Evidence Portfolio – Exposure Subcommittee, Question 2

What is the relationship between physical activity and cardiovascular disease mortality?

a. Is there a dose-response relationship? If yes, what is the shape of the relationship?
b. Does the relationship vary by age, sex, race/ethnicity, or socio-economic status?

Sources of Evidence: Existing Systematic Review, Meta-Analyses, and Pooled Analyses

Conclusion Statements and Grades

Strong evidence demonstrates that a strong inverse dose-response relation exists between amount of moderate-to-vigorous physical activity and cardiovascular disease mortality. The strength of the evidence is very unlikely to be modified by more studies of this outcome. **PAGAC Grade: Strong.**

Strong evidence demonstrates that the shape of the curve is nonlinear, with the greatest benefit seen early in the dose-response relationship. The relationship of moderate-to-vigorous physical activity and risk reduction has no lower limit. Risk appears to continue to decrease with increased exposure up to at least three to five times the amounts of moderate-to-vigorous physical activity recommended in the 2008 Guidelines (i.e., 150 minutes per week). The new data are consistent with those used to develop the 2008 Guidelines. **PAGAC Grade: Strong.**

Strong evidence demonstrates that these relationships do not vary by age, sex, race, or weight status. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether these relationships vary by ethnicity or socioeconomic status. **PAGAC Grade: Not assignable.**

Description of the Evidence

An initial search for systematic reviews, meta-analyses, pooled analyses, and reports identified sufficient literature to answer the research question as determined by the Exposure Subcommittee. Additional searches for original research were not needed.

Existing Systematic Reviews, Meta-Analyses, and Pooled Analyses

Overview

A total of 6 existing reviews were included: 1 systematic review,[1] 3 meta-analyses,[2-4] and 2 pooled analyses.[5, 6] The reviews were published from 2008 to 2017.

The systematic review[1] included 121 studies and a timeframe from 1983 to 2013.

The meta-analyses included a range of 16 to 36 studies and covered an extensive timeframe: Ekelund et al,[2] from inception to 2015; Hamer and Chida[3] and Wahid et al[4] from 1970s and 1980s to 2007 and 2014 respectively.

The pooled analyses included data from 11 cohorts, each from different population surveys.[5, 6]

Exposures

The majority of the included reviews examined self-reported physical activity in leisure time. Most reviews assessed physical activity in metabolic equivalent of task (MET) minutes or hours per week. One pooled analysis[6] examined a "weekend warrior" category (meeting the physical activity guidelines in 1 or 2 sessions) in addition to the usual physical activity categories (insufficiently active and regularly active). Two reviews addressed specific types of physical activity: dancing[5] and habitual walking.[3]

Outcomes

All of the included reviews addressed cardiovascular disease mortality and four of them also assessed all-cause mortality in addition to other outcomes.

Populations Analyzed

The table below lists the populations analyzed in each article.

Table 1. Populations Analyzed by All Sources of Evidence

	Sex	Race/ Ethnicity	Age	Weight Status	Chronic Conditions	Other
Ekelund, 2016			Adults			
Hamer, 2008	Female, Male		Adults >20			
Meron, 2016			Adults >40			
Milton, 2014			Adults			
O'Donovan, 2017	Female, Male		Adults >40	Obese	Hypertension status	Smoking status
Wahid, 2016			Adults 19–79			

Supporting Evidence

Existing Systematic Reviews, Meta-Analyses, and Pooled Analyses

Table 2. Existing Systematic Reviews, Meta-Analyses, and Pooled Analyses Individual Evidence Summary Tables

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Ekelund U, Steene-Johannessen J, Brown WJ. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonized meta-analysis of data from more than 1 million men and women. Lancet. 2016;388:1302-1310. doi:10.1016/S0140-6736(16)30370-1.</td></tr>
<tr><td>Purpose: To examine the joint and stratified associations of sedentary behavior and PA with all-cause mortality.</td><td rowspan="4">Abstract: High amounts of sedentary behaviour have been associated with increased risks of several chronic conditions and mortality. However, it is unclear whether physical activity attenuates or even eliminates the detrimental effects of prolonged sitting. We examined the associations of sedentary behaviour and physical activity with all-cause mortality. We did a systematic review, searching six databases (PubMed, PsycINFO, Embase, Web of Science, Sport Discus, and Scopus) from database inception until October, 2015, for prospective cohort studies that had individual level exposure and outcome data, provided data on both daily sitting or TV-viewing time and physical activity, and reported effect estimates for all-cause mortality, cardiovascular disease mortality, or breast, colon, and colorectal cancer mortality. We included data from 16 studies, of which 14 were identified through a systematic review and two were additional unpublished studies where pertinent data were available. All study data were analysed according to a harmonised protocol, which categorised reported daily sitting time and TV-viewing time into four standardised groups each, and physical activity into quartiles (in metabolic equivalent of task [MET]-hours per week). We then combined data across all studies to analyse the association of daily sitting time and physical activity with all-cause mortality, and estimated summary hazard ratios using Cox regression. We repeated these analyses using TV-viewing time instead of daily sitting time. Of the 16 studies included in the meta-analysis, 13 studies provided data on sitting time and all-cause mortality. These studies included 1 005 791 individuals who were followed up for 2-18.1 years, during which 84 609 (8.4%) died. Compared with the referent group (ie, those sitting <4 h/day and in the most active quartile [>35.5 MET-h per week]), mortality rates during follow-up were 12-59% higher in the two lowest quartiles of physical activity (from HR=1.12, 95% CI 1.08-1.16, for the second lowest quartile of physical activity [<16 MET-h per week] and sitting <4 h/day; to HR=1.59, 1.52-1.66, for the lowest quartile of physical activity [<2.5 MET-h per week] and sitting >8 h/day). Daily sitting time was not associated with increased all-cause mortality in those in the most active quartile of physical activity. Compared with the referent (<4 h of sitting per day and highest quartile of physical activity [>35.5 MET-h per week]), there was no increased risk of mortality during follow-up in those who sat for more than 8 h/day but who also reported >35.5 MET-h per week of activity (HR=1.04; 95% CI 0.99-1.10). By contrast, those who sat the least (<4 h/day) and were in the lowest activity quartile (<2.5 MET-h per week) had a significantly increased risk of dying during follow-up (HR=1.27, 95% CI 1.22-1.31). Six studies had data on TV-viewing time (N=465 450; 43 740 deaths). Watching TV for 3 h or more per day was associated with increased mortality regardless of</td></tr>
<tr><td>Timeframe: Inception–2015</td></tr>
<tr><td>Total # of Studies: 16</td></tr>
<tr><td>Exposure Definition: Self-reported leisure time PA and walking was assessed. Participation in moderate and vigorous intensity PA was assessed in metabolic equivalent of task hours per week and categorized into quartiles.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: All-cause, cardiovascular disease, and cancer mortality.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
</table>

	physical activity, except in the most active quartile, where mortality was significantly increased only in people who watched TV for 5 h/day or more (HR=1.16, 1.05-1.28). High levels of moderate intensity physical activity (ie, about 60-75 min per day) seem to eliminate the increased risk of death associated with high sitting time. However, this high activity level attenuates, but does not eliminate the increased risk associated with high TV-viewing time. These results provide further evidence on the benefits of physical activity, particularly in societies where increasing numbers of people have to sit for long hours for work and may also inform future public health recommendations.
Populations Analyzed: Adults	**Author-Stated Funding Source:** No funding source used

