Exposure

Chair: Bill Kraus

Members: Wayne Campbell, John Jakicic, Kathy Janz, Ken Powell

Experts and Consultants

- Consultant:
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  Stanford University

Subcommittee Questions

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

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

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

Subcommittee Questions

4. What is the relationship between bout duration of continuous aerobic physical activity and cardiorespiratory fitness and health outcomes?

5. What is the relationship between step count per day and (1) mortality (i.e., all-cause or cause-specific) and (2) disease incidence (e.g., coronary heart disease, type 2 diabetes)?

6. What is the relationship between high intensity interval training and reduction in cardiometabolic risk?

Question # 3

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

- Source of evidence to answer question:
  - Systematic reviews
  - Meta-analyses

Analytical Framework

Systematic Review Questions

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

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

Common Inclusion/ Exclusion Criteria

- Language
  - Exclude: Studies that do not have full text in English
- Publication Status
  - Include: Studies published in peer-reviewed journals, PAGAC-approved reports
  - Exclude: Grey literature
- Study Subjects
 - Exclude: Studies of animals only

Inclusion/Exclusion Criteria

- Date of Publication
  - Existing Sources: Include 2006 - Present
- Study Subjects
  - Include: Only studies conducted in general population.
  - Exclude: Studies on patients with existing cardiovascular disease or on high performance athletes.
- Study Design
  - Include: Systematic reviews, Meta-analyses, PAGAC-Approved reports
  - Exclude: Narrative reviews, Commentaries, Editorials
- Exposure/Intervention
  - Include: All types and intensities of physical activity
  - Exclude: Missing physical activity, Single, acute session of exercise, Therapeutic exercise, Physical fitness as the exposure, Only used as confounding variable, Sedentary behavior
- Outcome
  - Include: Cardiovascular disease incidence:
    - Coronary heart disease/ischemic heart disease
    - Coronary artery disease
    - Stroke of all types
    - Heart failure
  - Exclude: Congenital heart disease

Search Terms

- Physical Activity Terms
  - "Aerobic activities", "Aerobic activity", "Cardiovascular activities", "Cardiovascular activity", "Endurance activities", "Endurance activity", "Energy expenditure", "Exercise" OR "Physical activity", "Resistance training", "Sedentary lifestyle", "strength training", "physical conditioning", "walking.

- Outcome Terms
  - "Arteriosclerosis", "Cerebral infarction", "Cerebrovascular diseases", "Cerebrovascular disease", "Coronary heart disease", "Heart failure", "Intracerebral Hemorrhage", "Intracerebral Hemorrhages", "Intracranial hemorrhage", "Intracranial hemorrhages", "Myocardial ischemia", "myocardial infarction", "Stroke", "Subarachnoid hemorrhage", "Subarachnoid hemorrhages", "Ischemic heart diseases", "Ischemic heart disease".

Search Results: High-Quality Reviews[1]
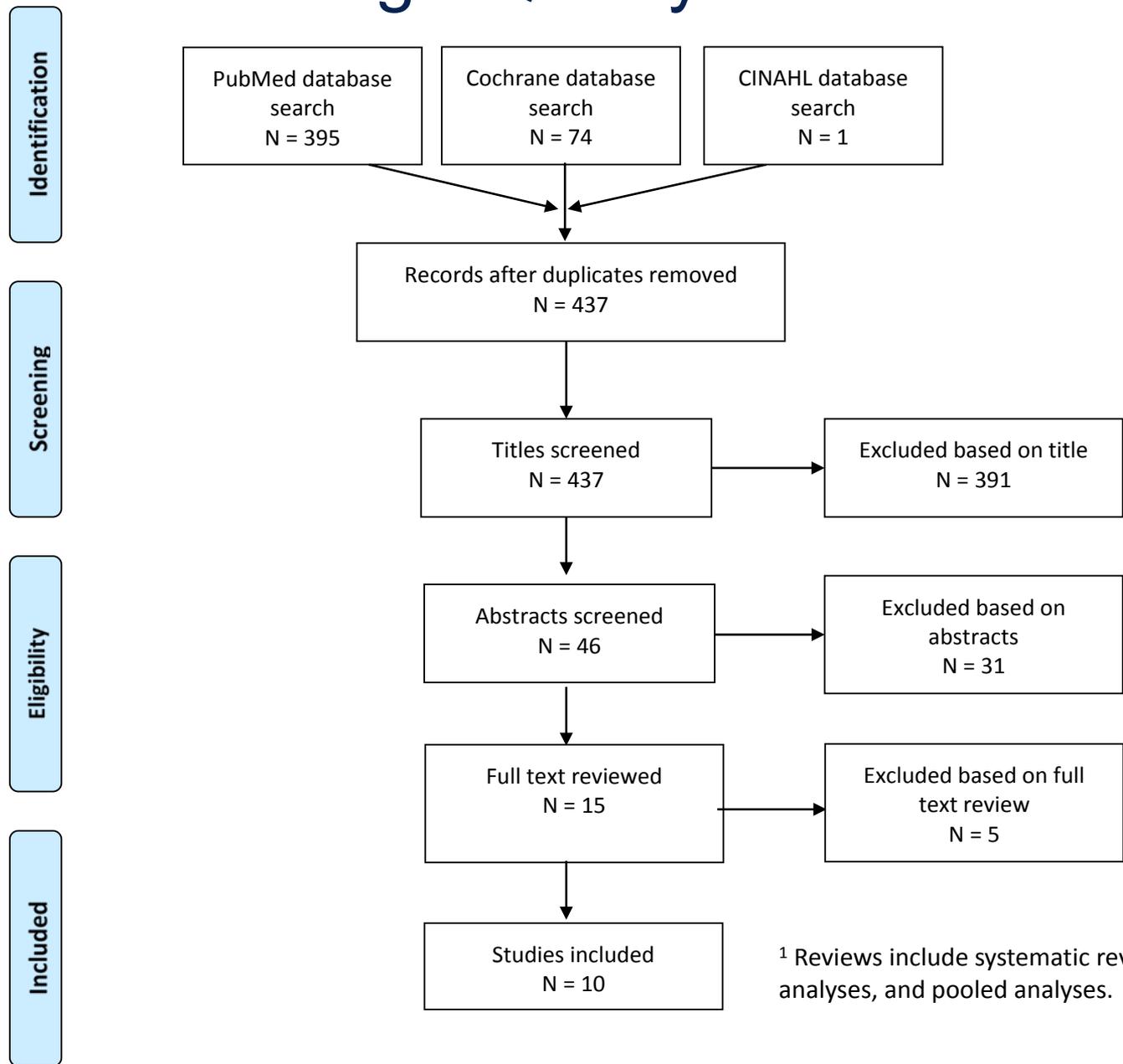
Identification

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Records after duplicates removed
N = 437

Screening

Titles screened
N = 437

Excluded based on title
N = 391

Eligibility

Abstracts screened
N = 46

Excluded based on abstracts
N = 31

Full text reviewed
N = 15

Excluded based on full text review
N = 5

Included

Studies included
N = 10

[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

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Description of the Evidence

- Included reviews (n=10)
  - 1 systematic review and 9 meta-analyses
  - Published 2008-2016
- Some studies examined sub-group effects:
  - Gender, Age groups (<55, >55; ≥30)
- Exposure
  - Mostly self-reported PA
  - Different domains assessed (leisure, occupational, transportation PA)
- Mostly longitudinal cohort studies

