Dose-Response Relationships of Step Count Metrics with All-Cause Mortality and Cardiovascular Diseases: A Meta-Analysis

Short title: Step count metrics and health outcomes

Niels A. Stens MSc [a,b] (Niels.Stens@radboudumc.nl)

Esmée A. Bakker PhD [a,c] (Esmee.Bakker@radboudumc.nl)

Asier Mañas PhD [d,e,f,g] (Asier.Manas@uclm.es)

Laurien M. Buffart PhD [a] (Laurien.Buffart@radboudumc.nl)

Francisco B. Ortega PhD [c,h,i] (ortegaf@ugr.es)

Duck-chul Lee PhD [j] (dclee@iastate.edu)

Paul D. Thompson, MD [k] (pthomps1947@gmail.com)

Dick H.J. Thijssen PhD [a,l] (Dick.Thijssen@radboudumc.nl)

Thijs M.H. Eijsvogels PhD [a] (Thijs.Eijsvogels@radboudumc.nl)

[a] Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, the Netherlands

[b] Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands

[c] Department of Physical Education and Sports, Faculty of Sports Science, Sport and Health University Research Institute (iMUDS), University of Granada, Granada, Spain

[d] GENUD Toledo Research Group, University of Castilla-La Mancha, Toledo, Spain

[e] CIBER of Frailty and Healthy Aging (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain.

[f] Center UCM-ISCIII for Human Evolution and Behavior, Madrid, Spain.

[g] Faculty of Education, Complutense University of Madrid, Madrid, Spain.

[h] CIBERobn Physiopathology of Obesity and Nutrition, Granada, Spain.

[i] Faculty of Sport and Health Sciences University of Jyväskylä, Jyväskylä, Finland.

[j] Department of Kinesiology, Iowa State University, Iowa, USA

[k] Division of Cardiology, Hartford Hospital, Hartford, United States of America

[l] Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

Funding

FBO's research activity on this topic is supported by the Grant PID2020-120249RB-I00 funded by MCIN/AEI/10.13039/501100011033 and by the Andalusian Government (Junta de Andalucía, Plan Andaluz de Investigación, ref. P20_00124).

EAB has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No [101064851].

Disclosures

None to declare.

Corresponding author: Thijs M.H. Eijsvogels PhD, Department of Medical BioSciences (928), Radboud university medical center, P.O. box 9101, 6500 HB, Nijmegen, The Netherlands, Email: Thijs.Eijsvogels@radboudumc.nl, Phone: +31 (0)24 36 13674, Fax: +31 (0)24 366 83 40, Twitter @ThijsEijsvogels

Word count: 5,141

Number of Tables: 0 (+ 4 Supplemental Tables)

Number of Figures: 5 (+ 10 Supplemental Figures and 1 Central Illustration)

ACKNOWLEDGEMENTS

The authors thank dr. Gerjon Hannink (department of Evidence-based Surgery, Radboud University Medical Center, Nijmegen, The Netherlands) for his statistical expertise and help during the analyses.

STRUCTURED ABSTRACT

BACKGROUND: The minimal and optimal daily step counts for health improvements remain unclear.

OBJECTIVES: A meta-analysis was performed to quantify dose-response associations of objectively-measured step count metrics in the general population.

METHODS: Electronic databases were searched from inception to October 2022. Primary outcomes included all-cause mortality and incident cardiovascular disease (CVD). Study results were analysed with generalized least squares and random effects models.

RESULTS: 111,309 individuals from 12 studies were included. Significant risk reductions were observed at 2,517 steps/day for all-cause mortality (adjusted hazard ratio (aHR): 0.92, 95% confidence interval (CI): 0.84, 0.999) and 2,735 steps/day for incident CVD (aHR: 0.89, 95% CI: 0.79, 0.999) compared with 2,000 steps/day (reference). Additional steps resulted in non-linear risk reductions of all-cause mortality and incident CVD with an optimal dose at 8,763 (aHR 0.40, 95% CI: 0.38, 0.43) and 7,126 steps/day (aHR 0.49, 95% CI: 0.45, 0.55), respectively. Increments from a low to an intermediate or high cadence were independently associated with risk reductions of all-cause mortality. Sex did not impact the dose-response associations, but after stratification for assessment device and wear location, pronounced risk reductions were observed for hip-worn accelerometers compared to pedometers and wrist-worn accelerometers.

CONCLUSIONS: As little as 2,517 and 2,735 steps/day yields significant mortality and CVD benefits, with progressive risk reductions up to 8,763 and 7,126 steps/day respectively. Additional mortality benefits were found at a moderate-to-high *versus* low step cadence. These findings can extent contemporary physical activity prescriptions given the easy-to-understand concept of step count.

PROSPERO REGISTRATION NUMBER: CRD42021244747.

CONDENSED ABSTRACT

Step count-based physical activity goals may represent a promising public health tool. This meta-analysis quantifies dose-response associations of objectively-measured step count metrics in the general population. Our results highlight that as little as ~2,500-2,700 steps/day already yields significant mortality and cardiovascular disease benefits, with progressive risk reductions up to ~7,100-8,800 steps/day. Step count targets were similar when stratified for sex, assessment device and wear location. These findings can extent contemporary physical activity prescriptions given the easy-to-understand concept of step count.

KEYWORDS: Walking, Public Health, Physical Activity, Exercise, Health Outcomes, Population

ABBREVIATION LIST

CI = confidence interval

CVD = cardiovascular disease

aHR = adjusted hazard ratio

IQR = interquartile range

MOOSE = Meta-analysis of Observational Studies in Epidemiology

SD = standard deviation

INTRODUCTION

Regular physical activity reduces the risk of cardiovascular diseases (CVD) and all-cause mortality in the general population[1,2]. Walking is an accessible type of physical activity that can be easily and accurately measured via commercially-available smartphones or smartwatches[3], pedometers[4], and accelerometers[5,6]. Daily step count represents an easy-to-use metric for the general population, and may therefore have the potential to improve physical activity adherence and subsequent clinical outcomes[7]. Indeed, studies found that performing an additional 1,000 daily steps is associated with a 12-15% reduced risk of all-cause mortality [8,9] and lower odds for frailty[10]. Despite the potential of walking to improve health, the 2020 World Health Organization Guidelines on Physical Activity and Sedentary Behaviour do not include step count thresholds[11]. Several meta-analyses have qualitatively examined the dose-response association of daily step count[8,9,12-15], but objective data extraction to identify minimum and optimum step count doses have not yet been fully established. To enable the integration of evidence-based thresholds in future physical activity guidelines, the role of potential effect modifiers such as walking intensity (i.e., step cadence [16]) should also be delineated as previous studies reported mixed results[17-19]. Therefore, this systematic review and meta-analysis examines the dose-response association of objectively-measured step count metrics with all-cause mortality and incident CVD in the general population. In addition, the moderating effects of 1) sex, 2) step cadence and 3) device and wear location of the step count assessment were explored.

METHODS

This systematic review was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist[20] and registered at the PROSPERO database (CRD42021244747).