Meta-Analysis **Citation:** Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. *Br J Sports Med.* 2008;42(4):238-243.	
Purpose: To quantify the association between walking and the risk of cardiovascular disease (CVD) and all-cause mortality in healthy men and women.	**Abstract:** OBJECTIVE: To quantify the association between walking and the risk of cardiovascular disease (CVD) and all-cause mortality in healthy men and women. DATA SOURCES: Medline, Cochrane Database of Systematic Reviews, and Web of Science databases were searched to May 2007. STUDY SELECTION: Prospective epidemiological studies of walking and CVD and all-cause mortality. RESULTS: 18 prospective studies were included in the overall analysis, which incorporated 459 833 participants free from CVD at baseline with 19 249 cases at follow-up. From the meta-analysis the pooled hazard ratio of CVD in the highest walking category compared with the lowest was 0.69, (95% CI 0.61 to 0.77, p<0.001), and 0.68 (0.59 to 0.78, p<0.001) for all-cause mortality. These effects were robust among men and women, although there was evidence of publication biases for the associations with CVD risk. Walking pace was a stronger independent predictor of overall risk compared with walking volume (48% versus 26% risk reductions, respectively). There was also evidence of a dose-response relationship across the highest, intermediate, and lowest walking categories in relation to the outcome measures. CONCLUSIONS: The results suggest walking is inversely associated with clinical disease endpoints and largely support the current guidelines for physical activity. The mechanisms that mediate this relationship remain largely unknown and should be the focus of future research.
Timeframe: 1970–2007	
Total # of Studies: 18	
Exposure Definition: Walking: measures of habitual walking volume (time/distance) or intensity. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: CVD: fatal and nonfatal, including death from coronary causes, myocardial infarction, angina pectoris, stroke, congestive heart failure, and coronary revascularization procedures. All-cause mortality. **Examine Cardiorespiratory Fitness as Outcome:** No	
Populations Analyzed: Male, Female; Adults >20	**Author-Stated Funding Source:** British Heart Foundation

<table>
<tr><td colspan="2">Pooled Analysis
Citation: Merom D, Ding D, Stamatakis E. Dancing participation and cardiovascular disease mortality: a pooled analysis of 11 population-based British cohorts. Am J Prev Med. 2016;50(6):756-760. doi:10.1016/j.amepre.2016.01.004.</td></tr>
<tr><td>Purpose: To examine whether dance participation offers a greater protection against cardiovascular mortality than walking.

Total # of Studies: 11

Exposure Definition: PA was measured with a validated questionnaire. PA, dancing, and walking were measured in metabolic equivalent of task (MET). Total PA metabolic equivalent of task hours were calculated (MET/hours/week).
Measures Steps: No
Measures Bouts: No
Examines HIIT: No

Outcomes Addressed: Cardiovascular disease mortality.
Examine Cardiorespiratory Fitness as Outcome: No</td><td>Abstract: INTRODUCTION: Little is known about whether cardiovascular benefits vary by activity type. Dance is a multidimensional physical activity of psychosocial nature. The study aimed to examine the association between dancing and cardiovascular disease mortality. METHODS: A cohort study pooled 11 independent population surveys in the United Kingdom from 1995 to 2007, analyzed in 2014. Participants were 48,390 adults aged >/=40 years who were free of cardiovascular disease at baseline and consented to be linked to the National Death Registry. Respondents reported participation in light- or moderate-intensity dancing and walking in the past 4 weeks. Physical activity amount was calculated based on frequency, duration, and intensity of participation in various types of exercise. The main outcome was cardiovascular disease mortality based on ICD-9 codes 390-459 or ICD-10 codes I01-I99. RESULTS: During 444,045 person-years, 1,714 deaths caused by cardiovascular disease were documented. Moderate-intensity, but not light-intensity, dancing and walking were both inversely associated with cardiovascular disease mortality. In Cox regression models, the hazard ratios for cardiovascular disease mortality, adjusted for age, sex, SES, smoking, alcohol, BMI, chronic illness, psychosocial distress, and total physical activity amount, were 0.54 (95% CI=0.34, 0.87) for moderate-intensity dancing and 0.67 (95% CI=0.52, 0.87) for moderate-intensity walking. CONCLUSIONS: Moderate-intensity dancing was associated with a reduced risk for cardiovascular disease mortality to a greater extent than walking. The association between dance and cardiovascular disease mortality may be explained by high-intensity bouts during dancing, lifelong adherence, or psychosocial benefits.</td></tr>
<tr><td>Populations Analyzed: Adults >40</td><td>Author-Stated Funding Source: No funding source used</td></tr>
</table>

<table>
<tr><td colspan="2">Systematic Review
Citation: Milton K, Macniven R, Bauman A. Review of the epidemiological evidence for physical activity and health from low- and middle-income countries. Glob Public Health. 2014;9(4):369-381. doi:10.1080/17441692.2014.894548.</td></tr>
<tr><td>Purpose: To identify and summarize the epidemiological evidence for PA and health from developing countries.</td><td rowspan="4">Abstract: Almost 80% of deaths from non-communicable diseases (NCDs) occur in low- and middle-income countries. Physical inactivity is a key risk factor for NCDs. Enhancing understanding of the scientific evidence linking physical activity and health in low- and middle-income countries is important for supporting national efforts to promote physical activity and reduce NCDs in these countries. A systematic review of three electronic databases was conducted in July 2013, including large population-based epidemiological studies with adult participants, conducted in low- and middle-income countries, and published in the past 30 years. Physical activity was consistently associated with a reduced risk of all-cause mortality, cardiovascular disease (CVD), diabetes and several types of cancer. Positive associations were also found between physical activity and body composition (including overweight and obesity), blood pressure, cholesterol, metabolic indices and bone mineral density. Overall, the results confirm that the epidemiological research into the health benefits of physical activity in low- and middle-income countries is consistent with previous research conducted in high-income countries. This summary of the available research can be used as an advocacy tool in low- and middle-income countries to support greater prominence of physical activity in NCD policies.</td></tr>
<tr><td>Timeframe: 1983–2013</td></tr>
<tr><td>Total # of Studies: 121</td></tr>
<tr><td>Exposure Definition: PA: assessed mainly through self-report. A few of the included studies (N=5) used objective methods (pedometer, accelerometer, or other).
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: All-cause mortality. Cardiovascular disease. Diabetes. Cancer.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Adults</td><td>Author-Stated Funding Source: Not Reported</td></tr>
</table>

Pooled Analysis

Citation: O'Donovan G, Lee IM, Hamer M, Stamatakis E. Association of "weekend warrior" and other leisure time physical activity patterns with risks for all-cause, cardiovascular disease, and cancer mortality. *JAMA Intern Med.* 2017;177:335-342. doi:10.1001/jamainternmed.2016.8014.

