Evidence Portfolio – Exposure Subcommittee, Question 3

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

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 and Meta-Analyses

Conclusion Statements and Grades

Strong evidence demonstrates a significant relationship between greater amounts of physical activity and decreased incidence of cardiovascular disease, stroke, and heart failure. The strength of the evidence is unlikely to be modified by more studies of these outcomes. **PAGAC Grade: Strong.**

Strong evidence demonstrates a significant dose-response relationship between physical activity and cardiovascular disease, stroke, and heart failure. When exposures are expressed as energy expenditure (MET-hours per week), the shape of the curve for incident CVD appears to be nonlinear, with the greatest benefit seen early in the dose-response relationship. It is unclear whether the shapes of the relations for incident stroke and heart failure are linear or nonlinear. There is no lower limit for the relation of MPVA and risk reduction. Risk appears to continue to decrease with increased exposure up to at least five times the current recommended levels of moderate-to-vigorous physical activity. **PAGAC Grade: Strong.**

Insufficient evidence is available to determine whether these relationships vary by age, sex, race, ethnicity, socioeconomic status, or weight 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 Review and Meta-Analyses

Overview

A total of 10 existing reviews were included: 1 systematic review[1] and 9 meta-analyses.[2-10] The reviews were published from 2008 to 2016.

The systematic review[1] included 254 studies published between 1950 and 2008.

The meta-analyses included a range of 12 to 43 studies. Most meta-analyses covered an extensive timeframe: from inception to 2013,[9] from 1954 and 1966 to 2007,[7, 10] and from the 1980s and 1990s to 2005–2016.[2-6, 8]

Exposures

The majority of included reviews examined self-reported physical activity (PA). Different domains of PA were also assessed, including total PA[4]; occupational and leisure PA[3]; occupational, leisure, and transport PA[6]; and leisure PA only.[7] Some reviews also established specific PA dose categories in metabolic equivalent minutes or hours per week.[4, 5, 8, 10] Other reviews used minimal or low vs. moderate or high PA levels as reported in individual studies.[1, 2, 7] Two meta-analyses examined specific types of PA: Tai Chi Chuan[9] and walking.[10]

Outcomes

Included reviews addressed the incidence of cardiovascular disease in a variety of ways, including risk of stroke,[2, 4, 9] heart failure incidence and risk,[3, 5] and risk and incidence of coronary heart disease.[6, 7, 10]

Populations Analyzed

The table below lists the populations analyzed in each article.

Table 1. Populations Analyzed by All Sources of Evidence

	Sex	Age	Other
Diep, 2010	Female, Male	Adults	
Echouffo-Tcheugui, 2015	Female, Male	Adults	Region: U.S., non-U.S.
Kyu, 2016		Adults	
Pandey, 2015	Female, Male	Adults <55, ≥55	Region: U.S., Europe
Sattelmair, 2011	Female, Male	Adults	
Sofi, 2008	Female, Male	Adults 20–88	
Wahid, 2016		Adults 19–79	
Warburton, 2010		Adults 19–65	
Zheng, 2015		Adults ≥30	
Zheng, 2009	Female, Male	Adults <55, ≥55	

Supporting Evidence

Existing Systematic Review and Meta-Analyses

Table 2. Existing Systematic Review and Meta-Analyses Individual Evidence Summary Tables

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Diep L, Kwagyan J, Kurantsin-Mills J, Weir R, Jayam-Trouth A. Association of physical activity level and stroke outcomes in men and women: a meta-analysis. J Womens Health (Larchmt). 2010;19(10):1815-1822. doi:10.1089/jwh.2009.1708.</td></tr>
<tr><td>Purpose: To perform a comprehensive meta-analysis of studies to (1) quantify the association between physical activity (PA) level and risk of stroke outcomes and (2) test the hypothesis that the association of PA level with stroke outcomes will be similar between men and women.</td><td rowspan="5">Abstract: OBJECTIVE: The protective effect of physical activity (PA) on risk of stroke remains controversial as a result of lack of insight into the sources of heterogeneity between studies. We performed a comprehensive meta-analysis of studies to (1) quantify the association between PA level and risk of stroke outcomes and (2) test the hypothesis that the association of PA level with stroke outcomes will be similar between men and women. The outcome measures are stroke incidence, stroke mortality, or both. METHODS: Cohort studies were identified by searching MEDLINE and EMBASE (from 1986 to 2005) and meta-analysis conducted according to meta-analysis of Observational Studies in Epidemiology (MOOSE) group recommendations. Data were reported as pooled relative risk (RR) and 95% confidence intervals (CI) using random-effects models to assess the association of stroke outcomes with PA level. Heterogeneity was investigated, and sensitivity analysis was performed. Stratified analysis by gender was performed. RESULTS: Of 992 articles, 13 satisfied all eligibility criteria and were studied. Compared with low PA, moderate PA caused an 11% reduction in risk of stroke outcome (RR = 0.89, 95% CI 0.86-0.93, $p < 0.01$) and high PA a 19% reduction (RR = 0.81, CI 0.77-0.84, $p < 0.01$). Among the men, results showed a 12% reduction in risk associated with moderate PA (RR = 0.88, CI 0.82-0.94, $p < 0.01$) and 19% reduction for high PA (RR = 0.81, CI 0.75-0.87, $p < 0.01$). Among the women, results showed a 24% reduction in risk for high PA (RR = 0.76, CI 0.64-.89, $p < 0.01$). There was, however, no significant risk reduction associated with a moderate PA level in women. CONCLUSIONS: Increased PA level appears beneficial in reduction of risk of stroke and related outcomes. However, higher levels of PA may be required in women to achieve as significant a risk reduction as in men. An exercise regimen tailored to women to improve related physiological mechanisms will likely be beneficial.</td></tr>
<tr><td>Timeframe: January 1986–September 2005</td></tr>
<tr><td>Total # of Studies: 13</td></tr>
<tr><td>Exposure Definition: Physical Activity: differed by studies, many used self-report questionnaires. PA was categorized for analysis as low, moderate, and high level.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Risk of first stroke or stroke death: Outcome assessment varied by study, either death certificate, medical record, or confirmed by radiographic evaluation. Relative risk estimates calculated for analysis.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Male, Female, Adults</td><td>Author-Stated Funding Source: National Institutes of Health National Center for Research Resources, Howard University, AAASPS, and PROFESS Study on Stroke Patients.</td></tr>
</table>

