Evidence Portfolio – Exposure Subcommittee, Question 1

What is the relationship between physical activity and all-cause 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 Reviews, Meta-Analyses, and Pooled Analyses

Conclusion Statements and Grades

Strong evidence demonstrates a clear inverse dose-response relationship between the amount of moderate-to-vigorous physical activity and all-cause mortality. The strength of the evidence is very unlikely to be modified by more studies of these outcomes. **PAGAC Grade: Strong.**

Strong evidence demonstrates a dose-response relationship between physical activity and all-cause mortality. 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 the lower bound 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 the dose-response relationships between moderate-to-vigorous physical activity and all-cause mortality 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

Existing Systematic Reviews, Meta-Analyses, and Pooled Analyses

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.

Overview

A total of twelve 12 existing reviews were included: 2 systematic reviews,[1, 2] 7 meta-analyses,[3-9] and 3 pooled analyses.[10-12] The reviews were published from 2008 to 2017.

The systematic reviews included a large number of studies: 121[1] and 254.[2] They also covered extensive timeframes (from 1990 to 2013 and from 1950 to 2008, respectively).

The meta-analyses included a range of 9 to 80 studies. Most meta-analyses covered an extensive timeframe: from inception to one year before publication,[3, 5, 8, 9] from 1945 to 2013,[6] and from 1970s and 1960s to 2007 and 2006.[4, 7]

The pooled analyses include data from 6 prospective cohort studies[10, 11] and from 11 cohorts.[12]

Exposures

The majority of the included reviews examined self-reported physical activity in leisure time. Most reviews also established specific physical activity dose categories in metabolic equivalent of task (MET) minutes or hours per week using quartiles or a variety of categories such as inactive and low, medium, and high levels of physical activity, or high vs. low levels of physical activity. One pooled analysis[12] 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). Three reviews addressed specific types of physical activity: cycling and walking,[6] domain-specific physical activity,[8] and habitual walking.[4]

Outcomes

All the included reviews addressed all-cause mortality as an outcome and 5 of them also examined cardiovascular disease mortality.

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	Socioeconomic Status	Weight Status	Chronic Conditions	Other
Arem, 2015	Female, Male	White, Black/African American	Adults <50, 50–<60, 60–<70, 70 and older	Educational attainment	Overweight, Obese	History of cancer, History of heart disease	
Ekelund, 2016			Adults				
Hamer, 2008	Female, Male		Adults >20				
Hupin, 2015			Adults >60				
Kelly, 2014			Adults 20–93				
Lollgen, 2009	Female, Male		Adults				
Milton, 2014			Adults				
Moore, 2012	Female, Male	White, Black/African American	Adults 21–90	Educational attainment		History of cancer, History of heart disease	Smoking status
O'Donovan, 2017	Female, Male		Adults >40		Obese	Hypertension status	Smoking status
Samitz, 2011	Female, Male		Adults 28–85				
Warburton, 2010			Adults 19–65				
Woodcock, 2011			Adults 20–88				