Purpose: To investigate associations between PA patterns and all-cause, cardiovascular disease, and cancer mortality among adults.

Total # of Studies: 11

Exposure Definition: Self-reported leisure time PA, separated into patterns: inactive (no moderate- or vigorous-intensity PA); insufficiently active (<150 minutes/week moderate and <75 minutes/week vigorous); weekend warrior (at least 150 minutes/week moderate or 75 minutes/week vigorous from 1 or 2 sessions); regularly active (at least 150 minutes/week moderate or 75 minutes/week vigorous from 3 or more sessions). 3.0 to 5.9 metabolic equivalents of task (METs) classified moderate activities and 6.0 or more METs classified vigorous activities.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No

Outcomes Addressed: All-cause, cardiovascular disease, and cancer mortality ascertained from death certificates.
Examine Cardiorespiratory Fitness as Outcome: No

Abstract: Importance More research is required to clarify the association between physical activity and health in "weekend warriors" who perform all their exercise in 1 or 2 sessions per week.Objective To investigate associations between the weekend warrior and other physical activity patterns and the risks for all-cause, cardiovascular disease (CVD), and cancer mortality.Design, Setting, and Participants This pooled analysis of household-based surveillance studies included 11 cohorts of respondents to the Health Survey for England and Scottish Health Survey with prospective linkage to mortality records. Respondents 40 years or older were included in the analysis. Data were collected from 1994 to 2012 and analyzed in 2016.Exposures Self-reported leisure time physical activity, with activity patterns defined as inactive (reporting no moderate- or vigorous-intensity activities), insufficiently active (reporting <150 min/wk in moderate-intensity and <75 min/wk in vigorous-intensity activities), weekend warrior (reporting ≥150 min/wk in moderate-intensity or ≥75 min/wk in vigorous-intensity activities from 1 or 2 sessions), and regularly active (reporting ≥150 min/wk in moderate-intensity or ≥75 min/wk in vigorous-intensity activities from ≥3 sessions). The insufficiently active participants were also characterized by physical activity frequency.Main Outcomes and Measures All-cause, CVD, and cancer mortality ascertained from death certificates.Results Among the 63 591 adult respondents (45.9% male; 44.1% female; mean [SD] age, 58.6 [11.9] years), 8802 deaths from all causes, 2780 deaths from CVD, and 2526 from cancer occurred during 561 159 person-years of follow-up. Compared with the inactive participants, the hazard ratio (HR) for all-cause mortality was 0.66 (95% CI, 0.62-0.72) in insufficiently active participants who reported 1 to 2 sessions per week, 0.70 (95% CI, 0.60-0.82) in weekend warrior participants, and 0.65 (95% CI, 0.58-0.73) in regularly active participants. Compared with the inactive participants, the HR for CVD mortality was 0.60 (95% CI, 0.52-0.69) in insufficiently active participants who reported 1 or 2 sessions per week, 0.60 (95% CI, 0.45-0.82) in weekend warrior participants, and 0.59 (95% CI, 0.48-0.73) in regularly active participants. Compared with the inactive participants, the HR for cancer mortality was 0.83 (95% CI, 0.73-0.94) in insufficiently active participants who reported 1 or 2 sessions per week, 0.82 (95% CI, 0.63-1.06) in weekend warrior participants, and 0.79 (95% CI, 0.66-0.94) in regularly active participants.Conclusions and Relevance Weekend warrior and other leisure time physical activity patterns characterized by 1 or 2 sessions per week may be sufficient to reduce all-cause, CVD, and cancer mortality risks regardless of adherence to prevailing physical activity guidelines.

Populations Analyzed: Male, Female; Adults >40; Obese (BMI: 30 and above); Hypertension Status; Smoking Status	**Author-Stated Funding Source:** National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care—East Midlands, Leicester Clinical Trials Unit (United Kingdom)

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Wahid A, Manek N, Nichols M. Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and meta-analysis. J Am Heart Assoc. 2016;5(9):e002495. doi:10.1161/JAHA.115.002495.</td></tr>
<tr><td>Purpose: To draw together the epidemiological studies that assesses the independent association between PA levels and both cardiovascular disease and type 2 diabetes mellitus outcomes, using a single continuous metric and adjusting for body weight.</td><td rowspan="5">Abstract: BACKGROUND: The relationships between physical activity (PA) and both cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) have predominantly been estimated using categorical measures of PA, masking the shape of the dose-response relationship. In this systematic review and meta-analysis, for the very first time we are able to derive a single continuous PA metric to compare the association between PA and CVD/T2DM, both before and after adjustment for a measure of body weight. METHODS AND RESULTS: The search was applied to MEDLINE and EMBASE electronic databases for all studies published from January 1981 to March 2014. A total of 36 studies (3 439 874 participants and 179 393 events, during an average follow-up period of 12.3 years) were included in the analysis (33 pertaining to CVD and 3 to T2DM). An increase from being inactive to achieving recommended PA levels (150 minutes of moderate-intensity aerobic activity per week) was associated with lower risk of CVD mortality by 23%, CVD incidence by 17%, and T2DM incidence by 26% (relative risk [RR], 0.77 [0.71-0.84]), (RR, 0.83 [0.77-0.89]), and (RR, 0.74 [0.72-0.77]), respectively, after adjustment for body weight. CONCLUSIONS: By using a single continuous metric for PA levels, we were able to make a comparison of the effect of PA on CVD incidence and mortality including myocardial infarct (MI), stroke, and heart failure, as well as T2DM. Effect sizes were generally similar for CVD and T2DM, and suggested that the greatest gain in health is associated with moving from inactivity to small amounts of PA.</td></tr>
<tr><td>Timeframe: 1981–2014</td></tr>
<tr><td>Total # of Studies: 36</td></tr>
<tr><td>Exposure Definition: Exposure data for PA was converted to a common continuous metric of metabolic equivalent of task hours per week.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Incidence of cardiovascular disease, stroke, type 2 diabetes mellitus, and mortality from those chronic conditions.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Adults 19–79</td><td>Author-Stated Funding Source: British Heart Foundation</td></tr>
</table>