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Echouffo-Tcheugui JB, Butler J, Yancy CW, Fonarow GC. Association of physical activity or fitness with incident heart failure: a systematic review and meta-analysis. Circ Heart Fail. 2015. 8(5):853-861. doi:10.1161/CIRCHEARTFAILURE.115.002070.</td></tr>
<tr><td>Purpose: To examine the association of physical activity (PA) and the incidence of heart failure, as well as the effect of fitness on heart failure occurrence.</td><td rowspan="5">Abstract: BACKGROUND: Previous studies have shown that high levels of physical activity are associated with lower risk of risk factors for heart failure (HF), such as coronary heart disease, hypertension, and diabetes mellitus. However, the effects of physical activity or fitness on the incidence of HF remain unclear. METHODS AND RESULTS: MEDLINE and EMBASE were systematically searched until November 30, 2014. Prospective cohort studies reporting measures of the association of physical activity (n=10) or fitness (n=2) with incident HF were included. Extracted effect estimates from the eligible studies were pooled using a random-effects model meta-analysis, with heterogeneity assessed with the I(2) statistic. Ten cohort studies on physical activity eligible for meta-analysis included a total of 282 889 participants followed for 7 to 30 years. For the physical activity studies, maximum versus minimal amount of physical activity groups were used for analyses; with a total number of participants (n=165 695). The pooled relative risk (95% confidence interval [CI]) for HF among those with a regular exercise pattern was 0.72 (95% CI, 0.67-0.79). Findings were similar for men (0.71 [95% CI, 0.61-0.83]) and women (0.72 [95% CI, 0.67-0.77]) and by type of exercise. There was no evidence of publication bias (P value for Egger test=0.34). The pooled associated effect of physical fitness on incident HF was 0.79 (95% CI, 0.75-0.83) for each unit increase in metabolic equivalent of oxygen consumption. CONCLUSIONS: Published literature support a significant association between increased physical activity or fitness and decreased incidence of HF.</td></tr>
<tr><td>Timeframe: 1990–November 2014</td></tr>
<tr><td>Total # of Studies: 12</td></tr>
<tr><td>Exposure Definition: Included studies categorized participants on the basis of occupational and leisure time PA, vigorous PA, and cumulative/total PA. The extreme groups (i.e., maximum versus minimal amount of PA) were used for the meta-analyses, with the highest group as the referent. Only the estimate for total physical activity was used. Physical fitness: continuous measure reported by study.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Heart failure incidence: assessment varied by study, including discharge ICD-9 or ICD-10 codes, death certificate, self-report by physician, and Framingham criteria. Pooled relative risks were estimated.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Male, Female; Adults; Region: U.S., non-U.S.</td><td>Author-Stated Funding Source: Not Reported</td></tr>
</table>

Meta-Analysis

Citation: Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ*. 2016;354:i3857. doi:10.1136/bmj.i3857.

Purpose: To quantify the dose-response associations between total physical activity (PA) and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events.

Timeframe: 1980–2016

Total # of Studies: 174 (43 for ischemic heart disease and 26 for ischemic stroke).

Exposure Definition: Total PA—in metabolic equivalent (MET) minutes/week—was estimated from all included studies. Continuous and categorical dose-response between PA and outcomes conducted. Categorical compared insufficiently active (<600 MET minutes/week), low active (600–3,999 MET minutes), moderately active (4000–7,999 MET minutes), and highly active (≥8,000 MET minutes).

Measures Steps: No

Measures Bouts: No

Examines HIIT: No

Outcomes Addressed: Risk of ischemic heart disease, ischemic stroke, breast cancer, colon cancer, and diabetes. Pooled relative risk estimated for analyses.

Examine Cardiorespiratory Fitness as Outcome: No

Abstract: OBJECTIVE: To quantify the dose-response associations between total physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events. DESIGN: Systematic review and Bayesian dose-response meta-analysis. DATA SOURCES: PubMed and Embase from 1980 to 27 February 2016, and references from relevant systematic reviews. Data from the Study on Global AGEing and Adult Health conducted in China, Ghana, India, Mexico, Russia, and South Africa from 2007 to 2010 and the US National Health and Nutrition Examination Surveys from 1999 to 2011 were used to map domain specific physical activity (reported in included studies) to total activity. ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Prospective cohort studies examining the associations between physical activity (any domain) and at least one of the five diseases studied. RESULTS: 174 articles were identified: 35 for breast cancer, 19 for colon cancer, 55 for diabetes, 43 for ischemic heart disease, and 26 for ischemic stroke (some articles included multiple outcomes). Although higher levels of total physical activity were significantly associated with lower risk for all outcomes, major gains occurred at lower levels of activity (up to 3000-4000 metabolic equivalent (MET) minutes/week). For example, individuals with a total activity level of 600 MET minutes/week (the minimum recommended level) had a 2% lower risk of diabetes compared with those reporting no physical activity. An increase from 600 to 3600 MET minutes/week reduced the risk by an additional 19%. The same amount of increase yielded much smaller returns at higher levels of activity: an increase of total activity from 9000 to 12 000 MET minutes/week reduced the risk of diabetes by only 0.6%. Compared with insufficiently active individuals (total activity <600 MET minutes/week), the risk reduction for those in the highly active category (>/=8000 MET minutes/week) was 14% (relative risk 0.863, 95% uncertainty interval 0.829 to 0.900) for breast cancer; 21% (0.789, 0.735 to 0.850) for colon cancer; 28% (0.722, 0.678 to 0.768) for diabetes; 25% (0.754, 0.704 to 0.809) for ischemic heart disease; and 26% (0.736, 0.659 to 0.811) for ischemic stroke. CONCLUSIONS: People who achieve total physical activity levels several times higher than the current recommended minimum level have a significant reduction in the risk of the five diseases studied. More studies with detailed quantification of total physical activity will help to find more precise relative risk estimates for different levels of activity.

