The relationship between step count and all-cause mortality and cardiovascular events: A dose–response meta-analysis

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Running head: Step count and cardiovascular events

SUPPLEMENTAL MATERIAL

Supplementary File 1

Literature search strategy

Cochrane Central Register of Controlled Trials (Issue 7 of 12, July 2021)

((step count) OR (steps per day) OR (daily steps)) AND ((cardiovascular disease) OR (cardiovascular events) OR (heart disease) OR (cerebrovascular accident) OR (angina) OR (stroke) OR (myocardial infarction) OR (heart infarction) OR (ischemic heart disease)) -in Abstract

EMBASE

('step count'/exp OR 'step count' OR 'daily steps' OR 'steps per day') AND ('heart disease'/exp OR 'heart disease' OR 'cardiovascular disease'/exp OR 'cardiovascular disease' OR 'cardiovascular events' OR 'heart infarction'/exp OR 'heart infarction' OR 'ischemic heart disease'/exp OR 'ischemic heart disease' OR 'cerebrovascular accident'/exp OR 'cerebrovascular accident' OR 'heart failure'/exp OR 'heart failure' OR 'angina'/exp OR angina OR 'stroke'/exp OR stroke OR 'myocardial infarction' OR 'coronary artery disease'/exp OR 'coronary artery disease' OR 'death'/exp OR death OR 'cause of death'/exp OR 'cause of death' OR 'mortality'/exp OR mortality)

OVID

9 Resources selected: 1) Journals@Ovid Full Text <July 07, 2021>, 2) JBI EBP Database <Current to June 30, 2021>, 3) EBM Reviews-ACP Journal Club <1991 to June 2021>, 4) EBM Reviews-Cochrane Central Register of Controlled Trials <June 2021>, 5) EBM Reviews-Cochrane Database of Systematic Reviews <2005 to July 8, 2021>, 6) Embase <1974 to 2021July 08>, 7) Ovid Emcare <1995 to 2021 Week 26>, 8) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 08, 2021>, 9) APA PsycInfo <1987 to July Week 1 2021>.

#1 (cardiovascular disease or myocardial infarction or coronary or cardiovascular events or heart disease or ischemic heart disease or cerebrovascular accident or angina or stroke or heart infarction or death or mortality or cause of death or all-cause of death or all-cause mortality).af.

#2 (cohort or prospective or trial or clinical trial or follow-up).af.

#3 (step count or steps per day or daily steps).af.

#1 and #2 and #3

PubMed

((step count) OR (steps per day) OR (daily steps)) AND ((cardiovascular disease) OR (cardiovascular events) OR (heart disease) OR (cerebrovascular accident) OR (angina) OR (stroke) OR (myocardial infarction) OR (heart infarction) OR (ischemic heart disease) OR (mortality) OR (cause of death) OR (all-cause mortality) OR (all-cause death) OR (death)) AND (cohort OR prospective OR trial OR (clinical trial) OR (follow-up))

Scopus

(("step count" OR "steps per day" OR "daily steps") AND ("cardiovascular disease" OR "cardiovascular events" OR "heart disease" OR "ischemic heart disease" OR

"cerebrovascular accident" OR arrhythmias OR "heart failure" OR "myocardial ischemia" OR stroke OR "myocardial infarction" OR mortality OR "cause of death" OR "all-cause of death" OR "all-cause mortality" OR death) AND (cohort OR prospective OR "clinical trial" OR "follow-up")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Adult"))

Web of Science

TS = (("step count" OR "steps per day" OR daily steps) AND ("cardiovascular disease" OR "cardiovascular events" OR "heart disease" OR "ischemic heart disease" OR cerebrovascular accident OR angina OR stroke OR "heart infarction" OR myocardial infarction OR mortality OR "cause of death" OR "all-cause of death" OR "all-cause mortality" OR death) AND (cohort OR prospective OR trial OR clinical trial OR follow-up))

Supplementary File 2

Literature Search result

After the exclusion of duplicates and studies that did not fulfill the inclusion criteria, 23 remaining articles seemed to be relevant for this meta-analysis. After evaluating the full texts of these 23 publications, we excluded 7 articles as follows:

Two articles[1, 2] were excluded owing to lack of sufficient data for estimation of RRs. Four articles[3-6] were excluded because they did not separately report step count. We also excluded one article[7] because only its abstract was written in English.

The final meta-analysis included 16 publications. Among these 16 publications, 12 publications provided statistical effects relevant to the meta-analyses on all-cause mortality, 4 articles on total CVD, 1 article on stroke[8]. One article[9] was a randomized controlled trial, and others were prospective cohort studies.

We included 3 conference papers in the final meta-analysis.[10-12] Indeed, we could not assure the quality and reliability of these findings without peer review. However, journals that sponsored these conferences had a high impact factor, and sufficient data we need was reported on the meeting abstract. Therefore, we decided to include these conference papers.

Supplementary Table 1. Step count and all-cause mortality.

