

Evidence Portfolio – Cardiometabolic Health and Weight Management Subcommittee, Question 3

In adults without diabetes, what is the relationship between physical activity and type 2 diabetes?

- 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, socio-economic status, or weight status?
- c. Does the relationship vary based on: frequency, duration, intensity, type (mode), or how physical activity is measured?

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

Conclusion Statements and Grades

Strong evidence demonstrates a significant relationship between a higher volume of physical activity and lower incidence of type 2 diabetes. **PAGAC Grade: Strong.**

Strong evidence demonstrates that an inverse curvilinear dose-response relationship exists between the volume of physical activity and incidence of type 2 diabetes, with a decreasing slope at higher levels of physical activity. **PAGAC Grade: Strong.**

Moderate evidence indicates no effect modification by weight status. An inverse relationship exists between a higher volume of physical activity and lower incidence of type 2 diabetes for people who have normal weight, overweight, or obesity. **PAGAC Grade: Moderate.**

Limited evidence suggests that the relationship between a higher volume of physical activity and lower incidence of type 2 diabetes is not influenced by age, sex, or race/ethnicity. **PAGAC Grade: Limited.**

Insufficient evidence is available to determine whether the relationship between physical activity and the incidence of type 2 diabetes varies by socioeconomic status. **PAGAC Grade: Not assignable.**

Insufficient evidence is available to determine whether the relationship between physical activity and the incidence of type 2 diabetes varies by the frequency, intensity, duration, or type of physical activity, or how physical activity is measured. **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 Cardiometabolic Health and Weight Management Subcommittee. Additional searches for original research were not needed.

Existing Systematic Reviews, Meta-Analyses, and Pooled Analysis

Overview

A total of 12 existing reviews were included: 4 systematic reviews,¹⁻⁴ 7 meta-analyses,⁵⁻¹¹ and 1 pooled analysis.¹² The reviews were published between 2007 and 2016.

The systematic reviews included a range of 5 to 20 studies that examined physical activity and type 2 diabetes. Reviews covered the following timeframes: 1950 to 2008,⁴ 1980 to May 2012,³ 1990 to May 2009,¹ and 1999 to August 2008.²

The meta-analyses included a range of 3 to 81 studies that examined physical activity and type 2 diabetes. The meta-analyses covered an extensive timeframe: inception to March 2015,⁵ inception to June 2014,⁷ inception to June 2012,¹⁰ inception to March 2006,⁸ 1980 to 2016,⁹ 1981 to 2014,¹¹ and 1989 to November 2011.⁶

The pooled analysis included 2 studies that examined physical activity and type 2 diabetes.

Exposures

All included reviews examined physical activity. Four reviews assessed physical activity types such as leisure-time physical activity, active commuting, household, and occupational physical activity.^{4-6, 9} One meta-analysis⁷ specifically examined leisure-time physical activity and 1 meta-analysis⁸ examined physical activity of moderate intensity.

Outcomes

All included reviews examined risk or incidence of type 2 diabetes as an outcome.

Populations Analyzed

The table below lists the populations analyzed in each article.

Table 1. Populations Analyzed by All Sources of Evidence

	Sex	Race/ Ethnicity	Age	Weight Status	Other
Aune, 2015			All ages		
Cloostermans, 2015			Adults 25–65	Normal/healthy weight (BMI: 18.5–24.9), Overweight (BMI: 25–29.9), Obese (BMI: 30 and above)	
Fogelholm, 2010,			Adults ≥18	Normal weight vs. overweight vs. obese	
Huai, 2016			Not reported		
Jeon, 2007	Male, Female				U.S. vs. Non-U.S. cohorts
Kyu, 2016			Adults		
Merlotti, 2014			Not reported		
Qin, 2010			Not reported		
Reiner, 2013			Adults 18–85		
Wahid, 2016			Adults 19–79		
Warburton, 2010			Adults 19–65		
Xu, 2015	Male, Female	Asian	Ages 35–49, 50–64, ≥65		Urban

Supporting Evidence

Existing Systematic Reviews, Meta-Analyses, and Pooled Analyses

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

<p>Meta-Analysis Citation: Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis. <i>Eur J Epidemiol.</i> 2015;30(7):529-542. doi:10.1007/s10654-015-0056-z.</p>	
<p>Purpose: To explore associations with specific types of PA, assess a possible dose-response relationship, and address potential confounding.</p>	<p>Abstract: We investigated the association between specific types of physical activity and the risk of type 2 diabetes in a systematic review and meta-analysis of published studies. PubMed, Embase and Ovid databases were searched for prospective studies and randomized trials up to 2nd of March 2015. Summary relative risks (RRs) were calculated using a random effects model. Eighty-one studies were included. The summary RRs for high versus low activity were 0.65 (95 % CI 0.59-0.71, I(2) = 18 %, n = 14) for total physical activity, 0.74 (95 % CI 0.70-0.79, I(2) = 84 %, n = 55) for leisure-time activity, 0.61 (95 % CI 0.51-0.74, I(2) = 73 %, n = 8) for vigorous activity, 0.68 (95 % CI 0.52-0.90, I(2) = 93 %, n = 5) for moderate activity, 0.66 (95 % CI 0.47-0.94, I(2) = 47 %, n = 4) for low intensity activity, and 0.85 (95 % CI 0.79-0.91, I(2) = 0 %, n = 7) for walking. Inverse associations were also observed for increasing activity over time, resistance exercise, occupational activity and for cardiorespiratory fitness. Nonlinear relations were observed for leisure-time activity, vigorous activity, walking and resistance exercise (p nonlinearity < 0.0001 for all), with steeper reductions in type 2 diabetes risk at low activity levels than high activity levels. This meta-analysis provides strong evidence for an inverse association between physical activity and risk of type 2 diabetes, which may partly be mediated by reduced adiposity. All subtypes of physical activity appear to be beneficial. Reductions in risk are observed up to 5-7 h of leisure-time, vigorous or low intensity physical activity per week, but further reductions cannot be excluded beyond this range.</p>
<p>Timeframe: Inception–March 2015</p>	
<p>Total # of Studies: 87 publications (81 studies)</p>	
<p>Exposure Definition: PA. Separate dose-response analyses for studies reporting metabolic equivalent (MET) hours per week and studies reporting on kilocalories of energy expenditure. Subgroups include dose-response analysis of leisure-time PA and total PA; different intensities of PA, including moderate (3–5.9 METs), vigorous (≥ 6 METs), and low intensity PA (1.6–2.9 METs); walking; resistance exercise; and occupational physical activity.</p>	
<p>Measures Steps: No Measures Bouts: No Examines HIIT: No</p>	
<p>Outcomes Addressed: Risk of type 2 diabetes. Examine Cardiorespiratory Fitness as Outcome: No</p>	
<p>Populations Analyzed: All ages</p>	<p>Author-Stated Funding Source: Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.</p>