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">Pooled Analysis
Citation: Arem H, Moore SC, Patel A, et al. 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.</td></tr>
<tr><td>Purpose: To quantify the dose-response association between leisure time PA and mortality and define the upper limit of benefit or harm associated with increased levels of PA.</td><td rowspan="4">Abstract: IMPORTANCE: The 2008 Physical Activity Guidelines for Americans recommended a minimum of 75 vigorous-intensity or 150 moderate-intensity minutes per week (7.5 metabolic-equivalent hours per week) of aerobic activity for substantial health benefit and suggested additional benefits by doing more than double this amount. However, the upper limit of longevity benefit or possible harm with more physical activity is unclear. OBJECTIVE: To quantify the dose-response association between leisure time physical activity and mortality and define the upper limit of benefit or harm associated with increased levels of physical activity. DESIGN, SETTING, AND PARTICIPANTS: We pooled data from 6 studies in the National Cancer Institute Cohort Consortium (baseline 1992-2003). Population-based prospective cohorts in the United States and Europe with self-reported physical activity were analyzed in 2014. A total of 661,137 men and women (median age, 62 years; range, 21-98 years) and 116,686 deaths were included. We used Cox proportional hazards regression with cohort stratification to generate multivariable-adjusted hazard ratios (HRs) and 95% CIs. Median follow-up time was 14.2 years. EXPOSURES: Leisure time moderate- to vigorous-intensity physical activity. MAIN OUTCOMES AND MEASURES: The upper limit of mortality benefit from high levels of leisure time physical activity. RESULTS: Compared with individuals reporting no leisure time physical activity, we observed a 20% lower mortality risk among those performing less than the recommended minimum of 7.5 metabolic-equivalent hours per week (HR, 0.80 [95% CI, 0.78-0.82]), a 31% lower risk at 1 to 2 times the recommended minimum (HR, 0.69 [95% CI, 0.67-0.70]), and a 37% lower risk at 2 to 3 times the minimum (HR, 0.63 [95% CI, 0.62-0.65]). An upper threshold for mortality benefit occurred at 3 to 5 times the physical activity recommendation (HR, 0.61 [95% CI, 0.59-0.62]); however, compared with the recommended minimum, the additional</td></tr>
<tr><td>Total # of Studies: 6</td></tr>
<tr><td>Exposure Definition: Self-reported leisure time PA of moderate and vigorous intensity was converted into estimated metabolic-equivalent hours per week.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Mortality risks associated with very high levels of exercise. Mortality dose-response for moderate- and vigorous-intensity leisure time PA. Date of death obtained from National Death Index, death certificates, or medical records.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
</table>

Populations Analyzed: Male, Female; White, Black or African American; Adults <50, 50–<60, 60–<70, ≥70; Socioeconomic Status: Less Than High School, Some College or Post High School Training, College Graduate; BMI: Normal (BMI: 18.5–24.9), Overweight (BMI: 25–29.9), Obese (BMI: ≥30); History of Cancer; Heart Disease; Smoking Status	benefit was modest (31% vs 39%). There was no evidence of harm at 10 or more times the recommended minimum (HR, 0.69 [95% CI, 0.59-0.78]). A similar dose-response relationship was observed for mortality due to cardiovascular disease and to cancer. CONCLUSIONS AND RELEVANCE: Meeting the 2008 Physical Activity Guidelines for Americans minimum by either moderate- or vigorous-intensity activities was associated with nearly the maximum longevity benefit. We observed a benefit threshold at approximately 3 to 5 times the recommended leisure time physical activity minimum and no excess risk at 10 or more times the minimum. In regard to mortality, health care professionals should encourage inactive adults to perform leisure time physical activity and do not need to discourage adults who already participate in high-activity levels.
	Author-Stated Funding Source: Intramural Research Program of the Division of Cancer Epidemiology and Genetics and the Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Ekelund U, Steene-Johannessen J, Brown WJ, et al.; Lancet Physical Activity Series 2 Executive Committee; Lancet Sedentary Behaviour Working Group. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet. 2016;388(10051):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="5">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 physical activity, except in the most active quartile, where mortality was significantly increased only in</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>