Draft Key Findings

- 3# reviews of 95 studies assessed CVD in n>500,000 plus 3.6M

- 2# reviews of 36 studies assessed stroke in n=210,000 plus 3.6M

- 3# reviews of 48 studies assessed heart failure in n=350,000 plus 3.6M

- Tai Chi and Stroke

- Walking and CVD
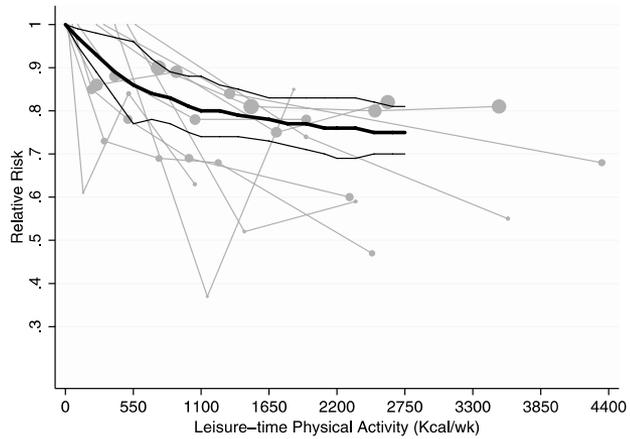
Sattelmair, J.,Pertman, J.,Ding, E. L.,Kohl, H. W., 3rd,Haskell, W.,Lee, I. M. (2011). Dose response between physical activity and risk of coronary heart disease: a meta-analysis Circulation, 124(7), 789-95

Men - Pooled Relative Risk of CHD by Kcal/wk of LTPA
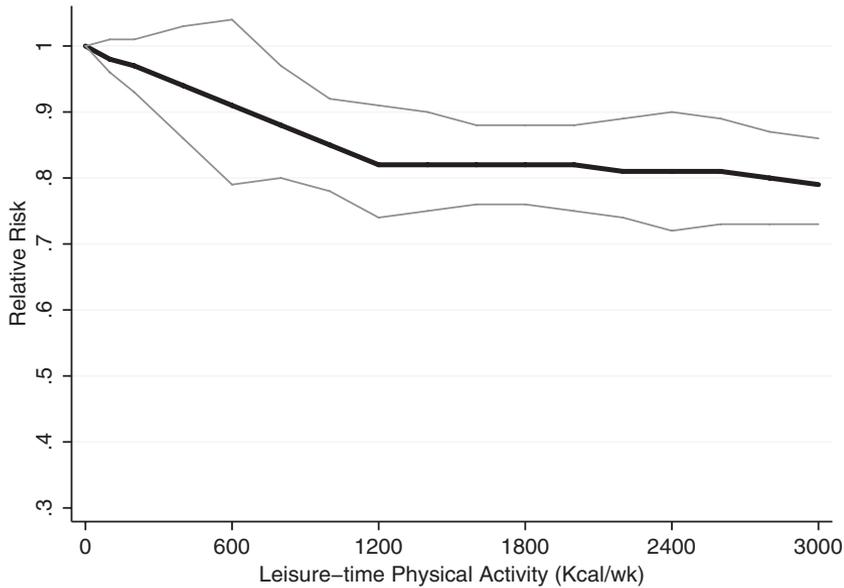
Women - Pooled Relative Risk of CHD by Kcal/wk of LTPA
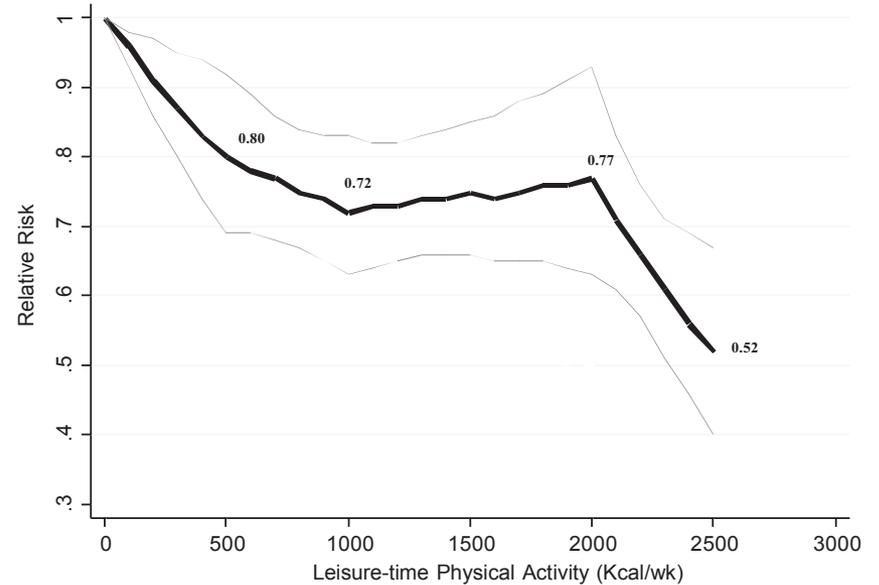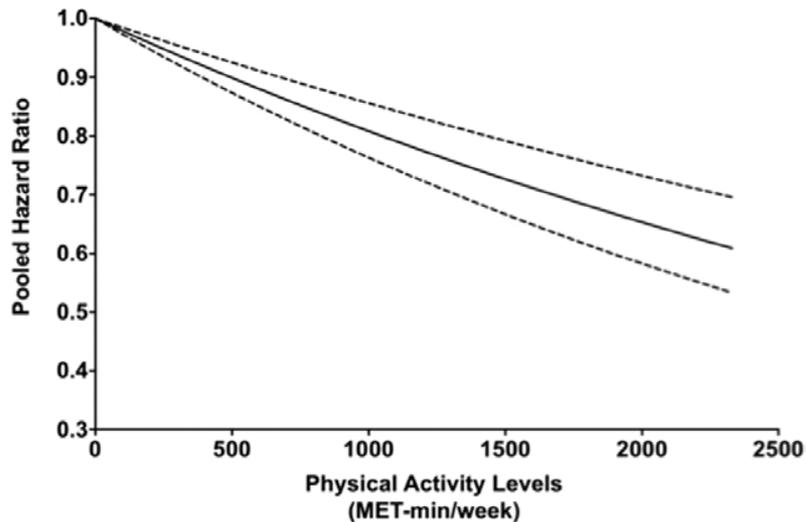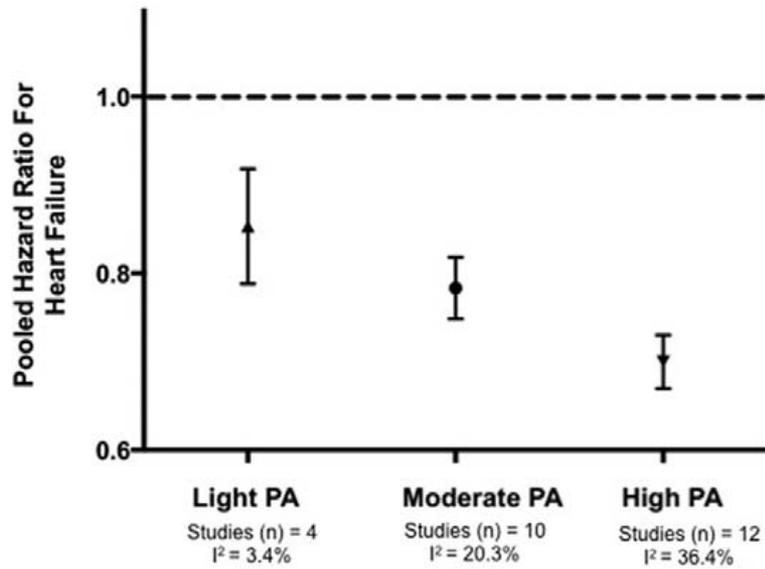
Pandey, A.,Garg, S.,Khunger, M.,Darden, D.,Ayers, C.,Kumbhani, D. J.,Mayo, H. G.,de Lemos, J. A.,Berry, J. D. (2015). Dose-Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis Circulation, 132(19), 1786-94