Study	Country; Study name; No of participants; No of cases	Age at baseline (years), Year of baseline assessment, Follow-up (years)	Case ascertainment	Pedometer or Accelerometer, Device(s), Location, Duration	Number of steps per day	Corresponding hazard ratio (95% CI)	Covariates	Quality assessment*
Dwyer et al. (2015)[13]	Australia; the Tasped Prospective Cohort Study; *n* = 2576 (1226 men, 1350 women); 219 cases	>18, 2000–05, 10.0 years	The Australian National Death Index	Pedometer, Digi-Walker SW-200 (YAMASA, Tokyo, Japan), HJ-003 and HJ-102(Omron, Tokyo, Japan), waist, 7 days	0–5550 5551–8000 8001–10000 10001–3500 13501–39164	1 0.43（0.30–0.62) 0.25 (0.16–0.38) 0.24 (0.15–0.37) 0.10 (0.05–0.18)	Age, sex, BMI at baseline, total energy intake from all sources(kJ) at baseline, current smoking status at baseline, alcohol consumption (g/day) at baseline, education at baseline and study cohort	8
Fox et al. (2015)[14]	The United Kingdom; project OPAL (Older People and Active Living); *n* = 213(109 men, 104 women); 33 cases	≥70, 2007–08, 4.2years	Medical records, death certificates	Accelerometer, GT1Ms (ActiGraph, Pensacola, FL, USA) waist,7 days	<3196 3196–5170 >5170	7.69 (1.43–41.20) 3.99 (0.80–20.01) 1	Age, gender, educational attainment, IMD, weight status, GP Management System and number of self-reported chronic illnesses at baseline	9
Yamamoto et al. (2018)[15]	Japan; study on the relationship between environmental factors and health outcomes in Niigata City, Japan; *n* = 419 (228 men,191 women); 76 cases	71, 1998–99, 9.8 years	Medical records, death certificates	Pedometer, EC-100S (YAMASA, Tokyo, Japan), waist,7 days	<4503 4503–6110 6111–7971 >7972	1 0.81(0.43–1.54) 1.26(0.70–2.26) 0.46(0.22–0.96)	Sex, body mass index (continuous variable), cigarette smoking (never-smokers, past smokers, current smokers), alcohol intake (non, 1–2 times/week, 3–5 times/week, 6–7 times/week), and medication use (yes, no)	8
German et al. (2019)[10]	The United States; the 2005–2006 NHANES survey; *n* = 4055 (1914 men, 2141 women); 474 cases	45.9, 2005–06 12 years	The National Death Index	Accelerometer, AM-7164 (ActiGraph, Pensacola, FL, USA), right hip, 7 days	<2500 2500–4999 5000–7500 7500–9999 >10000	1 0.50(0.36–0.68) 0.27(0.19–0.38) 0.20(0.10–0.38) 0.33(0.15–0.69)	Some adjustment factor [a]	7
Jefferis et al. (2019, UK)[16]	The United Kingdom; the British Regional Heart Study; *n* = 1181 men; 194 cases	71–92, 2010–12, 5.0 years	National Health Service central registers	Accelerometer GT3x (ActiGraph, Pensacola, FL, USA), right hip,7 days	121–2927 2928–4532 4533–6412 6413–17781	1 0.63(0.43–0.93) 0.59(0.39–0.90) 0.31(0.17–0.57)	Age, region of residence, season of wear, accelerometer wear time, social class, alcohol use, smoking, sleep time, living alone, body mass index, mobility disability.	9
Lee et al. (2019)[17]	The United States; the Women's Health Study (WHS); *n* = 16741 women; 504 cases	62–101, 2011–12, 4.3 years	Medical records, death certificates, or the National Death Index	Accelerometer, GT3X+ (ActiGraph, Pensacola, FL, USA), hip, 7 days	2128–3202 3992–4738 5493–6403 7580–9954	1 0.59(0.47–0.75) 0.54(0.41–0.72) 0.42(0.3–0.60)	Age, wear time, smoking status, alcohol use, intakes of saturated fat, fiber, fruits, and vegetables, hormone therapy, parental history of myocardial	9

							infarction, family history of cancer, general health, history of cardiovascular disease, history of cancer, and cancer screening.	
Hansen et al. (2020)[18]	Norway; a nationwide multicenter physical activity surveillance study; *n* = 2183(1026 men, 1157 women); 119cases	40–85, 2008–09, 9.1 years	The Norwegian Cause of Death Registry	Accelerometer, GT1M (ActiGraph, Pensacola, FL, USA), waist, 7 days	3495–5325 6388–7350 8215–9186 10556–13110	1 0.52(0.29–0.93) 0.50(0.27–0.94) 0.43(0.21–0.88)	Sex, wear time, VPA, education, body mass index, smoking (never/former/ current), alcohol intake, and number of medical conditions, excluding deaths within first 2 y (*n* = 9).	9
Oftedal et al. (2020)[19]	Australia; the Hunter Community Study (HCS); *n* = 1697 (860 men, 837 women); 204 cases	55–85, 2005–08, 9.6 years	Medical records, death certificates	Pedometer Digi-Walker SW-200 (YAMASA, Tokyo, Japan), waist, 7 days	Median (IQR)6678 (4689–8850)	0.93(0.88–0.98) per 1000–step increment	Mean age and diet quality score, and reference categories ‘low income’ and ‘current smoker’.	9
Paluch et al. (2020)[11]	The United States; the Coronary Artery Risk Development in Young Adults (CARDIA) study; *n* = 2027 (851 men, 1176 women); 67 cases	45.3±3.5, 2005–06, 10.8±0.9 years	The state health department	Accelerometer, 7164 (ActiGraph, Pensacola, FL, USA), hip, >4 days	5898–7452 8553–9489 10501–11472 12904–15660	1 0.43(0.20–0.90) 0.83(0.45–1.56) 0.48(0.23–0.99)	Wear time, age, sex, race, max education, center, healthy eating index, smoking status, alcohol intake, history of cardiovascular disease, type 2 diabetes, hypertension, obesity, hypercholesterolemia.	7
Saint-Maurice et al. (2020)[20]	The United States; the National Health and Nutrition Examination Survey (NHANES); *n* = 4840 (2405 men, 2435 women); 1165 cases	>40, 2003–06, 10.1 years	The National Death Index	Accelerometer, 7164 (ActiGraph, Pensacola, FL, USA), hip,7 days	4000 8000 12000	1 0.49(0.44–0.55) 0.35(0.28–0.45)	steps per day, sex, age, diet quality, race/ethnicity, body mass index, education, alcohol consumption, smoking status, diabetes, stroke, coronary heart disease, heart failure, cancer, chronic bronchitis, emphysema, mobility limitation, and self–reported general health.	9
Mañas et al. (2021)[21]	Spain; the Toledo Study for Healthy Aging (TSHA); *n* = 768 (354 men, 414 women); 89 cases	78.8 ± 4.9, 2015 − 17, 5.7 years	The Spanish National Death Index (Ministry of Health, Consumer Affairs and Social Welfare)	Accelerometer, wGT3X-BT, (ActiGraph, Pensacola, FL, USA), left hip, 7 days	5835 ± 3445 steps/day (mean ± SD)	0.87 (0.81–0.95) per additional 1000 steps	Accelerometer wear time (covariate excluded in the steps/min models), age, sex, BMI, education, income, marital status and comorbidities.	9
Schneider et al. (2021)[22]	The United Kingdom; the UK Biobank; *n* = 95974 (41903 men,54071 women); 2290 cases	37–73 2013–15 5.5 years	National death registries	Accelerometer, AX3 (Axivity, Newcastle upon Tyne, UK), wrist, 7 days	6500 8000 9250 12000	1 0.36(0.18–0.75) 0.29(0.13–0.64) 0.15(0.05–0.44)	Sex, age, BMI, and alcohol consumption	9

Notes: *Quality assessment according to Newcastle-Ottawa scale (range 0 − 9) for cohort studies (see supplementary material for further details).

