Do the associations of daily steps with mortality and incident cardiovascular disease differ by sedentary time levels? A device-based cohort study

Matthew N Ahmadi 1,2, Leandro F M Rezende 3,4, Gerson Ferrari 4,5, Borja Del Pozo Cruz 6,7,8, I-Min Lee 9, Emmanuel Stamatakis 1,2

ABSTRACT
Objectives This study aims to examine the associations of daily step count with all-cause mortality and incident cardiovascular disease (CVD) by sedentary time levels and to determine if the minimal and optimal number of daily steps is modified by high sedentary time.

Methods Using data from the UK Biobank, this was a prospective dose–response analysis of total daily steps across low (<10.5 hours/day) and high (≥10.5 hours/day) sedentary time (as defined by the inflection point of the adjusted absolute risk of sedentary time with the two outcomes). Mortality and incident CVD was ascertained through 31 October 2021.

Results Among 72 174 participants (age=61.1±7.8 years), 1633 deaths and 6190 CVD events occurred over 6.9 (±0.8) years of follow-up. Compared with the referent 2200 steps/day (5th percentile), the optimal dose (nadir of the curve) for all-cause mortality ranged between 9000 and 10 500 steps/day for high (HR 95% CI):0.61 (0.51 to 0.73)) and low (0.69 (0.52 to 0.92)) sedentary time. For incident CVD, there was a subtle gradient of association by sedentary time level with the lowest risk observed at approximately 9700 steps/day for high (0.79 (0.72 to 0.86)) and low (0.71 (0.61 to 0.83)) sedentary time. The minimal dose (steps/day associated with 50% of the optimal dose) of daily steps was between 4000 and 4500 steps/day across sedentary time groups for all-cause mortality and incident CVD.

Conclusions Any amount of daily steps above the referent 2200 steps/day was associated with lower mortality and incident CVD risk, for low and high sedentary time. Accruing 9000–10 500 steps/day was associated with the lowest mortality risk independent of sedentary time. For a roughly equivalent number of steps/day, the risk of incident CVD was lower for low sedentary time compared with high sedentary time.

INTRODUCTION
Greater daily steps have established protective effects on health, and its potential benefits have been associated with lower mortality and cardiovascular disease (CVD).1-4 Recent studies have found as few as 4000 to 10 000 steps are associated with lower mortality and morbidity with potentially continuing risk reductions for higher daily steps.1,2,4,5 In contrast, high amounts of sedentary time are associated with higher mortality and morbidity risk.6,7 Previous meta-analyses reported a 30%–50% increase in all-cause mortality and CVD from high levels of sedentary time (eg, >10–14 hours/day).6,7 Daily steps and sedentary time affect similar risk factors that contribute to the development of CVD and higher mortality risk, such as obesity, blood pressure and cholesterol.10,11 However, the current evidence on daily stepping comes from studies that did not consider whether (and to what extent) the association with mortality and incident CVD was modified or attenuated by levels of sedentary time.

Studies examining joint associations and effect modification have reported physical activity may offset or attenuate the higher risk of all-cause mortality12–15 and CVD16–18 associated with sedentary time. A meta-analysis of self-reported sedentary time and physical activity suggested that 60–75 min/day of moderate-to-vigorous physical activity (MVPA) lowered the detrimental associations of
high sedentary time,19 while data from the 45 and Up Study showed high sedentary time was only associated with higher mortality risk in those not attaining the minimum threshold of current recommendations (at least 150 MVPA min/week).18

A harmonised meta-analysis of hip worn accelerometer devices suggested that 30–40 min/day of MVPA attenuated the all-cause mortality risk attributed to sedentary time.20 Collectively, this body of evidence estimated time in intensity-specific physical activity needed to offset or substantially attenuate high levels of predominantly self-reported sedentary time. For many individuals, it may be challenging to recall time or estimate intensity to determine whether they are sufficiently active in relation to minute-based and intensity-based targets. Stepping-based information may provide a more tangible physical activity prescription that is easier to act on.

No study to date has examined if high sedentary time modifies the dose-response of daily steps with all-cause mortality and incident CVD. Such information can be used to advise the general public, inform guidelines and improve clinical intervention.21 22

We aimed to determine if sedentary time modified the optimal and minimal daily steps associated with all-cause mortality and incident CVD risk. We pursued these aims by examining the detailed dose response of daily steps across high and low sedentary time levels in a large cohort of UK adults using wrist-worn accelerometers.