CVD

MET (minutes/week)

CVA

MET (minutes/week)
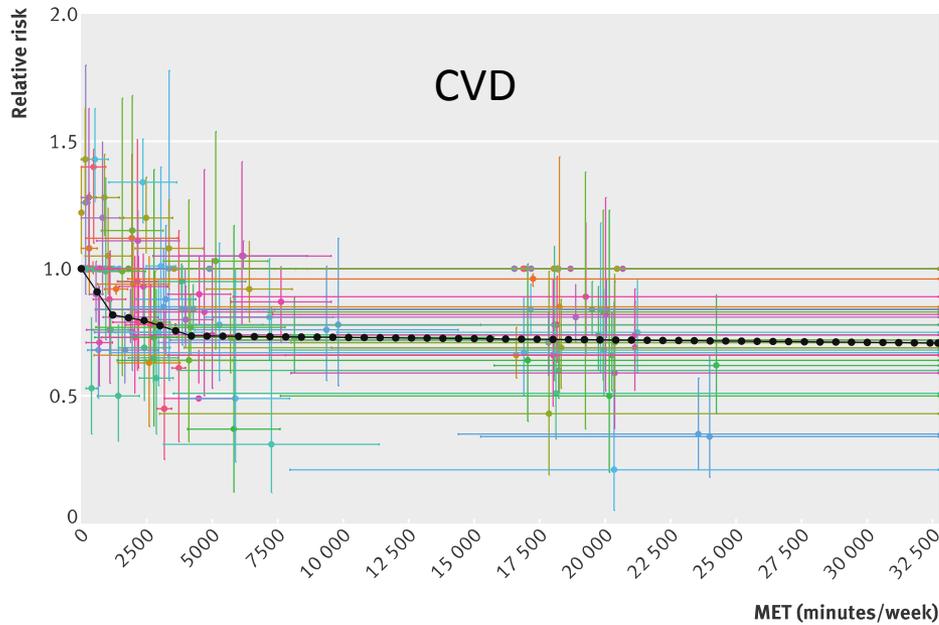
Kyu, H. H.,Bachman, V. F.,Alexander, et al. (2016). Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013 BMJ, 354.
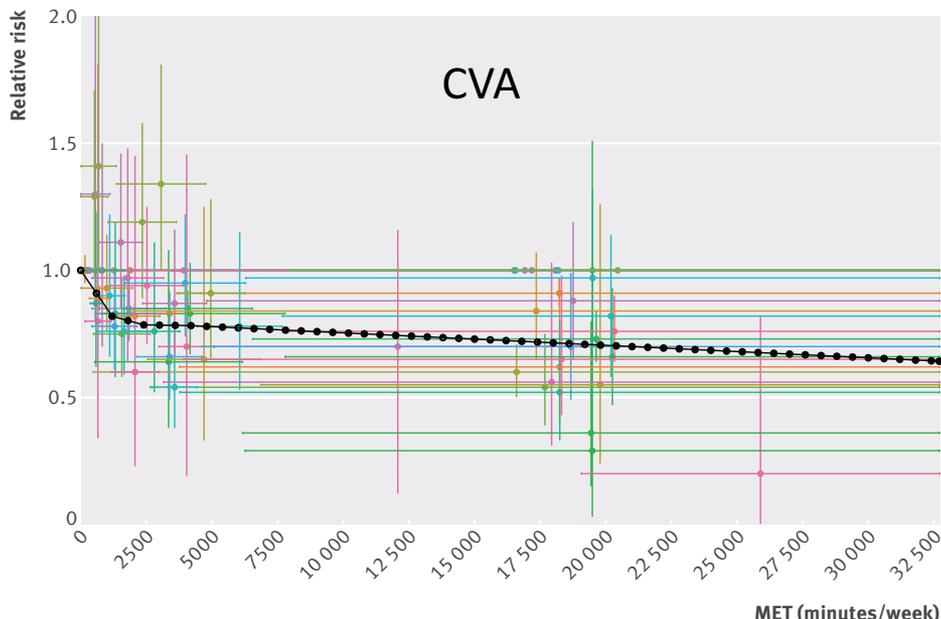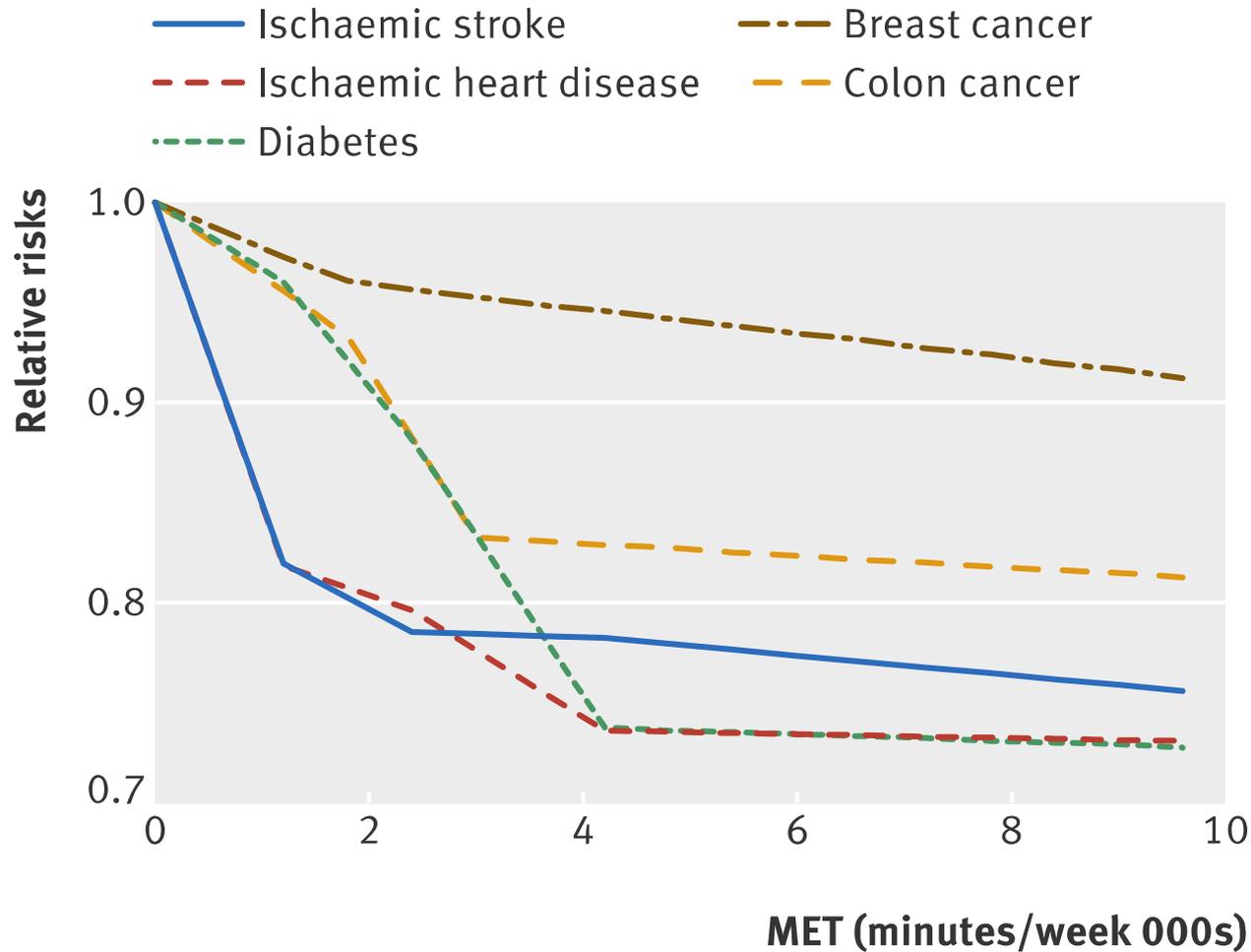
Kyu, H. H., Bachman, V. F., Alexander, L. et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013 BMJ, 354.