[a] Unclear, not mentioned in the meeting abstract.

Abbreviation: 95%CI = 95% confidence interval; BMI = body mass index; IMD = index of multiple deprivation; GP = general practitioner; VPA = take more vigorous intensity activity (e.g., jogging).

Supplementary Table 2. Step count and cardiovascular disease.

Study	Country; Study name; No of participants; No of cases	Age at baseline (years), Year of baseline assessment, Follow-up (years)	Case ascertainment	CVD incidence or mortality	Pedometer or Accelerometer, Device(s), Location, Duration	Number of steps per day	Corresponding hazard ratio (95%CI)	Covariates	Quality assessment*
Cochrane et al. (2017)[9]	The United States; the LIFE (Lifestyle Interventions and Independence for Elders) Study; *n* = 1590 (521 men, 1069 women); 234 cases	78.9±5.2, 2010—13, 2.7 years [b]	Hospital records included MI, silent MI, hospitalized angina, congestive heart failure, revascularization with bypass surgery or percutaneous angioplasty, aortic aneurysm, peripheral artery disease, stroke, and transient ischemic attack	Incidence	Accelerometer, GT3x (ActiGraph, Pensacola, FL, USA), hip, 7 days	2681±1475	0.90(0.85–0.96) per 500 steps	Accelerometer wear time, site and sex, randomization, race, age, education, living alone, and marital status, diabetes mellitus, cardiovascular disease, and antihypertensive use, ankle‐brachial index, systolic and diastolic blood pressure, and Pittsburgh Sleep Quality Index score.	9
Jefferis et al. (2019)[23]	The United Kingdom; the British Regional Heart Study (BRHS); *n* = 1181 men; 122 cases	71—92, 2010—12, 4.9 years	International Classification of Disease (ICD) 9 codes: MI 410–414 (ICD 10 codes I20–I25), Stroke 430–438, (ICD10 I60–69) and Heart Failure 428 (ICD10 I50); yearly reviews of primary care notes	Incidence and mortality	Accelerometer, GT3x (ActiGraph, Pensacola, FL, USA), right hip, 7 days	121–2943 2944–4540 4541–6406 6407–17781	1.00 0.75(0.47–1.20) 0.44(0.25–0.77) 0.34(0.17–0.67)	Age, region of residence, season of wear, accelerometer wear time, social class, alcohol use, smoking, sleep time, living alone, BMI, mobility disability	9
LaCroix et al. (2020)[12]	The United Kingdom; the OPACH Study; *n* = 6379 women; 175 cases	79±7, 2012–14, followed to March 31, 2017	National Death Index	Mortality	Accelerometer, GT3X+ (ActiGraph, Pensacola, FL, USA), waist, 7 days	2000(ref.)	1 0.48(0.32–0.73) 0.56(0.35–0.90) 0.25(0.11–0.54)	Age, race-ethnicity, education, smoking status, alcohol consumption, self-reported health, multimorbidity, and physical function	6
Moniruzzaman et al. (2020)[8]	Japan; Shiga Epidemiological Study of Subclinical Atheroscleros (SESSA); *n* = 680 men;145 cases	40–79, 2006–08, 5 years	The presence of CSVD was assessed in participants by brain MRI	Incidence	Pedometer Digi-Walker DW-200 (YAMASA, Tokyo, Japan), waist, 7 days	≤6060 6061–8174 8175–10614 ≥10615	1[a] 0.81(0.50–1.34) [a] 0.52(0.30–0.89) [a] 0.69(0.41–1.17) [a]	Adjusted for age, smoking and drinking status	9
Saint-Maurice et al. (2020)[20]	The United States; the National Health and Nutrition Examination Survey (NHANES); *n* = 4840 (2405 men,	>40, 2003–06, 10.1 years	International Classification of Diseases, 10th Revision (ICD–10) codes for cardiovascular disease (CVD; ICD–10 code 053–	Mortality	Accelerometer,7164 (ActiGraph, Pensacola, FL, USA), hip, 7 days	4000 8000 12000	1 0.49(0.40–0.60) 0.35(0.24–0.52)	Age, diet quality, sex, race-ethnicity, BMI, education, alcohol consumption, smoking status, diabetes, stroke,	9

	2435 women); 406 cases	075)		coronary heart disease, heart failure, cancer, chronic bronchitis, emphysema, mobility limitation, and self-reported general health.

Notes: *Quality assessment according to Newcastle-Ottawa scale (range 0 – 9) for cohort studies (see supplementary material for further details).
[a] Odds ratio with 95%CI
[b] Clinical Trial

Abbreviation: 95%CI = 95% confidence interval; BMI = body mass index; CVD = cardiovascular diseases; CSVD = cerebral small vessel disease; ICD = international classification of diseases; MI = myocardial infarction; MRI = magnetic resonance imaging. .