Information sources and search strategy. A systematic literature search was performed in PubMed and Embase (Ovid), from inception to October 2022, using the search terms daily step count, step

intensity, objective step-measuring methods, mortality, and incident CVD alone and in combination (**Supplemental Table 1)**.

Eligibility criteria. Studies were included if they 1) quantified daily step count using objective step-counting methods (i.e., accelerometry, pedometer), 2) examined the associations between step count and all-cause mortality or incident fatal or non-fatal CVD including ischemic/coronary heart disease, stroke, and/or heart failure, 3) had a prospective cohort study design, 4) were peer-reviewed, published in English and accessible online, and 5) included adults aged ≥18 years without CVD at baseline. Studies addressing congenital heart disease were excluded.

Data extraction and quality assessment. Studies were selected by two independent researchers (NS, EB). Potential articles were manually screened using titles and abstracts. Full-text publications were retrieved and reviewed. Both researchers discussed results to reach consensus. Reference lists of relevant studies and systematic reviews were checked to ensure no relevant studies were missing. Extracted descriptive data included the study's primary outcome, cohort name, covariates included in analysis, sample size, age, sex, number of events, body mass index, baseline step count, monitoring period, wear time, assessment device, wear location, follow-up duration and shape of the dose-response curve. Authors were contacted via email in case insufficient data was reported.

Two researchers (NS, EB) independently scored the risk of bias of included studies using the Newcastle-Ottawa Scale[21]. In case of disagreement, consensus was reached by consulting a third researcher (TE). Studies were scored for selection, comparability and outcome on a 0-9 point score, where 1-3, 4-6 and 7-9 points reflect a high, intermediate, or low risk of bias respectively.

Data synthesis and analysis. Categorical and continuous dose-response associations between step count and clinical outcomes were tested. In addition, we explored the moderator effects of sex, step cadence, assessment device, wear location.

Categorical dose-response analysis. Categorical dose-response analyses were performed for step count and cadence. Peak cadence represents the maximal number of steps performed during any specified period of time. Peak 30-minute cadence was included in our analyses, as this parameter was most frequently reported. We used a previously published approach[22,23] to pool study data and generate three categories for step count and cadence each (i.e., low, intermediate, and high; **Supplemental Methods)**. Fully-adjusted hazard ratios (aHRs) were used to control for confounding variables. Transformation of aHRs and 95% confidence intervals (CIs) by the natural logarithm was performed to allow accurate estimation of the 95% CI for the pooled estimate. In essence, we compared the high and intermediate to the low categories using random effects as previously described[24]. Additional analyses were performed to examine 1) the moderator effect of device type and wear location (i.e., pedometer, hip-worn and wrist-worn accelerometer) and 2) the interplay between step cadence and step count. Heterogeneity was assessed using the I^2 and tau^2, with an I^2>50% indicating significant heterogeneity. Publication bias was explored using funnel plots and Egger's tests.

Continuous dose-response analysis. aHRs and 95% CIs per 500 step increment (range 1,500-16,000 steps) were extracted from published dose-response curves using a graphical software program (WebPlotDigitizer version 4.5, Automeris LLC, Pacifica, USA)[25,26]. Continuous dose-response associations between daily step count and all-cause mortality or incident CVD were based on a generalized least squares regression model using the maximum likelihood method. Non-linearity was assessed by modelling step count using a restricted cubic spline. We tested three knots (at 5%, 50% and 95% of step count distribution)[27], four knots (at 5%, 35%, 65% and 95%), and five knots (at 5%, 27.5%, 50%, 72.5% and 95%), and subsequently compared the Akaike Information criteria to identify

the best fitting model. Linearity was tested using the Wald test. The reference level of the pooled dose-response curves was set at 2,000 steps, which was performed by subtracting the natural log-transformed aHR corresponding to 2,000 steps/day from the natural log-transformed aHRs of the full range of step counts. The dose where minimal risk reductions were observed, was set at the first step count where the lower and upper border of the 95% CI were both lower than 1. The optimal step count dose was defined as the maximal risk reduction at the least effort (steps/day), reflecting the lowest step count at which the lower border of the 95% CI exceeded the upper border of the 95% CI of the lowest aHR (i.e., overlap of confidence intervals). We repeated these analyses with incremental reference categories (+1,000 steps/day) to compose a heatmap of the dose-response association between 2,000 and 16,000 steps/day. Dose-response models were truncated at 16,000 steps/day because of a paucity of data above this value. To explore effect modification, we additionally investigated the role of sex and accelerometry wear location. To test the robustness of our results, we performed a sensitivity analysis including only high-quality studies (Newcastle-Ottawa Scale ≥ 7).

All analyses were performed in R version 4.02 (R Foundation for Statistical Computing, Vienna, Austria) using *meta* (version 5.1-1)[28] and *rms (*version 6.2-0*)*[29]. A two-tailed p-value<0.05 indicated statistical significance. Baseline study characteristics were weighted for sample size to better reflect the characteristics of the overall population. Data is presented as mean ± standard deviation (SD), median with interquartile range [IQR], or frequency and proportion.

RESULTS

Study selection. The systematic search identified 5,414 potential studies: 2,856 from PubMed and 2,558 from Embase (**Figure 1**). A total of 1,078 were duplicates, 4,307 articles were excluded based on title and abstract, leaving 29 articles which were screened for eligibility. Fifteen articles did not meet the inclusion criteria after reading the full-text and two articles[30,31] were excluded because of insufficient data, leaving 12 studies for inclusion. One study[32] shared unpublished data on the association between daily step count and cardiac hospitalizations. In total, eleven studies assessed the association between step count and all-cause mortality (n=111,309)[17-19,32-40]; four studies assessed step

count and incident CVD (n=85,261)[19,32,40,41] and four assessed step cadence and all-cause mortality (n=102,191)[17-19,40].

Study and population characteristics. The analytical cohort (**Supplemental Table 2**) objectively measured step count data from 111,309 individuals (60.8% women, 62.5±5.3 years old, body mass index 27.0±1.3 kg/m^2). Mean daily step count was 7,069±904 steps/day. Of the twelve included studies, one study included only women[17] and two included only men[33,41]. Step count was quantified using a pedometer (n=3)[35,37,38], or a hip-worn (n=8)[17-19,32-34,36,41] or wrist-worn (n=1)[40] accelerometer. All studies measured step count for 7 days, except for one cohort that measured for two days [38]. Most studies corrected for age (n=10), BMI (n=10), sex (n=10), smoking status (n=10), alcohol status (n=9), education level (n=7) and relevant comorbidities (n=8) within their fully-adjusted model. Most studies used national death registries[17-19,32-35,38,40,41] and death certificates[17] to assess endpoints.

Quality assessment and publication bias. All studies had a low risk of bias (Newcastle-Ottawa Scale ≥ 7), except for one[37] which had an intermediate risk of bias (Newcastle-Ottawa Scale = 6; **Supplemental Table 3**). Assessment of publication bias for the association between daily step count and all-cause mortality showed a symmetrical pattern suggesting minimal publication bias (**Supplemental Figure 1**).