	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

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med. 2008;42:238-243.</td></tr>
<tr><td>Purpose: To quantify the association between walking and the risk of cardiovascular disease (CVD) and all-cause mortality in healthy men and women.</td><td rowspan="5">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.</td></tr>
<tr><td>Timeframe: 1970–2007</td></tr>
<tr><td>Total # of Studies: 18</td></tr>
<tr><td>Exposure Definition: Walking: measures of habitual walking volume (time/distance) or intensity.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>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</td></tr>
<tr><td>Populations Analyzed: Male, Female; Adults >20</td><td>Author-Stated Funding Source: British Heart Foundation</td></tr>
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<table>
<tr><td colspan="2">Meta-Analysis
Citation: 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.</td></tr>
<tr><td>Purpose: To determine whether a dose of moderate-to-vigorous-intensity physical activity (MVPA) below the recommended level was effective in reducing mortality in older adults.</td><td rowspan="5">Abstract: BACKGROUND: The health benefits of 150 min a week of moderate-to-vigorous-intensity physical activity (MVPA) in older adults, as currently recommended, are well established, but the suggested dose in older adults is often not reached. OBJECTIVES: We aimed to determine whether a lower dose of MVPA was effective in reducing mortality, in participants older than 60 years. METHODS: The PubMed and Embase databases were searched from inception to February 2015. Only prospective cohorts were included. Risk ratios of death were established into four doses based on weekly Metabolic Equivalent of Task (MET)-minutes, defined as inactive (reference), low (1-499), medium (500-999) or high (>/=1000). Data were pooled and analyzed through a random effects model using comprehensive meta-analysis software. RESULTS: Of the 835 reports screened, nine cohort studies remained, totaling 122 417 participants, with a mean follow-up of 9.8+/-2.7 years and 18 122 reported deaths (14.8%). A low dose of MVPA resulted in a 22% reduction in mortality risk (RR=0.78 (95% CI 0.71 to 0.87) p<0.0001). MVPA beyond this threshold brought further benefits, reaching a 28% reduction in all-cause mortality in older adults who followed the current recommendations (RR=0.72 (95% CI 0.65 to 0.80) p<0.0001) and a 35% reduction beyond 1000 MET-min per week (RR=0.65 (95% CI 0.61 to 0.70) p<0.0001). CONCLUSIONS: A dose of MVPA below current recommendations reduced mortality by 22% in older adults. A further increase in physical activity dose improved these benefits in a linear fashion. Older adults should be encouraged to include even low doses of MVPA in their daily lives.</td></tr>
<tr><td>Timeframe: Inception–2015</td></tr>
<tr><td>Total # of Studies: 9</td></tr>
<tr><td>Exposure Definition: PA intensity was assessed in metabolic equivalent of task (MET) units, duration (minutes per day or week), and frequency (days per week). Exposure data was converted to MET-minutes of MVPA per week and categorized by 4 dose types (inactive, low, medium, and high).
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: All-cause mortality relative risk for participants engaging in low, medium, and moderate-to-vigorous-intensity PA compared to inactive participants.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Adults >60</td><td>Author-Stated Funding Source: Not Reported</td></tr>
</table>

<table>
<tr><td colspan="2">Meta-Analysis
Citation: 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.</td></tr>
<tr><td>Purpose: To determine the reduced risk for all-cause mortality from walking or cycling and the shape of the dose-response curve across the range of exposures for walking and cycling.</td><td rowspan="5">Abstract: BACKGROUND AND OBJECTIVE: Walking and cycling have shown beneficial effects on population risk of all-cause mortality (ACM). This paper aims to review the evidence and quantify these effects, adjusted for other physical activity (PA). DATA SOURCES: We conducted a systematic review to identify relevant studies. Searches were conducted in November 2013 using the following health databases of publications: Embase (OvidSP); Medline (OvidSP); Web of Knowledge; CINAHL; SCOPUS; SPORTDiscus. We also searched reference lists of relevant texts and reviews. STUDY ELIGIBILITY CRITERIA AND PARTICIPANTS: Eligible studies were prospective cohort design and reporting walking or cycling exposure and mortality as an outcome. Only cohorts of individuals healthy at baseline were considered eligible. STUDY APPRAISAL AND SYNTHESIS METHODS: Extracted data included study population and location, sample size, population characteristics (age and sex), follow-up in years, walking or cycling exposure, mortality outcome, and adjustment for other co-variables. We used random-effects meta-analyses to investigate the beneficial effects of regular walking and cycling. RESULTS: Walking (18 results from 14 studies) and cycling (8 results from 7 studies) were shown to reduce the risk of all-cause mortality, adjusted for other PA. For a standardized dose of 11.25 METhours per week (or 675 MET minutes per week), the reduction in risk for ACM was 11% (95% CI = 4 to 17%) for walking and 10% (95% CI = 6 to 13%) for cycling. The estimates for walking are based on 280,000 participants and 2.6 million person-years and for cycling they are based on 187,000 individuals and 2.1 million person-years. The shape of the dose-response relationship was modelled through meta-analysis of pooled relative risks within three exposure intervals. The dose-response analysis showed that walking or cycling had the greatest effect on risk for ACM in the first (lowest) exposure interval. CONCLUSIONS AND IMPLICATIONS: The analysis shows that walking and cycling have population-level health benefits even after adjustment for other PA. Public health approaches would have the biggest impact if they are able to increase walking and cycling levels in the groups that have the lowest levels of these activities. REVIEW REGISTRATION: The review protocol was registered with PROSPERO (International database of prospectively registered systematic reviews in health and social care) PROSPERO 2013: CRD42013004266.</td></tr>
<tr><td>Timeframe: 1945–2013</td></tr>
<tr><td>Total # of Studies: 18</td></tr>
<tr><td>Exposure Definition: Reported exposure levels for walking and cycling were converted into metabolic equivalent of task hours per week.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: All-cause mortality.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Adults 20–93</td><td>Author-Stated Funding Source: World Health Organization Regional Office for Europe</td></tr>
</table>