Supplementary Table 3. Stratified analysis on associations of step count with risk of all-cause mortality and CVD.

	n	RR (95%CI)[a]	I^2 (%)[b]	*p*[c]
All-cause mortality	**12**			
Location				
the United States	4	0.86 (0.84–0.87)	0.0	0.673
the United Kingdom	3	0.74 (0.62–0.89)	67.1	0.048
Europe	2	0.87 (0.82–0.93)	0.0	0.863
Australia	2	0.94 (0.91–0.97)	0.0	0.760
Japan	1	0.93 (0.84–1.03)	–	–
Sex				
Male and female	10	0.88 (0.84–0.92)	72.0	0.000
Male	1	0.84 (0.77–0.91)	–	–
Female	1	0.85 (0.80–0.90)	–	–
Follow-up duration				
>5 years	9	0.88 (0.85–0.92)	72.5	0.000
≤5years	3	0.84 (0.80–0.89)	12.7	0.318
Reduce chance of reverse causality				
Yes	7	0. 89 (0.86–0.93)	53.7	0.044
No	3	0.75 (0.61–0.91)	75.8	0.016
Unclear	2	0.87 (0.83–0.91)	0.0	0.384
All-cause mortality (only by accelerometer)	**9**			
Location				
the United States	4	0.86 (0.84–0.87)	0.0	0.673
the United Kingdom	3	0.74 (0.62–0.89)	67.1	0.048
Europe	2	0.87 (0.82–0.93)	70.0	0.863
Sex				
Male and female	7	0.85 (0.82–0.89)	45.2	0.090
Male	1	0.84 (0.77–0.91)	–	–
Female	1	0.85 (0.80–0.90)	–	–
Follow-up time				
>5 years	6	0.86 (0.83–0.89)	41.3	0.13
≤5 years	3	0.84 (0.80–0.89)—	12.7	0.318
Location of accelerometer				
Waist/hip	8	0.86(0.84–0.87)	0.0	0.703
Wrist	1	0.68(0.57–0.81)	–	–
Reduce chance of reverse causality				
Yes	4	0.86 (0.82–0.89)	0.0	0.875
No	3	0.75 (0.61–0.91)	75.8	0.016
Unclear	2	0.87 (0.83–0.91)	0.0	0.384
CVD	**5**			
Location				
the United States	2	0.93 (0.91–0.94)	4.0	0.307
the United Kingdom Japan	2	0.94 (0.91–0.97)	13.5	0.282

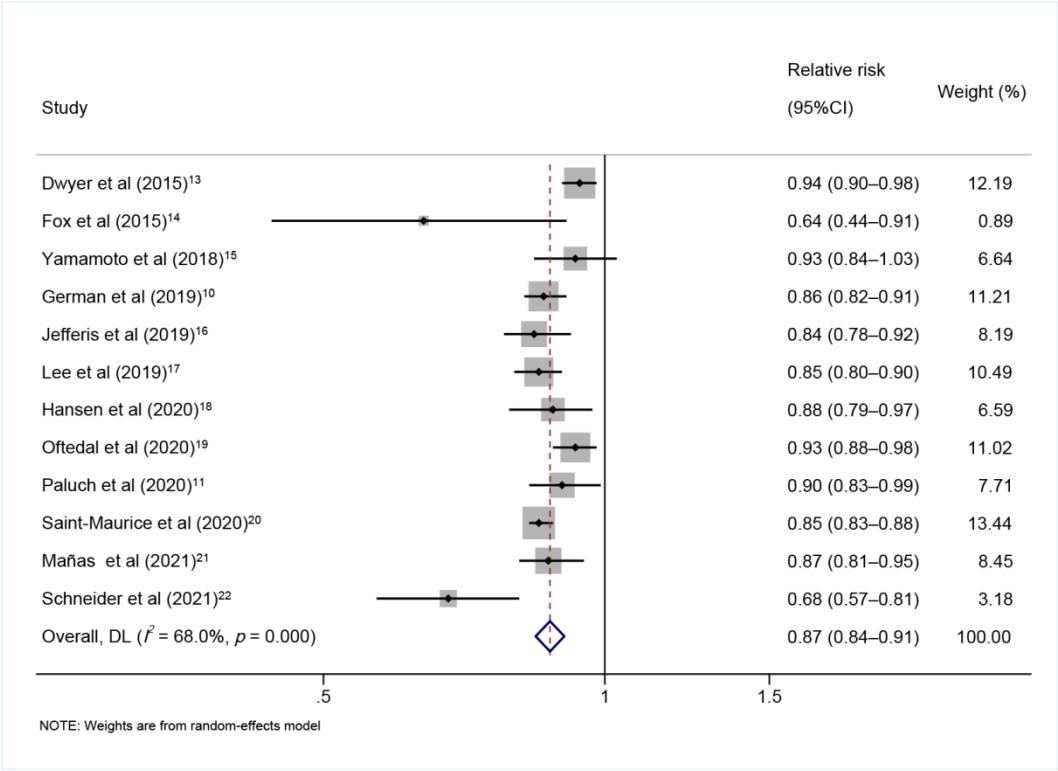
	1	0.98 (0.96–1.00)	–	–
Sex				
Male and female	2	0.93 (0.91–0.94)	4.0	0.307
Male	2	0.97 (0.94–1.00)	61.9	0.105
Female	1	0.92 (0.88–0.97)	–	–
Follow-up time				
>5 years	1	0.93 (0.92–0.95)	–	–
≤5 years	4	0.94 (0.91–0.98)	74.0	0.009
Type of wearable devices				
Pedometer	1	0.98 (0.96–1.00)	–	–
Accelerometer	4	0.93 (0.92–0.94)	0.0	0.392
Endpoints				
Total CVD	4	0.93 (0.92–0.94)	0.0	0.392
Single CVD endpoint	1	0.98 (0.96–1.00)	–	–
Reduce chance of reverse causality				
Yes	1	0.95 (0.92–0.98)	–	–
No	3	0.94 (0.90–0.98)	89.1	0.000
Unclear	1	0.92 (0.88–0.97)	–	–