Populations Analyzed: Adults

Author-Stated Funding Source: Bill and Melinda Gates Foundation

Meta-Analysis **Citation:** Pandey A, Garg S, Khunger M, et al. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation*. 2015. 132(19):1786-1794. doi:10.1161/CIRCULATIONAHA.115.015853.	
Purpose: To determine the categorical and quantitative dose-response association between physical activity (PA) and risk of heart failure. **Timeframe:** January 1995–September 2014 **Total # of Studies:** 12 **Exposure Definition:** Most included studies assessed PA by self report/questionnaires; continuous and categorical dose response between PA in metabolic equivalent minutes/week and outcome assessed. Categorical analyses: compared 4 categories of PA: lowest, light, moderate, and highest. Each PA category (highest, moderate, and light PA) was compared with the lowest PA. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No **Outcomes Addressed:** Risk of heart failure. Assessment of outcome varied by study: options included self-report, ICD-9/10 codes, medical records or patient chart review. Pooled hazard ratio or relative risk estimated for analyses. **Examine Cardiorespiratory Fitness as Outcome:** No	**Abstract:** BACKGROUND: Prior studies have reported an inverse association between physical activity (PA) and risk of heart failure (HF). However, a comprehensive assessment of the quantitative dose-response association between PA and HF risk has not been reported previously. METHODS AND RESULTS: Prospective cohort studies with participants >18 years of age that reported association of baseline PA levels and incident HF were included. Categorical dose-response relationships between PA and HF risk were assessed with random-effects models. Generalized least-squares regression models were used to assess the quantitative relationship between PA (metabolic equivalent [MET]-min/wk) and HF risk across studies reporting quantitative PA estimates. Twelve prospective cohort studies with 20 203 HF events among 370 460 participants (53.5% women; median follow-up, 13 years) were included. The highest levels of PA were associated with significantly reduced risk of HF (pooled hazard ratio for highest versus lowest PA, 0.70; 95% confidence interval, 0.67-0.73). Compared with participants reporting no leisure-time PA, those who engaged in guideline-recommended minimum levels of PA (500 MET-min/wk; 2008 US federal guidelines) had modest reductions in HF risk (pooled hazard ratio, 0.90; 95% confidence interval, 0.87-0.92). In contrast, a substantial risk reduction was observed among individuals who engaged in PA at twice (hazard ratio for 1000 MET-min/wk, 0.81; 95% confidence interval, 0.77-0.86) and 4 times (hazard ratio for 2000 MET-min/wk, 0.65; 95% confidence interval, 0.58-0.73) the minimum guideline-recommended levels. CONCLUSIONS: There is an inverse dose-response relationship between PA and HF risk. Doses of PA in excess of the guideline-recommended minimum PA levels may be required for more substantial reductions in HF risk.
Populations Analyzed: Male, Female; Adults <55, ≥55; Country/region: U.S. and Europe	**Author-Stated Funding Source:** University of Texas Southwestern Medical Center and the American Heart Association

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011. 124(7):789-795. doi:10.1161/CIRCULATIONAHA.110.010710.</td></tr>
<tr><td>Purpose: To pool results from prospective cohort studies to quantify the dose-response relationship between physical activity (PA) and risk of coronary heart disease (CHD), including both the amount of PA required and the magnitude of benefit to CHD risk.</td><td rowspan="5">Abstract: BACKGROUND: No reviews have quantified the specific amounts of physical activity required for lower risks of coronary heart disease when assessing the dose-response relation. Instead, previous reviews have used qualitative estimates such as low, moderate, and high physical activity. METHODS AND RESULTS: We performed an aggregate data meta-analysis of epidemiological studies investigating physical activity and primary prevention of CHD. We included prospective cohort studies published in English since 1995. After reviewing 3194 abstracts, we included 33 studies. We used random-effects generalized least squares spline models for trend estimation to derive pooled dose-response estimates. Among the 33 studies, 9 allowed quantitative estimates of leisure-time physical activity. Individuals who engaged in the equivalent of 150 min/wk of moderate-intensity leisure-time physical activity (minimum amount, 2008 U.S. federal guidelines) had a 14% lower coronary heart disease risk (relative risk, 0.86; 95% confidence interval, 0.77 to 0.96) compared with those reporting no leisure-time physical activity. Those engaging in the equivalent of 300 min/wk of moderate-intensity leisure-time physical activity (2008 U.S. federal guidelines for additional benefits) had a 20% (relative risk, 0.80; 95% confidence interval, 0.74 to 0.88) lower risk. At higher levels of physical activity, relative risks were modestly lower. People who were physically active at levels lower than the minimum recommended amount also had significantly lower risk of coronary heart disease. There was a significant interaction by sex (P=0.03); the association was stronger among women than men. CONCLUSIONS: These findings provide quantitative data supporting US physical activity guidelines that stipulate that "some physical activity is better than none" and "additional benefits occur with more physical activity."</td></tr>
<tr><td>Timeframe: January 1995–July 2009</td></tr>
<tr><td>Total # of Studies: 33</td></tr>
<tr><td>Exposure Definition: PA: All types of PA, including leisure time PA, walking time or pace, occupational PA, transport PA, total PA, and non-leisure PA were included. Analyses compared highest and lowest PA groups for each type of PA. Dose-response analysis also conducted for leisure time PA (kcal/week).
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: CHD incidence. Relative risks estimated in analyses.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Male, Female; Adults</td><td>Author-Stated Funding Source: NIH and Donald and Sue Pritzker Scholarship</td></tr>
</table>