Categorical dose-response association between daily step count and clinical outcomes. Among 111,309 individuals, 4,854 died (4.4%) during a median follow-up of 77.8 months [71.6–82.9]. Intermediate step counts (6,000 [5,392-6,775] steps/day) were associated with a significantly lower mortality risk (aHR 0.64, 95% CI: 0.56-0.72; **Figure 2**) compared to the lower tertile (3,166 [2,375-4,191] steps/day). The risk reduction for the association with all-cause mortality was largest (aHR 0.50, 95% CI: 0.42-0.60; **Figure 2**) in individuals in the highest tertile (10,000 [8,843-11,082] steps/day).

A total of 1,224 individuals (1.4%) developed a CVD event during 72.9 [66.4-80.4] months of follow-up. The intermediate (5,737 [5,449-6,000] steps/day) and high step count (11,000 [9,923-12,024] steps/day) categories were associated with a lower risk of CVD (aHR 0.58, 95% CI: 0.46-0.73 and aHR 0.42, 95% CI: 0.33-0.53, respectively) compared to the low step count category (2,022 [1,468-2,885] steps/day; **Figure 3**).

Continuous dose-response association between daily step count and clinical outcomes. The continuous dose-response analyses revealed non-linear trends (p-values for non-linearity <0.001) for the associations between step count versus all-cause mortality and incident CVD (**Central Illustration** and **Supplemental Figure 2**). Risk reductions became statistically significant for the associations with all-cause mortality and CVD at 2,517 steps/day (aHR: 0.92, 95% CI: 0.84-0.999) and 2,735 steps/day (aHR: 0.89, 95% CI: 0.79-0.999), respectively. The minimal effective step count for all-cause mortality and CVD was 479 [399, 644] and 735 [632, 1081] steps/day above the reference category for other cut-offs points (**Supplemental Table 4**). Further increases in step count were associated with a decreased mortality and CVD risk until 8,763 steps/day (aHR: 0.40, 95% CI: 0.38-0.43) and 7,126 (aHR: 0.49, 95% CI: 0.45-0.55) after which additional reductions in mortality and incident CVD risk were not statistically significant (16,000 vs 2,000 steps: aHR 0.35 [95% CI: 0.30-0.40], and aHR 0.42 [95% CI: 0.33-0.53], respectively; **Central Illustration**). Changes in risk estimates following increases or decreases of 1,000 steps/day were strongly dependent on baseline step count (**Figure 4**).

Comparable results were observed when only high-quality studies were examined (**Supplemental Figure 3**). Likewise, no important differences in risk reductions were observed between men and women (**Supplemental Figures 4, 5** and **6**). Studies using hip-worn accelerometry were associated with more pronounced mortality risk reductions than studies using wrist-worn accelerometers (**Supplemental Figures 7, 8** and **9**) and pedometers (**Supplemental Figure 9**).

Step cadence and mortality. Intermediate (63 [63-63] steps/min) and high (88 [88-88] steps/min) cadences were associated with a lower mortality risk (aHR 0.67, 95% CI: 0.56-0.80; and aHR 0.62, 95% CI: 0.40-0.97) than a low cadence (29 [28-30] steps/min, **Supplemental Figure 10**). Additional adjustment for step count attenuated these associations (intermediate cadence: aHR 0.78, 95% CI: 0.65-0.93; and high cadence: aHR 0.79, 95% CI: 0.67-0.94; **Figure 5**).

DISCUSSION

Our meta-analyses quantified the dose-response association of objectively-measured daily step count metrics with all-cause mortality and incident CVD in the general population. A minimal dose of 2,517 and 2,735 steps/day was associated with an 8% reduction in all-cause mortality and a 11% reduction in CVD risk, respectively, compared to individuals accumulating 2,000 steps/day. The optimal doses were found at 8,763 steps/day for all-cause mortality (i.e., 60% risk reduction) and 7,126 steps/day for incident CVD (i.e., 51% risk reduction). Increasing from low to intermediate and high cadence were also associated with a decreased all-cause mortality risk (33% and 38% risk reduction, respectively), even after adjustment for daily step count (22% and 21% risk reduction, respectively). Risk reductions were greater for hip-worn accelerometers than for pedometers and wrist-worn accelerometers. There were no important differences in risk reductions with step count between men and women. Findings from this meta-analysis may optimize physical activity prescription in daily practice given the easy-to-understand concept of step count from a public health perspective.

Minimal dose. We found that the minimal step count dose needed to elicit significant health benefits was ~2,500 steps/day for all-cause mortality and ~2,700 steps/day for incident CVD in comparison to individuals who accumulated 2,000 steps/day. These findings highlight that behaviour changes from physical inactivity to a lifestyle with some physical activity may already produce risk reductions for all-cause mortality and incident CVD. It is important to highlight that such activity levels are feasible for the majority of the general population, including older adults and individuals with chronic

diseases[42]. Increases of 1,000 steps/day were associated with additional health benefits (**Figure 4**), especially among those with a low number of baseline steps (**Supplemental Table 4)**, highlighting that every step counts.

Optimal dose. The optimal step count dose was observed at ~8,800 and ~7,100 steps for all-cause mortality and incident CVD, respectively. Step counts beyond our optimal dose minimally improved health outcomes. This plateau suggests that most benefits were achieved at step counts less then 10,000 per day, which aligns with observations from recent other meta-analyses[12,14]. Although higher step volumes beyond this level were not associated with additional health benefits, there is no reason to discourage individuals from such behaviour as a highly physically-active lifestyle may provide other benefits, such as joy, improved quality of life, sleep and mental health[43,44].

Stepping cadence. We found that an intermediate and high cadence was associated with a reduced risk of mortality and CVD morbidity, even after additional adjustment for daily steps. These findings underline that both volume (steps/day) and intensity (cadence, steps/min) are independently associated with health and that their risk reductions are additive. Cadence can be considered a proxy for fitness, since a higher cadence requires a greater oxygen consumption[45,46] and higher fitness is associated with better event-free survival [47,48]. Similarly, a greater proportion of vigorous physical activity, relative to the total amount of physical activity, is associated with a reduced mortality risk[49-51]. Hence, accruing step volumes at a higher step cadence may provide additional benefits compared to low cadence.

Device type and wear location. Reductions in mortality and CVD risks were larger for hip-worn accelerometers than pedometers and wrist-worn accelerometers. Hip-mounted devices are potentially more likely to accurately measure steps given their close proximity to locomotion acceleration. Alternatively, this observation may also relate to differences in cohort characteristics (i.e., age,

follow-up time, event rate), as we included only one study using a wrist-worn device. The lower risk estimate for pedometers may be due to underestimation of step count compared to accelerometers[52], especially at slower cadences[53]. Nevertheless, the impact of these findings may be limited for future guidelines, since the minimal and optimal dose were not affected by the device type or wear location. Therefore, a uniform step count prescription may be adopted using different devices.