Notes: [a] Obtained from the random-effects model

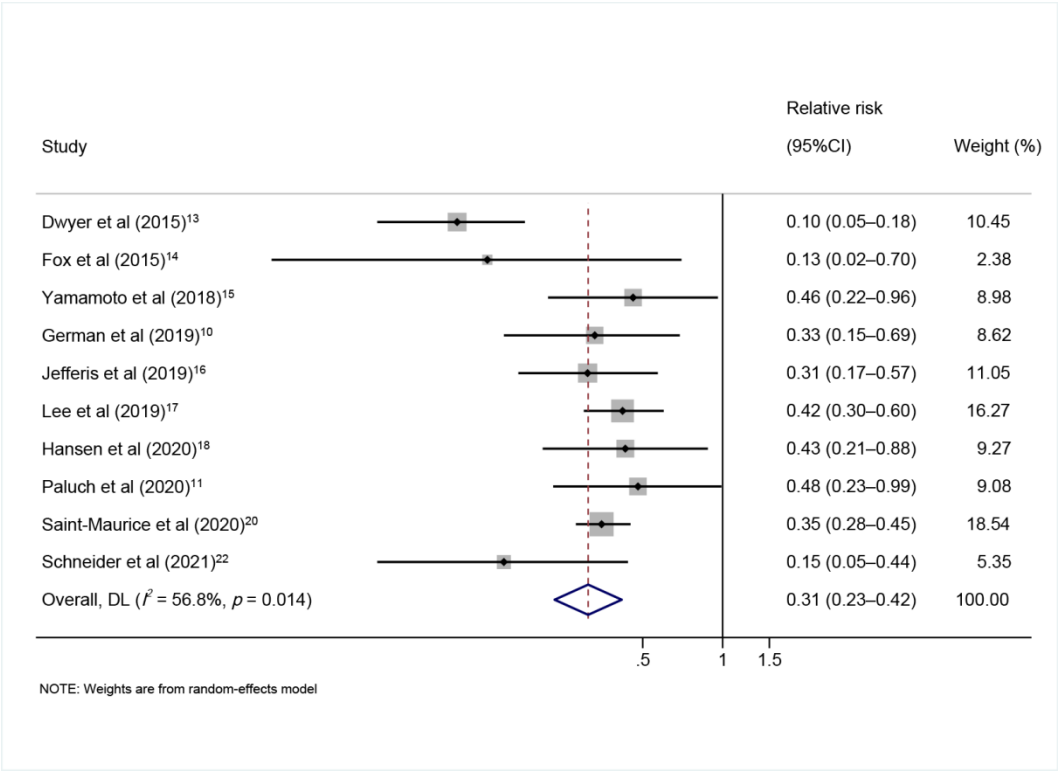
[b] Inconsistency- percentage of variation across studies due to heterogeneity

[c] Obtained from the *Q* test

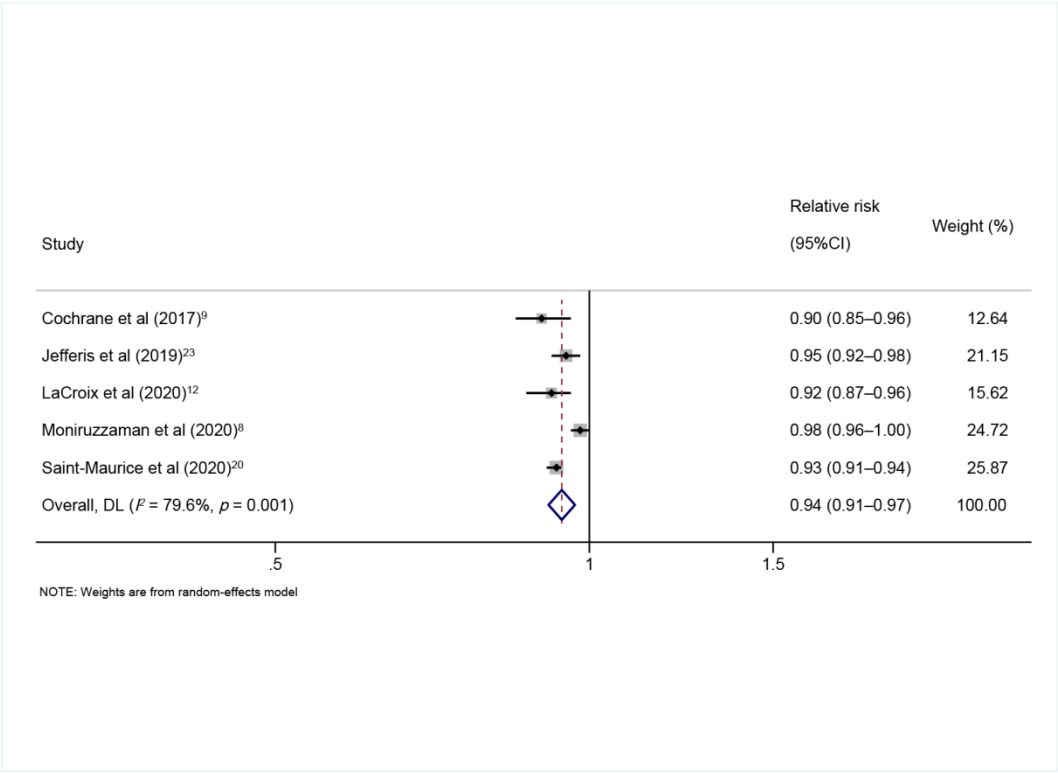
Abbreviation: RR = relative risk- 95%CI = 95% confidence interval; CVD = cardiovascular diseases.