Meta-Analysis **Citation:** Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil.* 2008. 15(3):247-257. doi:10.1097/HJR.0b013e3282f232ac.	
Purpose: To evaluate all the available prospective cohort studies that examined the effect of leisure time physical activity (LTPA) on the primary prevention of coronary heart disease (CHD) among men and women, considering that only LTPA can really be influenced by the recommendations of guidelines. **Timeframe:** 1966–May 2007 **Total # of Studies:** 22 **Exposure Definition:** Included studies that assessed LTPA in various ways. Analyses compared lowest to highest group of LTPA and lowest to moderate (middle) group of LTPA. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No **Outcomes Addressed:** Risk of CHD. Subgroup analyses conducted by follow up time (<13 years, >13 years). Relative risk calculated for analyses. **Examine Cardiorespiratory Fitness as Outcome:** No	**Abstract:** BACKGROUND: A vast body of evidence during the last decades has shown the clear preventive role of physical activity in cardiovascular disease. The real magnitude of the association between physical activity during leisure time (LTPA) and primary prevention of coronary heart disease (CHD) has, however, not been completely defined. DESIGN: Meta-analysis of prospective cohort studies. METHODS: Studies were included if they reported relative risks and their corresponding 95% confidence intervals (CI), for categories of LTPA in relation to CHD. The LTPA categories of the selected studies were grouped into three levels of intensity: high, moderate and low. The high level of physical activity was determined, to obtain a level of intensity attainable by the general population. RESULTS: Data were available for 26 studies, incorporating 513,472 individuals (20,666 CHD events), followed up for 4-25 years. Under a random-effects model, the overall analysis showed that individuals who reported performing a high level of LTPA had significant protection against CHD [relative risk 0.73 (95% CI 0.66-0.80), P<0.00001]. A similar significant protection against CHD, for individuals who practised a moderate level of LTPA, has been also demonstrated [relative risk 0.88 (95% CI 0.83-0.93), P<0.0001]. CONCLUSIONS: The current meta-analysis reports significant protection against the occurrence of CHD resulting from moderate-to-high levels of physical activity. These results strengthen the recommendations of guidelines that indicate the protective effect against cardiovascular disease of physical activity profiles that are attainable by ordinary people.
Populations Analyzed: Male, Female; Adults 20–88; Region: U.S. vs. non-U.S.	**Author-Stated Funding Source:** Not Reported

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Wahid A, Manek N, Nichols M, et al. 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 assess the independent association between physical activity (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 equivalents (hours per week).
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Incidence of cardiovascular disease, stroke, and 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>

Systematic Review **Citation:** Warburton DE, Charlesworth, 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 physical activity (PA) and chronic disease. **Timeframe:** 1950–2008 **Total # of Studies:** 254 **Exposure Definition:** Any form of physical activity/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	**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.
Populations Analyzed: Adults 19–65	**Author-Stated Funding Source:** Public Health Agency of Canada

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Zheng G, Huang M, Liu F, Li S, Tao J, Chen L. Tai chi chuan for the primary prevention of stroke in middle-aged and elderly adults: a systematic review. Evid Based Complement Alternat Med. 2015;2015:742152. doi:10.1155/2015/742152.</td></tr>
<tr><td>Purpose: To attempt to conduct a systematic review and meta-analysis of the existing studies on Tai Chi Chuan (TCC) exercise as an intervention for the primary prevention of stroke in middle-aged and elderly adults, to draw more useful conclusions about the safety and efficacy of TCC in preventing stroke, and to offer recommendations for future research.</td><td rowspan="5">Abstract: Background. Stroke is a major healthcare problem with serious long-term disability and is one of the leading causes of death in the world. Prevention of stroke is considered an important strategy. Methods. Seven electronic databases were searched. Results. 36 eligible studies with a total of 2393 participants were identified. Primary outcome measures, TCC exercise combined with other intervention had a significant effect on decreasing the incidence of nonfatal stroke (n = 185, RR = 0.11, 95% CI 0.01 to 0.85, P = 0.03) and CCD (n = 125, RR = 0.33, 95% CI 0.11 to 0.96, P = 0.04). For the risk factors of stroke, pooled analysis demonstrated that TCC exercise was associated with lower body weight, BMI, FBG level, and decreasing SBP, DBP, plasma TC, and LDL-C level regardless of the intervention period less than half a year or more than one year and significantly raised HDL-C level in comparison to nonintervention. Compared with other treatments, TCC intervention on the basis of the same other treatments in patients with chronic disease also showed the beneficial effect on lowering blood pressure. Conclusion. The present systematic review indicates that TCC exercise is beneficially associated with the primary prevention of stroke in middle-aged and elderly adults by inversing the high risk factors of stroke.</td></tr>
<tr><td>Timeframe: Inception–2013</td></tr>
<tr><td>Total # of Studies: 36</td></tr>
<tr><td>Exposure Definition: Tai Chi Chuan exercise for at least 30 minutes and 3 times per week for 4 weeks.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Primary outcome of incidence of fatal or nonfatal stroke or cardia-cerebrovascular disease. Secondary outcomes included any modification risk factor of stroke (e.g., blood pressure, blood lipids, fasting blood glucose).
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Adults ≥30</td><td>Author-Stated Funding Source: State Administration of Traditional Chinese Medicine of China</td></tr>
</table>