**METHODS**

**Study participants**

Participants were included from the UK Biobank Study, a prospective cohort of 502,629 participants between 40 and 69 years. All participants were enrolled between 2006 and 2010 and provided informed written consent. Participants completed physical examinations by trained staff and touchscreen questionnaires. We excluded participants with diagnosed CVD or cancer (ascertained through self-report, hospital admission and cancer registry records) prior to accelerometer measurement, missing covariate data or an event within the first 12 months from the ascertainment methods. 23 24

We calculated daily steps with all-hip accelerometer devices (Axivity AX3 accelerometer) worn on their dominant wrist for 24 hours/day for 7 days to measure physical activity. Prior to being mailed, the AX3 accelerometers were initialised to collect data with a sampling frequency of 100 Hz and a dynamic range between ±8 g. Participants returned the devices by mail and the data were calibrated and non-wear periods were identified according to standard procedures.25 24

Monitoring days were considered valid if wear time was greater than 16 hours. In this study, participants were required to have at least three valid monitoring days, with at least one of those days being a weekend day, and have worn the monitor during sleep periods. Physical activity type was classified with a validated accelerometer-based activity machine learning scheme covering sedentary behaviour, small utilitarian movements, walking and running,25 26 consistent with previously published studies.3 5 27 We calculated steps during periods of ambulation using a tuned signal peak detection method38 29 used in previous studies3 5 and in validation studies shown to have a step detection accuracy of 89%.29

Mortality and cardiovascular disease ascertainment

Participants were followed up to 30 September 2021 (England and Wales) or 31 October 2021 (Scotland), with deaths obtained through linkage with the NHS Digital of England and Wales or the NHS Central Register and National Records of Scotland. Inpatient hospitalisation data (England: 30 September 2021; Scotland: 31 July 2021; Wales 28 February 2018) were provided by either the Hospital Episode Statistics for England, the Patient Episode Database for Wales or the Scottish Morbidity Record for Scotland. CVD was defined as diseases of the circulatory system, excluding hypertension, diseases of arteries and lymphatic system. Online supplemental table 1 describes in detail CVD ascertainment methods.

**Covariates**

Our selection of covariates was based on previous daily stepping and sedentary time literature (online supplemental figure 2) and included age, sex, ethnicity, education, smoking status, alcohol consumption, fruit and vegetable consumption (servings per day), parental history of CVD and cancer, medication use (cholesterol, insulin and hypertension) and accelerometer-measured sleep time (hours/day). In sensitivity analyses, we included clinical factors that may be potential mediators: waist circumference, glycaated haemoglobin A1C, high-density and low-density lipoprotein, diastolic and systolic blood pressure, and triglycerides. Complete covariate definitions are provided in online supplemental table 2.

**Analyses**

We calculated the adjusted dose–response absolute risk for all-cause mortality and incident CVD per 10,000 person-years, and crude risk percent (categorical). We used Cox proportional hazards regression models to estimate HR with 95% CIs for all-cause mortality. Fine-Gray subdistribution method was used for incident CVD analyses with non-cardiovascular deaths treated as a competing risk. In both sets of analyses, we used restricted cubic splines with knots at the 10th, 50th and 90th percentile to model the dose–response associations. No violations in any of the assumptions of Cox proportional hazard model were observed. Specifically, we checked for assumptions of Cox proportional hazard model including Schoenfeld residual, independence of survival times for individuals, linearity of covariates, continuous survival time, multicollinearity and independence of censoring date, and no violations were observed. Effect modification was tested by fitting an interaction term between sedentary time and daily steps. We examined the dose response for the optimal (nadir of the curve) and minimal (defined as 50% of the optimal dose3 5 27; (1–optimal dose HR)/2) number of steps for high and low sedentary time. In all analyses, we set the reference data point to be the 5th percentile of daily steps among all participants (eg, 2200 steps).