Draft Conclusion Statement

- ## **Conclusion Statements:**
  - There is strong evidence that greater amounts of physical activity are associated with decreased risks for CVD, stroke and heart failure.
  - The strength of the evidence is unlikely to be modified by more studies.

Yet to be done

- Evaluate for stratification by age, gender, race, ethnicity, SES, BMI.
- Evaluate for intensity, amount and mode.
- Position dose-response curves for CVD, HF and stroke.

Committee Discussion

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

Bouts, Steps and High Intensity Interval Training (HIIT)

- Search Strategies

Search Terms (Combined search SR/MA)
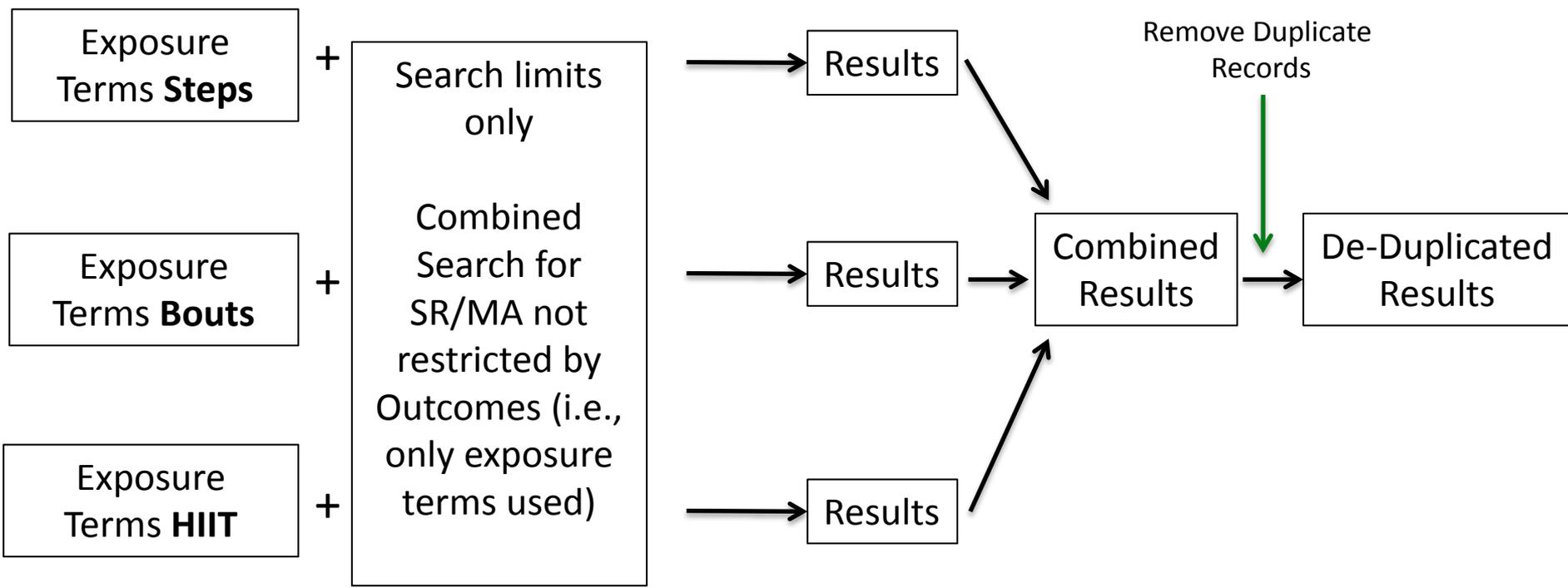
Exposure Terms

- Steps: "Pedometer", "Step count", "Steps/day", "Daily steps", "Walking".

- Bouts: "intermittent activity", intermittent exercise", "accumulated activity", "bouts"

- HIIT: "High intensity activity", "Interval training", "high intensity interval training", "High intensity" AND "training".

Search Terms (Adding outcome terms for Steps and Bouts original research search)

Outcome Terms

- **CVD OR Type 2 Diabetes:** Arterisoclero*, "Arteriosclerosis", "Cerebral infarction", "Cerebrovascular diseases", "Cerebrovascular disease", "Coronary heart disease", "Heart failure", "Intracerebral Hemorrhage", "Intracerebral Hemorrhages", "Intracranial hemorrhage", "Intracranial hemorrhages", "Myocardial ischemia", "myocardial infarction", "Stroke", "Subarachnoid hemorrhage", "Subarachnoid hemorrhages", "Ischemic heart diseases", "Ischemic heart disease", "insulin resistance", "Blood glucose", Hyperglycemia, "Diabetes Mellitus, Type 2".

- **Incidence OR Mortality:** "risk", "risks", "Incidence", "incident", "Death", "Dying", Fatal*, Mortalit*, "Mortality", "Postmortem".