Table 3. Existing Systematic Reviews, Meta-Analyses, and Pooled Analyses Quality Assessment Chart

AMSTARExBP: SR/MA						
	Ekelund, 2016	Hamer, 2008	Merom, 2016	Milton, 2014	O'Donovan, 2017	Wahid, 2016
Review questions and inclusion/exclusion criteria delineated prior to executing search strategy.	Yes	Yes	Yes	Yes	Yes	Yes
Population variables defined and considered in methods.	Yes	Yes	Yes	No	Yes	Yes
Comprehensive literature search performed.	Yes	Yes	N/A	Partially Yes	N/A	Yes
Duplicate study selection and data extraction performed.	Yes	No	N/A	No	N/A	Yes
Search strategy clearly described.	Yes	Yes	N/A	Yes	N/A	Yes
Relevant grey literature included in review.	Yes	No	N/A	No	N/A	No
List of studies (included and excluded) provided.	No	No	N/A	Yes	N/A	Yes
Characteristics of included studies provided.	Yes	Yes	No	No	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	Yes	Yes	No	N/A	Yes	No
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	Yes	No	No	Yes	Yes
Results depended on study quality, either overall, or in interaction with moderators.	Yes	Yes	N/A	N/A	Yes	Yes
Scientific quality used appropriately in formulating conclusions.	Yes	Yes	N/A	N/A	Yes	Yes
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	Yes	No	N/A	No	Yes
Effect size index chosen justified, statistically.	Yes	Yes	Yes	N/A	Yes	Yes
Individual-level meta-analysis used.	Yes	No	No	N/A	No	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	Yes	Yes	N/A	No	N/A	Yes
Conflict of interest disclosed.	Yes	Yes	No	No	Yes	Yes

Appendices

Appendix A: Analytical Framework

Topic Area
Exposure

Systematic Review Questions

What is the relationship between physical activity and cardiovascular disease mortality?

a. Is there a dose-response relationship? If yes, what is the shape of the relationship?
b. Does the relationship vary by age, sex, race/ethnicity, or socio-economic status?

Population
Adults, 18 years and older

Exposure
All types and intensities of physical activity, including lifestyle activities/leisure activities

Comparison
Adults who participate in varying levels of physical activity

Endpoint Health Outcomes

- Cardiovascular disease mortality

Key Definitions

- Dose-response: The relation between the dose of physical activity and the health or fitness outcome of interest.
- Dose: The amount of physical activity performed by the subject or participants. The dose can be measured in terms of a single component of activity (e.g., frequency, duration, intensity) or as the total amount.
- Intensity: How much work is being performed or the magnitude of the effort required to perform an activity or exercise. Intensity can be expressed either in *absolute* or *relative* terms.

Appendix B: Final Search Strategy

Search Strategy: PubMed (Systematic Reviews, Meta-Analyses, Pooled Analyses, and High-Quality Reports)

Database: PubMed Search 1 (Mortality AND PA AND Limits); Date of Search: 1/03/2017; 220 results

Search 2 (Mortality AND CVD AND PA AND Limits); Date of Search: 1/03/2017; 69 additional results

Set	Search Strategy
Mortality	((Death[mh] OR Mortality[mh]) OR ((Death[tiab] OR Dying[tiab] OR Fatal*[tiab] OR Mortalit*[tiab] OR Postmortem[tiab]) NOT medline[sb]))
CVD	AND (("Aortic aneurysm and dissection"[tiab] OR Arteriosclerosis[mh] OR Cardiomyopathies[mh] OR "cerebral-Hemorrhage"[mh] OR "Coronary artery disease"[mh] OR Death, sudden, cardiac[mh] OR "Heart failure"[mh] OR "Intracranial hemorrhages"[mh] OR "Myocardial ischemia"[mh] OR "myocardial infarction"[mh] OR Stroke[mh] OR "Subarachnoid hemorrhage"[mh]) OR ((Arteriosclero*[tiab] OR Atherosclero*[tiab] OR Cardiomyopathies[tiab] OR Cardiomyopathy[tiab] OR "cerebral Hemorrhages"[tiab] OR "cerebral Hemorrhage"[tiab] OR "Cerebral infarction"[tiab] OR "Cerebrovascular diseases"[tiab] OR "Cerebrovascular disease"[tiab] OR "Coronary heart disease"[tiab] OR "Heart failure"[tiab] OR "Hypertensive heart disease"[tiab] OR "Hypertensive renal disease"[tiab] OR "Intracerebral Hemorrhage"[tiab] OR "Intracerebral Hemorrhages"[tiab] OR "Intracranial hemorrhage"[tiab] OR "Intracranial hemorrhages"[tiab] OR "Ischemic heart diseases"[tiab] OR "Ischemic heart disease"[tiab] OR "myocardial infarction"[tiab] OR Stroke[tiab] OR "Subarachnoid hemorrhages"[tiab] OR "Subarachnoid hemorrhage"[tiab]) NOT medline[sb]))
Physical Activity	AND ((("Activity bouts"[tiab] OR "Daily steps"[tiab] OR "High intensity activity"[tiab] OR "Pedometer"[tiab] OR "Step count"[tiab] OR "Steps/day"[tiab]) OR (("Interval training"[tiab] OR "Walk"[tiab] OR "Walking"[tiab] OR ("High intensity"[tiab] AND "training"[tiab])) NOT medline[sb])) OR (("2006/01/01"[PDAT] : "2016/12/31"[PDAT]) AND (("Active living"[tiab] OR "Active travel"[tiab] OR "Exercise"[mh] OR "High intensity activities"[tiab] OR "Light intensity activity"[tiab] OR "Low intensity activity" [tiab] OR "Moderate to Vigorous Activities"[tiab] OR "Moderate to Vigorous Activity"[tiab] OR "Physical endurance"[mh] OR "Physical fitness"[mh] OR "Physical inactivity"[tiab] OR "Sedentary lifestyle"[mh] OR "Weight lifting"[mh] OR "Active commute"[tiab] OR "Active commuting"[tiab] OR "Moderate Activities" [tiab] OR "Moderate Activity" [tiab] OR "Vigorous Activities"[tiab] OR "Vigorous Activity"[tiab]) OR (("Aerobic activities"[tiab] OR "Aerobic activity"[tiab] OR "Anaerobic training"[tiab] OR "Cardiorespiratory activity"[tiab] OR "Cardiorespiratory fitness"[tiab] OR "Cardiovascular activities"[tiab] OR "Cardiovascular activity"[tiab] OR "Cardiovascular fitness" [tiab] OR "Endurance activities"[tiab] OR "Endurance activity"[tiab] OR "Energy expenditure"[tiab] OR "Exercise"[tiab] OR "Physical