Meta-Analysis **Citation:** Löllgen H, Böckenhoff 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.	
Purpose: To investigate the effect of PA with different intensity categories on all-cause mortality.	**Abstract:** In a meta-analysis we investigated the effect of physical activity with different intensity categories on all-cause mortality. Many studies have reported positive effects of regular physical activity on primary prevention. This recent meta-analysis analyzed all-cause mortality with special reference to intensity categories. A computerized systematic literature search was performed in EMBASE, PUBMED, and MEDLINE data bases (1990-2006) for prospective cohort studies on physical leisure activity. Thirty-eight studies were identified and evaluated. The presentation refers to studies with 3 or 4 different intensities of regular physical activity according to a standard questionnaire. There was a significant association of lower all-cause mortality for active individuals compared with sedentary persons. For studies with three activity categories (mildly, moderately, and highly active) and multivariate-adjusted models, highly active men had a 22% lower risk of all-cause mortality (RR=0.78; 95% CI: 0.72 to 0.84) compared to mildly active men. For women, the relative risk was 0.69 (95% CI: 0.53 to 0.90). We observed similar results in moderately active persons compared to mildly active individuals (RR=0.81 for men and RR=0.76 for women). This association of activity to all-cause mortality was similar and significant in older subjects. Regular physical activity over longer time is strongly associated with a reduction in all-cause mortality in active subjects compared to sedentary persons. There is a dose-response curve especially from sedentary subjects to those with mild and moderate exercise with only a minor additional reduction with further increase in activity level.
Timeframe: 1990–2006	
Total # of Studies: 38	
Exposure Definition: PA in leisure time: kilocalories expended or metabolic equivalent of task. Only studies reporting type of PA and two or more intensity categories were included. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: All-cause mortality. **Examine Cardiorespiratory Fitness as Outcome:** No	
Populations Analyzed: Male, Female; Adults	**Author-Stated Funding Source:** Not Reported

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.	
Purpose: To identify and summarize the epidemiological evidence for PA and health from developing countries. **Timeframe:** 1983–2013 **Total # of Studies:** 121 **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 **Outcomes Addressed:** All-cause mortality. Cardiovascular disease. Diabetes. Cancer. **Examine Cardiorespiratory Fitness as Outcome:** No	**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.
Populations Analyzed: Adults	**Author-Stated Funding Source:** Not Reported

<table>
<tr><td colspan="2">Pooled Analysis
Citation: Moore SC, Patel AV, Matthews CE. 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.</td></tr>
<tr><td>Purpose: To examine distinct levels of leisure time PA of moderate to vigorous intensity in relation to mortality risk and life expectancy.
Total # of Studies: 6
Exposure Definition: Leisure time PA of moderate or vigorous intensity using metabolic equivalents of tasks (METs). MET hours/week calculated for each study.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No
Outcomes Addressed: Hazard ratios for mortality and life expectancy.
Examine Cardiorespiratory Fitness as Outcome: No</td>
<td>Abstract: BACKGROUND: Leisure time physical activity reduces the risk of premature mortality, but the years of life expectancy gained at different levels remains unclear. Our objective was to determine the years of life gained after age 40 associated with various levels of physical activity, both overall and according to body mass index (BMI) groups, in a large pooled analysis. METHODS AND FINDINGS: We examined the association of leisure time physical activity with mortality during follow-up in pooled data from six prospective cohort studies in the National Cancer Institute Cohort Consortium, comprising 654,827 individuals, 21-90 y of age. Physical activity was categorized by metabolic equivalent hours per week (MET-h/wk). Life expectancies and years of life gained/lost were calculated using direct adjusted survival curves (for participants 40+ years of age), with 95% confidence intervals (CIs) derived by bootstrap. The study includes a median 10 y of follow-up and 82,465 deaths. A physical activity level of 0.1-3.74 MET-h/wk, equivalent to brisk walking for up to 75 min/wk, was associated with a gain of 1.8 (95% CI: 1.6-2.0) y in life expectancy relative to no leisure time activity (0 MET-h/wk). Higher levels of physical activity were associated with greater gains in life expectancy, with a gain of 4.5 (95% CI: 4.3-4.7) y at the highest level (22.5+ MET-h/wk, equivalent to brisk walking for 450+ min/wk). Substantial gains were also observed in each BMI group. In joint analyses, being active (7.5+ MET-h/wk) and normal weight (BMI 18.5-24.9) was associated with a gain of 7.2 (95% CI: 6.5-7.9) y of life compared to being inactive (0 MET-h/wk) and obese (BMI 35.0+). A limitation was that physical activity and BMI were ascertained by self report. CONCLUSIONS: More leisure time physical activity was associated with longer life expectancy across a range of activity levels and BMI groups. Please see later in the article for the Editors' Summary.</td></tr>
<tr><td>Populations Analyzed: Male, Female; Race: White, Black or African American; Adults 21–90; Education: High School or Less, Some College or Post High School Training, College Graduate; Any Cancer; History of Heart Disease; Smoking Status</td>
<td>Author-Stated Funding Source: Intramural Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health</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(3):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)