Practical implications. This study revealed reversed J-shaped dose-response curves between daily steps and health outcomes, with progressive risk reductions for mortality and CVD at a higher number of daily steps, independent of sex. The optimal dose of ~8,800 steps/day for mortality and ~7,100 for CVD may be used in future physical activity guidelines. Step count based targets may enhance adherence to physical activity recommendations since measurement devices are commercially available and provide reliable measurement of walking activity[54]. Physicians may stimulate individuals, even those who are moderately active, to increase their physical activity with at least 1,000 steps/day, as this target is feasible and can be achieved during ~10 minutes of walking activity[55]. Since walking is accessible to the majority of the population, including those with chronic disease or with a lower social economic status, and can be adjusted to a pace that matches the individual level of fitness, step count based physical activity goals may become a promising public health tool.

Strengths and limitations. The strengths include the large sample size (n=111,309) and the ability to model continuous dose-response associations, while the risk of bias was low with minimal evidence of publication bias. Nonetheless, several limitations should be considered. First, daily step counts were only investigated at baseline, but physical activity behaviour may change over time and is influenced by various factors (e.g., age, sex, socio-economic status, and disease state)[56,57]. Repeated measures of daily step count could further strengthen the evidence. Second, we were not able to quantify the effects of reverse causation and other relevant factors that influence daily step count, due

to restrictions in available and published dose-response curves. Nonetheless, ten out of 12 studies concluded that their results were not likely to be affected by reverse causation when removing the first[17,33,35,41], second[18,32,34,38,40] or third[37] follow-up year(s). Third, only four studies investigated the additive effects of step cadence to total step count. Future studies are warranted to confirm our results. Fourth, observations from this study may not directly be extrapolated to chronically diseased, older and low-income populations. Whilst the minimal and optimal step count may represent relevant targets for these populations, the magnitude of risk reductions may be different as distinct dose-response relationship between physical activity and health were previously presented for individuals with CVD *versus* healthy controls[58].

CONCLUSIONS

A lower risk for all-cause mortality and incident CVD may already be experienced after 2,517 and 2,735 steps/day, respectively. Additional increments of 1,000 steps/day (~10 minutes walking) enhance risk reductions in a non-linear fashion (reversed J-shaped curve). Optimal health benefits were achieved at 8,763 steps/day for all-cause mortality and 7,126 steps/day for incident CVD. A higher cadence provides additional health benefits beyond the total step volume. As health benefits of daily steps were similar between men and women and step count targets were independent of wear location and device, the integration of uniform daily step targets in future physical activity guidelines may be relevant from a public health perspective as “Every Step Counts”.

CLINICAL PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Using data from 111,309 individuals, minimum (2,517 and 2,735 steps/day) and optimum (8,763 and 7,126 steps/day) step counts were identified to reduce all-cause mortality and incident cardiovascular disease, respectively. These targets were independent of sex, wear location and device type.

TRANSLATIONAL OUTLOOK: Given the easy-to-understand concept of daily steps from a public health perspective, step count metrics may be used to prescribe the minimal and optimal volume (i.e., steps/day) and intensity (i.e., step cadence) of physical activity for health improvement.

DATA AVAILABILITY

The data underlying this article will be shared upon reasonable request to the corresponding author.

REFERENCES

1. Lee D-c, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-Time Running Reduces All-Cause and Cardiovascular Mortality Risk. Journal of the American College of Cardiology 2014;64:472-481.

2. Eijsvogels TM, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the Extremes: The Amount of Exercise to Reduce Cardiovascular Events. J Am Coll Cardiol 2016;67:316-29.

3. Case MA, Burwick HA, Volpp KG, Patel MS. Accuracy of smartphone applications and wearable devices for tracking physical activity data. Jama 2015;313:625-6.

4. Hasson RE, Haller J, Pober DM, Staudenmayer J, Freedson PS. Validity of the Omron HJ-112 pedometer during treadmill walking. Med Sci Sports Exerc 2009;41:805-9.

5. Esliger DW, Probert A, Connor Gorber S, Bryan S, Laviolette M, Tremblay MS. Validity of the Actical accelerometer step-count function. Med Sci Sports Exerc 2007;39:1200-4.

6. Fortune E, Lugade V, Morrow M, Kaufman K. Validity of using tri-axial accelerometers to measure human movement - Part II: Step counts at a wide range of gait velocities. Med Eng Phys 2014;36:659-69.

7. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. Int J Epidemiol 2011;40:1382-400.

8. Liu Y, Sun Z, Wang X, Chen T, Yang C. Dose-response association between the daily step count and all-cause mortality: A systematic review and meta-analysis. J Sports Sci 2022;40:1678-1687.

9. Jayedi A, Gohari A, Shab-Bidar S. Daily Step Count and All-Cause Mortality: A Dose-Response Meta-analysis of Prospective Cohort Studies. Sports Med 2021.

10. Lefferts EC, Bakker EA, Carbone S, Lavie CJ, Lee DC. Associations of total and aerobic steps with the prevalence and incidence of frailty in older adults with hypertension. Prog Cardiovasc Dis 2021;67:18-25.

11. World Health Organization. WHO guidelines on physical activity and sedentary behaviour. Geneva, 2020.

12. Paluch AE, Bajpai S, Bassett DR et al. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. Lancet Public Health 2022;7:e219-e228.

13. Sheng M, Yang J, Bao M et al. The relationships between step count and all-cause mortality and cardiovascular events: A dose-response meta-analysis. J Sport Health Sci 2021;10:620-628.

14. Paluch AE, Bajpai S, Ballin M et al. Prospective Association of Daily Steps With Cardiovascular Disease: A Harmonized Meta-Analysis. Circulation 2022.

15. Isath A, Virani SS, Wang Z et al. Meta-analysis of Per-Day Step Count and All-Cause Mortality. Am J Cardiol 2022;180:166-168.

16. Tudor-Locke C, Craig CL, Brown WJ et al. How many steps/day are enough? For adults. Int J Behav Nutr Phys Act 2011;8:79.

17. Lee IM, Shiroma EJ, Kamada M, Bassett DR, Matthews CE, Buring JE. Association of Step Volume and Intensity With All-Cause Mortality in Older Women. JAMA Intern Med 2019;179:1105-1112.

18. Paluch AE, Gabriel KP, Fulton JE et al. Steps per Day and All-Cause Mortality in Middle-aged Adults in the Coronary Artery Risk Development in Young Adults Study. JAMA Netw Open 2021;4:e2124516.

19. Saint-Maurice PF, Troiano RP, Bassett DR, Jr. et al. Association of Daily Step Count and Step Intensity With Mortality Among US Adults. Jama 2020;323:1151-1160.

20. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 2000;283:2008-12.

21. Wells GA, Wells G, Shea B et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. 2014.

22. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation 2014;129:643-59.

23. Pandey A, Salahuddin U, Garg S et al. Continuous Dose-Response Association Between Sedentary Time and Risk for Cardiovascular Disease: A Meta-analysis. JAMA Cardiol 2016;1:575-83.

24. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

25. Rohatgi A. WebPlotDigitizer: Version 4.5. 2022.

26. Drevon D, Fursa SR, Malcolm AL. Intercoder Reliability and Validity of WebPlotDigitizer in Extracting Graphed Data. Behav Modif 2017;41:323-339.

27. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010;29:1037-57.

28. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153-160.

29. Harrel F. rms: Regression Modeling Strategies. R package version 6.2-0. https://CRAN.R-project.org/package=rms. 2021.

30. Cochrane SK, Chen SH, Fitzgerald JD et al. Association of Accelerometry-Measured Physical Activity and Cardiovascular Events in Mobility-Limited Older Adults: The LIFE (Lifestyle Interventions and Independence for Elders) Study. J Am Heart Assoc 2017;6.

31. Yates T, Haffner SM, Schulte PJ et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. Lancet 2014;383:1059-66.

32. Mañas A, Del Pozo Cruz B, Ekelund U et al. Association of accelerometer-derived step volume and intensity with hospitalizations and mortality in older adults: A prospective cohort study. J Sport Health Sci 2021.

33. Jefferis BJ, Parsons TJ, Sartini C et al. Objectively measured physical activity, sedentary behaviour and all-cause mortality in older men: does volume of activity matter more than pattern of accumulation? Br J Sports Med 2019;53:1013-1020.

34. Hansen BH, Dalene KE, Ekelund U et al. Step by step: Association of device-measured daily steps with all-cause mortality-A prospective cohort Study. Scand J Med Sci Sports 2020;30:1705-1711.

35. Oftedal S, Holliday EG, Attia J et al. Daily steps and diet, but not sleep, are related to mortality in older Australians. J Sci Med Sport 2020;23:276-282.

36. Fox KR, Ku PW, Hillsdon M et al. Objectively assessed physical activity and lower limb function and prospective associations with mortality and newly diagnosed disease in UK older adults: an OPAL four-year follow-up study. Age Ageing 2015;44:261-8.

37. Yamamoto N, Miyazaki H, Shimada M et al. Daily step count and all-cause mortality in a sample of Japanese elderly people: a cohort study. BMC Public Health 2018;18:540.

38. Dwyer T, Pezic A, Sun C et al. Objectively Measured Daily Steps and Subsequent Long Term All-Cause Mortality: The Tasped Prospective Cohort Study. PLoS One 2015;10:e0141274.

39. Del Pozo Cruz B, Ahmadi MN, Lee IM, Stamatakis E. Prospective Associations of Daily Step Counts and Intensity with Cancer and Cardiovascular Disease Incidence and Mortality and All-Cause Mortality. JAMA Internal Medicine 2022:1DUMMY.

40. Del Pozo Cruz B, Ahmadi MN, Lee IM, Stamatakis E. Prospective Associations of Daily Step Counts and Intensity With Cancer and Cardiovascular Disease Incidence and Mortality and All-Cause Mortality. JAMA Intern Med 2022;182:1139-1148.

41. Jefferis BJ, Parsons TJ, Sartini C et al. Does total volume of physical activity matter more than pattern for onset of CVD? A prospective cohort study of older British men. Int J Cardiol 2019;278:267-272.

42. Tudor-Locke C, Craig CL, Aoyagi Y et al. How many steps/day are enough? For older adults and special populations. Int J Behav Nutr Phys Act 2011;8:80.

43. Wasfy MM, Lee I-M. Examining the Dose-Response Relationship between Physical Activity and Health Outcomes. NEJM Evidence 2022;1:EVIDra2200190.

44. Chekroud SR, Gueorguieva R, Zheutlin AB et al. Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study. Lancet Psychiatry 2018;5:739-746.

45. Tudor-Locke C, Aguiar EJ, Han H et al. Walking cadence (steps/min) and intensity in 21-40 year olds: CADENCE-adults. Int J Behav Nutr Phys Act 2019;16:8.

46. Tudor-Locke C, Ducharme SW, Aguiar EJ et al. Walking cadence (steps/min) and intensity in 41 to 60-year-old adults: the CADENCE-adults study. Int J Behav Nutr Phys Act 2020;17:137.

47. Laukkanen JA, Isiozor NM, Kunutsor SK. Objectively Assessed Cardiorespiratory Fitness and All-Cause Mortality Risk: An Updated Meta-analysis of 37 Cohort Studies Involving 2,258,029 Participants. Mayo Clin Proc 2022;97:1054-1073.

48. Kokkinos P, Faselis C, Samuel IBH et al. Cardiorespiratory Fitness and Mortality Risk Across the Spectra of Age, Race, and Sex. J Am Coll Cardiol 2022;80:598-609.

49. Ahmadi MN, Clare PJ, Katzmarzyk PT, Del Pozo Cruz B, Lee IM, Stamatakis E. Vigorous physical activity, incident heart disease, and cancer: how little is enough? Eur Heart J 2022;43:4801-4814.

50. Dempsey PC, Rowlands AV, Strain T et al. Physical activity volume, intensity, and incident cardiovascular disease. Eur Heart J 2022;43:4789-4800.

51. Wang Y, Nie J, Ferrari G, Rey-Lopez JP, Rezende LFM. Association of Physical Activity Intensity With Mortality: A National Cohort Study of 403 681 US Adults. JAMA Internal Medicine 2021;181:203-211.

52. Tudor-Locke C, Ainsworth BE, Thompson RW, Matthews CE. Comparison of pedometer and accelerometer measures of free-living physical activity. Med Sci Sports Exerc 2002;34:2045-51.

53. Martin JB, Krč KM, Mitchell EA, Eng JJ, Noble JW. Pedometer accuracy in slow walking older adults. Int J Ther Rehabil 2012;19:387-393.

54. Toth LP, Park S, Springer CM, Feyerabend MD, Steeves JA, Bassett DR. Video-Recorded Validation of Wearable Step Counters under Free-living Conditions. Med Sci Sports Exerc 2018;50:1315-1322.

55. Tudor-Locke C, Rowe DA. Using cadence to study free-living ambulatory behaviour. Sports Med 2012;42:381-98.

56. Hirvensalo M, Telama R, Schmidt MD et al. Daily steps among Finnish adults: variation by age, sex, and socioeconomic position. Scand J Public Health 2011;39:669-77.

57. Tudor-Locke C, Schuna JM, Jr., Barreira TV et al. Normative steps/day values for older adults: NHANES 2005-2006. J Gerontol A Biol Sci Med Sci 2013;68:1426-32.

58. Bakker EA, Lee DC, Hopman MTE et al. Dose-response association between moderate to vigorous physical activity and incident morbidity and mortality for individuals with a

501 different cardiovascular health status: A cohort study among 142,493 adults from the
502 Netherlands. PLoS Med 2021;18:e1003845.

503

FIGURE LEGENDS

Central Illustration. Dose-response associations of daily step count with clinical outcomes.