We calculated E-values for the optimal and minimal daily steps to estimate the plausibility of bias from unmeasured confounding.31 To assess the robustness of our findings, we
performed additional joint association analyses with 2200 daily steps (congruent with stratified analysis) and high sedentary time as the reference. In sensitivity analyses, we adjusted for clinical factors (see covariate section above) that could be considered mediators of the association between the exposures and outcomes. We further performed an analysis with alternate sedentary time groupings with the highest quartile (≥11.5 hours/day) categorised high sedentary time and the lowest three quartiles as low sedentary time. We also conducted sensitivity analyses to examine reverse causation bias by excluding underweight participants (body mass index <18.5 kg/m²), participants reporting self-rated fair or poor health, or participants with an event within the first 2 years of follow-up.34 35 We also assessed incident CVD risk using cause-specific analyses to provide estimates of direct effects.34 35 In addition, we assessed age subgroup differences for participants <60 years old and ≥60 years old using an interaction term for age in our incident CVD analysis.

We performed all analyses using R statistical software. We reported this study as per the Strengthening the Reporting of Observational Studies in Epidemiology guideline and the Checklist for Statistical Assessment of Medical Papers.36

**Patient and public involvement**

No patients or members of the public were involved in the planning, design, data collection, analysis or interpretation of results for this study.

**Equity, diversity and inclusion statement**

Our study sample representative of all participants who participated in the UK Biobank study with valid accelerometer data, reflecting the demographic, geographical and socioeconomic diversity of the participants.

**RESULTS**

Our analytical sample for mortality included 72174 participants (average age (SD)= 61.1 (7.8) years; 57.9% female) followed up for an average of 6.9±0.8 years with 1633 deaths. Our incident CVD analysis sample included 71441 participants with 6190 events. Median (IQR) total steps and sedentary time were 6222 (4102–9225) steps/day and 10.6 (9.7–11.6) hours/day, respectively. Participants wore the accelerometers for an average of 22.8 hours/day. Participant characteristics by sedentary time are provided in table 1. Participants classified as having high sedentary time (53.8% of the total sample) were more likely to be current smokers, use cholesterol and hypertension medication, and have higher central adiposity (waist circumference) compared with their low sedentary time counterparts. Within the high and low sedentary time levels, median daily steps were 4829 (3329, 6834) and 8362 (5883, 11 792), respectively.

**Absolute risks**

The sex-adjusted and age-adjusted sedentary time dose–response absolute risk for all-cause mortality and incident CVD is shown in figure 1. We used the dose–response results to categorise participants as having high or low sedentary, reflective of when risk became pronounced. Using the difference between adjacent absolute risk estimates in 30 min increments, we found risk became more pronounced for both all-cause mortality and incident CVD at 10.5 hours/day of sedentary time.

Online supplemental table 3 and figure 2 present the crude risk and the multivariable-adjusted dose response of all-cause mortality and incident CVD associated steps/day by sedentary time level, respectively. Within the high sedentary time level (≥10.5 hours/day), accumulating <4000 steps/day (tertile 1) was associated with a crude mortality risk of 5.41% (95% CI 5.32% to 5.50%), whereas accumulating >8000 steps/day (tertile 3) was associated with a 3.05% (95% CI 2.96% to 3.13%) crude risk. The corresponding crude risk for participants within the low sedentary time level (<10.5 hours/day) was 3.74% (95% CI 3.62% to 3.86%) and 2.27% (95% CI 2.24% to 2.30%).

**All-cause mortality**

Among participants with high sedentary time, we observed the nadir of the curve at 9000 steps/day corresponding to an HR (95%CI) of 0.61 (0.51 to 0.73), compared with the referent 2200 steps/day (figure 3; effect modification p=0.756). The minimal dose was at 4100 steps/day with an HR of 0.80 (0.74 to 0.87). Among participants with low sedentary time, we observed an attenuation in the magnitude of the steps/day dose–response association with the nadir of the curve at 10300 steps/day (0.69 (0.52 to 0.92)). We observed the minimal dose at 4400 steps/day with a corresponding HR of 0.84 (0.74 to 0.97). In our joint dose–response analysis (online supplemental figure 3), we observed consistent nadir and minimal dose values between the two sedentary time levels. The mortality risk was similar (eg, HR difference ≤0.03 units) between high and low sedentary time levels at 6000 steps/day and continued to be similar up to 9500 steps/day.