Meta-Analysis **Citation:** 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.	
Purpose: To quantify relationships between all-cause mortality and different domains of PA.	**Abstract:** BACKGROUND: The dose-response relation between physical activity and all-cause mortality is not well defined at present. We conducted a systematic review and meta-analysis to determine the association with all-cause mortality of different domains of physical activity and of defined increases in physical activity and energy expenditure. METHODS: MEDLINE, Embase and the Cochrane Library were searched up to September 2010 for cohort studies examining all-cause mortality across different domains and levels of physical activity in adult general populations. We estimated combined risk ratios (RRs) associated with defined increments and recommended levels, using random-effects meta-analysis and dose-response meta-regression models. RESULTS: Data from 80 studies with 1 338 143 participants (118 121 deaths) were included. Combined RRs comparing highest with lowest activity levels were 0.65 [95% confidence interval (95% CI) 0.60-0.71] for total activity, 0.74 (95% CI 0.70-0.77) for leisure activity, 0.64 (95% CI 0.55-0.75) for activities of daily living and 0.83 (95% CI 0.71-0.97) for occupational activity. RRs per 1-h increment per week were 0.91 (95% CI 0.87-0.94) for vigorous exercise and 0.96 (95% CI 0.93-0.98) for moderate-intensity activities of daily living. RRs corresponding to 150 and 300 min/week of moderate to vigorous activity were 0.86 (95% CI 0.80-0.92) and 0.74 (95% CI 0.65-0.85), respectively. Mortality reductions were more pronounced in women. CONCLUSION: Higher levels of total and domain-specific physical activity were associated with reduced all-cause mortality. Risk reduction per unit of time increase was largest for vigorous exercise. Moderate-intensity activities of daily living were to a lesser extent beneficial in reducing mortality.
Timeframe: Inception–2010	
Total # of Studies: 80	
Exposure Definition: Total PA or domain-specific PA, recorded as activity levels in units of time, kilocalories, or in metabolic equivalent of task hours (studies grouped according to measure used for dose-response analysis —not converted to a common metric). **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: All-cause mortality. **Examine Cardiorespiratory Fitness as Outcome:** No	
Populations Analyzed: Male, Female; Adults 28–85	**Author-Stated Funding Source:** University of Vienna and University of Bern