- **Cardiometabolic risk factors OR Cardiorespiratory fitness (for bouts only):** "blood pressure", "systolic pressure", "diastolic pressure", "mean arterial", "bp response", "bp decrease", "bp reduction", "normotensive", "hypertension", "hypotension", "normotension", "hypertensive", "hypotensive", "Body weight", "Body composition", "Body Mass Index", "Waist circumference", "Body weight change", "Weight gain", "Weight status", "Overweight", "Weight Control", "Weight maintenance", "Weight regulation", "Weight stability", "Body composition", "Body Mass Index", "Waist circumference", "glucose intolerance", "glucose control", "insulin resistance", "prediabetes", "pre-diabetes", "(diabetes AND ("type 2" OR "type II", "lipoproteins", "cholesterol", "triglycerides", "triglyceride", "blood lipids", "lipoprotein", "Cardiorespiratory fitness", "VO2 max", "maximal oxygen uptake", "peak oxygen uptake", "aerobic capacity".

Question # 4 Bouts

- What is the relationship between bout duration of continuous aerobic physical activity and cardiorespiratory fitness OR health outcomes (e.g., death, CAD, diabetes) OR risk factors for death or disease (e.g., BP, HDL, insulin sensitivity)?

- Source of evidence to answer question:
  - Combination of SR/MA/Existing report and de novo systematic review of original articles

Analytical Framework

Systematic Review Questions

Q5. What is the relationship between bout duration of continuous aerobic physical activity and cardiorespiratory fitness and health outcomes?

Population
Adults, 18 years and older

Exposure

- Physical activity (PA) performed in short bouts
- PA exposure of at least 12 weeks (intervention studies).

Comparison
Different PA bout durations

Endpoint Health Outcomes

- All-cause and CVD mortality
- CVD incidence
- Incidence of Type 2 Diabetes
- Cardiorespiratory fitness
- Cardio metabolic risk factors:
  - Blood Pressure
  - Blood lipids (total cholesterol, HDL- cholesterol, LDL- cholesterol, triglycerides.
  - Body mass, BMI
  - Waist circumference

Inclusion/Exclusion Criteria

- Date of Publication
  - Original Research: 1990-Present
- Study Subjects
  - Include: Only studies conducted in general population.
  - Exclude: Studies on patients with existing cardiovascular disease or on high performance athletes.
- Study Design
  - Include: Randomized controlled trials, Non-randomized controlled trials, Prospective cohort studies, Retrospective cohort studies, Before-and-after studies, Cross-sectional studies, Systematic reviews, Meta-analyses, Pooled analyses, PAGAC-Approved reports.
  - Exclude: Narrative reviews, Commentaries, Editorials,.
- Exposure/Intervention
  - Include:
    - Intervention or observational studies that use accelerometer or other objective measures to assess physical activity (PA) performed in short bouts. Bouts should be spread throughout the day (not within the same session of exercise).
    - Studies with any bout duration ideally less than 10 minutes.
    - For intervention studies the duration of the PA exposure should be at least 12 weeks.
- Outcome
  - Include:
    - All-cause and CVD mortality
    - CVD incidence
    - Type 2 Diabetes
    - Cardio metabolic risk factors and Cardiorespiratory fitness
  - Exclude: Congenital heart disease and studies on progression of CVD.

Search Results Q5 BOUTS: High-Quality Reviews[1]
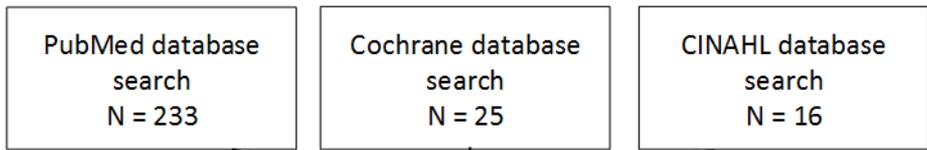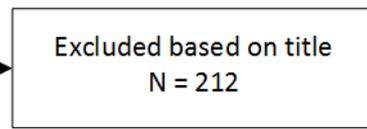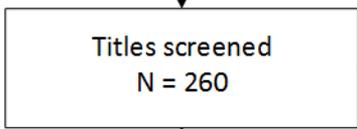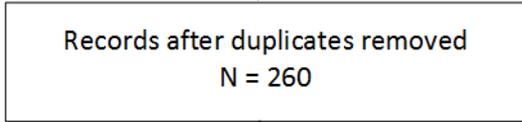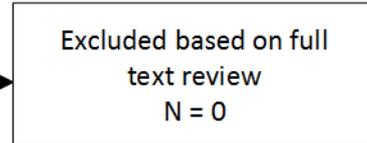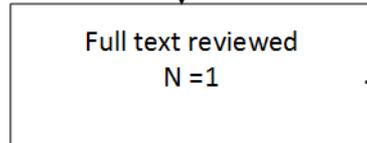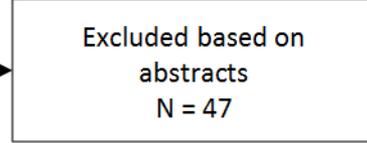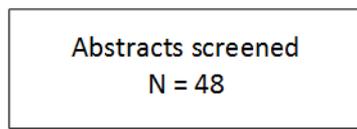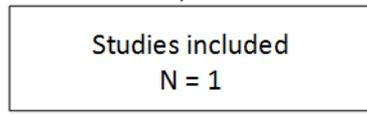
Identification

| PubMed database search N = 233 | Cochrane database search N = 25 | CINAHL database search N = 16 |

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Records after duplicates removed
N = 260

Screening

Titles screened
N = 260 → Excluded based on title
N = 212

Eligibility

Abstracts screened
N = 48 → Excluded based on abstracts
N = 47

Full text reviewed
N = 1 → Excluded based on full text review
N = 0

Included

Studies included
N = 1

[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

29

Search Results Q5 BOUTS: Original Research

Identification

PubMed database search
N = 1087

Cochrane database search
N = 101

CINAHL database search
N = 433

Records after duplicates removed
N = 1242

Screening

Titles screened
N = 1242

Excluded based on title
N = 1144

Abstracts screened
N = 98

Excluded based on abstracts
N = 70

Eligibility

Full text reviewed (in progress)
N =29

Excluded based on full text review
N = TBD

Included

Studies included
N = TBD

Description of the Evidence

- 27 of the 29 studies appear to be included
  - Design
    - 13 cross-sectional
    - 1 prospective
    - 13 intervention
  - Duration
    - 20 with durations $\geq$10 minutes per bout
    - 15 with durations <10 minutes per bout

Description of the Evidence

- Outcomes
  - 19 = weight, body composition, adiposity
  - 9 = lipids
  - 8 = blood pressure
  - 8 = glucose, insulin, etc.
  - 7 = fitness
  - 6 = metabolic syndrome
  - 2 = other cardiovascular risk outcomes

Committee Discussion

- What is the relationship between bout duration of continuous aerobic physical activity and cardiorespiratory fitness OR health outcomes (e.g., death, CAD, diabetes) OR risk factors for death or disease (e.g., BP, HDL, insulin sensitivity)?

Question # 5 Steps

- What is the relationship between step count per day and (1) mortality (i.e., all-cause or cause-specific) and (2) disease incidence (e.g., coronary heart disease, type 2 diabetes)?

