restricted to the search fields of the title and the abstract. Independent searches will be conducted for the nine NCDs under consideration. The search is adapted to the special features of the three databases (e.g. the use of medical subject heading terms in PubMed). It should be noted that the search is not filtered for observational studies, as reference lists of systematic reviews and meta-analyses are eligible for additional manual searching. The concrete search terms used can be found in Supplementary File 2.

Data management

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

Selection of eligible studies

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

Data extraction

Data of the full texts will be independently extracted by two reviewers using an Excel table (Supplementary File 3). This table has been pilot-tested with a number of eligible articles from four reviewers (AR, EM, LM, WG). The ensuing discussion secured a mutual understanding of the variables, the standardisation of the Excel data mask and a uniform system of data extraction. The results of the double data extraction will be checked for consistency. Any disagreements will be openly discussed by the three reviewers. Multiple

publications with the same or very similar content will only be considered once; duplicates with smaller sample sizes and shorter follow-up durations will be excluded.

Data items

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

Outcomes

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

Risk of bias assessment

Assessment of bias across the included studies is very important, as the results can affect the variability among single studies and consequently, the meta-analysis.[21] We will use the Cochrane ROBINS-I for assessing bias.[22] This tool pays particular attention to the internal validity of a study by comparing it to a hypothetical randomised controlled trial (RCT). The external validity of the study is not considered in this tool, and any generalisability, applicability or ethical issues will not affect our judgement.

ROBINS-I is a domain-based method of assessing the risk of bias. Seven domains are included in total. Confounding factors and selection bias have always been a matter of

importance in observational study designs, and both of these elements constitute two essential domains of ROBINS-I.[23] The additional domains of ROBINS-I include the classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results.[24] Through ROBINS-I, systematic appraisal is conducted in three phases:

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

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

Phase 3: The final stage focuses on the actual appraisal in the seven domains that expose the study to the risk of bias. This instrument contains five options to answer the signalling questions – namely, yes, probably yes, no, probably not and no information. In the same manner, the domain-specific judgments are based on five categories – namely, low, moderate, serious, critical risk and no information.

Each study will be independently rated by two reviewers, and any disagreement will be first noted and then followed by a discussion and consultation with a third group member. The final assessment will result in a table that includes all of the studies along with the domain-specific and overall conclusions reached by the reviewers.

Meta-biases assessment

We are aware of the implication of meta-biases (e.g. sampling, selection and data extraction bias) for the internal validity of this study.[25] To minimise meta-biases, the entire process will follow the suggestions of the above guidelines. Retrieval bias will be minimised with a comprehensive and representative search strategy. If the number of included studies permits this, publication bias will be assessed via funnel plots.[26] To minimise selection bias, inclusion criteria were selected on the basis of a comprehensive discussion. Furthermore, we will employ a double-check screening method against a clearly defined and specific criterion for eligibility. To address extractor biases, we will use a double-check approach of data extraction, which has been proven to improve the extraction process.[27,28] This review is limited to peer-reviewed published literature. A supplementary search for unpublished studies and literature will not occur, thus meaning that, to a certain extent, this review is susceptible to grey literature bias.[29]

Synthesis of results

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

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

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

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

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

Patient and public involvement

As the systematic review will be based on published studies, patient or public involvement is not applicable.

Limitations

Some potential limitations are to be expected. First, prospective observational cohort studies fail to provide conclusive evidence of a causal relationship between physical activity and mortality.[20, 39-41] Consequently, our review of cohort studies does not provide a conclusive answer as to whether the reported relationships between physical activity and mortality are actually causal or only correlative. According to Hill et al.,[42] however, confidence in a causal relationship increases when (1) a clear dose-response curve, (2) a strong association or a high effect size and (3) consistency of results in different studies are given. These three factors will be examined in our systematic review. Thus, this work can contribute to estimations of the likelihood of the causal influence of physical activity on mortality rates. Second, we will only include studies published in English. Studies published in other languages and grey, unpublished literature will not be included. Third, the wide range of tools available to measure physical activity in terms of their psychometric properties and the domains that they assess may present another challenge. This variability in measurement instruments may present difficulties in generating one single energy metric unit of physical activity, thus questioning the inclusion of all the eligible studies in the dose-response analysis. However, we will consider any form of physical activity by representing it in associated energy consumption units, and we will not consider potential differences between different intensities (i.e. light vs. moderate vs. vigorous) or between physical activity in different contexts (e.g. leisure time physical activity vs. occupational physical activity). Fourth, this study will only consider activity behaviour, not sedentary behaviour, even if there is a clear interaction between physical activity and sedentary behaviour with regard to mortality in healthy individuals.[43]