Systematic Review **Citation:** 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.	
Purpose: To examine critically the current literature to determine whether or not a dose-response relationship exists between habitual PA and chronic disease.	**Abstract:** This systematic review examines critically the scientific basis for Canada's Physical Activity Guide for Healthy Active Living for adults. Particular reference is given to the dose-response relationship between physical activity and premature all-cause mortality and seven chronic diseases (cardiovascular disease, stroke, hypertension, colon cancer, breast cancer, type 2 diabetes (diabetes mellitus) and osteoporosis). The strength of the relationship between physical activity and specific health outcomes is evaluated critically. Literature was obtained through searching electronic databases (e.g., MEDLINE, EMBASE), cross-referencing, and through the authors' knowledge of the area. For inclusion in our systematic review articles must have at least 3 levels of physical activity and the concomitant risk for each chronic disease. The quality of included studies was appraised using a modified Downs and Black tool. Through this search we identified a total of 254 articles that met the eligibility criteria related to premature all-cause mortality (N = 70), cardiovascular disease (N = 49), stroke (N = 25), hypertension (N = 12), colon cancer (N = 33), breast cancer (N = 43), type 2 diabetes (N = 20), and osteoporosis (N = 2). Overall, the current literature supports clearly the dose-response relationship between physical activity and the seven chronic conditions identified. Moreover, higher levels of physical activity reduce the risk for premature all-cause mortality. The current Canadian guidelines appear to be appropriate to reduce the risk for the seven chronic conditions identified above and all-cause mortality.
Timeframe: 1950–2008	
Total # of Studies: 254	
Exposure Definition: Any form of PA/exercise measurement (e.g., self-report, pedometer, accelerometer, maximal aerobic power [VO2 max]) was eligible for inclusion. High vs. lower levels of PA/fitness were used as exposure. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: All-cause mortality, cardiovascular disease, stroke, hypertension, colon cancer, breast cancer, type 2 diabetes, and osteoporosis. **Examine Cardiorespiratory Fitness as Outcome:** No	
Populations Analyzed: Adults 19–65	**Author-Stated Funding Source:** Public Health Agency of Canada

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Woodcock J, Franco OH, Orsini N, Robert 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.</td></tr>
<tr><td>Purpose: To quantify and characterize the nature of the association between nonvigorous PA and all-cause mortality.</td><td rowspan="5">Abstract: BACKGROUND: Although previous studies have found physical activity to be associated with lower mortality, the dose-response relationship remains unclear. In this systematic review and meta-analysis we quantify the dose-response relationship of non-vigorous physical activity and all-cause mortality. METHODS: We aimed to include all cohort studies in adult populations with a sample size of more than 10 000 participants that estimated the effect of different levels of light or moderate physical activity on all-cause mortality. We searched Medline, Embase, Cochrane (DARE), Web of Science and Global Health (June 2009). We used dose-response meta-regression models to estimate the relation between non-vigorous physical activity and mortality. RESULTS: We identified 22 studies that met our inclusion criteria, containing 977 925 (334 738 men and 643 187 women) people. There was considerable variation between the studies in their categorization of physical activity and adjustment for potential confounders. We found that 2.5 h/week (equivalent to 30 min daily of moderate intensity activity on 5 days a week) compared with no activity was associated with a reduction in mortality risk of 19% [95% confidence interval (CI) 15-24], while 7 h/week of moderate activity compared with no activity reduced the mortality risk by 24% (95% CI 19-29). We found a smaller effect in studies that looked at walking alone. CONCLUSION: Being physically active reduces the risk of all-cause mortality. The largest benefit was found from moving from no activity to low levels of activity, but even at high levels of activity benefits accrue from additional activity.</td></tr>
<tr><td>Timeframe: Inception-June 2009</td></tr>
<tr><td>Total # of Studies: 22</td></tr>
<tr><td>Exposure Definition: Light or moderate PA assessed by frequency, duration, and distance, or a combination of these factors, and measured by metabolic equivalent of task hours/week.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: All-cause mortality.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Adults 20–88</td><td>Author-Stated Funding Source: Not Reported</td></tr>
</table>

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

AMSTARExBP: SR/MA						
	Arem, 2015	Ekelund, 2016	Hamer, 2008	Hupin, 2015	Kelly, 2014	Lollgen, 2009
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	Yes	Yes	Yes
Comprehensive literature search performed.	N/A	Yes	Yes	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	N/A	Yes	No	Yes	Yes	Yes
Search strategy clearly described.	N/A	Yes	Yes	Yes	Yes	Yes
Relevant grey literature included in review.	N/A	Yes	No	No	Yes	No
List of studies (included and excluded) provided.	N/A	No	No	No	No	Yes
Characteristics of included studies provided.	Yes	Yes	Yes	Yes	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	Yes	Yes	Yes	Yes	Yes	Yes
Scientific quality (risk of bias) of included studies assessed and documented.	No	Yes	Yes	Yes	Yes	Partially Yes
Results depended on study quality, either overall, or in interaction with moderators.	N/A	Yes	Yes	Yes	Yes	Yes
Scientific quality used appropriately in formulating conclusions.	N/A	Yes	Yes	Yes	Yes	Yes
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	Yes	Yes	Yes	Yes	Yes
Effect size index chosen justified, statistically.	Yes	Yes	Yes	Yes	Yes	Yes
Individual-level meta-analysis used.	Yes	Yes	No	No	No	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	N/A	Yes	Yes	No	Yes	No
Conflict of interest disclosed.	Yes	Yes	Yes	No	Yes	No