<table>
<tr><td colspan="2">Meta-Analysis
Citation: Zheng H, Orsini N, Amin J, Wolk A, Nguyen VT, Ehrlich F. Quantifying the dose-response of walking in reducing coronary heart disease risk: meta-analysis. Eur J Epidemiol. 2009;24(4):181-192. doi:10.1007/s10654-009-9328-9.</td></tr>
<tr><td>Purpose: To examine the relationship between dose of walking and response in reducing coronary heart disease (CHD) risk for both men and women in the general population.</td><td rowspan="5">Abstract: The evidence for the efficacy of walking in reducing the risk of and preventing coronary heart disease (CHD) is not completely understood. This meta-analysis aimed to quantify the dose-response relationship between walking and CHD risk reduction for both men and women in the general population. Studies on walking and CHD primary prevention between 1954 and 2007 were identified through Medline, SportDiscus and the Cochrane Database of Systematic Reviews. Random-effect meta-regression models were used to pool the relative risks from individual studies. A total of 11 prospective cohort studies and one randomized control trial study met the inclusion criteria, with 295,177 participants free of CHD at baseline and 7,094 cases at follow-up. The meta-analysis indicated that an increment of approximately 30 min of normal walking a day for 5 days a week was associated with 19% CHD risk reduction (95% CI = 14-23%; P-heterogeneity = 0.56; I (2) = 0%). We found no evidence of heterogeneity between subgroups of studies defined by gender (P = 0.67); age of the study population (P = 0.52); or follow-up duration (P = 0.77). The meta-analysis showed that the risk for developing CHD decreases as walking dose increases. Walking should be prescribed as an evidence-based effective exercise modality for CHD prevention in the general population.</td></tr>
<tr><td>Timeframe: 1954–September 2007</td></tr>
<tr><td>Total # of Studies: 12</td></tr>
<tr><td>Exposure Definition: Walking: included studies that used various assessments of walking (distance walked, frequency, time, pace, etc.). All measures converted to metabolic equivalent (MET) hours per week. Dose-response analyses conducted by type of walking measurement (MET hours/week, kilometers/hour, and hours/week).
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Risk of CHD: fatal and nonfatal myocardial infarction and angina pectoris. Subgroup analyses by: follow-up duration, <6 years or >6 years. Relative risk estimated.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Male, Female; Adults <55, >55</td><td>Author-Stated Funding Source: Not Reported</td></tr>
</table>

Table 3. Existing Systematic Review and Meta-Analyses Quality Assessment Chart

AMSTARExBP: SR/MA					
	Diep, 2010	Echouffo-Tcheugui, 2015	Kyu, 2016	Pandey, 2015	Sattelmair, 2011
Review questions and inclusion/exclusion criteria delineated prior to executing search strategy.	Yes	Yes	Yes	Yes	Yes
Population variables defined and considered in methods.	Yes	Yes	Yes	Yes	Yes
Comprehensive literature search performed.	Yes	Yes	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	Yes	Yes	Yes	Yes	Yes
Search strategy clearly described.	Yes	Yes	Yes	Yes	Yes
Relevant grey literature included in review.	No	No	No	No	No
List of studies (included and excluded) provided.	No	No	No	No	No
Characteristics of included studies provided.	Yes	Yes	Yes	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	No	No	Yes	Yes	Yes
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	Yes	Yes	Yes	No
Results depended on study quality, either overall, or in interaction with moderators.	No	Yes	Yes	Yes	N/A
Scientific quality used appropriately in formulating conclusions.	Yes	Yes	Yes	Yes	N/A
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	Yes	Yes	Yes	Yes
Effect size index chosen justified, statistically.	Yes	Yes	Yes	Yes	Yes
Individual-level meta-analysis used.	No	No	No	No	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	Yes	Yes	Yes	Yes	Yes
Conflict of interest disclosed.	Yes	Yes	Yes	Yes	Yes

Table 3. Existing Systematic Review and Meta-Analyses Quality Assessment Chart (continued)

AMSTARExBP: SR/MA					
	Sofi, 2008	Wahid, 2016	Warburton, 2010	Zheng, 2015	Zheng, 2009
Review questions and inclusion/exclusion criteria delineated prior to executing search strategy.	Yes	Yes	Yes	Yes	Yes
Population variables defined and considered in methods.	Yes	Yes	Yes	No	Yes
Comprehensive literature search performed.	Yes	Yes	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	No	Yes	Yes	Yes	Yes
Search strategy clearly described.	Yes	Yes	Yes	Yes	Yes
Relevant grey literature included in review.	No	No	No	Yes	Yes
List of studies (included and excluded) provided.	No	Yes	No	Yes	No
Characteristics of included studies provided.	Yes	Yes	Yes	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	No	No	N/A	No	Yes
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	Yes	Yes	Yes	No
Results depended on study quality, either overall, or in interaction with moderators.	Yes	Yes	Yes	No	N/A
Scientific quality used appropriately in formulating conclusions.	Yes	Yes	Yes	Yes	N/A
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	Yes	N/A	Yes	Yes
Effect size index chosen justified, statistically.	Yes	Yes	N/A	Yes	Yes
Individual-level meta-analysis used.	No	No	N/A	No	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	Yes	Yes	No	No	Yes
Conflict of interest disclosed.	No	Yes	Yes	Yes	No

Appendices

Appendix A: Analytical Framework

Topic Area
Exposure

Systematic Review Questions

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

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 incidence

Key Definitions

Scope of CVD:

- Coronary heart disease/ischemic heart disease.
- Coronary artery disease
- Stroke
- Heart failure

Exclusion:

- Congenital heart disease

Appendix B: Final Search Strategy

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

Database: PubMed; Date of Search: 2/16/2017; 395 results

Set	Search Strategy
Cardiovascular Disease	(("Arteriosclerosis"[mh] OR "Heart failure"[mh] OR "Myocardial ischemia"[mh] OR "myocardial infarction"[mh] OR "Stroke"[mh] OR "Subarachnoid hemorrhage"[mh] OR "Intracranial hemorrhages"[mh]) OR ((Arterioscler o*[tiab] OR Atherosclero*[tiab] OR "Cerebral infarction"[tiab] OR "Cerebrovascular diseases"[tiab] OR "Cerebrovascular disease"[tiab] OR "Coronary heart disease"[tiab] OR "Heart failure"[tiab] OR "Intracerebral Hemorrhage"[tiab] OR "Intracerebral Hemorrhages"[tiab] OR "Intracranial hemorrhage"[tiab] OR "Intracranial hemorrhages"[tiab] OR "myocardial infarction"[tiab] OR "Stroke"[tiab] OR "Subarachnoid hemorrhages"[tiab] OR "Subarachnoid hemorrhage"[tiab] OR "Ischemic heart diseases"[tiab] OR "Ischemic heart disease"[tiab]) NOT medline[sb]))
Risk	AND ("risk"[tiab] OR "risks"[tiab] OR "Incidence"[tiab] OR "incident"[tiab] OR "incidents"[tiab] OR "risk"[mh] OR "Incidence"[mh])
Physical Activity	AND (("Exercise"[mh] OR "Exercise"[tiab] OR "Physical activity"[tiab] OR "Sedentary lifestyle"[mh]) OR (("Aerobic activities"[tiab] OR "Aerobic activity"[tiab] OR "Cardiovascular activities"[tiab] OR "Cardiovascular activity"[tiab] OR "Endurance activities"[tiab] OR "Endurance activity"[tiab] OR "Energy expenditure"[tiab] OR "Resistance training"[tiab] OR "strength training"[tiab] OR "physical conditioning"[tiab] OR "walking"[tiab]) NOT medline[sb]))
Limit: Publication Type Include Systematic Reviews/Meta-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 Systematic Reviews/Meta-Analyses	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]))

Set	Search Strategy
Limit: Publication Date	AND ("2006/01/01"[PDAT] : "3000/12/31"[PDAT])

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

Database: CINAHL; Date of Search: 2/17/2017; 1 unique result
Terms searched in title or abstract

Set	Search Strategy
Cardiovascular Disease	("Arteriosclerosis" OR "Cerebral infarction" OR "Cerebrovascular diseases" OR "Cerebrovascular disease" OR "Coronary heart disease" OR "Heart failure" OR "Intracerebral Hemorrhage" OR "Intracerebral Hemorrhages" OR "Intracranial hemorrhage" OR "Intracranial hemorrhages" OR "Myocardial ischemia" OR "myocardial infarction" OR "Stroke" OR "Subarachnoid hemorrhage" OR "Subarachnoid hemorrhages" OR "Ischemic heart diseases" OR "Ischemic heart disease")
Risk	AND ("risk" OR "risks" OR "Incidence" OR "incident" OR "incidents" OR "risk" OR "Incidence")
Physical Activity	AND ("Aerobic activities" OR "Aerobic activity" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Endurance activities" OR "Endurance activity" OR "Energy expenditure" OR "Exercise" OR "Physical activity" OR "Resistance training" OR "Sedentary lifestyle" OR "strength training" OR "physical conditioning" OR "walking")
Systematic Reviews and Meta-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

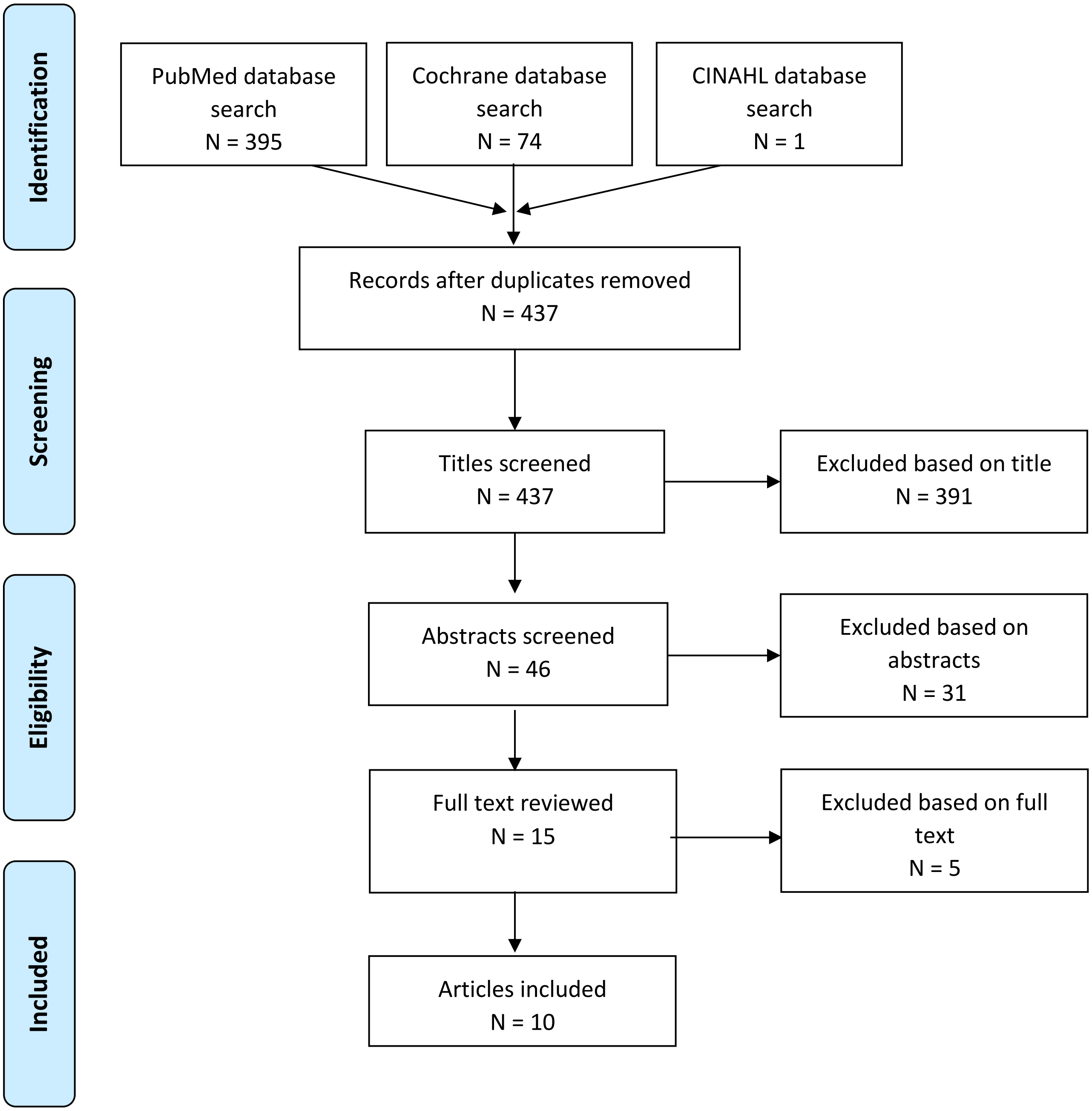
Search Strategy: Cochrane (Systematic Reviews, Meta-Analyses, Pooled Analyses, and High-Quality Reports)