Set	Search Strategy
	activity"[tiab] OR "Physical conditioning"[tiab] OR "Physical fitness"[tiab] OR "Resistance training"[tiab] OR "Sedentary lifestyle"[tiab] OR "Strength training"[tiab] OR "Weight training"[tiab]) NOT medline[sb])))))
Limit: Language	AND (English[lang])
Limit: Exclude animal only	NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))
Limit: Systematic Reviews, Meta-Analyses, and Pooled Analyses	AND (systematic[sb] OR meta-analysis[pt] OR “systematic review”[tiab] OR “systematic literature review”[tiab] OR metaanalysis[tiab] OR "meta-analysis"[tiab] OR metanalyses[tiab] OR "meta analyses"[tiab] OR "pooled analysis"[tiab] OR “pooled analyses”[tiab] OR "pooled data"[tiab])
Limit: Publication Type Exclude	NOT (“comment”[Publication Type] OR “editorial”[Publication Type])
Limit: Exclude child only	NOT (("infant"[Mesh] OR "child"[mesh] OR "adolescent"[mh]) NOT (("infant"[Mesh] OR "child"[mesh] OR "adolescent"[mh]) AND "adult"[Mesh]))
Limit: Exclude subheadings	NOT (ad[sh] OR aa[sh] OR ci[sh] OR cn[sh] OR dh[sh] OR de[sh] OR dt[sh] OR em[sh] OR en[sh] OR es[sh] OR eh[sh] OR ge[sh] OR hi[sh] OR is[sh] OR ip[sh] OR lj[sh] OR ma[sh] OR mi[sh] OR og[sh] OR ps[sh] OR py[sh] OR pk[sh] OR pd[sh] OR po[sh] OR re[sh] OR rt[sh] OR rh[sh] OR st[sh] OR sd[sh] OR tu[sh] OR th[sh] OR tm[sh] OR tr[sh] OR ut[sh] OR ve[sh] OR vi[sh])

Search Strategy: CINAHL (Systematic Reviews, Meta-Analyses, Pooled Analyses, and High-Quality Reports)

Database: CINAHL Search 1; Date of Search: 1/3/2017; 13 results
CINAHL Search 2; Date of Search: 1/3/2017; 2 results
Terms searched in title or abstract

Set	Search Strategy
Mortality	(Death OR Dying OR Fatal* OR Mortalit* OR Postmortem)
CVD	AND ("Aortic aneurysm and dissection" OR Arteriosclero* OR Atherosclero* OR Cardiomyopathies OR Cardiomyopathy OR "cerebral Hemorrhages" OR "cerebral Hemorrhage" OR "Cerebral infarction" OR "Cerebrovascular diseases" OR "Cerebrovascular disease" OR "Coronary heart disease" OR "Heart failure" OR "Hypertensive heart disease" OR "Hypertensive renal disease" OR "Intracerebral Hemorrhage" OR "Intracerebral Hemorrhages" OR "Intracranial hemorrhage" OR "Intracranial hemorrhages" OR "Ischemic heart diseases" OR "Ischemic heart disease" OR "myocardial infarction" OR Stroke OR "Subarachnoid hemorrhages" OR "Subarachnoid hemorrhage" OR "Myocardial ischemia")
Physical Activity	AND ("Activity bouts" OR "Daily steps" OR "High intensity activity" OR "Interval training" OR "Pedometer" OR "Step count" OR "Steps/day" OR "Walk" OR "Walking" OR ("High intensity" AND "training") OR "Active living" OR "Active travel" OR "Aerobic activities" OR "Aerobic activity" OR "Anaerobic training" OR "Cardiorespiratory activity" OR "Cardiorespiratory fitness" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Cardiovascular fitness" OR "Endurance activities" OR "Endurance activity" OR "Energy expenditure" OR "Exercise" OR "High intensity activities" OR "Light intensity activity" OR "Low intensity activity" OR "Moderate to Vigorous Activities" OR "Moderate to Vigorous Activity" OR "Physical activity" OR "Physical conditioning" OR "Physical fitness" OR "Physical inactivity" OR "Resistance training" OR "Sedentary lifestyle" OR "Strength training" OR "Weight training" OR "Active commute" OR "Active commuting" OR "Moderate Activities" OR "Moderate Activity" OR "Vigorous Activities" OR "Vigorous Activity")
Systematic Reviews, Meta-Analyses, and Pooled Analyses	AND ("systematic review" OR "systematic literature review" OR metaanalysis OR "meta analysis" OR metanalyses OR "meta analyses"" OR "pooled analysis" OR "pooled analyses" OR "pooled data")
Limits	2006-present English language Peer reviewed Exclude Medline records Human

Search Strategy: Cochrane (Systematic Reviews, Meta-Analyses, Pooled Analyses, and High-Quality Reports)

Database: Cochrane Search 1; Date of Search: 12/5/16; 121 Results
Search 2; Date of Search: 12/5/16; 38 Results
Terms searched in title, abstract, or keywords