Meta-Analysis	
Citation: Cloostermans L, Wendel-Vos W, Doornbos G, et al. Independent and combined effects of physical activity and body mass index on the development of type 2 diabetes—a meta-analysis of 9 prospective cohort studies. <i>Int J Behav Nutr Phys Act.</i> Dec 2015;147. doi:10.1186/s12966-015-0304-3.	
Purpose: To examine both the independent and combined effects of PA and body mass index on the development of type 2 diabetes.	Abstract: BACKGROUND: The aim of this harmonized meta-analysis was to examine the independent and combined effects of physical activity and BMI on the incidence of type 2 diabetes. METHODS: Our systematic literature review in 2011 identified 127 potentially relevant prospective studies of which 9 fulfilled the inclusion criteria (total N = 117,878, 56.2 % female, mean age = 50.0 years, range = 25-65 years). Measures of baseline physical activity (low, intermediate, high), BMI-category [BMI < 18.4 (underweight), 18.5-24.9 (normal weight), 25.0-29.9 (overweight), 30+ (obese)] and incident type 2 diabetes were harmonized across studies. The associations between physical activity, BMI and incident type 2 diabetes were analyzed using Cox regression with a standardized analysis protocol including adjustments for age, gender, educational level, and smoking. Hazard ratios from individual studies were combined in a random-effects meta-analysis. RESULTS: Mean follow-up time was 9.1 years. A total of 11,237 incident type 2 diabetes cases were recorded. In mutually adjusted models, being overweight or obese (compared with normal weight) and having low physical activity (compared with high physical activity) were associated with an increased risk of incident type 2 diabetes (hazard ratios 2.33, 95 % CI 1.95-2.78; 6.10, 95 % CI: 4.63-8.04, and 1.23, 95 % CI: 1.09-1.39, respectively). Individuals who were both obese and had low physical activity had 7.4-fold (95 % CI 3.47-15.89) increased risk of type 2 diabetes compared with normal weight, high physically active participants. CONCLUSIONS: This harmonized meta-analysis shows the importance of maintaining a healthy weight and being physically active in diabetes prevention.
Timeframe: 1989–September 2011	
Total # of Studies: 9	
Exposure Definition: PA measures (frequency, intensity, and duration), leisure time PA (including walking, gardening, shopping, and home maintenance), and active commuting. Minutes per week spent in low (sum of PA-minutes/week = 0), medium (0 minutes < sum of PA-minutes/week < 150 minutes), and high PA (sum of PA-minutes/week ≥ 150 minutes) categorized.	
Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Incidence of type 2 diabetes: measured glucose levels or self-report. Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Adults 25–65, Normal/healthy weight (BMI: 18.5–24.9), Overweight (BMI: 25–29.9), Obese (BMI: 30 and above)	Author-Stated Funding Source: Medical Research Council, British Heart Foundation, Economic and Social Research Council (UK); Australian Government Department of Health; American Cancer Society; National Institutes of Health.

Systematic Review Citation: Fogelholm M. Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors. A systematic review. <i>Obes Rev.</i> 2010;11(3):202-221. doi:10.1111/j.1467-789X.2009.00653.x.	
Purpose: To study the relative risks, including type 2 diabetes incidence, of physical inactivity in normal-weight people vs. obesity in individuals with high PA.	Abstract: The purpose of this systematic review was to study the relative health risks of poor cardio-respiratory fitness (or physical inactivity) in normal-weight people vs. obesity in individuals with good cardio-respiratory fitness (or high physical activity). The core inclusion criteria were: publication year 1990 or later; adult participants; design prospective follow-up, case-control or cross-sectional; data on cardio-respiratory fitness and/or physical activity; data on BMI (body mass index), waist circumference or body composition; outcome data on all-cause mortality, cardiovascular disease mortality, cardiovascular disease incidence, type 2 diabetes or cardiovascular and type 2 diabetes risk factors. Thirty-six publications filled the criteria for inclusion. The data indicate that the risk for all-cause and cardiovascular mortality was lower in individuals with high BMI and good aerobic fitness, compared with individuals with normal BMI and poor fitness. In contrast, having high BMI even with high physical activity was a greater risk for the incidence of type 2 diabetes and the prevalence of cardiovascular and diabetes risk factors, compared with normal BMI with low physical activity. The conclusions of the present review may not be applicable to individuals with BMI > 35.
Timeframe: 1990–May 2009	
Total # of Studies: 36 (6 with PA exposure and type 2 diabetes outcome)	
Exposure Definition: PA. Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Type 2 diabetes incidence. Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Age ≥18, Normal weight vs. overweight vs. obese	Author-Stated Funding Source: Not reported.

Meta-Analysis	
Citation: Huai P, Han H, Reilly KH, Guo X, Zhang J, Xu A. Leisure-time physical activity and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. <i>Endocrine</i> . 2016;52(2):226-230. doi:10.1007/s12020-015-0769-5.	
Purpose: To determine the relationship between leisure-time physical activity (LTPA) and type 2 diabetes.	Abstract: Published articles reported controversial results about the association between leisure-time physical activity (LTPA) and risk of type 2 diabetes. A meta-analysis of prospective cohort studies was conducted to explore the effect of LTPA on the incidence of type 2 diabetes. PubMed and Embase databases were searched from its inception to June 13, 2014. Fixed or random effects models were used to calculate the pooled effect sizes based on between-study heterogeneity that was examined by the Q test and I (2) statistic. A total of eight studies, including 296,395 participants and 10,815 incident cases, were included in this study. Both high-level LTPA [high vs. low: hazard ratio (HR) 0.69, 95 % confidence interval (CI) 0.61-0.78] and moderate-level LTPA (moderate vs. low: HR 0.79, 95 % CI 0.70-0.89) were associated with decreased incidence of type 2 diabetes. In conclusion, LTPA was significantly associated with decreased risk of diabetes; high-level LTPA is more beneficial in decreasing the incidence of type 2 diabetes than moderate-level LTPA.
Timeframe: Inception–June 2014	
Total # of Studies: 8	
Exposure Definition: LTPA. For studies with ≥ 3 levels of PA, the lowest level was defined as low-level LTPA, the highest level as high-level LTPA, and all categories in-between as moderate level LTPA. For studies that reported 2 levels of LTPA, LTPA was categorized into low-level and high-level.	
Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Type 2 diabetes. Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Not reported	Author-Stated Funding Source: Risk Factor and Intervention Strategy of Life Expectancy in Shandong Province.