Dose-response curves for the association between daily step count versus all-cause mortality (left panel) and incidence of cardiovascular diseases (CVD; right panel). Adjusted hazard ratios from published dose-response curves were extracted and pooled using restricted cubic spline models. Compared to the reference level of 2,000 steps/day, the minimum dose to significantly reduce the risk for adverse outcomes was 2,517 steps/day for all-cause mortality and 2,735 steps/day for incident CVD. The optimum dose, defined as the maximal risk reduction at the least effort, was established at 8,763 steps/day for all-cause mortality and 7,126 steps/day for incident CVD. Shaded areas indicate the corresponding 95% confidence interval. aHR adjusted hazard ratio, CVD cardiovascular disease.

Figure 1. PRISMA flowchart of the review process of potential articles.

Figure 2. Association between daily step count tertiles and all-cause mortality. *Individuals in the intermediate (6,000 [5,392-6,775] steps/day) and high step count tertile (10,000 [8,843-11,082] steps/day) had a significantly lower mortality risk (36 and 50%, respectively) compared to the low step count tertile (3,166 [2,375-4,191] steps/day). For each study, red vertical and horizontal lines represent the effect estimate and 95% confidence intervals. Study weights were obtained via a random-effects analysis and were presented as red squares and percentages. The red diamond represents the pooled estimate and its 95% confidence interval. The low, intermediate and high step counts reflect the average step count of the subjects in the respective group. CI = confidence interval, aHR = adjusted hazard ratio, IQR = interquartile range.*

Figure 3. Association between daily step count tertiles and incident CVD.

Individuals in the intermediate (5,737 [5,449-6,000] steps/day) and high step count tertile (11,000 [9,923-12,024] steps/day) had a lower risk for incident CVD (42 and 58%, respectively) compared to the low step count tertile (2,022 [1,468-2,885] steps/day). For each study, blue vertical and horizontal lines represent the effect estimate and 95% confidence intervals. Study weights were obtained via a random-effects analysis and were presented as blue squares and percentages. The blue diamond represents the pooled estimate and its 95% confidence interval. The low, intermediate and high step counts reflect the average step count of the subjects in the respective group. CI confidence interval, CVD cardiovascular disease, aHR adjusted hazard ratio, IQR interquartile range.

Figure 4. Associations between different step count volumes and clinical outcomes.

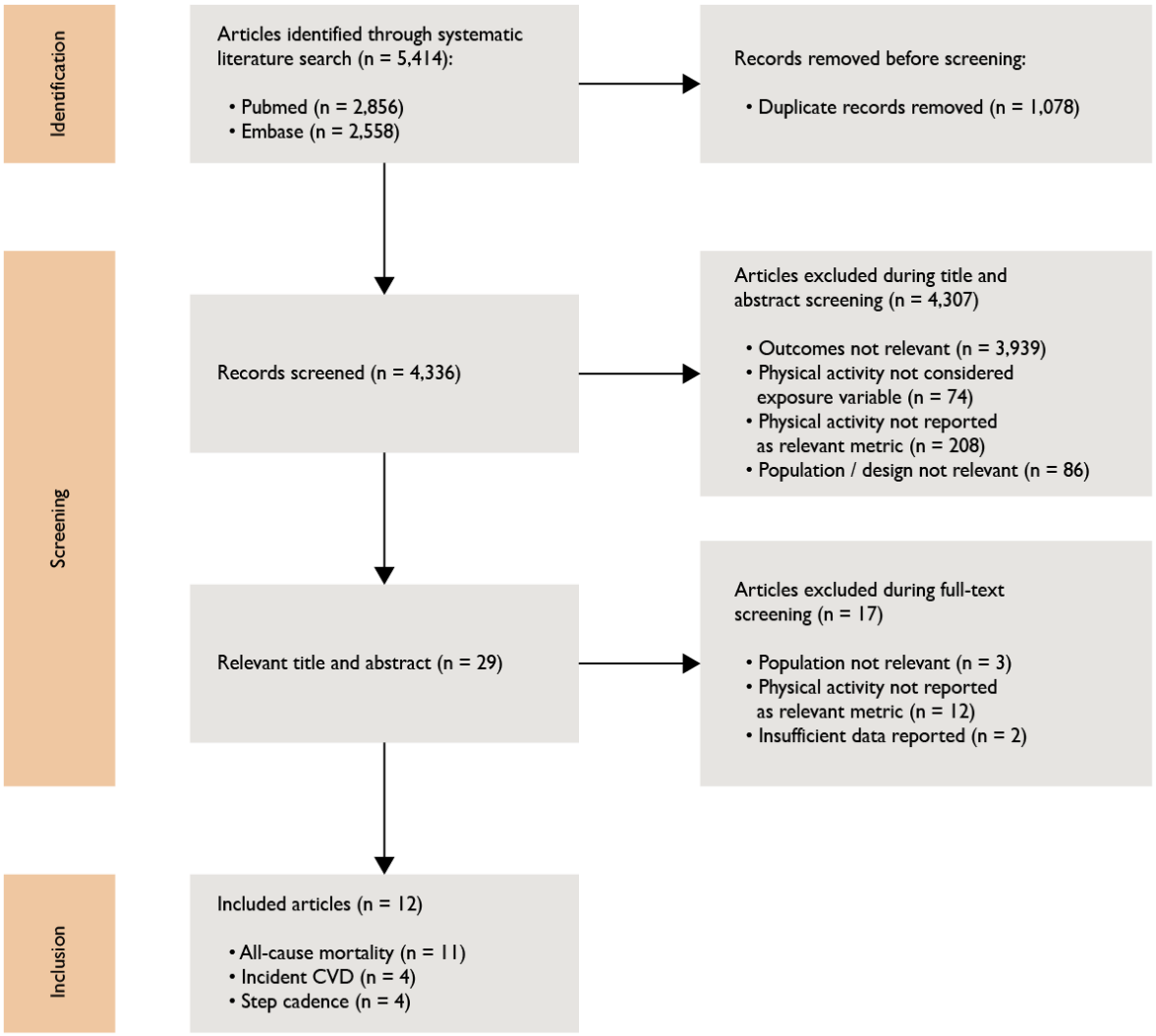
Heatmap visualization of the interplay between different step count volumes with all-cause mortality (left heatmap) and incident CVD risk (right heatmap). Heatmaps should be interpreted row-wise. Green and red values indicate significant reductions and increases in risk, respectively, whereas grey cells indicate no significant difference compared to the reference level. aHR adjusted hazard ratio, CVD cardiovascular disease, REF reference level.

Figure 5. Association between step cadence tertiles and all-cause mortality.

Forest plot highlighting the association between 30-minute peak cadence with all-cause mortality, adjusted for confounders and total step count. Individuals in the intermediate (66 [63-67] steps/min) and high step cadence tertile (90 [89-90] steps/min) had a significantly lower mortality risk (22 and 21% respectively) compared to the low step cadence tertile (25 [25-25] steps/min) after adjustment for total step count. For each study, red vertical and horizontal lines represent the effect estimate and 95% confidence intervals. Study weights were obtained via a random-effects analysis and are presented as red squares and

percentages. The red diamond represents the pooled estimate and its 95% confidence interval. The low, intermediate and high step cadence reflect the average step cadence of the subjects in the respective group. CI confidence interval, aHR adjusted hazard ratio, IQR interquartile range.