- Source of evidence to answer question:
  - Combination of SR/MA/Existing report and de novo systematic review of original articles.

Analytical Framework

Systematic Review Questions

Q4. What is the relationship between step count per day and (1) mortality (i.e., all-cause and CVD) and (2) disease incidence (e.g., CVD, type 2 diabetes)?

Population
Adults, 18 years and older

Exposure
- PA in **step counts** per day

Endpoint Health Outcomes
- All-cause and CVD mortality
- CVD incidence
- Incidence of Type 2 Diabetes

Common Inclusion/ Exclusion Criteria

- Language
  - Exclude: Studies that do not have full text in English

- Publication Status
  - Include: Studies published in peer-reviewed journals, PAGAC-approved reports
  - Exclude: Grey literature

- Study Subjects
  - Exclude: Studies of animals only

Inclusion/Exclusion Criteria

- Date of Publication
  - Existing Sources: Include Inception – Present
  - Original Research: 2011-Present
- Study Subjects
  - Include: Only studies conducted in general population.
  - Exclude: Studies on patients with existing cardiovascular disease or on high performance athletes.
- Study Design
  - Include: Randomized controlled trials, Non-randomized controlled trials, Prospective cohort studies, Retrospective cohort studies, Before-and-after studies, Systematic reviews, Meta-analyses, Pooled analyses, PAGAC-Approved reports
  - Exclude: Narrative reviews, Commentaries, Editorials, Cross-sectional studies.
- Exposure/Intervention
  - Include: Studies that qualify (objectively) steps per day as an exposure.
  - Exclude: Missing physical activity, Single, acute session of exercise, Therapeutic exercise, Physical fitness as the exposure, Only used as confounding variable, Sedentary behavior
- Outcome
  - Include:
    - All-cause and CVD mortality
    - CVD incidence
    - Type 2 Diabetes
  - Exclude: Congenital heart disease and studies on progression of CVD.

Search Results Q4 STEPS: High-Quality Reviews[1]

Identification

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Records after duplicates removed
N = 260

Screening

Titles screened
N = 260

Excluded based on title
N = 212

Eligibility

Abstracts screened
N = 48

Excluded based on abstracts
N = 45

Full text reviewed
N = 3

Excluded based on full text review
N = 1

Included

Studies included
N = 2
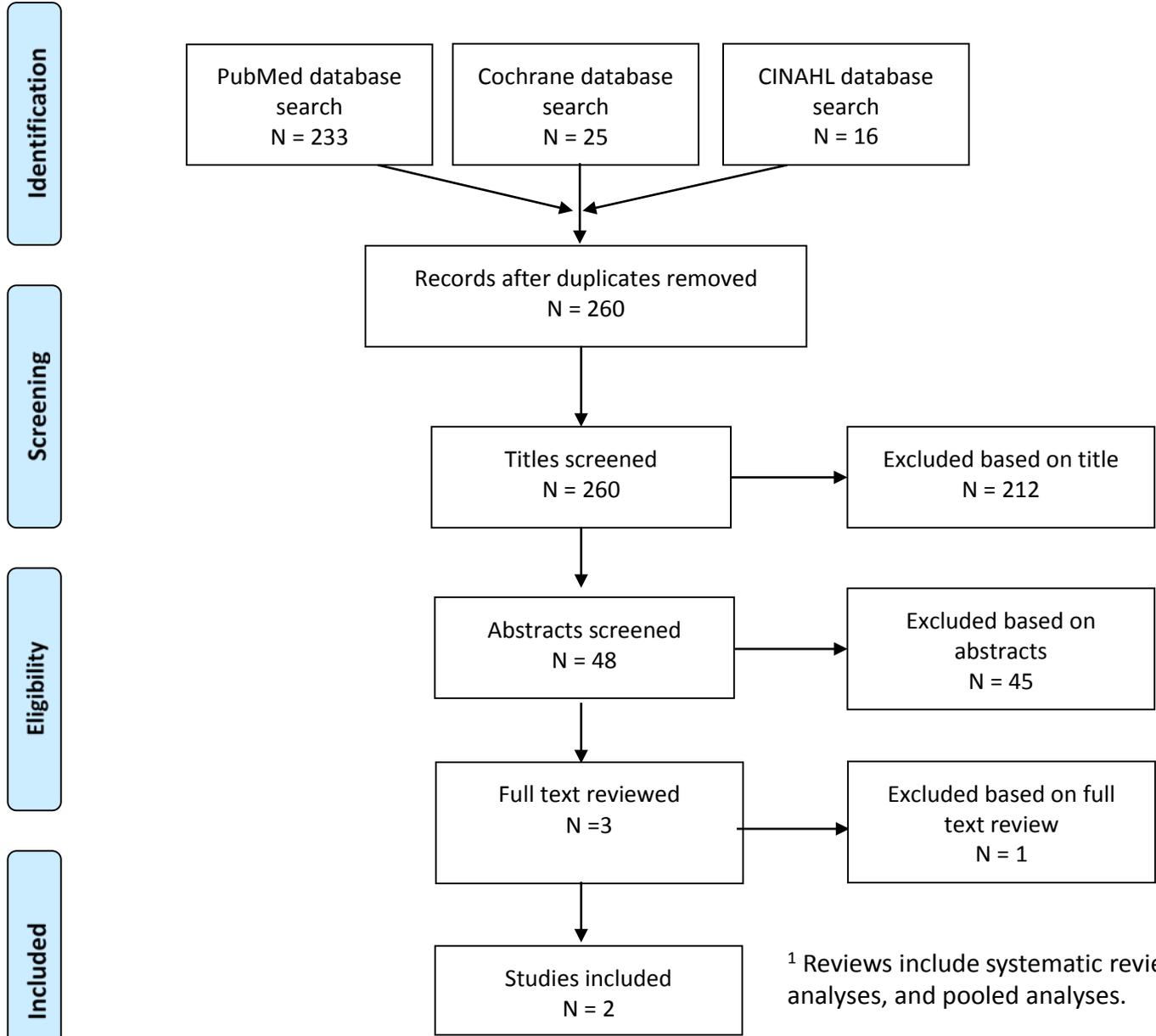
[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Search Results Q4 STEPS: Original Research

PubMed database search N = 454	Cochrane database search N = 26	CINAHL database search N = 286