**Incident cardiovascular disease**

In the dose–response association between steps/day and incident CVD, we observed lower risk for the low sedentary time group, for an equivalent steps/day, compared with the high sedentary time group (figure 4; effect modification p=0.725). The HR differences between the two groups increased up to the nadir of both curves. The minimal dose was at 4300 steps/day for both high and low sedentary time with corresponding HRs of 0.90 (95% CI 0.86 to 0.94) and 0.86 (95% CI 0.80 to 0.92). For high sedentary time, the optimal dose (nadir) was at 9700 steps/day with an HR of 0.79 (95% CI 0.72 to 0.86). In comparison, among participants with low sedentary time, we observed a similar optimal dose (9800 steps/day), with a lower corresponding HR of 0.71 (95% CI 0.61 to 0.83). In our joint dose–response analysis (online supplemental figure 4), the lower risk for an equivalent steps/day for low sedentary time compared with high sedentary time was consistent with our main analysis when steps/day exceeded 3700.

**Additional and sensitivity analyses**

When adjusting for waist circumference, glycated haemoglobin A1C, high-density and low-density lipoprotein, blood pressure and triglycerides, the association patterns remained consistent, although the magnitude was attenuated for high sedentary time and all-cause mortality (online supplemental figure 5). Exclusion of participants who had fair or poor self-rated health, were underweight or had an event within the first 2 years of follow-up showed generally consistent associations as our main analysis (online supplemental figure 6). For example, in the high sedentary time group 8700 steps/day was associated with the lowest all-cause mortality risk, and among the low sedentary time group the lowest risk was observed at 11 000 steps/day. Alternate sedentary time grouping with the highest quartile (≥11.5 hours/day; high sedentary time) and lowest three quartiles (low sedentary time) showed a consistent dose–response association pattern for incident CVD, and
### Table 1  Participant characteristics by sedentary time

<table>
<thead>
<tr>
<th></th>
<th>Low (&lt;10.5)</th>
<th>High (≥10.5)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>33338</td>
<td>38336</td>
<td>72174</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td>7.0 (0.8)</td>
<td>6.9 (0.8)</td>
<td>6.9 (0.8)</td>
</tr>
<tr>
<td>Age, years</td>
<td>60.5 (7.8)</td>
<td>62.1 (7.7)</td>
<td>61.1 (7.8)</td>
</tr>
<tr>
<td>Steps, (median (IQR))</td>
<td>8362.2 (5883.0–11 791.9)</td>
<td>4829.8 (3329.5–6834.1)</td>
<td>6222.5 (4102.1–9225.4)</td>
</tr>
<tr>
<td>Sedentary time, (median (IQR))</td>
<td>9.6 (8.9–10.1)</td>
<td>11.5 (11.0–12.2)</td>
<td>10.6 (9.7–11.6)</td>
</tr>
<tr>
<td>Sleep, hours, (median (IQR))</td>
<td>7.8 (6.9–8.6)</td>
<td>7.1 (6.0–7.9)</td>
<td>7.4 (6.4–8.2)</td>
</tr>
<tr>
<td>Male, %</td>
<td>12780 (38.3)</td>
<td>17570 (45.2)</td>
<td>30350 (42.1)</td>
</tr>
</tbody>
</table>

### Smoking history, %

- Never: 1880 (59.6) 22290 (57.4) 42170 (58.4)
- Previous: 11347 (34.0) 13700 (35.3) 25047 (34.7)
- Current: 2111 (6.3) 2846 (7.3) 4957 (6.9)

### Alcohol consumption, %

- Never: 897 (2.7) 1137 (2.9) 2034 (2.8)
- Previous: 776 (2.3) 1116 (2.9) 1892 (2.6)
- Occasional: 6408 (19.2) 8287 (21.3) 14695 (20.4)
- Within guidelines: 12576 (37.7) 14163 (36.5) 26739 (37.0)
- Double guidelines: 8113 (24.3) 8804 (22.7) 16917 (23.4)
- More than double guidelines: 4568 (13.7) 5329 (13.7) 9897 (13.7)

### Education, %

- College/University: 14485 (43.4) 17715 (45.6) 32200 (44.6)
- A/A/S: 4904 (13.5) 5171 (13.3) 9675 (13.4)
- O levels: 6978 (20.9) 7623 (19.6) 14601 (20.2)
- CSE: 1624 (4.9) 1322 (3.4) 2946 (4.1)
- NVQ/HND/HNC: 1708 (5.1) 1988 (5.1) 3696 (5.1)
- Other: 4039 (12.1) 5017 (12.9) 9056 (12.5)