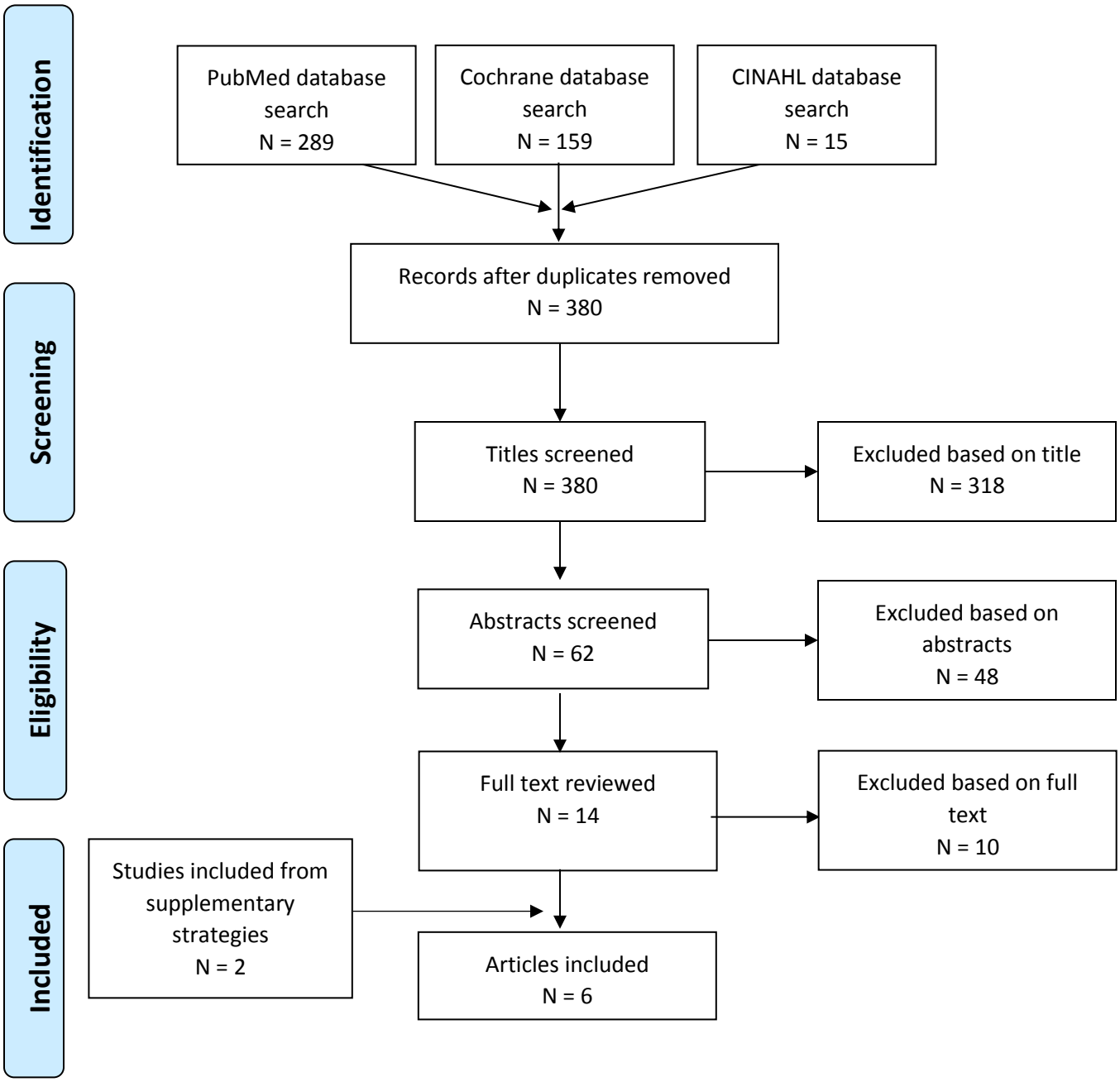
Set	Search Terms
Mortality	(“Mortality” OR “Death”)
CVD	AND ("Aortic aneurysm and dissection" OR Arteriosclero* OR Atherosclero* OR Cardiomyopathies OR Cardiomyopathy OR "cerebral Hemorrhages" OR "cerebral Hemorrhage" OR "Cerebral infarction" OR "Cerebrovascular diseases" OR "Cerebrovascular disease" OR "Coronary heart disease" OR "Heart failure" OR "Hypertensive heart disease" OR "Hypertensive renal disease" OR "Intracerebral Hemorrhage" OR "Intracerebral Hemorrhages" OR "Intracranial hemorrhage" OR "Intracranial hemorrhages" OR "Ischemic heart diseases" OR "Ischemic heart disease" OR "myocardial infarction" OR Stroke OR "Subarachnoid hemorrhages" OR "Subarachnoid hemorrhage" OR "Myocardial ischemia")
Physical Activity	AND ("Active living" OR "Active travel" OR "Aerobic activities" OR "Aerobic activity" OR "Anaerobic training" OR "Cardiorespiratory activity" OR "Cardiorespiratory fitness" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Cardiovascular fitness" OR "Endurance activities" OR "Endurance activity" OR "Energy expenditure" OR "Exercise" OR "High intensity activities" OR "Light intensity activity" OR "Low intensity activity" OR "Moderate to Vigorous Activities” OR "Moderate to Vigorous Activity” OR "Physical activity" OR "Physical conditioning" OR "Physical fitness" OR "Physical inactivity" OR "Resistance training" OR "Sedentary lifestyle" OR "Strength training" OR "Weight training" OR “Active commute” OR “Active commuting” OR “Moderate Activities” OR “Moderate Activity” OR “Vigorous Activities” OR “Vigorous Activity”)
Limits	2006-present Word variations not searched Cochrane Reviews and Other Reviews

Supplementary Strategies:

At full text review two supplementary search strategies were conducted: hand search and expert consultation. Hand search consisted of scanning the reference lists from included studies to identify additional relevant reviews. For expert consultation the members of the Physical Activity Guidelines Exposure Subcommittee were asked to suggest relevant reviews that were not captured by the search strategies. One review[3] and one pooled analysis[6] were identified.

Appendix C: Literature Tree

Existing Systematic Reviews, Meta-Analyses, Pooled Analyses, and Reports Literature Tree



Appendix D: Inclusion/Exclusion Criteria

Exposure Subcommittee
What is the relation between physical activity and cardiovascular disease mortality?

a. Is there a dose-response relationship? If yes, what is the shape of the relationship?
b. Does the relationship vary by age, sex, race/ethnicity, or socio-economic status?

Category	Inclusion/Exclusion Criteria	Notes/Rationale
Publication Language	**Include:** • Studies published with full text in English	
Publication Status	**Include:** • Studies published in peer-reviewed journals • Reports determined to have appropriate suitability and quality by PAGAC **Exclude:** • Grey literature, including unpublished data, manuscripts, abstracts, conference proceedings	
Research Type	**Include:** • Original research • Meta-analyses • Systematic reviews • Reports determined to have appropriate suitability and quality by PAGAC	
Study Subjects	**Include:** • Human subjects	
Age of Study Subjects	**Include:** • 18 years of age and above	
Health Status of Study Subjects	**Include:** • Only studies conducted in general population. • Studies referring to "walkers" or "runners" that are not clearly high performance athletes **should be included.** **Exclude:** • Studies on patients with specific conditions. • Studies on high performance athletes.	
Comparison	**Include studies in which the comparison is:** • Adults exposed to different doses of physical activity.	
Date of Publication	**Include:** • Studies published after 2006 • No date limit for specific terms related to steps, high intensity interval training, and bouts.	

Study Design/Type of research	**Include:** • Systematic reviews • Meta-analyses • Pooled analyses • Reports **Exclude:** • Original research articles • Literature reviews • Commentaries	
Size of Study Groups	**Include:** • All	
Intervention/ Exposure	**Include studies that:** • Assess all types and intensities of physical activity, including lifestyle, leisure, occupational, and transportation activity. • All measures of PA dose or exposure will be considered EXCEPT for fitness (see exclusion criteria). **Exclude:** • Exposure measured by a single measure of physical fitness (cardiovascular fitness, strength, flexibility, **walking speed in older adults**): Where the measure of physical activity is based only on physical fitness measures (single or combined variables). • Studies that assess sedentary behavior as exposure (TV viewing, computer games, sitting-time, sleep, other). • Studies that do not include physical activity (or the lack thereof) as the primary exposure variable or used solely as a confounding variable. • Studies of a specific therapeutic exercise (range of motion exercise, inspiratory muscle training).	
Outcome	**Include studies in which the outcome is:** • Cardiovascular disease mortality	
Multiple Publications of Same Data	**Include:** More than one article per data set. **Note if re-analysis of dataset evaluated for 2008 **Exclude:** No restriction.	