Meta-Analysis	
Citation: Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. <i>Diabetes Care</i> . 2007;30(3):744-752. doi:10.2337/dc06-1842.	
Purpose: To systematically review the epidemiological evidence on the association between PA of moderate intensity and risk of type 2 diabetes.	Abstract: OBJECTIVE: To systematically evaluate the evidence for an association between physical activity of moderate intensity and risk of type 2 diabetes. RESEARCH DESIGN AND METHODS: We searched EMBASE and Medline through March 2006 and examined reference lists of retrieved articles. We excluded studies that did not assess physical activity of moderate intensity independent of activities of vigorous intensity (more than six times the resting metabolic rate). Information on study design, participant characteristics, assessment of physical activity, and outcomes and estimates of associations were extracted independently by two investigators. We calculated summary relative risks (RRs) using a random-effects model for the highest versus the lowest reported duration of activities. RESULTS: We identified 10 prospective cohort studies of physical activity of moderate intensity and type 2 diabetes, including a total of 301,221 participants and 9,367 incident cases. Five of these studies specifically investigated the role of walking. The summary RR of type 2 diabetes was 0.69 (95% CI 0.58-0.83) for regular participation in physical activity of moderate intensity as compared with being sedentary. Similarly, the RR was 0.70 (0.58-0.84) for regular walking (typically > or = 2.5 h/week brisk walking) as compared with almost no walking. The associations remained significant after adjustment for BMI. Similar associations were observed in men and women and in the U.S. and Europe. CONCLUSIONS: These findings indicate that adherence to recommendations to participate in physical activities of moderate intensity such as brisk walking can substantially reduce the risk of type 2 diabetes.
Timeframe: Inception–March 2006	
Total # of Studies: 10	
Exposure Definition: Moderately intense PA, defined as requiring a metabolic equivalent task score of 3.0–6.0. Typical activity of moderate intensity is "brisk" walking at 5.6 km/h on a flat surface, playing golf, leisure bicycling at <10 km/h, and gardening.	
Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Incidence and prevalence of type 2 diabetes. Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Male, Female, U.S. vs. Non-U.S. cohorts	Author-Stated Funding Source: Not reported.

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. <i>BMJ</i> . 2016;354:i3857. doi:10.1136/bmj.i3857.	
Purpose: To quantify the dose-response associations between total PA and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events.	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.
Timeframe: 1980–2016	
Total # of Studies: 174 (55 for diabetes)	
Exposure Definition: Total PA in metabolic equivalent (MET) minutes/week were 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 (4,000–7,999 MET minutes), and highly active (≥8,000 MET minutes).	
Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Diabetes Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Adults	Author-Stated Funding Source: Bill and Melinda Gates Foundation.

Meta-Analysis	
Citation: Merlotti, C, Morabito, A, Pontiroli, AE. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. <i>Diabetes Obes Metab.</i> 2014. 16(8):719-27	
Purpose: To evaluate the effectiveness of different strategies in prevention of type 2 diabetes mellitus.	Abstract: AIM: Different intervention strategies can prevent type 2 diabetes (T2DM). Aim of the present systematic review and meta-analysis was to evaluate the effectiveness of different strategies. METHODS: Studies were grouped into 15 different strategies: 1: diet plus physical activity; 2: physical activity; 3-6: anti-diabetic drugs [glitazones, metformin, beta-cell stimulating drugs (sulphonylureas, glinides), alfa-glucosidase inhibitors]; 7-8: cardiovascular drugs (ACE inhibitors, ARB, calcium antagonists); 9-14 [diets, lipid-affecting drugs (orlistat, bezafibrate), vitamins, micronutrients, estrogens, alcohol, coffee]; 15: bariatric surgery. Only controlled studies were included in the analysis, whether randomized, non-randomized, observational studies, whether primarily designed to assess incident cases of diabetes, or performed with other purposes, such as control of hypertension, of ischemic heart disease or prevention of cardiovascular events. Appropriate methodology [preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement] was used. Seventy-one studies (490 813 subjects), published as full papers, were analysed to identify predictors of new cases of T2DM, and were included in a meta-analysis (random-effects model) to study the effect of different strategies. Intervention effect (new cases of diabetes) was expressed as odds ratio (OR), with 95% confidence intervals (C.I.s). Publication bias was formally assessed. RESULTS: Body mass index was in the overweight range for 13 groups, obese or morbidly obese in lipid-affecting drugs and in bariatric surgery. Non-surgical strategies, except for beta-cell stimulating drugs, estrogens and vitamins, were able to prevent T2DM, with different effectiveness, from 0.37 (C.I. 0.26-0.52) to 0.85 (C.I. 0.77-0.93); the most effective strategy was bariatric surgery in morbidly obese subjects [0.16 (C.I. 0.11,0.24)]. At meta-regression analysis, age of subjects and amount of weight lost were associated with effectiveness of intervention. CONCLUSIONS: These data indicate that several strategies prevent T2DM, making it possible to make a choice for the individual subject.
Timeframe: Inception–June 2012	
Total # of Studies: 71 (20 with PA)	
Exposure Definition: PA (grouped into diet + PA and PA or education). Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Incidence of type 2 diabetes (as a means to develop an odds ratio and evaluate likelihood of development as a product of exposure effectiveness). Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Not reported	Author-Stated Funding Source: Not reported.

<p>Systematic Review Citation: Qin L, Knol MJ, Corpeleijn E, Stolck RP. Does physical activity modify the risk of obesity for type 2 diabetes: a review of epidemiological data. <i>Eur J Epidemiol.</i> 2010;25(1):5-12. doi:10.1007/s10654-009-9395-y.</p>	
<p>Purpose: To summarize the evidence on the interaction between obesity and physical inactivity as they contribute to risk of type 2 diabetes.</p>	<p>Abstract: Obesity and physical inactivity are both risk factors for type 2 diabetes. Since they are strongly associated, it has been suggested that they might interact. In this study, we summarized the evidence on this interaction by conducting a systematic review. Two types of interaction have been discerned, statistical and biological interaction, which could give different results. Therefore, we calculated both types of interaction for the studies in our review. Cohort studies, published between 1999 and 2008, that investigated the effects of obesity and physical activity on the risk of type 2 diabetes were included. We calculated both biological and statistical interaction in these studies. Eight studies were included of which five were suitable to calculate interaction. All studies showed positive biological interaction, meaning that the joint effect was more than the sum of the individual effects. However, there was inconsistent statistical interaction; in some studies the joint effect was more than the product of the individual effects, in other studies it was less. The results show that obesity and physical inactivity interact on an additive scale. This means that prevention of either obesity or physical inactivity, not only reduces the risk of diabetes by taking away the independent effect of this factor, but also by preventing the cases that were caused by the interaction between both factors. Furthermore, this review clearly showed that results can differ depending on what method is used to assess interaction.</p>
<p>Timeframe: 1999–August 2008</p>	
<p>Total # of Studies: 8</p>	
<p>Exposure Definition: Self-reported physical inactivity and PA (in tandem with obesity status) were reported in categories or metabolic equivalent (MET) hours. Physically active was defined as ≥ 21.8 MET hours/week and physically inactive was defined as <2.1 MET hours/week.</p> <p>Measures Steps: No Measures Bouts: No Examines HIIT: No</p>	
<p>Outcomes Addressed: Relative risk of type 2 diabetes mellitus: relative risk representing the individual effect of obesity (the risk in obese and physically active individuals relative to the risk in normal weight and physically active individuals), the relative risk representing the individual effect of physical inactivity (the risk in normal weight and physically inactive individuals relative to the risk in normal weight and physically active individuals), the relative risk representing the joint effect of obesity and physical inactivity (the risk in obese and physically inactive individuals relative to the risk in normal weight and physically active individuals). Examine Cardiorespiratory Fitness as Outcome: No</p>	
<p>Populations Analyzed: Not reported</p>	<p>Author-Statement Funding Source: Not reported.</p>