Database: Cochrane; Date of Search: 2/16/17; 74 results
Terms searched in title, abstract, or keywords

Set	Search Terms
Cardiovascular Disease	("Arteriosclerosis" OR "Cerebral infarction" OR "Cerebrovascular diseases" OR "Cerebrovascular disease" OR "Coronary heart disease" OR "Heart failure" OR "Intracerebral Hemorrhage" OR "Intracerebral Hemorrhages" OR "Intracranial hemorrhage" OR "Intracranial hemorrhages" OR "Myocardial ischemia" OR "myocardial infarction" OR "Stroke" OR "Subarachnoid hemorrhage" OR "Subarachnoid hemorrhages" OR "Ischemic heart diseases" OR "Ischemic heart disease")
Risk	AND ("risk" OR "risks" OR "Incidence" OR "incident" OR "incidents" OR "risk" OR "Incidence")
Physical Activity	AND ("Aerobic activities" OR "Aerobic activity" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Endurance activities" OR "Endurance activity" OR "Energy expenditure" OR "Exercise" OR "Physical activity" OR "Resistance training" OR "Sedentary lifestyle" OR "strength training" OR "physical conditioning" OR "walking")
Limits	2006-present Word variations not searched Cochrane Reviews and Other Reviews

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 relationship between physical activity and cardiovascular disease incidence?

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 existing cardiovascular disease. • 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	

Study Design/Type of Research	**Include:** • Systematic reviews • Meta-analyses • Report • Pooled analysis **Exclude:** • Original research articles • Literature reviews • Commentaries	
Size of Study Groups	**Include:** • All **Exclude:** • No criteria	
Intervention/ Exposure	**Include studies that:** • Assess all types and intensities of physical activity, including lifestyle, leisure, occupational, and transportation activity. • All measures of physical activity dose or exposure will be considered EXCEPT for fitness (see exclusion criteria). **Exclude:** • Studies of a specific therapeutic or rehabilitation exercise for patients with existing cardiovascular disease. • 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.	

Outcome	**Include studies in which the outcome is:**
	• Cardiovascular disease incidence:
	    ○ Coronary heart disease/ischemic heart disease
	    ○ Coronary artery disease
	    ○ Stroke of all types
	    ○ Heart failure
	Exclude:
	• Congenital heart disease
	• Studies on progression of cardiovascular disease	

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			
Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev.* 2008; 13(2):245-269.		X		X	
Audrey S, Procter S, Cooper A, et al. Employer schemes to encourage walking to work: feasibility study incorporating an exploratory randomized controlled trial. In: *Public Health Research*, No. 3.4. Southampton, UK: NIHR Journals Library; 2015. doi: 10.3310/phr03040.			X		
Boodhwani, M, Andelfinger, G, Leipsic, J, et al. Canadian Cardiovascular Society position statement on the management of thoracic aortic disease. *Can J Cardiol.* 2014;30(6):577-589. doi: 10.1016/j.cjca.2014.02.018.		X			
Borges, JP, Lessa, MA. Mechanisms involved in exercise-induced cardioprotection: a systematic review. *Arq Bras Cardiol.* 2015;105(1):71-81. doi:10.5935/abc.20150024.					X
Burtscher, M, Ponchia, A. The risk of cardiovascular events during leisure time activities at altitude. *Prog Cardiovasc Dis.* 2010;52(6):507-511. doi:10.1016/j.pcad.2010.02.008.					X
Cassar K. Peripheral arterial disease. *BMJ Clinical Evidence*. 2011;2011:0211.		X		X	
Chiu M, Austin PC, Manuel DG, Tu JV. Comparison of cardiovascular risk profiles among ethnic groups using population health surveys between 1996 and 2007. *CMAJ*. 2010;182(8):E301-E310. doi:10.1503/cmaj.091676.			X		
Chou R, Arora B, Dana T, Fu R, Walker M, Humphrey L. Screening asymptomatic adults for coronary heart disease with resting or exercise electrocardiography: systematic review to update the 2004 U.S. Preventive Services Task Force recommendation. In: *Evidence Synthesis No. 88.* AHRQ Publication No. 11-05158-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; September 2011.				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.					
Conraads VM, Van Craenenbroeck EM, De Maeyer C, Van Berendoncks AM, Beckers PJ, Vrints CJ. Unraveling new mechanisms of exercise intolerance in chronic heart failure: role of exercise training. *Heart Fail Rev*. 2013;18(1):65-77. doi: 10.1007/s10741-012-9324-0.			X		
Dalusung-Angosta, A. The impact of Tai Chi exercise on coronary heart disease: a systematic review. *J Am Acad Nurse Pract.* 2011;23(7):376-381. doi: 10.1111/j.1745-7599.2011.00597.x.					X
Desveaux L, Beauchamp M, Goldstein R, Brooks D. Community-based exercise programs as a strategy to optimize function in chronic disease: a systematic review. *Med Care.* 2014; 52(3):216-226. doi:10.1097/MLR.0000000000000065.	X				
Dupree CS. Primary prevention of heart failure: an update. *Curr Opin Cardiol.* 2010;25(5):478-483. doi:10.1097/HCO.0b013e32833cd550.					X
e Silva Ade S, da Mota MP. Effects of physical activity and training programs on plasma homocysteine levels: a systematic review. *Amino Acids.* 2014;46(8):1795-1804. doi:10.1007/s00726-014-1741-z.	X				
Ebrahim S, Taylor F, Ward K, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database Syst Rev.* 2011;1:CD001561. doi:0.1002/14651858.CD001561.pub3.				X	
Englert HS, Diehl HA, Greenlaw RL, Willich SN, Aldana S. The effect of a community-based coronary risk reduction: the Rockford CHIP. *Prev Med.* 2007;44(6):513-519.			X		
Fuentes B, Gallego J, Gil-Nunez A, et al. Guidelines for the preventive treatment of ischaemic stroke and TIA (I). Update on risk factors and life style. *Neurologia.* 2012;27(9):560-574. doi: 10.1016/j.nrl.2011.06.002.					X
Gjevestad GO, Holven KB, Ulven SM. Effects of exercise on gene expression of inflammatory markers in human peripheral blood cells: a systematic review. *Curr Cardiovasc Risk Rep.* 2015;9(7):34.	X				
Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research					X