Appendix E: Rationale for Exclusion at Abstract or Full-Text Triage for Existing Systematic Reviews, Meta-Analyses, Pooled Analyses, and Reports

The table below lists the excluded articles with at least one reason for exclusion, but may not reflect all possible reasons.

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
Arena R, Myers J, Forman DE, Lavie CJ, Guazzi M. Should high-intensity-aerobic interval training become the clinical standard in heart failure? *Heart Fail Rev.* 2013;18(1):95-105. doi:10.1007/s10741-012-9333-z.		X			
Asberg AN, Hench I, Hagen K. The mortality associated with chronic widespread musculoskeletal complaints: a systematic review of the literature. *Musculoskeletal Care*. 2016;15(2):104-113. doi:10.1002/msc.1156.				X	
Aspelund T, Gudnason V, Magnusdottir BT, et al. Analyzing the large decline in coronary heart disease mortality in the Icelandic population aged 25–74 between the years 1981 and 2006. *PLoS One.* 2010;5(11):e13957. doi:10.1371/journal.pone.0013957.			X	X	
Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. fatness on all-cause mortality: a meta-analysis. *Prog Cardiovasc Dis.* 2014;56(4):382-390. doi:10.1016/j.pcad.2013.09.002.				X	
Arem H, Moore SC, Patel A. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* 2015;175(6):959-967. doi:10.1001/jamainternmed.2015.0533.	X				
Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363(23):211-2219. doi:363(23):2211-2219.				X	
Biddle SJ, Bennie JA, Bauman AE, et al. Too much sitting and all-cause mortality: is there a causal link? *BMC Public Health*. 2016;16:635. doi:10.1186/s12889-016-3307-3.				X	
Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med.* 2015;162(2):123-132. doi:10.7326/M14-1651.				X	
Brinkley A, McDermott H, Munir F. What benefits does team sport hold for the workplace? A systematic review. *J Sports Sci.* 2017;35(2):136-148.	X				
Campkin LM, Boyd JM, Campbell DJT. Coronary artery disease patient perspectives		X		X	

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
on exercise participation. *J Cardiopulm Rehabil Prev.* 2017;37(5):305-314. doi:10.1097/HCR.0000000000000195.					
Chau JY, Grunseit AC, Chey T, et al. Daily sitting time and all-cause mortality: a meta-analysis. *PLoS One.* 2013;8(11):e80000. doi:10.1371/journal.pone.0080000.				X	
Cole JA, Smith SM, Hart N, Cupples ME. Systematic review of the effect of diet and exercise lifestyle interventions in the secondary prevention of coronary heart disease. *Cardiol Res Pract.* 2011;2011:232351. doi:10.4061/2011/232351.				X	
Cooper R, Kuh D, Hardy R; Mortality Review Group; FALCon and HALCyon Study Teams. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ*. 2010;341:c4467. doi:10.1136/bmj.c4467.				X	
Cox JF III. ACP Journal Club. Review: Exercise reduces mortality compared with drugs in stroke but not in CHD, HF, or prediabetes. *Ann Intern Med.* 2014;160(8):JC3. doi:10.7326/0003-4819-160-8-201404150-02003.	X				
Cramer H, Lauche R, Paul A, Langhorst J, Michalsen A, Dobos G. Mind-body medicine in the secondary prevention of coronary heart disease. *Dtsch Arztebl Int.* 2015;112(45):759-767. doi:10.3238/arztebl.2015.0759.		X		X	
Dahabreh IJ, Paulus JK. Association of episodic physical and sexual activity with triggering of acute cardiac events: systematic review and meta-analysis. *JAMA*. 2011;305(12):1225-1233. doi:10.1001/jama.2011.336.				X	
Danaei G, Ding EL, Mozaffarian D, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med.* 2009;6(4):e1000058. doi:10.1371/journal.pmed.1000058.			X		
de Rezende LF, Rey-Lopez JP, Matsudo VK, do Carmo Luiz O. Sedentary behavior and health outcomes among older adults: a systematic review. *BMC Public Health.* 2014;14:333. doi:10.1186/1471-2458-14-333.				X	
Ekelund U, Ward HA, Norat T, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC). *Am J Clin Nutr.* 2015;101(3):613-621. doi:10.3945/ajcn.114.100065.			X		

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
Fuzeki E, Vogt L, Banzer W. [Sedentary behaviour and health]. *Gesundheitswesen*. 2015;77(3):148-160.				X	
Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *JAMA*. 2011;305(23):2448-2455. doi:10.1001/jama.2011.812.				X	
Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2014;5:CD010072. doi:10.1002/14651858.CD010072.pub2.	X				
Hartley L, Flowers N, Lee MS, Ernst E, Rees K. Tai chi for primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2014;9(4):CD010366. doi:10.1002/14651858.CD010366.pub2.	X				
Hartley L, Lee MS, Kwong JS, et al. Qigong for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2015;(6):CD010390. doi:10.1002/14651858.CD010390.pub2.				X	
Hupin D, Roche F, Gremeaux V, et al. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥60 years: a systematic review and meta-analysis. *Br J Sports Med.* 2015;49(19):1262-1267. doi:10.1136/bjsports-2014-094306.	X				
Hupin D, Roche F, Oriol M, et al. Physical activity for older adults: even a little is good! *Ann Phys Rehabil Med*. 2016;59(suppl):e58. doi:10.1016/j.rehab.2016.07.135.			X		
Jenkins F, Jenkins C, Gregoski MJ, Magwood GS. Interventions promoting physical activity in African American women: an integrative review. *J Cardiovasc Nurs*. 2017;32(1):22-29.				X	
Jewiss D, Ostman C, Smart NA. The effect of resistance training on clinical outcomes in heart failure: a systematic review and meta-analysis. *Int J Cardiol.* 2016;221:674-681. doi:10.1016/j.ijcard.2016.07.046.		X			
Kelly P, Kahlmeier S, Götschi T, et al. Systematic review and meta-analysis of reduction in all-cause mortality from walking and cycling and shape of dose response relationship. *Int J Behav Nutr Phys Act.* 2014;11:132. doi:10.1186/s12966-014-0132-x.	X				
Keteyian SJ. Exercise training in congestive heart failure: risks and benefits. *Prog Cardiovasc Dis.* 2011;53(6):419-428. doi:10.1016/j.pcad.2011.02.005.		X			
Koba S, Tanaka H, Maruyama C, et al. Physical activity in the Japan population: association with blood lipid levels and effects in reducing				X	