Records after duplicates removed
N = 632

Screening

Titles screened
N = 632 → Excluded based on title N =TBD

Eligibility

Abstracts screened
N = TBD → Excluded based on abstracts N = TBD

Full text reviewed
N =TBD → Excluded based on full text review N = TBD

Included

Studies included
N = TBD

39
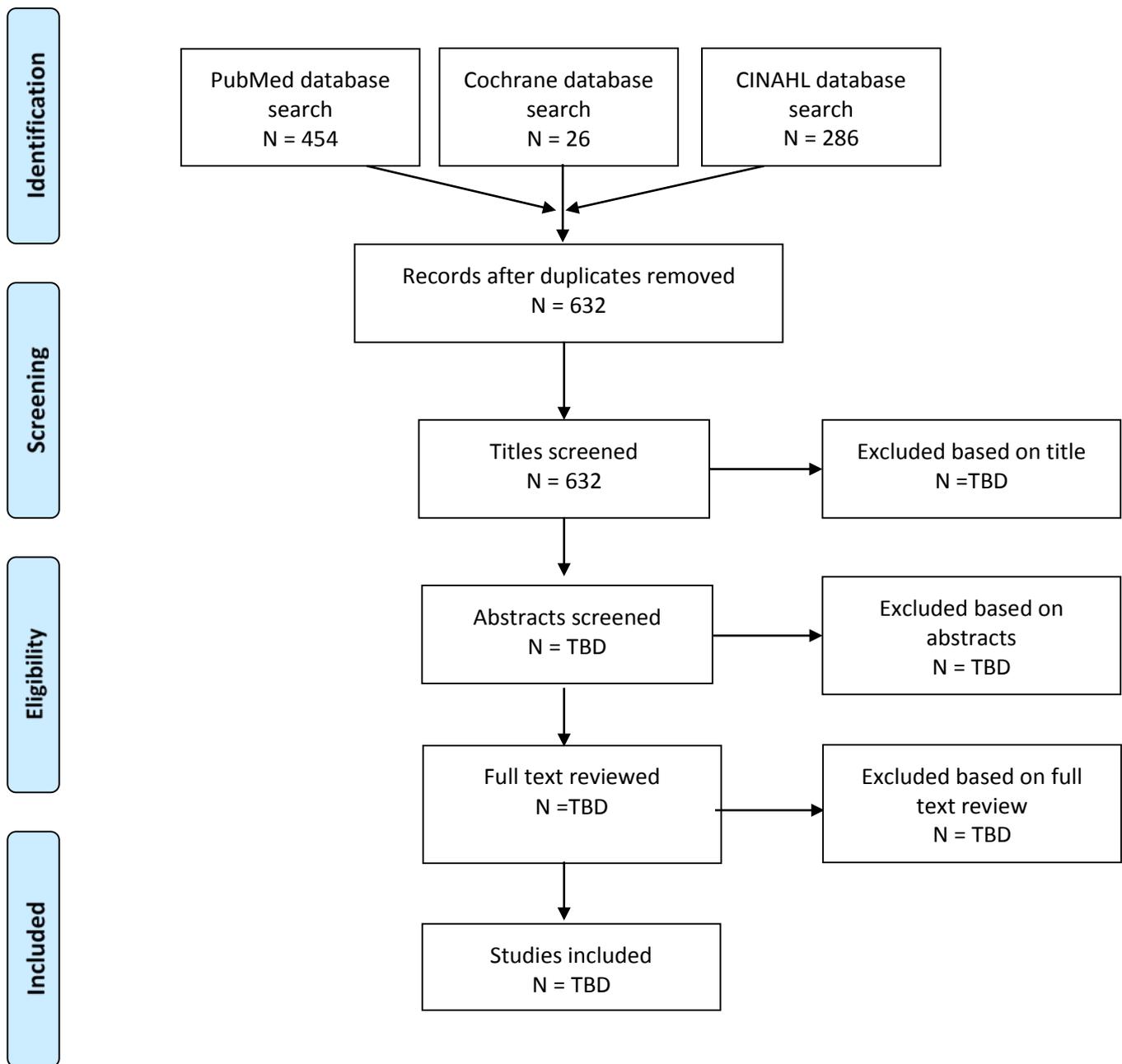
Description of the Evidence

- Included reviews (n=2) Same Group
  - 1 systematic review of adult normative counts/d
  - 1 systematic review of older adult normative counts/d
- Some studies examined sub-group effects:
  - Gender, Age Groups, Ethnicity, Nationality
- Exposure
  - Pedometer-measured steps
- Dose-response
  - Addressed as narrative review, not tabulated or critiqued
- Original Research Not As Yet Triaged

Committee Discussion

- What is the relationship between step count per day and (1) mortality (i.e., all-cause or cause-specific) and (2) disease incidence (e.g., coronary heart disease, type 2 diabetes)?

Question # 6

- What is the relationship between high intensity interval training and reduction in cardiometabolic risk?

- **Definition:** interval training as non-steady-state aerobic training on an aerobic device. Periods of high intensity training are interspersed by recovery periods. The entire bout exposure takes place in one "session."

- Source of evidence to answer question:
  - Systematic reviews
  - Meta-analyses

Question # 6

- What is the relationship between high intensity interval training and reduction in cardiometabolic risk?
  - Is there a dose-response relationship? If yes, what is the shape of the relationship?
  - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?

Analytical Framework

Systematic Review Questions

Q6. What is the relationship between high intensity interval training and reduction in cardiometabolic risk?

Population
Adults, 18 years and older

Exposure
- PA performed as high-intensity interval training.

Comparison
- Different PA intensities

Endpoint Health Outcomes
- All-cause and CVD mortality
- CVD incidence
- Incidence of Type 2 Diabetes
- Cardiorespiratory fitness
- Cardio metabolic risk factors:
    - Blood Pressure
    - Blood lipids (total cholesterol, HDL- cholesterol, LDL- cholesterol, triglycerides.
    - Body mass, BMI
    - Waist circumference

Search Results Q6 HIIT: High-Quality Reviews[1]

Identification

| PubMed database search N = 233 | Cochrane database search N = 25 | CINAHL database search N = 16 |