### Diet, servings/day

Mean: 8.3 (4.5) 8.0 (4.4) 8.1 (4.4)

### Parental history of CVD

- Never: 8200 (24.6) 9820 (25.3) 18020 (25.0)
- Previous: 776 (2.3) 1116 (2.9) 1892 (2.6)
- Occasional: 6408 (19.2) 8287 (21.3) 14695 (20.4)
- Within guidelines: 12576 (37.7) 14163 (36.5) 26739 (37.0)
- Double guidelines: 8113 (24.3) 8804 (22.7) 16917 (23.4)
- More than double guidelines: 4568 (13.7) 5329 (13.7) 9897 (13.7)

### Medication use, %

- Cholesterol: 2859 (8.6) 5150 (13.3) 8009 (11.1)
- Blood pressure: 3549 (10.6) 6431 (16.6) 9980 (13.8)
- Insulin: 147 (0.4) 272 (0.7) 419 (0.6)

### Biomarkers

- Glycated haemoglobin: 34.7 (4.6) 35.5 (5.8) 35.1 (5.3)
- High density lipoprotein: 1.5 (0.4) 1.5 (0.4) 1.5 (0.4)
- Low density lipoprotein: 3.6 (0.8) 3.6 (0.8) 3.6 (0.8)
- Triglycerides: 1.6 (0.9) 1.7 (1.0) 1.6 (1.0)

### Self-rated health, %

- Excellent: 8554 (25.7) 8333 (21.5) 16887 (23.4)
- Good: 20393 (61.2) 23481 (60.5) 43874 (60.8)
- Fair: 3887 (11.7) 6112 (15.7) 9999 (13.9)
- Poor: 466 (1.4) 852 (2.2) 1318 (1.8)

### Blood pressure, mm Hg

- Systolic: 136.5 (19.0) 139.3 (19.2) 138.0 (19.1)
- Diastolic: 80.8 (10.5) 82.3 (10.6) 81.6 (10.5)

### Waist circumference, cm

- Male: 92.8 (9.8) 96.4 (11.0) 94.9 (10.6)
- Female: 80.2 (10.7) 84.4 (12.1) 82.4 (11.6)

Values represent mean (SD) unless stated otherwise.

CVD, cardiovascular disease; HNC, higher national certificate; HND, higher National diploma; NVQ, national vocational qualification.
a higher magnitude of association for low sedentary time with all-cause mortality (online supplemental figures 7 and 8). Our E-values suggest a moderate degree of unmeasured confounding would be required to reduce our observed associations for mortality and incident CVD. For example, the minimal steps/day dose E-value ranged from 1.67 (1.21) to 1.81 (1.56) for all-cause mortality and 1.46 (1.32) to 1.60 (1.39) for incident CVD (online supplemental table 4). Cause-specific hazard analysis for incident CVD risk was similar to Fine-Gray subdistribution hazard analysis. For example, in cause-specific analysis the optimal dose was approximately 9600 steps/day for high sedentary time, and 9800 steps/day for low sedentary time (online supplemental figure 9). Subgroup analysis by age showed no association...
between steps and incident CVD risk among young participants (<60 years old) with low sedentary time. However, among young participants with high sedentary time, there was an inverse association with no upper limit for daily steps and lower incident CVD risk. Among older participants (≥60 years old), we observed lower risk for both low and high sedentary time, with lowest risk observed among older participants with low sedentary time (eg. <10.5 hours/day) at an equal number of daily steps. For older adults with high sedentary time, the lowest risk was observed at approximately 8500 steps/day (online supplemental figure 10; effect modification p=0.153).

**DISCUSSION**

Our study adds new evidence to the literature by examining the dose–response association of daily steps with mortality and incident CVD risk in high and low sedentary time groups. For all-cause mortality, the optimal dose occurred between 9000 and 10 500 steps/day across sedentary time groups. Within the high sedentary time group we observed lower risk compared with the low sedentary time group at an equivalent number of daily steps. We found a lower incident CVD risk for an equivalent number of daily steps within the low sedentary time group compared with the high sedentary time group. There was consistency in the optimal

---

**Figure 3** Stratified dose–response association of all-cause mortality and steps by sedentary time. Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin and hypertension) and sleep duration. Shaded area represents 95% CI. Square=minimum dose (ED50); circle=optimum dose (nadir of curve). CVD, cardiovascular disease.