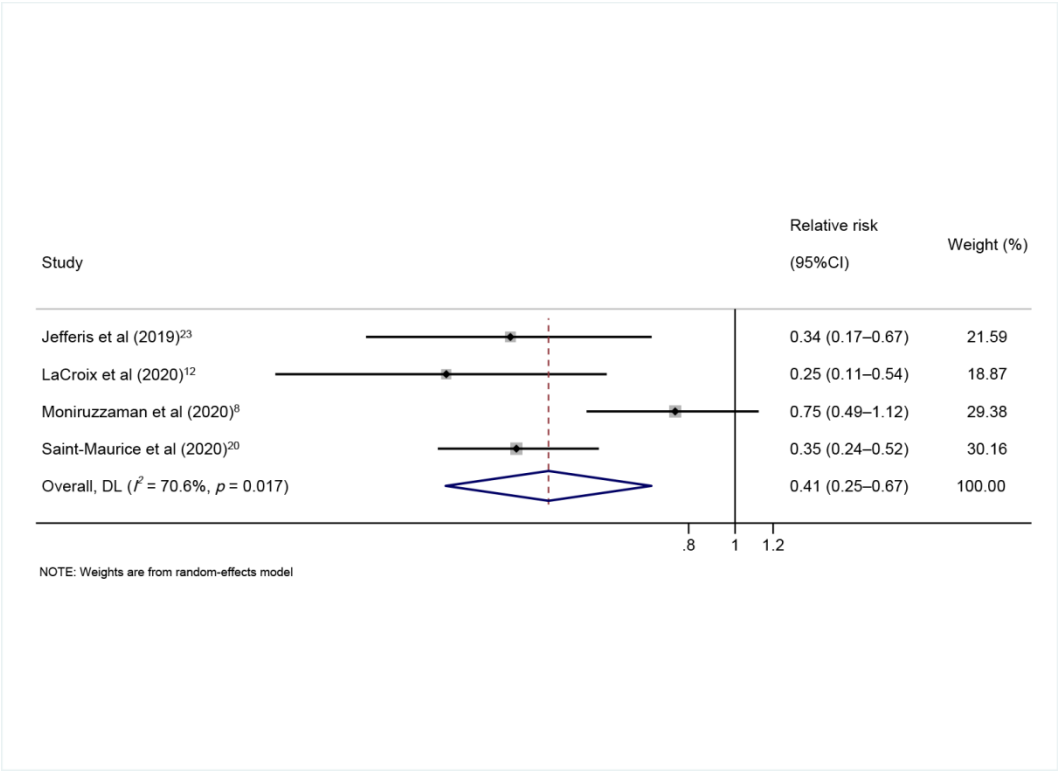
Supplementary Fig. 1. Forest plot of step count and risk of all‐cause mortality per 1000-step increment.



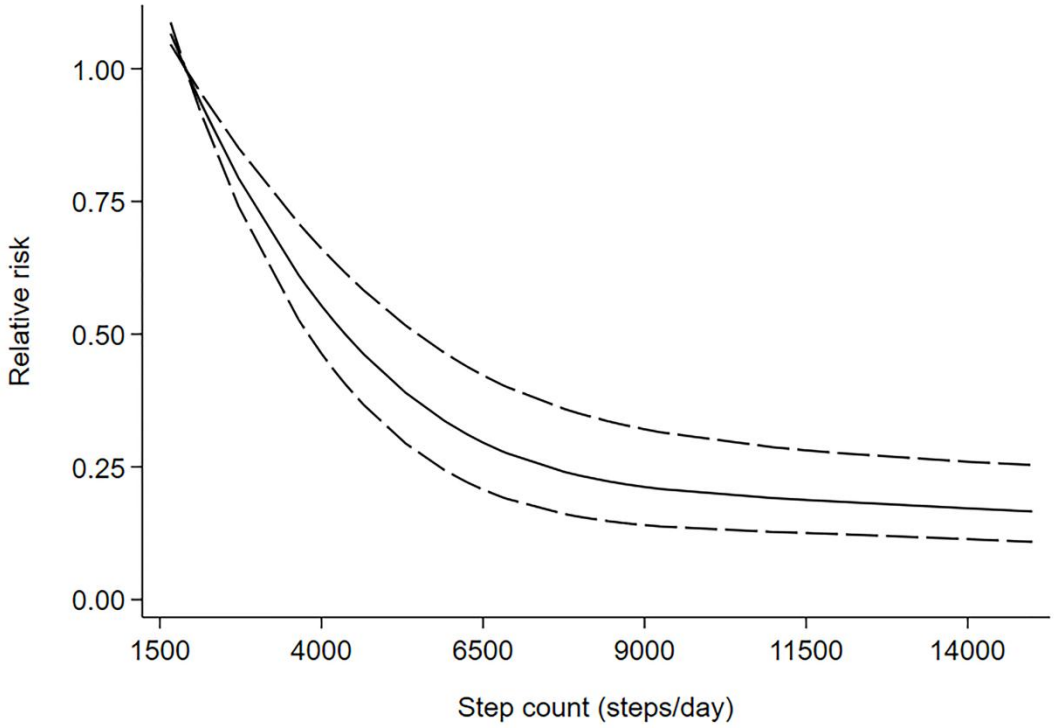
Supplementary Fig. 2 Step count and all-cause mortality, highest vs. lowest analysis.



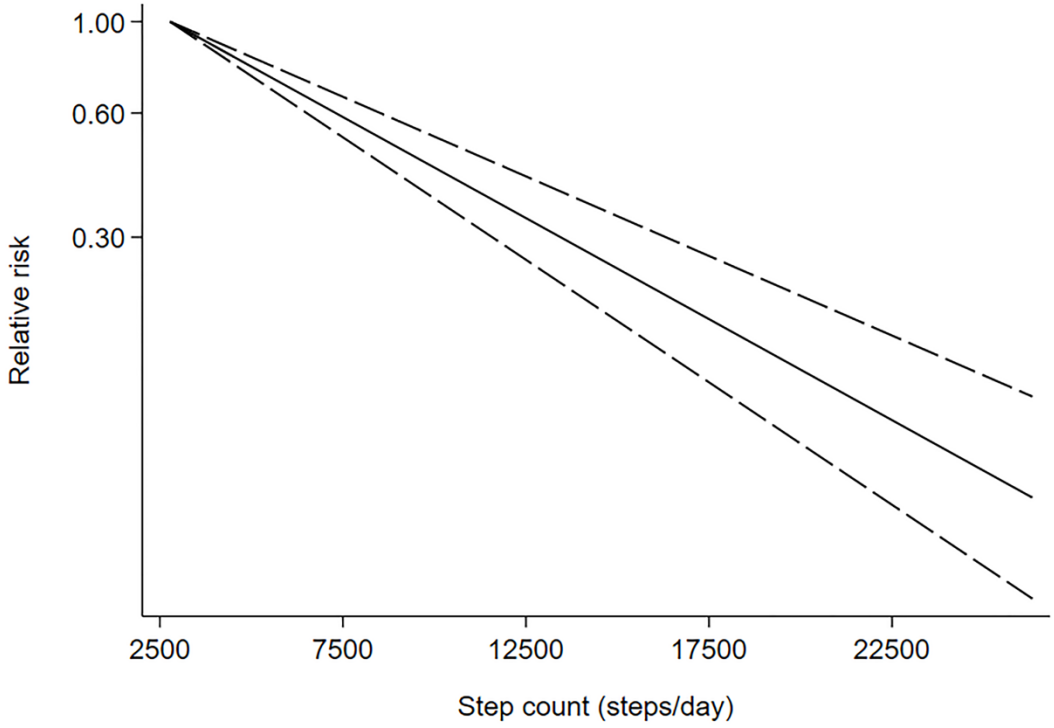
Supplementary Fig. 3. Forest plot of step count and risk of cardiovascular disease per 500-step increment.