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
cardiovascular and all-cause mortality. *J Atheroscler Thromb.* 2011;18(10):833-845.					
Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301(19):2024-2035. doi:10.1001/jama.2009.681.				X	
Kohl HW III. Is the association of walking with cardiovascular risk and all-cause mortality consistent? A meta-analysis. *Clin J Sport Med*. 2009;19(4):336-337.			X		
Kwong JS, Lau HL, Yeung F, Chau PH. Yoga for secondary prevention of coronary heart disease. *Cochrane Database Syst Rev*. 2015;7:CD009506. doi:10.1002/14651858.CD009506.pub4.		X			
Lawrence M, Kerr S, McVey C, Godwin J. A systematic review of the effectiveness of secondary prevention lifestyle interventions designed to change lifestyle behavior following stroke. *JBI Libr Syst Rev*. 2011;9(43):1226-1269. doi:10.11124/01938924-201109430-00001.	X	X			
Liu B, Hu X, Zhang Q, et al. Usual walking speed and all-cause mortality risk in older people: a systematic review and meta-analysis. *Gait Posture.* 2016;44:172-177. doi:10.1016/j.gaitpost.2015.12.008.				X	
Lollgen H, Bockenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. *Int J Sports Med.* 2009;30(3):213-224. doi:10.1055/s-0028-1128150.	X				
McHugh MD. Fit or fat? A review of the debate on deaths attributable to obesity. *Public Health Nurs.* 2006;23(3):264-270.				X	
Meader N, King K, Moe-Byrne T, et al. A systematic review on the clustering and co-occurrence of multiple risk behaviors. *BMC Public Health.* 2016;16:657. doi:10.1186/s12889-016-3373-6.	X				
Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med.* 2012;9(11):e1001335. doi:10.1371/journal.pmed.1001335.	X				
Morris DR, Rodriguez AJ, Moxon JV, et al. Association of lower extremity performance with cardiovascular and all-cause mortality in patients with peripheral artery disease: a systematic review and meta-analysis. *J Am*		X			

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
Heart Assoc. 2014;3(4):e001105. doi:10.1161/JAHA.114.001105.					
Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil.* 2008;15(3):239-246. doi:10.1097/HJR.0b013e3282f55e09.					X
Peeters A. BMI and cardiorespiratory fitness predicted mortality in older adults. *ACP J Club*. 2008;148(3):12.				X	
Peng L, Li S, Tang X, et al. The prognostic value of exercise-induced ventricular arrhythmias in patients with and without coronary artery disease: a meta-analysis. *Int J Cardiol.* 2016;218:225-232. doi:10.1016/j.ijcard.2016.05.052.		X		X	
Perreault K, Bauman A, Johnson N, Britton A, Rangul V, Stamatakis E. Does physical activity moderate the association between alcohol drinking and all-cause, cancer and cardiovascular diseases mortality? A pooled analysis of eight British population cohorts. *Br J Sports Med.* 2017;51(8):651-657. doi:10.1136/bjsports-2016-096194.				X	
Rai M, Thompson PD. The definition of exertion-related cardiac events. *Br J Sports Med.* 2011;45(2):130-131. doi:10.1136/bjsm.2009.057653.	X				
Reimers CD, Knapp G, Reimers AK. Does physical activity increase life expectancy? A review of the literature. *J Aging Res.* 2012;2012:243958. doi:10.1155/2012/243958.	X				
Rezende LFM, Sá TH, Mielke GI, Viscondi JYK, Rey-López JP, Garcia LMT. All-cause mortality attributable to sitting time: analysis of 54 countries worldwide. *Am J Prev Med.* 2016;51(2):253-263. doi:10.1016/j.amepre.2016.01.022.				X	
Ross R, Blair SN, Arena R, et al; American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699.				X	

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. *J Hypertens.* 2012;30(7):1277-1288. doi:10.1097/HJH.0b013e3283544669.		X			
Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol.* 2011;40(5):1382-1400. doi:10.1093/ije/dyr112.	X				
Scribbans TD, Vecsey S, Hankinson PB, Foster WS, Gurd BJ. The effect of training intensity on VO2max in young healthy adults: a meta-regression and meta-analysis. *Int J Exerc Sci.* 2016;9(2):230-247.	X				
Smith D. Review: increased physical activity and combined dietary changes reduce mortality in coronary artery disease. *ACP J Club.* 2006;144(1):16.		X			X
Thomas S, Mackintosh S, Halbert J. Does the 'Otago exercise programme' reduce mortality and falls in older adults? A systematic review and meta-analysis. *Age Ageing.* 2010;39(6):681-687. doi:10.1093/ageing/afq102.				X	
Voors AA. [The value of physical training in patients with heart failure]. *Ned Tijdschr Geneeskd.* 2009;153:A666.		X			
Waite O, Smith A, Madge L, Spring H, Noret N. Sudden cardiac death in marathons: a systematic review. *Phys Sportsmed*. 2016;44(1):79-84. doi:10.1080/00913847.2016.1135036.		X		X	
Warburton DE, Charlesworth S, Ivey A, Nettlefold L, Bredin SS. A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. *Int J Behav Nutr Phys Act.* 2010;7:39. doi:10.1186/1479-5868-7-39.	X				
Woodcock J, Franco OH, Orsini N, Roberts I. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. *Int J Epidemiol.* 2011;40(1):121-138. doi:10.1093/ije/dyq104.	X				

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1. Milton K, Macniven R, Bauman A. Review of the epidemiological evidence for physical activity and health from low- and middle-income countries. *Glob Public Health*. 2014;9(4):369-381. doi:10.1080/17441692.2014.894548.

2. Ekelund U, Steene-Johannessen J, Brown WJ. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonized meta-analysis of data from more than 1 million men and women. *Lancet*. 2016;388:1302-1310. doi:10.1016/S0140-6736(16)30370-1.

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5. Merom D, Ding D, Stamatakis E. Dancing participation and cardiovascular disease mortality: a pooled analysis of 11 population-based British cohorts. *Am J Prev Med*. 2016;50(6):756-760. doi:10.1016/j.amepre.2016.01.004.

6. O'Donovan G, Lee IM, Hamer M, Stamatakis E. Association of "weekend warrior" and other leisure time physical activity patterns with risks for all-cause, cardiovascular disease, and cancer mortality. *JAMA Intern Med*. 2017;177:335-342. doi:10.1001/jamainternmed.2016.8014.