Screening

Records after duplicates removed
N = 260

Titles screened
N = 260 → Excluded based on title N = 212

Eligibility

Abstracts screened
N = 48 → Excluded based on abstracts N = 37

Full text reviewed
N =11 → Excluded based on full text review N = 8

Included

Studies included
N = 3
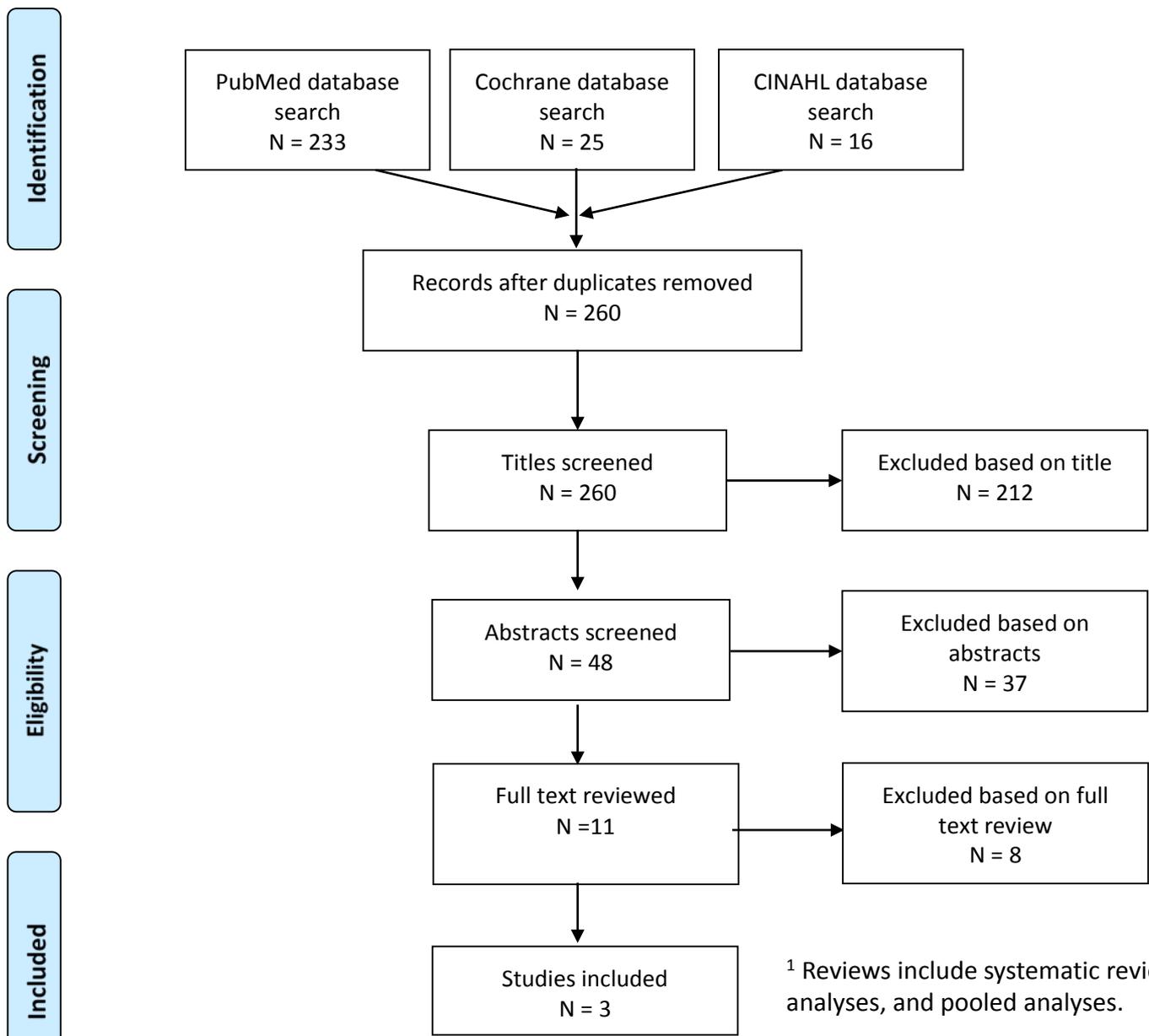
[1] Reviews include systematic reviews, meta-analyses, and pooled analyses.

Description of the Evidence

Three systematic reviews and (or) meta-analyses.

Participants: predominantly men and women ages 18 years and older.

Exposure: physical activity performed as high-intensity interval training.

Outcomes of interest: all-cause and cardiovascular disease mortality; cardiovascular disease and type 2 diabetes incidences; cardiorespiratory fitness; and cardiometabolic disease risk factors.

- The 2018 PAGAC assessment and evaluation specifically focuses on outcomes related to cardiometabolic disease risk factors (e.g., blood pressure, fasting blood lipids and lipoproteins, fasting blood glucose and insulin, and body mass index), due to a lack of information regarding mortality and cardiometabolic morbidities.

Description of the Evidence

Batacan Jr., et. al. [2017]:
- 65 studies, 2164 participants (936 who performed HIIT).
- This SR/MA included randomized and non-randomized clinical trials and comparative studies in groups without (46 of 65 studies) or with (19 or 65 studies) a diagnosed, current medical condition.
- The studies were categorized based on exercise training duration and participant BMI classification.

Jelleyman, et al. [2015]:
- 50 studies, 2033 participants (1383 who performed HIIT).
- Assessed effects of HIIT on indexes of blood glucose control and insulin resistance, compared with continuous training or control conditions.
- Included controlled (n=36, 72%) and uncontrolled (n=14, 28%) studies.
- Sub-group analyses were done based on weight status and health status (MetS/type 2 diabetes).

Description of the Evidence

Kessler et al. [2012]:

- Quasi-systematic, qualitative review of 24 RCTs (14 with continuous moderate-intensity exercise (CME) control groups; 14 with non-exercise (SED) control groups).
- Participants had various weight status and health status (healthy [17 studies], cardiovascular disease [5 studies], metabolic syndrome [1 study], type 2 diabetes [1 study].
- HIIT was categorized into two sub-types:
    - aerobic interval training (AIT, 19 studies)
    - sprint interval training (SIT, 5 studies)

For the purpose of the 2018 PAGAC assessment, results only from AIT studies are described. This was because of the low number of SIT studies included in the Kessler et al. [2012] review.

Draft Key Findings

- HIIT effectively improves cardiorespiratory fitness (increase VO_2max) in adults with varied body weight and health status [Batacan Jr., et al. 2017; Jelleyman et al. 2015; Kessler et al. 2012].

- HIIT-induced improvements in insulin sensitivity [Jelleyman et al. 2015; Kessler et al. 2012], blood pressure [Batacan Jr., et al. 2017; Kessler et al. 2012], and body composition [Batacan Jr., et al. 2017; Jelleyman et al. 2015; Kessler et al. 2012] more consistently occur in adults with overweight/obesity status and (or) high risk for cardiovascular disease and diabetes, especially with training ≥12 weeks.

- Healthy adults with normal weight status and lower risk for cardiometabolic disease do not typically show improvements in insulin sensitivity, blood pressure and body composition with HIIT. Blood lipids and lipoproteins apparently are not influenced by HIIT.

Draft Conclusion Statement

- **Overall Conclusion:**

Moderate evidence indicates that high-intensity interval training can effectively improve cardiorespiratory fitness in adults with varied body weight and health status and improve insulin sensitivity, blood pressure, and body composition in adults with overweight/obesity status and (or) high risk for cardiovascular disease and diabetes, especially with training durations ≥12 weeks.

- **Grade: Moderate**

Draft Conclusion Statement

- **Dose-response:**

Limited evidence suggests that dose-response relationships do not exist between the quantity of HIIT and several risk factors for cardiovascular disease and diabetes.

- **Grade: Limited**

- **Age, gender, race/ethnicity, socioeconomic status:**

Insufficient evidence is available to determine whether the effects of high-intensity interval training on cardiometabolic risk factors are influenced by age, sex, race/ethnicity, or socio-economic status.

- **Grade: Grade not assignable**

Draft Conclusion Statement

- **Weight status:**

There is moderate evidence that weight status influences the effectiveness of high-intensity interval training to reduce cardiometabolic disease risk; adults with overweight or obesity are more responsive than adults with normal weight to improve insulin sensitivity, blood pressure, and body composition.

- **Grade: Moderate**

- Conduct randomized clinical trials, with racially/ethnically diverse groups of adults who are overweight or obese and (or) at high risk for cardiovascular disease or type 2 diabetes, to assess dose-response relationships between the duration of high-intensity interval training and changes in cardiometabolic disease risk factors.

Committee Discussion

- What is the relationship between high intensity interval training and reduction in cardiometabolic risk?

  - Is there a dose-response relationship? If yes, what is the shape of the relationship?

  - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?