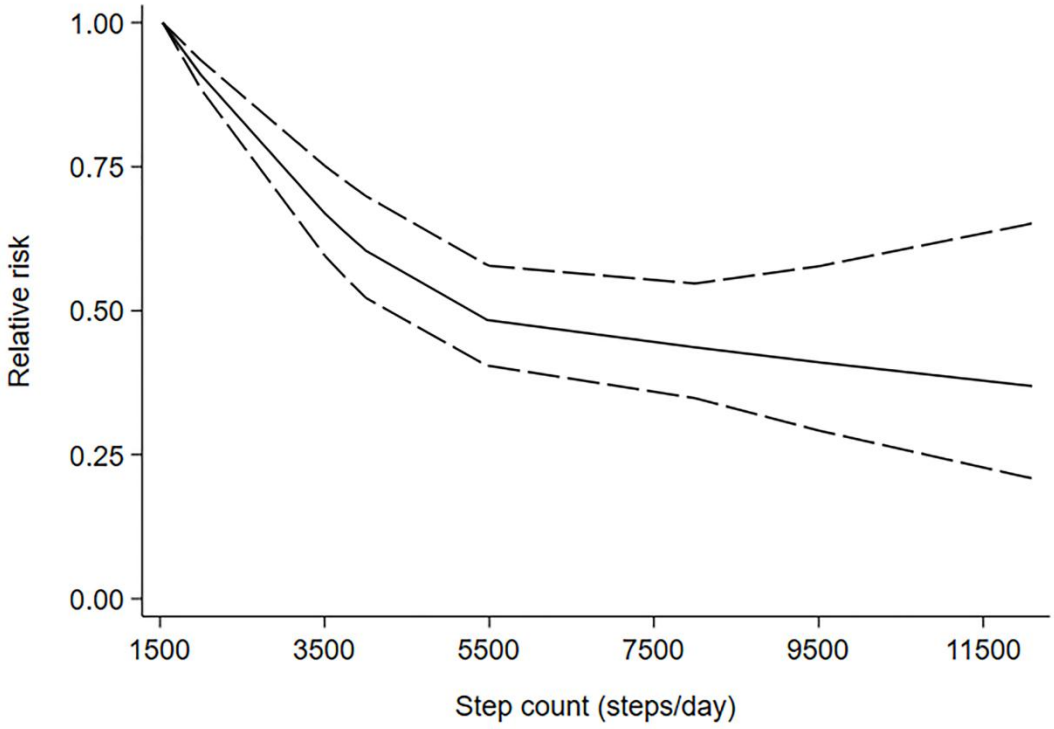
Supplementary Fig. 4. Step count and CVD, highest vs. lowest analysis.



Supplementary Fig. 5 Non-linear dose–response analysis of step count and all-cause mortality by accelerometer.

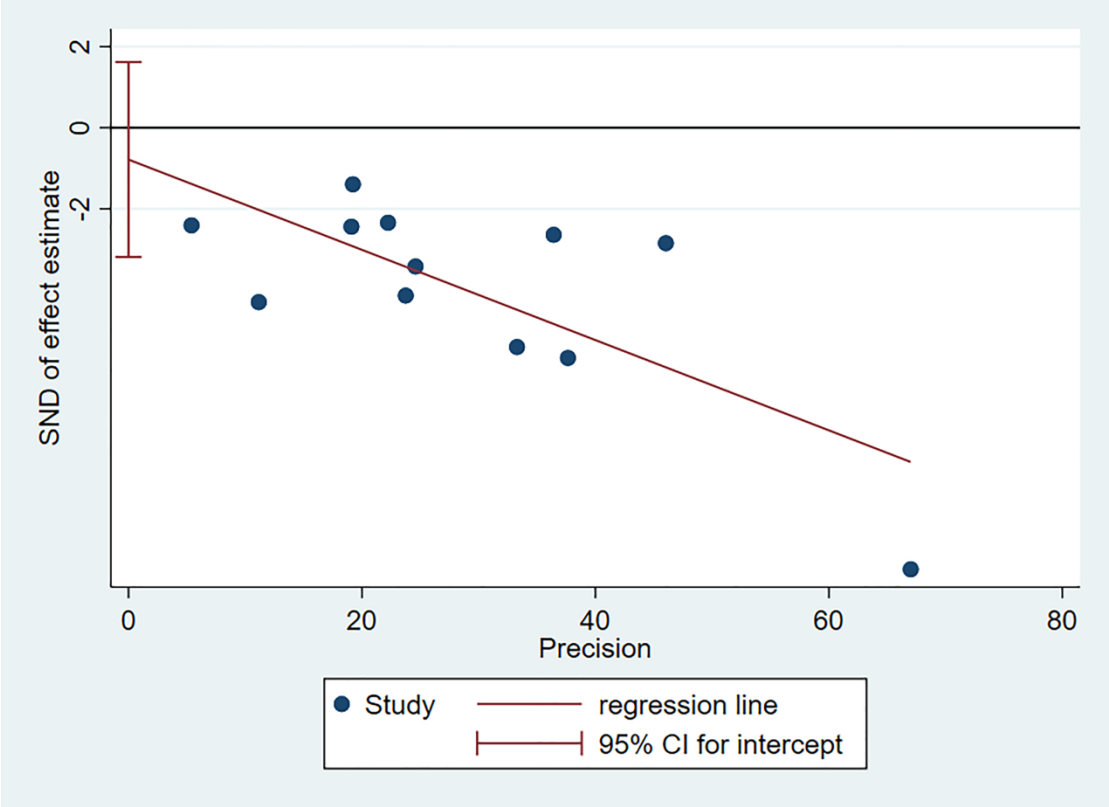


Supplementary Fig. 6 Linear dose–response analysis of step count and all-cause mortality by pedometer.