Systematic Review Citation: Reiner M, Niermann C, Jekauc D, Woll A. Long-term health benefits of physical activity—a systematic review of longitudinal studies. <i>BMC Public Health</i> . Sept 2013;813. doi:10.1186/1471-2458-13-813.	
Purpose: To review long-term effects of PA on the development of weight gain and obesity, coronary heart disease, and type 2 diabetes mellitus in healthy adults.	Abstract: BACKGROUND: The treatment of noncommunicable diseases (NCD), like coronary heart disease or type 2 diabetes mellitus, causes rising costs for the health system. Physical activity is supposed to reduce the risk for these diseases. Results of cross-sectional studies showed that physical activity is associated with better health, and that physical activity could prevent the development of these diseases. The purpose of this review is to summarize existing evidence for the long-term (>5 years) relationship between physical activity and weight gain, obesity, coronary heart disease, type 2 diabetes mellitus, Alzheimer's disease and dementia. METHODS: Fifteen longitudinal studies with at least 5-year follow up times and a total of 288,724 subjects (>500 participants in each study), aged between 18 and 85 years, were identified using digital databases. Only studies published in English, about healthy adults at baseline, intentional physical activity and the listed NCDs were included. RESULTS: The results of these studies show that physical activity appears to have a positive long-term influence on all selected diseases. CONCLUSIONS: This review revealed a paucity of long-term studies on the relationship between physical activity and the incidence of NCD.
Timeframe: 1980–May 2012	
Total # of Studies: 18 (5 type 2 diabetes mellitus outcome)	
Exposure Definition: Self-reported intentional PA or intentional activities of daily living over the long term (5 or more years). Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Incident risk of type 2 diabetes mellitus. Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Adults 18–85	Author-Stated Funding Source: Not reported.

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. <i>J Am Heart Assoc.</i> 2016;5(9). pii:e002495. doi:10.1161/JAHA.115.002495.	
Purpose: Draw together the epidemiological studies that assesses the independent association between PA levels and both cardiovascular disease and type 2 diabetes mellitus outcomes, using a single continuous metric and adjusting for body weight.	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.
Timeframe: 1981–2014	
Total # of Studies: 36 (3 related to type 2 diabetes)	
Exposure Definition: Exposure data for PA was converted to a common continuous metric of metabolic equivalent hours per week. Measures Steps: No Measures Bouts: No Examines HIIT: No	
Outcomes Addressed: Type 2 diabetes mellitus Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Adults 19–79	Author-Stated Funding Source: British Heart Foundation.

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. <i>Int J Behav Nutr Phys Act.</i> 2010;7:39. doi:10.1186/1479-5868-7-39.9	
Purpose: 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 (70 with type 2 diabetes as an outcome)	
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: Type 2 diabetes Examine Cardiorespiratory Fitness as Outcome: No	
Populations Analyzed: Adults 19–65	Author-Stated Funding Source: Public Health Agency of Canada.

<p>Pooled Analysis Citation: Xu F, Wang Y, Ware RS, et al. Joint impact of physical activity and family history on the development of diabetes among urban adults in Mainland China: a pooled analysis of community-based prospective cohort studies. <i>Asia Pac J Public Health</i>. 2015;27(2):NP372-381. doi:10.1177/1010539512443700.</p>	
<p>Purpose: To examine the joint effect of PA and parental history of diabetes on the risk of developing type II diabetes by pooling data from 2 community-based cohorts of urban adults living in a large regional city in Mainland China.</p>	<p>Abstract: To examine the joint influences of physical activity (PA) and family history (FH) of diabetes on subsequent type 2 diabetes (T2D), the authors pooled and analyzed data from 2 community-based urban adult prospective cohort studies in 2011 in Nanjing, China. Among 4550 urban participants, the 3-year cumulative incidence of T2D was 5.1%. After adjustment for potential confounders, compared with those with FH+ and insufficient PA, the adjusted odds ratio (95% confidence interval) of developing T2D was 0.42 (0.18, 0.98) for participants with sufficient PA and FH+, 0.32 (0.22, 0.46) for participants with insufficient PA and FH-, and 0.15 (0.08, 0.28) for participants with sufficient PA and FH-. Such significant graduated associations between PA/FH and risk of developing T2D were also identified in either men or women, separately. Sufficient PA and FH- may jointly reduce the risk of developing T2D in urban Chinese adults.</p>
<p>Total # of Studies: 2</p>	
<p>Exposure Definition: Self-reported frequency and duration of PA using Chinese short version of International Physical Activity Questionnaire. Total PA time was calculated as the sum of the time spent performing moderate PA plus double the time spent in vigorous PA. Total PA time equal to or greater than 150 minutes/week was classified as sufficient PA, and less than 150 minutes/week was classified as insufficient PA.</p> <p>Measures Steps: No Measures Bouts: No Examines HIIT: No</p>	
<p>Outcomes Addressed: Type II diabetes mellitus; odds ratio of incident risk of type II diabetes. Examine Cardiorespiratory Fitness as Outcome: No</p>	
<p>Populations Analyzed: Male; Female; Asian; Ages 35–49, 50–64, ≥65; Urban</p>	
<p>Author-Stated Funding Source: Nanjing Medical Science and Technique Development Foundation and Jiangsu Provincial Science and Technology Foundation.</p>	