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

AMSTARExBP: SR/MA						
	Milton, 2014	Moore, 2012	O'Donovan, 2017	Samitz, 2011	Warburton, 2010	Woodcock, 2011
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.	No	Yes	Yes	Yes	Yes	Yes
Comprehensive literature search performed.	Partially Yes	N/A	N/A	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	No	N/A	N/A	Yes	Yes	Yes
Search strategy clearly described.	Yes	N/A	N/A	Yes	Yes	Yes
Relevant grey literature included in review.	No	N/A	N/A	No	No	Yes
List of studies (included and excluded) provided.	Yes	N/A	N/A	Yes	No	Yes
Characteristics of included studies provided.	No	Yes	Yes	No	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	N/A	Yes	Yes	Yes	N/A	No
Scientific quality (risk of bias) of included studies assessed and documented.	No	No	Yes	Partially Yes	Yes	Yes
Results depended on study quality, either overall, or in interaction with moderators.	N/A	N/A	Yes	Yes	Yes	Yes
Scientific quality used appropriately in formulating conclusions.	N/A	N/A	Yes	No	Yes	Yes
Data appropriately synthesized and if applicable, heterogeneity assessed.	N/A	Yes	No	Yes	N/A	Yes
Effect size index chosen justified, statistically.	N/A	Yes	Yes	Yes	N/A	Yes
Individual-level meta-analysis used.	N/A	No	No	No	N/A	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	No	N/A	N/A	Yes	No	Yes
Conflict of interest disclosed.	No	Yes	Yes	Yes	Yes	No

Appendices

Appendix A: Analytical Framework

<u>Topic Area</u>
Exposure

<u>Systematic Review Questions</u>

What is the relationship between physical activity and all-cause 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?

<u>Population</u>
Adults, 18 years and older

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

<u>Comparison</u>
Adults who participate in varying levels of physical activity

<u>Endpoint Health Outcomes</u>

- All-cause mortality

<u>Key Definitions</u>

- 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 Terms
Mortality	((Mortality[mh]) OR ((Mortalit*[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 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]))))
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

Set	Search Terms
	"Ischemic heart disease"[tiab] OR "myocardial infarction"[tiab] OR Stroke[tiab] OR "Subarachnoid hemorrhages"[tiab] OR "Subarachnoid hemorrhage"[tiab]) NOT medline[sb]))
Limit: Publication Type Include 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: Language	AND (English[lang])
Limit: Exclude animal only	NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))
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]))

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 Terms
Mortality	(Death OR Dying OR Fatal* OR Mortalit* OR Postmortem)
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”)
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")
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