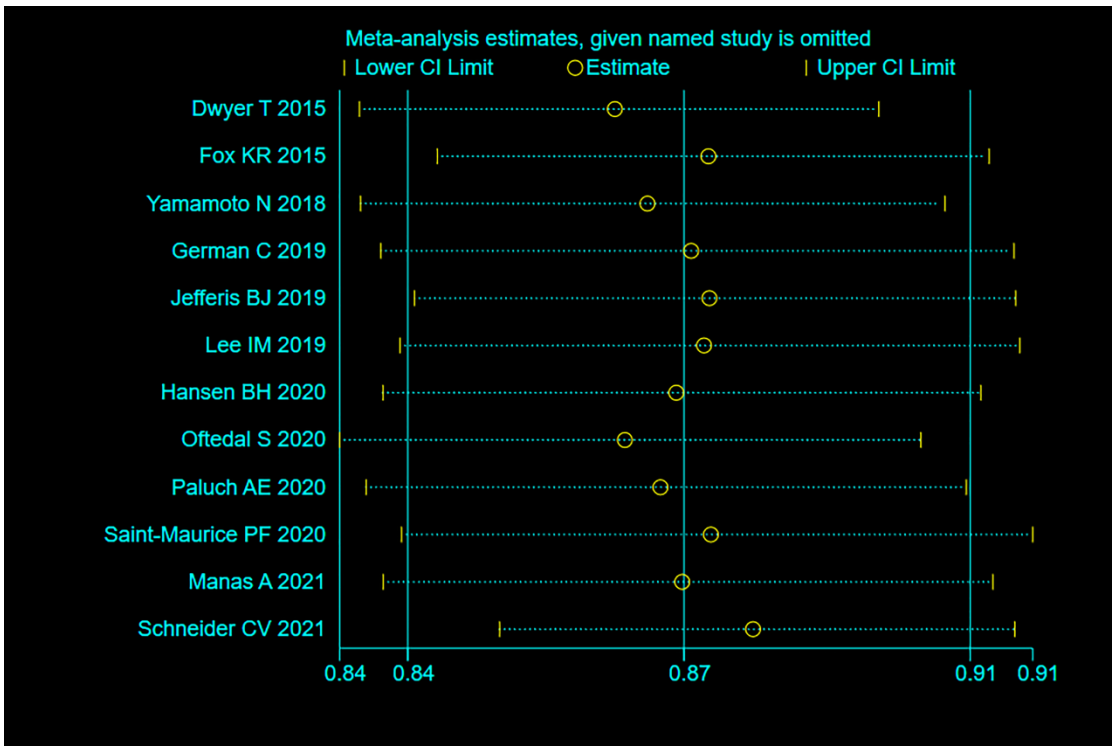


Supplementary Fig. 7 Non-linear dose–response analysis of step count and cardiovascular events

by accelerometer.

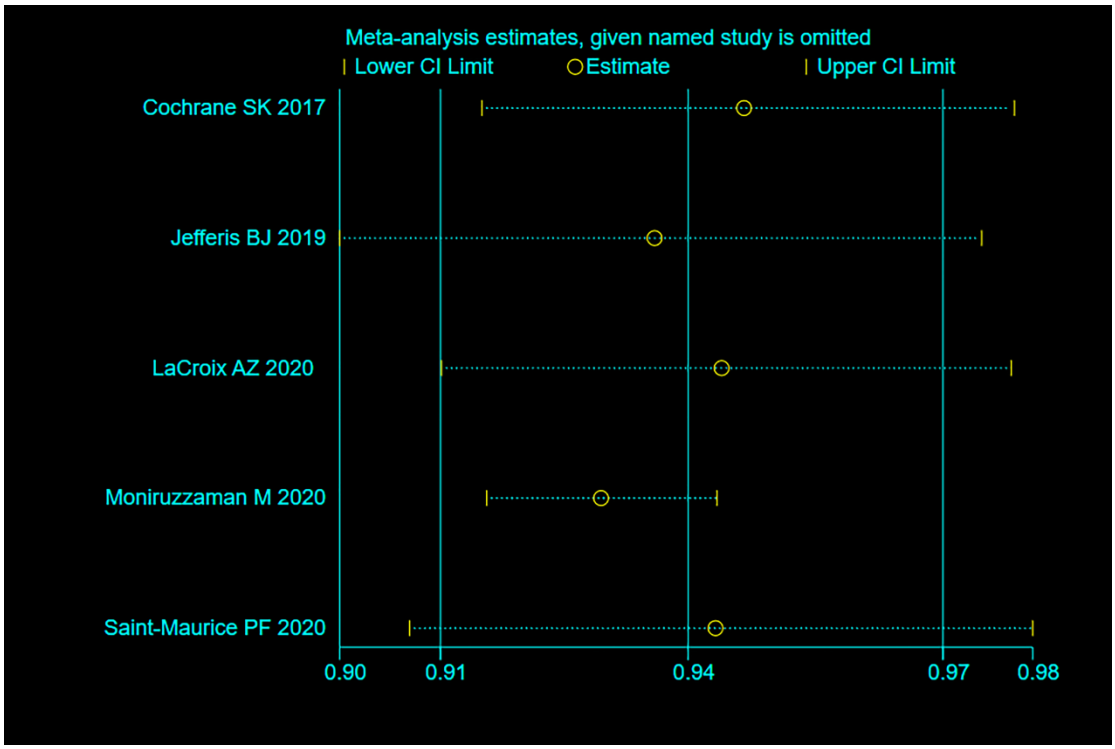


Supplementary Fig. 8. The funnel plot for publication bias of step count and all-cause mortality produced by Egger's test.



Supplementary Fig. 9. Sensitive analysis of step count and all-cause mortality per 1000-step

increment.



Supplementary Fig. 10. Sensitive analysis of step count and CVD per 500-step increment

References

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