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

AMSTARExBP: SR/MA						
	Aune, 2015	Cloostermans, 2015	Fogelholm, 2010	Huai, 2016	Jeon, 2007	Kyu, 2016
Review questions and inclusion/exclusion criteria delineated prior to executing search strategy.	Yes	Yes	Yes	Yes	Yes	Yes
Population variables defined and considered in methods.	Yes	Yes	No	No	Yes	Yes
Was a comprehensive literature search performed?	Yes	Partially Yes	Partially Yes	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	No	No	No	Yes	Yes	Yes
Search strategy clearly described.	Yes	Yes	Yes	Yes	Yes	Yes
Relevant grey literature included in review.	No	No	No	No	No	No
List of studies (included and excluded) provided.	Yes	No	No	No	No	No
Characteristics of included studies provided.	Yes	Yes	Yes	No	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	Yes	No	N/A	No	No	Yes
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	No	No	Partially Yes	No	Yes
Results depended on study quality, either overall, or in interaction with moderators.	Yes	N/A	N/A	No	N/A	Yes
Scientific quality used appropriately in formulating conclusions.	Yes	N/A	N/A	No	N/A	Yes
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	Yes	N/A	Yes	Yes	Yes
Effect size index chosen justified, statistically.	Yes	Partially Yes	N/A	Yes	Yes	Yes
Individual-level meta-analysis used.	No	No	N/A	No	No	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	Yes	No	No	Yes	Yes	Yes
Conflict of interest disclosed.	Yes	Yes	No	Yes	No	Yes

AMSTARExBP: SR/MA						
	Merlotti, 2014	Qin, 2010	Reiner, 2013	Wahid, 2016	Warburton, 2010	Xu, 2015
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	No	Yes	Yes	Yes
Was a comprehensive literature search performed?	Yes	Partially Yes	Partially Yes	Yes	Yes	N/A
Duplicate study selection and data extraction performed.	Yes	No	No	Yes	Yes	N/A
Search strategy clearly described.	Yes	Yes	Yes	Yes	Yes	N/A
Relevant grey literature included in review.	Yes	No	No	No	No	N/A
List of studies (included and excluded) provided.	No	No	No	Yes	No	N/A
Characteristics of included studies provided.	Yes	Yes	Yes	Yes	Yes	No
FITT defined and examined in relation to outcome effect sizes.	No	N/A	N/A	No	N/A	No
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	No	No	Yes	Yes	No
Results depended on study quality, either overall, or in interaction with moderators.	No	N/A	N/A	Yes	Yes	N/A
Scientific quality used appropriately in formulating conclusions.	Yes	N/A	N/A	Yes	Yes	N/A
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	N/A	N/A	Yes	N/A	No
Effect size index chosen justified, statistically.	Yes	N/A	N/A	Yes	N/A	No
Individual-level meta-analysis used.	No	N/A	N/A	No	N/A	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	Yes	No	No	Yes	No	N/A
Conflict of interest disclosed.	No	No	No	Yes	Yes	Yes

Appendices

Appendix A: Analytical Framework

Topic Area

Cardiometabolic Health and Weight Management

Systematic Review Question

In adults without diabetes, what is the relationship between physical activity and type 2 diabetes?

- 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, socio-economic status, or weight status?
- c. Does the relationship vary based on frequency, duration, intensity, type (mode), or how physical activity is measured?

Population

Adults, ages 18 and older without diabetes

Exposure

All types and intensities of physical activity, including lifestyle activities, leisure activities, and sedentary behavior

Comparison

Adults who participate in varying levels of physical activity, including no reported physical activity

Endpoint Health Outcomes

Type 2 diabetes

Key Definitions

- Non-diabetic/normal: Having an A1C below 5.7%, fasting blood glucose less than 100 mg/dL, and an OGTT 2-hour blood glucose lower than 140 mg/dL.
- Prediabetes: Having an A1C of 5.7%–6.4%, fasting blood glucose of 100–125 mg/dl, and an OGTT 2-hour blood glucose of 140 mg/dL–199 mg/dL.
- Diabetes: Having an A1C of 6.5% or higher, fasting blood glucose of 126 mg/dL or higher, and an OGTT 2-hour blood glucose of 200 mg/dL or higher.

Appendix B: Final Search Strategy

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

Database: PubMed; Date of Search: 5/11/17; 972 results

Set	Search Strategy
Limit: Language	(English[lang])
Limit: Exclude animal only	NOT ("Animals"[mh] NOT ("Animals"[mh] AND "Humans"[mh]))
Limit: Exclude child only	NOT (("infant"[mh] OR "child"[mh] OR "child, preschool"[mh] OR "adolescent"[mh]) NOT (("infant"[mh] OR "child"[mh] OR "child, preschool"[mh] OR "adolescent"[mh]) AND "adult"[mh]))
Limit: Publication Date (Systematic Reviews/Meta-Analyses)	AND ("2006/01/01"[PDAT] : "3000/12/31"[PDAT])
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])
Physical Activity	AND (("Aerobic endurance"[tiab] OR "Bicycl*"[tiab] OR "Endurance training"[tiab] OR "Exercise"[mh] OR "Exercise"[tiab] OR "Exercises"[tiab] OR "Free living activities"[tiab] OR "Free living activity"[tiab] OR "Functional training"[tiab] OR "Leisure-time physical activity"[tiab] OR "Lifestyle activities"[tiab] OR "Lifestyle activity"[tiab] OR "Muscle stretching exercises"[mh] OR "Physical activity"[tiab] OR "Qi gong"[tiab] OR "Recreational activities"[tiab] OR "Recreational activity"[tiab] OR "Resistance training"[tiab] OR "Running"[tiab] OR "Sedentary lifestyle"[mh] OR "Speed training"[tiab] OR "Strength training"[tiab] OR "Tai chi"[tiab] OR "Tai ji"[mh] OR "Tai ji"[tiab] OR "Training duration"[tiab] OR "Training frequency"[tiab] OR "Training intensity"[tiab] OR "Treadmill"[tiab] OR "Walking"[tiab] OR "Weight lifting"[tiab] OR "Weight training"[tiab] OR "Yoga"[mh] OR "Yoga"[tiab]) 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 "Physical activities"[tiab] OR "Physical conditioning"[tiab] OR "Sedentary"[tiab]) NOT medline[sb]))
Outcome	AND ("Diabetes"[tiab] OR "diabetes mellitus"[mh])

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

Database: CINAHL; Date of Search: 5/11/17; 29 results

Terms searched in title or abstract

Set	Search Terms
Physical Activity	("Aerobic endurance" OR "Bicycl*" OR "Endurance training" OR "Exercise" OR "Exercises" OR "Free living activities" OR "Free living activity" OR "Functional training" OR "Leisure-time physical activity" OR "Lifestyle activities" OR "Lifestyle activity" OR "Muscle stretching exercises" OR "Physical activity" OR "Qi gong" OR "Recreational activities" OR "Recreational activity" OR "Resistance training" OR "Running" OR "Sedentary lifestyle" OR "Speed training" OR "Strength training" OR "Tai chi" OR "Tai ji" OR "Tai ji" OR "Training duration" OR "Training frequency" OR "Training intensity" OR "Treadmill" OR "Walking" OR "Weight lifting" OR "Weight training" OR "Yoga" OR "Aerobic activities" OR "Aerobic activity" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Endurance activities" OR "Endurance activity" OR "Physical activities" OR "Physical conditioning" OR "Sedentary")
Outcomes	AND ("Diabetes" OR "diabetes mellitus")
Systematic Reviews and Meta-Analyses	("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)