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
Interdisciplinary Working Group. *Stroke*. 2006;37(6):1583-1633.					
Haffey TA. How to avoid a heart attack: putting it all together. *J Am Osteopath Assoc.* 2009;109(5 suppl):S14-S20.			X		
Hartley L, Lee MS, Kwong JSW, Flowers N, Todkill D, Ernst E, Rees K. Qigong for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2015;6:CD010390. doi:10.1002/14651858.CD010390.pub2.					X
Harvard Medical School. Walk more to slash your stroke risk. New research confirms that regular walking helps to prevent stroke. How many steps are required to make a difference?. *Harv Mens Health Watch.* 2014;18(8):1,7.			X		
Kelley GA, Kelley KS. Efficacy of aerobic exercise on coronary heart disease risk factors. *Prev Cardiol.* 2008;11(2):71-75.	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			
Korczak D, Dietl M, Steinhauser G. Effectiveness of programmes as part of primary prevention demonstrated on the example of cardiovascular diseases and the metabolic syndrome. *GMS Health Technology Assessment*. 2011;7:Doc02. doi:10.3205/hta000093.				X	
Lin JS, O'Connor E, Whitlock E, et al. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: update of the evidence for the U.S. Preventive Services Task Force. *Evidence Synthesis No. 79.* AHRQ Publication No. 11-05149-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; December 2010.				X	
Loomba RS, Arora R. Prevention of coronary heart disease in women. *Ther Adv Cardiovasc Dis.* 2008;2(5):321-327. doi:10.1177/1753944708093511.				X	X
McKelvie RS. Heart failure. *BMJ Clin Evid.* 2011. pii:0204.				X	
Palmefors H, DuttaRoy S, Rundqvist B, Borjesson M. The effect of physical activity or exercise on key biomarkers in atherosclerosis-a systematic review. *Atherosclerosis*. 2014;235(1):150-161. doi:10.1016/j.atherosclerosis.2014.04.026.	X				
Reimers CD, Knapp G, Reimers AK. Exercise as stroke prophylaxis. *Dtsch Arztebl Int.* 2009;106(44):715-721. doi:10.3238/arztbl.2009.0715.					X
Ricciardi AC, Lopez-Cancio E, Perez de la Ossa N, et al. Prestroke physical activity is associated with good functional outcome and arterial recanalization after	X	X			

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search
stroke due to a large vessel occlusion. *Cerebrovasc Dis.* 2014;37(4):304-311. doi:10.1159/000360809.					
Vinereanu D. Risk factors for atherosclerotic disease: present and future. *Herz*. 2006;31(3 suppl):5-24.			X		
Walden R, Tomlinson B. Cardiovascular disease. In: Benzie IFF, Wachtel-Galor S, eds. *Herbal Medicine: Biomolecular and Clinical Aspects.* 2nd ed. Boca Raton, FL: CRC Press/Taylor & Francis; 2011. Chapter 16. Available from: https://www.ncbi.nlm.nih.gov/books/NBK92767/			X		
Wang J, Wen X, Li W, Li X, Wang Y, Lu W. Risk factors for stroke in the Chinese population: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* 2017;26(3):509-517.					X

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4. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ*. 2016;354:i3857. doi:10.1136/bmj.i3857.

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7. Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil*. 2008;15(3):247-257. doi:10.1097/HJR.0b013e3282f232ac.

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9. Zheng G, Huang M, Liu F, Li S, Tao J, Chen L. Tai chi chuan for the primary prevention of stroke in middle-aged and elderly adults: a systematic review. *Evid Based Complement Alternat Med*. 2015;2015:742152. doi:10.1155/2015/742152.

10. Zheng H, Orsini N, Amin J, Wolk A, Nguyen VT, Ehrlich F. Quantifying the dose-response of walking in reducing coronary heart disease risk: meta-analysis. *Eur J Epidemiol*. 2009;24(4):181-192. doi:10.1007/s10654-009-9328-9.