559


Identification
Articles identified through systematic literature search (n = 5,414):
• Pubmed (n = 2,856)
• Embase (n = 2,558)
Records removed before screening:
• Duplicate records removed (n = 1,078)
Screening
Records screened (n = 4,336)
Articles excluded during title and abstract screening (n = 4,307)
• Outcomes not relevant (n = 3,939)
• Physical activity not considered exposure variable (n = 74)
• Physical activity not reported as relevant metric (n = 208)
• Population / design not relevant (n = 86)
Relevant title and abstract (n = 29)
Articles excluded during full-text screening (n = 17)
• Population not relevant (n = 3)
• Physical activity not reported as relevant metric (n = 12)
• Insufficient data reported (n = 2)
Inclusion
Included articles (n = 12)
• All-cause mortality (n = 11)
• Incident CVD (n = 4)
• Step cadence (n = 4)

560

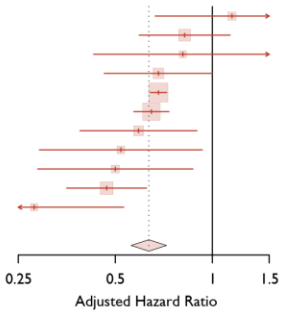
561

562

Intermediate vs low step count tertile

Study	Publishing year	Sample size (n)	Events (%)	Low step count (steps/day)	Intermediate step count (steps/day)	aHR [95% CI]	Weight
Fox et al.	2015	201	16.4	2,208	4,183	1.15 [0.66, 1.99]	4.4%
Oftedal et al.	2020	1,697	12.0	3,166	6,688	0.82 [0.59, 1.13]	9.6%
Yamamoto et al.	2018	419	18.1	3,394	5,310	0.81 [0.43, 1.53]	3.4%
Dwyer et al.	2015	2,576	8.5	4,381	7,552	0.68 [0.46, 1.00]	7.6%
Saint−Maurice et al.	2020	4,840	24.1	4,000	6,000	0.68 [0.64, 0.72]	24.6%
Del Pozo Cruz et al.	2022	78,500	2.8	1,289	6,000	0.65 [0.57, 0.73]	20.7%
Jefferis et al.	2019	1,274	15.2	1,524	5,472	0.59 [0.39, 0.90]	6.8%
Hansen et al.	2020	2,183	5.5	4,651	6,862	0.52 [0.29, 0.93]	4.0%
Mañas et al.	2021	768	11.6	2,542	5,311	0.50 [0.29, 0.87]	4.3%
Lee et al.	2019	16,741	3.0	2,718	5,905	0.47 [0.35, 0.63]	11.2%
Paluch et al.	2021	2,110	3.4	5,837	8,502	0.28 [0.15, 0.53]	3.4%
Random effects model						**0.64 [0.56, 0.72]**	**100.0%**

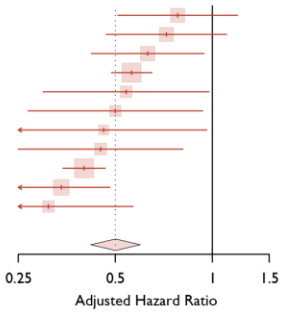
Heterogeneity: I^2 = 53% [95%CI: 7%, 76%], τ^2 = 0.02 [95% CI: 0.00, 0.22]
Test for overall effect: $z = -7.02$ ($p < 0.01$)



High vs low step count tertile

Study	Publishing year	Sample size (n)	Events (%)	Low step count (steps/day)	High step count (steps/day)	aHR [95% CI]	Weight
Fox et al.	2015	201	16.4	2,208	6,158	0.78 [0.51, 1.20]	9.0%
Dwyer et al.	2015	2,576	8.5	4,381	10,520	0.72 [0.47, 1.11]	9.0%
Oftedal et al.	2020	1,697	12.0	3,166	11,644	0.63 [0.42, 0.94]	9.6%
Del Pozo Cruz et al.	2022	78,500	2.8	1,289	10,000	0.56 [0.49, 0.65]	16.7%
Mañas et al.	2021	768	11.6	2,542	9,015	0.54 [0.30, 0.98]	6.1%
Hansen et al.	2020	2,183	5.5	4,651	8,670	0.50 [0.27, 0.93]	5.7%
Yamamoto et al.	2018	419	18.1	3,394	10,241	0.46 [0.22, 0.96]	4.4%
Paluch et al.	2021	2,110	3.4	5,837	11,815	0.45 [0.25, 0.81]	6.2%
Saint−Maurice et al.	2020	4,840	24.1	4,000	10,000	0.40 [0.34, 0.47]	16.5%
Lee et al.	2019	16,741	3.0	2,718	8,442	0.34 [0.24, 0.48]	11.0%
Jefferis et al.	2019	1,274	15.2	1,524	12,097	0.31 [0.17, 0.57]	5.9%
Random effects model						**0.50 [0.42, 0.60]**	**100.0%**

Heterogeneity: I^2 = 62% [95% CI: 26%, 80%], τ^2 = 0.04 [95% CI: 0.00, 0.21]
Test for overall effect: $z = -7.63$ ($p < 0.01$)



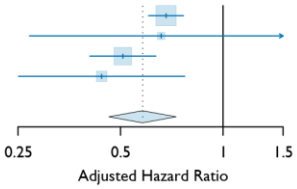
563

564

Intermediate vs low step count tertile

Study	Publishing year	Sample size (n)	Events (%)	Low step count (steps/day)	Intermediate step count (steps/day)	aHR [95% CI]	Weight
Saint−Maurice et al.	2020	4,840	8.3	4,000	6,000	0.68 [0.60, 0.77]	46.5%
Mañas et al.	2021	740	4.3	2,513	5,373	0.66 [0.27, 1.60]	5.8%
Del Pozo Cruz et al.	2022	78,500	0.8	1,276	6,000	0.51 [0.41, 0.63]	35.2%
Jefferis et al.	2019	1,181	10.3	1,532	5,474	0.44 [0.25, 0.77]	12.5%
Random effects model						**0.58 [0.46, 0.73]**	**100.0%**

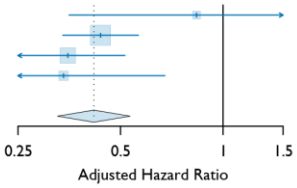
Heterogeneity: I^2 = 56% [95% CI: 0%, 85%], τ^2 = 0.03 [95% CI: 0.00, 0.68]
Test for overall effect: $z = -4.68$ ($p < 0.01$)