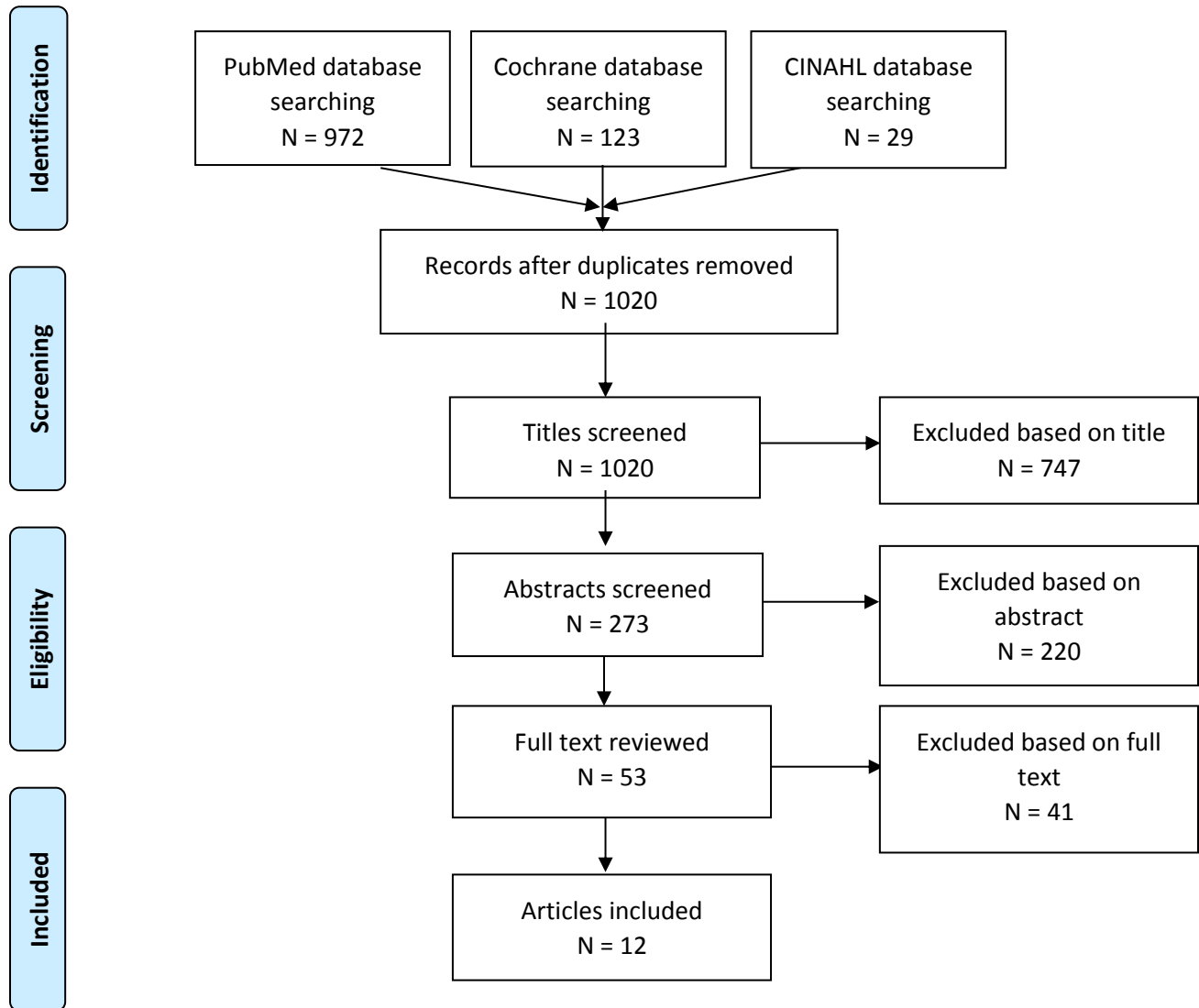
Database: Cochrane; Date of Search: 5/11/17; 123 results

Terms searched in title, abstract, or keywords

Set	Search Terms
Physical Activity	("Aerobic endurance" OR "Bicycl*" OR "Endurance training" OR "Exercise" OR "Exercises" OR "Free living activities" OR "Free living activity" OR "Functional training" OR "Leisure-time physical activity" OR "Lifestyle activities" OR "Lifestyle activity" OR "Muscle stretching exercises" OR "Physical activity" OR "Qi gong" OR "Recreational activities" OR "Recreational activity" OR "Resistance training" OR "Running" OR "Sedentary lifestyle" OR "Speed training" OR "Strength training" OR "Tai chi" OR "Tai ji" OR "Tai ji" OR "Training duration" OR "Training frequency" OR "Training intensity" OR "Treadmill" OR "Walking" OR "Weight lifting" OR "Weight training" OR "Yoga" OR "Aerobic activities" OR "Aerobic activity" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Endurance activities" OR "Endurance activity" OR "Physical activities" OR "Physical conditioning" OR "Sedentary")
Outcomes	AND ("Diabetes" OR "diabetes mellitus")
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

Cardiometabolic Health and Weight Management Subcommittee

Systematic Review Question: In adults without diabetes, what is the relationship between physical activity and type 2 diabetes?

- 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, socio-economic status, or weight status?
- c. Does the relationship vary based on frequency, duration, intensity, type (mode), or how physical activity is measured?