**Figure 4** Stratified dose–response association of cardiovascular disease incidence and steps by sedentary time. Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin and hypertension) and sleep duration. Shaded area represents 95% CI. Square=minimum dose (ED50); circle=optimum dose (nadir of curve). CVD, cardiovascular disease.
and minimal steps/day association with incident CVD risk between the two groups at just under 10 000 steps/day and 4500 steps/day, respectively.

**All-cause mortality**

Previous prospective studies examining daily steps did not consider the potential effects of differing sedentary time levels on the association with health risks.1 37 Given the established dynamic between physical activity and sedentary time,17 18 such an exclusion may lead to overestimation of effect estimates and underestimation of the minimal and optimal steps/day dose response. Studies and meta-analyses assessing daily steps and all-cause mortality, which did not consider sedentary time, showed a curvilinear dose response that suggested between 6000 and 10 000 steps/day was associated with lower all-cause mortality.1–4 38 Our analyses expands on previous research and examines the influence of sedentary time on the daily stepping dose-response association. Between 6000 and 10 500 steps/day, we found mortality risk was about 10% lower for an equivalent number of steps in the high sedentary time group compared with the low sedentary time group. Our findings emphasise the importance of increasing daily steps particularly among adults who are highly sedentary. In the high sedentary time group, the stronger association could be attributable to the more pronounced impact of daily step accumulation in individuals who are at a higher risk of mortality from the adverse effects of sedentary time. Among the high sedentary time group, being sufficiently active through daily step accumulation may ameliorate downstream effects of sedentary time, lowering the risk of developing comorbidities and subsequently leading to lower mortality risk.19 40 If confirmed in future studies, our dose–response findings may help to improve health messaging and goal setting for the most at-risk individuals in the population.

**Incident cardiovascular disease**

We observed lower incident CVD risk for an equivalent number of daily steps for low sedentary time compared with high sedentary time, although with overlapping 95% CIs. This graded association pattern may be due to the separate contributions of sedentary time and daily steps (eg, physical activity) to cardiovascular health, leading to an additive effect on CVD risk. Our cause-specific hazards dose–response analysis, which provides a direct effect estimation, was comparable to our Fine–Gray subdistribution hazards analysis that provides an estimation of the direct and indirect effect estimation.34 Studies have demonstrated prolonged sedentary time contributes to increased inflammation, oxidative stress and induces adverse effects on cardiovascular autonomic nervous system function.41–43 In contrast, higher daily steps can lead to cardioprotective adaptations.44–46 We did not find evidence that daily steps could compensate for excess sitting time. This contrasts prior studies that have found MVPA can lower the risk of high sedentary time to be comparable to low sedentary time.17 18 47 The majority of daily steps occur at a light intensity1 3 and may explain in part the disparate findings between our study and MVPA intensity focused studies. Taken together, this suggests an important role of physical activity intensity to reduce the risks of sedentary time for CVD prevention.

Among the high sedentary time group, we found a 10%–21% lower CVD risk when daily step accumulation was between 4000 and 10 000 steps/day. The magnitude in the dose–response association we observed for steps/day with CVD risk was attenuated in comparison with two prior meta-analyses that did not account for differing levels of sedentary time.37 48 In addition, a prior meta-analysis37 of eight cohorts found there was no association between daily steps and lower incident CVD risk among participants <60 years old. Our results extend on this prior finding to provide nuanced information on the influence of sedentary time. Indeed, among adults <60 years old with low sedentary time (<10.5 hours/day), we did not find an association between daily steps and incident CVD risk. However, among adults <60 years old with high sedentary time, we observed an inverse linear association. This finding further highlights the potential health-benefits of increasing daily steps to mitigate CVD risk among highly sedentary adults. The absence of an association among adults <60 years old with low sedentary time could be due to the latency period for CVD to progress towards clinical endpoints of hospitalisations and death compared with their counterparts who have high sedentary time and are at a higher risk of cardiovascular events earlier in adulthood. Collectively, our results underscore the importance for a combination of decreasing sedentary time and increasing daily steps to improve cardiovascular health.