List of abbreviations

NCD: Noncommunicable Disease

WHO: World Health Organization

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols

PICO: Population, Intervention, Control, Outcome

MOOSE: Meta-analysis Of Observational Studies in Epidemiology

COPD: Chronic Obstructive Pulmonary Disease

LBP: Low Back Pain

MET: Metabolic Equivalent Tasks

SQ: Signalling Question

RoB: Risk of Bias

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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

of this study protocol. All authors contributed substantially to the drafting of the paper and its revisions. All authors have read and approved the final manuscript.

Funding statement

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

Competing interests

The authors declare no conflict of interests.

Provenance and peer review

This research was not commissioned and was externally peer reviewed.

Data sharing statement

Data (including the extracted contents from the searched articles) are available upon reasonable request from Dr. Wolfgang Geidl; mail: wolfgang.geidl@fau.de

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.#)
ADMINISTRATIVE INFORMATION			
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	
INTRODUCTION			
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
METHODS			
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 τ)	
	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"

#31 “myocardial infarction”
#32 #26 OR #27 OR #28 OR #29 OR #30 OR #31

Major depressive disorder

#33 “depression” [MeSH Terms]
#34 “depressive disorder, major” [MeSH Terms]
#35 “depressive disorder”
#36 “depressive symptoms”
#37 “emotional depression”
#38 #33 OR #34 OR #35 OR #36 OR #37

Low back pain

#39 “low back pain” [MeSH Terms]
#40 “lumbago”
#41 “low backache”
#42 #39 OR #40 OR #41

Stroke

#43 “stroke” [MeSH Terms]
#44 “cerebrovascular accident”
#45 “CVA”
#46 “apoplexy”
#47 “brain vascular accident”
#48 #43 OR #44 OR #45 OR #46 OR #47

Osteoarthritis

#49 “osteoarthritis” " [MeSH Terms]
#50 “osteoarthrosis”
#51 “osteoarthritides”
#52 “arthritis degenerative”
#53 #49 OR #50 OR #51 OR #52

Lung cancer

#54 “lung neoplasm” [MeSH Terms]
#55 “pulmonary neoplasm”
#56 “lung cancer”
#57 “pulmonary cancer”
#58 #54 OR #55 OR #56 OR #57

Intervention (Exposure)

#59 “human activities” [MeSH Terms]
#60 “motor activities” [MeSH Terms]
#61 “leisure activities” [MeSH Terms]
#62 “exercises” [MeSH Terms]
#63 “running” [MeSH Terms]
#64 “walking” [MeSH Terms]
#65 “bicycling” [MeSH Terms]

#66 “gardening” [MeSH Terms]
#67 “sports” [MeSH Terms]
#68 “activities of daily living” [MeSH Terms]
#69 “human activity”
#70 “motor activity”
#71 “leisure activity”
#72 “exercise”
#73 “sport”
#74 “physical activity
#74 “physical activities
#75 “nonexercise activity”
#76 “nonexercise activities”
#77 “energy expenditure”
#78 “caloric expenditure”
#79 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78

Comparator

None.

Outcome

#79 “mortality” [MeSH Terms]
#80 “death”
#81 “survival”
#82 “life expectancy”
#83 “years of life lost”
#84 #79 OR #80 OR #81 OR #82 OR #83

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

Scpous 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