Category	Inclusion/Exclusion Criteria	Notes/Rationale
Publication Language	Include: <ul style="list-style-type: none"> • Studies published with full text in English 	
Publication Status	Include: <ul style="list-style-type: none"> • Studies published in peer-reviewed journals • Reports determined to have appropriate suitability and quality by PAGAC Exclude: <ul style="list-style-type: none"> • Grey literature, including unpublished data, manuscripts, abstracts, conference proceedings 	
Research Type	Include: <ul style="list-style-type: none"> • Original research: Prospective (concurrent; longitudinal) cohort studies; randomized controlled trials • Meta-analyses • Systematic reviews • Pooled analyses • Reports determined to have appropriate suitability and quality by PAGAC 	
Study Subjects	Include: <ul style="list-style-type: none"> • Human subjects 	
Age of Study Subjects	Include: <ul style="list-style-type: none"> • Adults ages 18 and older • When data are analyzed by age groups, only data with lower age range of 18 may be included (e.g., in a study with individuals 13–21 where data are presented for multiple age groups, only data for 18 and older may be included) 	
Health Status of Study Subjects	Include: <ul style="list-style-type: none"> • Healthy adults without diabetes • People who are overweight or obese • Adults with pre-diabetes or impaired glucose tolerance Exclude:	

	<ul style="list-style-type: none"> • Studies of adults with any chronic condition (obesity is ok) • Hospitalized patients • Smokers only 	
Comparison	<p>Include:</p> <ul style="list-style-type: none"> • Adults who participate in varying levels of physical activity, including no reported physical activity • Recreational athletes (marathons ok as long as the study looks at a diverse group of runners—not just the elites) <p>Exclude:</p> <ul style="list-style-type: none"> • High-performance athletes • Studies comparing athletes to non-athletes • Studies comparing athlete types (e.g., comparing runners to soccer players) 	
Date of Publication	<p>Include:</p> <ul style="list-style-type: none"> • Original research published from 2006 to 2017 • Systematic reviews and meta-analyses published from 2006 to 2017 	
Study Design	<p>Include:</p> <ul style="list-style-type: none"> • Randomized trials • Prospective cohort studies • Systematic reviews • Meta-analyses • Pooled analyses • PAGAC approved reports <p>Exclude:</p> <ul style="list-style-type: none"> • Non-randomized trials • Retrospective cohort studies • Case-control studies • Before-After studies • Narrative reviews • Commentaries • Editorials • Cross-sectional studies • Time series 	
Intervention/ Exposure	<p>Include studies in which the exposure or intervention is:</p> <ul style="list-style-type: none"> • All types and intensities of physical activity, including lifestyle activities, leisure activities, and sedentary behavior <p>Exclude:</p>	

	<ul style="list-style-type: none"> • Studies that do not include physical activity (or the lack thereof) as the primary exposure variable or used solely as a confounding variable • Studies missing physical activity (mental games such as Sudoku instead of physical activities) 	
Outcome	Include studies in which the outcome is: <ul style="list-style-type: none"> • Type 2 diabetes 	
Study Duration (Original Research)	<ul style="list-style-type: none"> • Minimum 1 year for observational studies 	

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	Other
Abdulameer SA, Sulaiman SA, Hassali MA, Subramaniam K, Sahib MN. Osteoporosis and type 2 diabetes mellitus: what do we know, and what we can do? <i>Patient Prefer Adherence</i> . 2012;6:435-448. doi:10.2147/PPA.S32745.		X				
Abubakari AR, Bhopal RS. Systematic review on the prevalence of diabetes, overweight/obesity and physical inactivity in Ghanaians and Nigerians. <i>Public Health</i> . 2008;122(2):173-182. doi:10.1016/j.puhe.2007.06.012.				X		
Abubakari AR, Lauder W, Jones MC, Kirk A, Agyemang C, Bhopal RS. Prevalence and time trends in diabetes and physical inactivity among adult West African populations: the epidemic has arrived. <i>Public Health</i> . 2009;123(9):602-614. doi:10.1016/j.puhe.2009.07.009.				X		
Adeniyi AF, Adeleye JO, Adeniyi CY. Diabetes, sexual dysfunction and therapeutic exercise: a 20 year review. <i>Curr Diabetes Rev</i> . 2010;6(4):201-206. doi:10.2174/157339910791658907.		X				
Afable A, Karingula NS. Evidence based review of type 2 diabetes prevention and management in low and middle income countries. <i>World J Diabetes</i> . 2016;7(10):209-229. doi:10.4239/wjd.v7.i10.209.		X				
Aguiar EJ, Morgan PJ, Collins CE, Plotnikoff RC, Callister R. Efficacy of interventions that include diet, aerobic and resistance training components for type 2 diabetes prevention: a systematic review with meta-analysis. <i>Int J Behav Nutr Phys Act</i> . Jan 2014;2. doi:10.1186/1479-5868-11-2.				X		
Ahmad S, Shanmugasagaram S, Walker KL, Prince SA. Examining sedentary time as a risk factor for cardiometabolic diseases and their markers in South Asian adults: a systematic review. <i>Int J Public Health</i> . 2017;62(4):503-515. doi:10.1007/s00038-017-0947-8.				X		
Al Tunajji H, Davis JC, Mackey DC, Khan KM. Population attributable fraction of type 2 diabetes due to physical inactivity in adults:	X					

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
a systematic review. <i>BMC Public Health</i> . May 2014;469. doi:10.1186/1471-2458-14-469.						
Aljasir B, Bryson M, Al-Shehri B. Yoga practice for the management of type II diabetes mellitus in adults: a systematic review. <i>Evid Based Complement Alternat Med</i> . 2010;7(4):399-408. doi:10.1093/ecam/nen027.		X				
Allothman S, Yahya A, Rucker J, Kluding PM. Effectiveness of interventions for promoting objectively measured physical activity of adults with type 2 diabetes: a systematic review. <i>J Phys Act Health</i> . 2017;14(5):408-415. doi:10.1123/jpah.2016-0528.		X				
Alouki K, Delisle H, Bermudez-Tamayo C, Jhori M. Lifestyle interventions to prevent type 2 diabetes: a systematic review of economic evaluation studies. <i>J Diabetes Res</i> . Jan 2016:2159890. doi:10.1155/2016/2159890.	X					
Alsairafi ZK, Taylor KM, Smith FJ, Alattar AT. Patients' management of type 2 diabetes in Middle Eastern countries: review of studies. <i>Patient Prefer Adherence</i> . June 2016:1051-1062. doi:10.2147/PPA.S104335.	X					
American Diabetes Association. Prevention or delay of type 2 diabetes. <i>Diabetes Care</i> . 2015;(38)(suppl 1):S31-S32. doi:10.2337/dc15-S008.			X			
Angermayr L, Melchart D, Linde K. Multifactorial lifestyle interventions in the primary and secondary prevention of cardiovascular disease and type 2 diabetes mellitus—a systematic review of randomized controlled trials. <i>Ann Behav Med</i> . 2010;40(1):49-64. doi:10.1007/s12160-010-9206-4.				X		
Antunes LC, Levandovski R, Dantas G, Caumo W, Hidalgo MP. Obesity and shift work: chronobiological aspects. <i>Nutr Res Rev</i> . 2010;23(1):155-168. doi:10.1017/S0954422410000016.				X		
Appuhamy JA, Kebreab E, Simon M, Yada R, Milligan LP, France J. Effects of diet and exercise interventions on diabetes risk factors in adults without diabetes: meta-analyses of controlled trials. <i>Diabetol Metab Syndr</i> . Nov 2014:127. doi:10.1186/1758-5996-6-127.				X		