**Implications**

Our findings provide new insights regarding the dose response of daily steps, sedentary time, mortality and CVD risk. Overall, between 9000 and 10 500 steps/day was the optimum dose to lower mortality and CVD risk across sedentary time groups. Our prospective results provide relevant findings that can be used to augment public health messaging and inform the first generation of stepping-based and device-based physical activity and sedentary guidelines. Daily stepping targets are a simple metric that clinicians and allied health providers can use to monitor and promote physical activity to their patients. Collectively, our findings may have important implications to help improve the efficacy of future trials and the precision of intervention treatments among individuals with varying physical activity and sedentary time levels.

Our results indicate sedentary time did not significantly modify the dose-response association of daily steps. We also found the amount of physical activity (eg, steps/day) needed to lower the risk of mortality and incident CVD may be lower than previously suggested using self-reported data.49 This is explained, in part, by differences in self-report and wearables-based measures. Self-reported physical activity is prone to over-reporting due to a combination of social desirability and recall bias,49 50 and being limited to measuring blocks of time where an individual may not be active throughout the duration. Wearables provide a continuous objective measure of movement that is not susceptible to the limitations of self-reported physical activity.

**Strengths and limitations**

To our knowledge, the current study is among the first aimed to determine the optimal and minimal number of daily steps to lower mortality and incident CVD risk across sedentary time levels. The large sample size and long follow-up allowed us to reduce the risk of reverse causation bias by removing participants with an event in the first 2 years of follow-up, prevalence of major disease, self-rated fair or poor health and who were underweight. Due to the observational design, we cannot rule out the presence of residual and unmeasured confounding. However, E-values indicate for the minimal dose an unmeasured confounder would need to have a moderate association, between 1.46 and 1.81, with the exposures and outcome for the observed relationships to be null. Covariate assessments...
Conclusions
In our population-based cohort study of over 70 000 individuals, we did not find an effect modification by sedentary time levels on the dose–response association of daily steps. We found an upper incidence of mortality and incident CVD independent of sedentary time. The minimal threshold associated with substantially lower mortality and CVD risk was between 4000 and 4500 steps/day. We found a lower incident CVD risk for an equivalent number of steps in the low sedentary time group compared with the high sedentary time group. These findings provide tangible targets that can be easily implemented in future steps-based and sedentary time-based interventions, and can inform the first generation of device-based guidelines.

Author affiliations
1Mackenzie Wearables Research Hub, Charles Perkins Centre, The University of Sydney, Sydney, New South Wales, Australia
2School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia
3Department of Preventive Medicine, Escola Paulista de Medicina, Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil
4Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Providencia, Chile
5Universidad de Santiago de Chile (USACH), Escuela de Ciencias de la Actividad Física, el Deporte y la Salud, Chile
6Department of Physical Education and Sports, Faculty of Education, University of Cádiz, Cádiz, Spain
7Biomedical Research and Innovation Institute of Cádiz (INiBICA) Research Unit, University of Cádiz, Cádiz, Spain
8Department of Sports Science and Clinical Biomathematics, University of Southern Denmark, Odense, Denmark
9Division of Preventive Medicine, Brigham and Women’s Hospital and Harvard Medical School; Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA

Twitter Emmanuel Stamatakis @M_Stamatakis

Acknowledgements This research has been conducted using the UK Biobank Resource under Application Number 25813. The authors would like to thank all the participants and professionals contributing to the UK Biobank.

Contributors All authors have reviewed the manuscript and approve of its submission to the journal. MNA and ES are the guarantors.

Funding This study is funded by an Australian National Health and Medical Research Council (NHMRC) Investigator Grant Leadership level 2 (APP 1194510) and a National Heart Foundation Fellowship (APP 107158). BDPC is supported by the Government of Andalusia, Research Talent Recruitment Programme (EMRIGA 2020/0013/15).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by National Health Service, National Research Ethics Service (Ref 11/NW/0382). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The UK Biobank data that support the findings of this study can be accessed by researchers on application (https://www.ukbiobank.ac.uk/register-apply/).

Supplemental material This content has been supplied by the author(s).