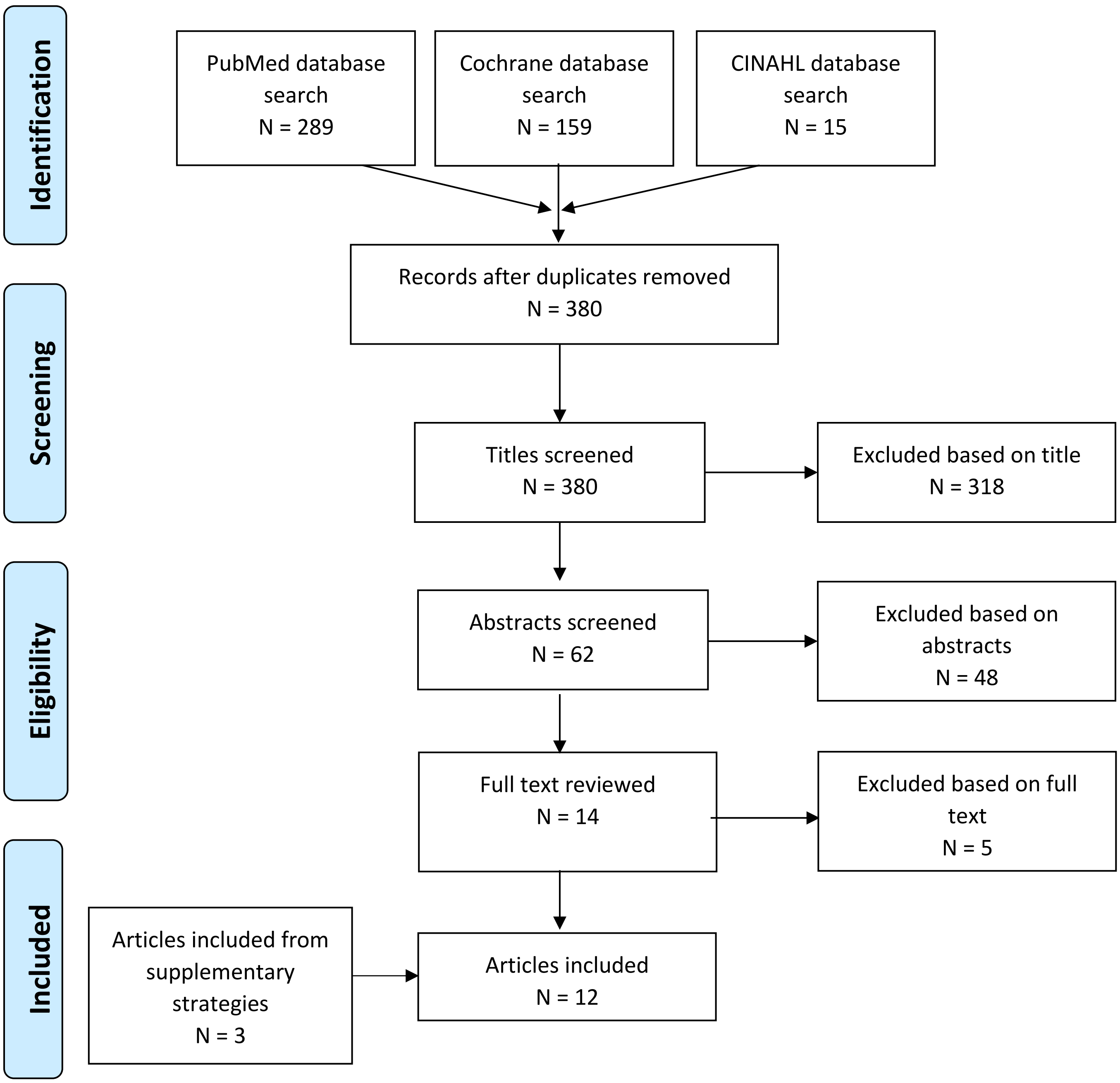
Set	Search Terms
Mortality	("Mortality" OR "Death")
Physical Activity	AND ("Active living" OR "Active travel" OR "Aerobic activities" OR "Aerobic activity" OR "Anaerobic training" OR "Cardiorespiratory activity" OR "Cardiorespiratory fitness" OR "Cardiovascular activities" OR "Cardiovascular activity" 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")
CVD	AND ("Aortic aneurysm and dissection" OR Arterioscler* OR Atheroscler* 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")
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[4] and two pooled analyses[11, 12] 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 all-cause 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:** • All-cause 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			
Åsberg AN, Heuch I, Hagen K. The mortality associated with chronic widespread musculoskeletal complaints: a systematic review of the literature. *Musculoskeletal Care*. 2017;15(2):104-113. doi:10.1002/msc.1156.				X	
Aspelund T, Gudnason V, Magnusdottir BT, et al. Analysing 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	
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):2211-2219. doi:10.1056/NEJMoa1000367.				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 DJ. Coronary artery disease patient perspectives on exercise participation. *J Cardiopulm Rehabil Prev.* 2017;37(5):305-314. doi:10.1097/HCR.0000000000000195.		X		X	
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				X	

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
coronary heart disease. *Cardiol Res Pract.* 2011;2011:232351. doi:10.4061/2011/232351.					
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Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
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Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
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