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
Arambepola C, Ricci-Cabello I, Manikavasagam P, Roberts N, French DP, Farmer A. The impact of automated brief messages promoting lifestyle changes delivered via mobile devices to people with type 2 diabetes: a systematic literature review and meta-analysis of controlled trials. <i>J Med Internet Res.</i> 2016;18(4):e86. doi:10.2196/jmir.5425.		X				
Avery L, Flynn D, Dombrowski SU, van Wersch A, Sniehotta FF, Trenell MI. Successful behavioural strategies to increase physical activity and improve glucose control in adults with type 2 diabetes. <i>Diabet Med.</i> 2015;32(8):1058-1062. doi:10.1111/dme.12738.		X				
Avery L, Flynn D, Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. <i>Diabetes Care.</i> 2012;35(12):2681-2689. doi:10.2337/dc11-2452.		X				
Baskerville R, Ricci-Cabello I, Roberts N, Farmer A. Impact of accelerometer and pedometer use on physical activity and glycaemic control in people with type 2 diabetes: a systematic review and meta-analysis. <i>Diabetic Medicine.</i> 2017;34(5):612-620. doi:10.1111/dme.13331.		X				
Bhurji N, Javer J, Gasevic D, Khan NA. Improving management of type 2 diabetes in South Asian patients: a systematic review of intervention studies. <i>BMJ Open.</i> 2016;6(4):e008986. doi:10.1136/bmjopen-2015-008986.		X				
Bian RR, Piatt GA, Sen A, et al. The effect of technology-mediated diabetes prevention interventions on weight: a meta-analysis. <i>J Med Internet Res.</i> 2017;19(3):e76. doi:10.2196/jmir.4709.				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. <i>Ann Intern Med.</i> 2015;162(2):123-132. doi:10.7326/M14-1651.				X		
Blaha MJ, Bansal S, Rouf R, Golden SH, Blumenthal RS, Defilippis AP. A practical "ABCDE" approach to the metabolic syndrome. <i>Mayo Clin Proc.</i> 2008;83(8):932-941. doi:10.4065/83.8.932.				X		

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
Bosomworth NJ. Approach to identifying and managing atherogenic dyslipidemia: a metabolic consequence of obesity and diabetes. <i>Can Fam Physician</i> . 2013;59(11):1169-1180.				X		
Bravata DM, Smith-Spangler C, Sundaram V, et al. Using pedometers to increase physical activity and improve health: a systematic review. <i>JAMA</i> . 2007;298(19):2296-2304. doi:10.1001/jama.298.19.2296.	X					
Brinks R, Hoyer A, Kuss O, Rathmann W. Projected effect of increased active travel in German urban regions on the risk of type 2 diabetes. <i>PLoS One</i> . 2015;10(4):e0122145. doi:10.1371/journal.pone.0122145.			X			
Brocklebank LA, Falconer CL, Page AS, Perry R, Cooper AR. Accelerometer-measured sedentary time and cardiometabolic biomarkers: a systematic review. <i>Prev Med</i> . 2015;76:92-102. doi:10.1016/j.ypmed.2015.04.013.	X					
Brown SA, Garcia AA, Brown A, et al. Biobehavioral determinants of glycemic control in type 2 diabetes: a systematic review and meta-analysis. <i>Patient Educ Couns</i> . 2016;99(10):1558-1567. doi:10.1016/j.pec.2016.03.020.		X				
Brunton SA, Rolla AR. Implementing intensified treatment strategies for patients with type 2 diabetes mellitus. <i>J Fam Pract</i> . 2007;56(11)(suppl):S9-S16.		X				
Brunton SA. The changing shape of type 2 diabetes. <i>Medscape J Med</i> . 2008;10(6):143; quiz 143.		X				
Byrne H, Caulfield B, De Vito G. Effects of self-directed exercise programmes on individuals with type 2 diabetes mellitus: a systematic review evaluating their effect on HbA1c and other metabolic outcomes, physical characteristics, cardiorespiratory fitness and functional outcomes. <i>Sports Med</i> . 2017;47(4):717-733. doi:10.1007/s40279-016-0593-y.		X				
Caffrey MK. Evidence builds on yoga, but no reimbursement yet. <i>Am J Manag Care</i> . 2014;20(8 Spec No.):E5.			X			
Cai H, Li G, Zhang P, Xu D, Chen L. Effect of exercise on the quality of life in type 2 diabetes mellitus: a systematic review. <i>Qual Life Res</i> . 2017;26(3):515-530. doi:10.1007/s11136-016-1481-5.		X				

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
Cai X, Qiu SH, Yin H, et al. Pedometer intervention and weight loss in overweight and obese adults with type 2 diabetes: a meta-analysis. <i>Diabet Med</i> . 2016;33(8):1035-1044. doi:10.1111/dme.13104.		X				
Cayley WE. The role of exercise in patients with type 2 diabetes. <i>Am Fam Physician</i> . 2007;75(3):335-336.		X				
Ceysens G, Rouiller D, Boulvain M. Exercise for diabetic pregnant women. <i>Cochrane Database Syst Rev</i> . 2006;(3):Cd004225. doi:10.1002/14651858.CD004225.pub2.		X				
Chapman A, Meyer C, Renehan E, Hill KD, Browning CJ. Exercise interventions for the improvement of falls-related outcomes among older adults with diabetes mellitus: a systematic review and meta-analyses. <i>J Diabetes Complications</i> . 2017;31(3):631-645. doi:10.1016/j.jdiacomp.2016.09.015.		X				
Chen L, Pei JH, Kuang J, et al. Effect of lifestyle intervention in patients with type 2 diabetes: a meta-analysis. <i>Metabolism</i> . 2015;64(2):338-347. doi:10.1016/j.metabol.2014.		X				
Christensen J, Valentiner LS, Petersen RJ, Langberg H. The effect of game-based interventions in rehabilitation of diabetics: a systematic review and meta-analysis. <i>Telemed J E Health</i> . 2016;22(10):789-797. doi:10.1089/tmj.2015.0165.		X				
Chudyk A, Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. <i>Diabetes Care</i> . 2011;34(5):1228-1237. doi:10.2337/dc10-1881.		X				
Cigolle CT, Blaum CS, Halter JB. Diabetes and cardiovascular disease prevention in older adults. <i>Clin Geriatr Med</i> . 2009;25(4):607-641, vii-viii. doi:10.1016/j.cger.2009.09.001.		X				
Colberg SR, Grieco CR. Exercise in the treatment and prevention of diabetes. <i>Curr Sports Med Rep</i> . 2009;8(4):169-175. doi:10.1249/JSR.0b013e3181ae0654.		X				
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