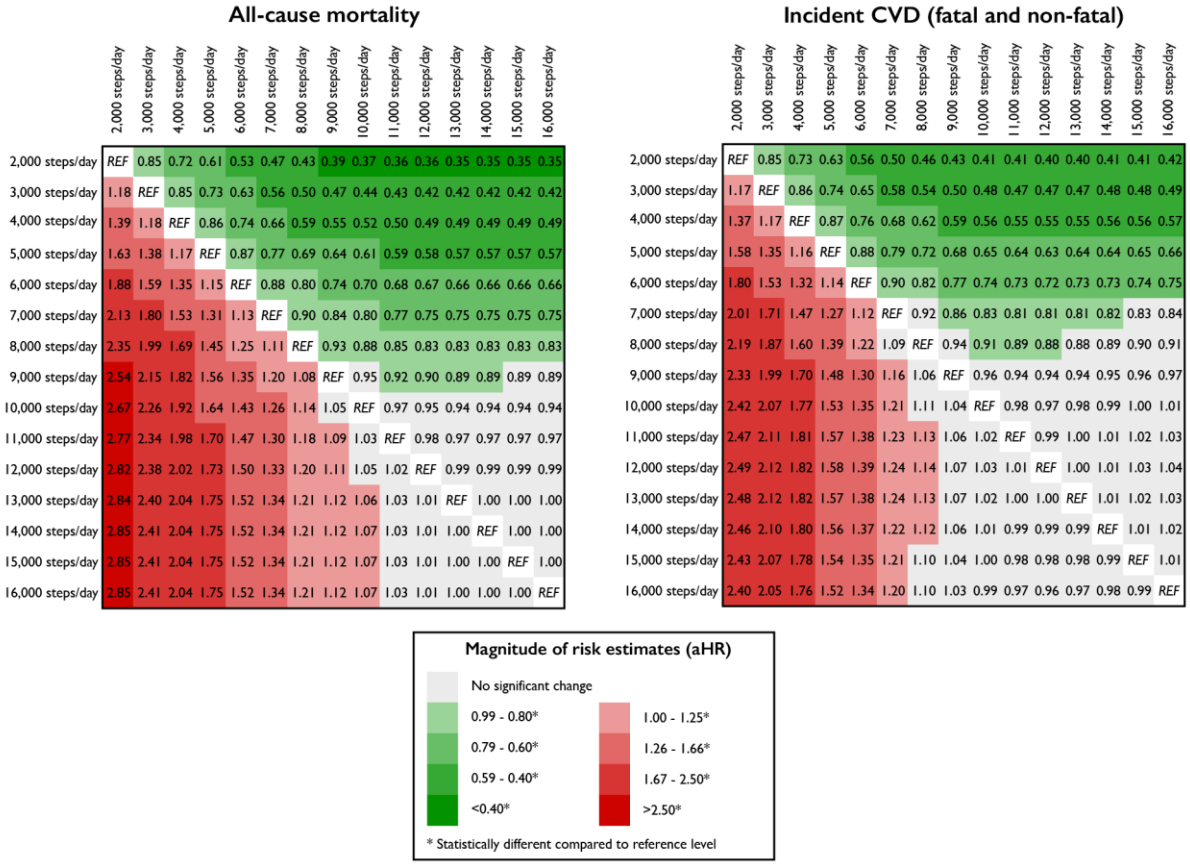
High vs low step count tertile

Study	Publishing year	Sample size (n)	Events (%)	Low step count (steps/day)	High step count (steps/day)	aHR [95% CI]	Weight
Mañas et al.	2021	740	4.3	2,513	9,691	0.84 [0.35, 1.98]	7.6%
Del Pozo Cruz et al.	2022	78,500	0.8	1,276	10,000	0.44 [0.34, 0.56]	51.0%
Saint−Maurice et al.	2020	4,840	8.3	4,000	12,000	0.35 [0.24, 0.52]	29.9%
Jefferis et al.	2019	1,181	10.3	1,532	12,094	0.34 [0.17, 0.67]	11.6%
Random effects model						**0.42 [0.33, 0.53]**	**100.0%**

Heterogeneity: I^2 = 20% [95% CI: 0%, 88%], τ^2 = 0.01 [95% CI: 0.00, 1.57]
Test for overall effect: $z = -6.96$ ($p < 0.01$)



568


All-cause mortality
Incident CVD (fatal and non-fatal)
2,000 steps/day
3,000 steps/day
4,000 steps/day
5,000 steps/day
6,000 steps/day
7,000 steps/day
8,000 steps/day
9,000 steps/day
10,000 steps/day
11,000 steps/day
12,000 steps/day
13,000 steps/day
14,000 steps/day
15,000 steps/day
16,000 steps/day
Magnitude of risk estimates (aHR)
No significant change
0.99 - 0.80*
0.79 - 0.60*
0.59 - 0.40*
<0.40*
1.00 - 1.25*
1.26 - 1.66*
1.67 - 2.50*
>2.50*
* Statistically different compared to reference level

569

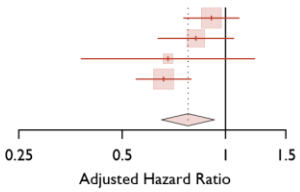
570

571

Intermediate vs low step cadence tertile

Study	Publishing year	Sample size (n)	Events (%)	Low step cadence	Intermediate step cadence	aHR [95% CI]	Weight
Saint−Maurice et al.	2020	4,840	24.1	28 steps/min	63 steps/min	0.91 [0.76, 1.10]	33.3%
Lee et al.	2019	16,741	3.0	31 steps/min	63 steps/min	0.82 [0.64, 1.06]	25.4%
Paluch et al.	2021	2,110	3.4	59 steps/min	76 steps/min	0.68 [0.38, 1.22]	7.9%
Del Pozo Cruz et al.	2022	78,500	2.8	25 steps/min	68 steps/min	0.66 [0.55, 0.79]	33.4%
Random effects model						**0.78 [0.65, 0.93]**	**100.0%**

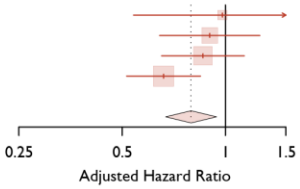
Heterogeneity: I^2 = 51% [95% CI: 0%, 84%], τ^2 = 0.02 [95% CI: 0.00, 0.38]
Test for overall effect: $z = -2.76$ ($p < 0.01$)



High vs low step cadence tertile

Study	Publishing year	Sample size (n)	Events (%)	Low step cadence	High step cadence	aHR [95% CI]	Weight
Paluch et al.	2021	2,110	3.4	59 steps/min	97 steps/min	0.98 [0.54, 1.78]	7.9%
Saint−Maurice et al.	2020	4,840	24.1	28 steps/min	89 steps/min	0.90 [0.64, 1.26]	22.7%
Lee et al.	2019	16,741	3.0	31 steps/min	88 steps/min	0.86 [0.65, 1.14]	31.5%
Del Pozo Cruz et al.	2022	78,500	2.8	25 steps/min	91 steps/min	0.66 [0.52, 0.85]	37.9%
Random effects model						**0.79 [0.67, 0.94]**	**100.0%**

Heterogeneity: I^2 = 13% [95% CI: 0%, 87%], τ^2 < 0.01 [95% CI: 0.00, 0.40]
Test for overall effect: $z = -2.64$ ($p < 0.01$)



572