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

ORCID iDs
Matthew N Ahmadi http://orcid.org/0000-0002-3115-338X
Leandro F M Rezende http://orcid.org/0000-0002-7469-1399
Gerson Ferrari http://orcid.org/0000-0003-3177-6576
Borja Del Pozo Cruz http://orcid.org/0000-0003-3944-2212
I-Min Lee http://orcid.org/0000-0002-1083-6907
Emmanuel Stamatakis http://orcid.org/0000-0001-7323-3225

REFERENCES


### Supplemental Document

<table>
<thead>
<tr>
<th>Page</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Supplemental Figure 1. Flow diagram of participants in the study</td>
</tr>
<tr>
<td>2</td>
<td>Supplemental Figure 2: Directed acyclic graph to guide covariate selection</td>
</tr>
<tr>
<td>3</td>
<td>Supplemental Figure 3: Joint dose-response association of steps and sedentary time with all-cause mortality</td>
</tr>
<tr>
<td>4</td>
<td>Supplemental Figure 4: Joint dose-response association of steps and sedentary time with cardiovascular disease incidence</td>
</tr>
<tr>
<td>5</td>
<td>Supplemental Figure 5: Stratified dose-response association of steps, all-cause mortality, and cardiovascular disease incidence by sedentary time. Adjustment for biomarkers</td>
</tr>
<tr>
<td>6</td>
<td>Supplemental Figure 6: Stratified dose-response association of steps, all cause mortality, and cardiovascular disease incidence by sedentary time. Exclusion of participants with fair or poor self-rated health, underweight, or had an event within the first two years of follow up</td>
</tr>
<tr>
<td>7</td>
<td>Supplemental Figure 7: Stratified dose-response association of all-cause mortality and steps by sedentary time; highest quartile and lowest three quartile grouping.</td>
</tr>
<tr>
<td>8</td>
<td>Supplemental Figure 8: Stratified dose-response association of cardiovascular disease incidence and steps by sedentary time; highest quartile and lowest three quartile grouping</td>
</tr>
<tr>
<td>9</td>
<td>Supplemental Figure 9: Stratified dose-response association of cardiovascular disease incidence and steps by sedentary time; cause-specific analysis</td>
</tr>
<tr>
<td>10</td>
<td>Supplemental Figure 10: Stratified dose-response association of cardiovascular disease incidence and steps by sedentary time; age subgroups.</td>
</tr>
<tr>
<td></td>
<td>Supplemental Table 1: Assessment of CVD and cancer incidence* and definition of diseases</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>12</td>
<td>Supplemental Table 2: Covariate definitions</td>
</tr>
<tr>
<td>13</td>
<td>Supplemental Table 3: Crude absolute risk stratified by steps and sedentary behaviour groups</td>
</tr>
<tr>
<td>14</td>
<td>Supplemental Table 4: E-values for optimal and minimal steps/day for all-cause mortality and cardiovascular disease incidence by sedentary time</td>
</tr>
<tr>
<td>15</td>
<td>Supplemental Text 1: Physical activity, sedentary behaviour, and step classification</td>
</tr>
</tbody>
</table>
Supplemental Figure 1. Flow diagram of participants in the study

Participants who wore accelerometer
(n=103,684)

Participants with valid wear time
(n=91,228)

Participants without valid wear time (<2 weekdays and <1 weekend day), not sufficiently calibrated (error >10mg), a faulty monitor (avg acceleration > 100 mg), or monitor wasn’t worn to sleep on each valid wear day
(n=12,456)

Participants with valid wear time
(n=91,228)

Participants with missing covariate data: ethnicity = 42; smoking history = 251; alcohol consumption = 491; diet = 1,235
(n=2,019)

Participants with complete covariate data
(n=89,209)

Participants without prevalent cancer or CVD
(n=72,251)

Death within the first 12 months of follow-up
(n=77)

All-cause mortality sample
(n=72,174; Total mortality=1,633)

CVD events within the first 12 months of follow-up
(n=810)

CVD incidence sample
(n=71,441; CVD events= 6,190)

1. Prevalent Cancer (n=9,386)
2. Prevalent CVD (n=10,030)
   *some participants had prevalent CVD and cancer
Supplemental Figure 2: Directed acyclic graph to guide covariate selection

Green= exposure; blue= outcome; grey= adjusted variables; white= unobserved variables
Supplemental Figure 3: Joint dose-response association of steps and sedentary time with all-cause mortality

All-cause mortality

Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension), sleep duration. Shaded area represents 95%CI.
Supplemental Figure 4: Joint dose-response association of steps and sedentary time with cardiovascular disease incidence

Cardiovascular disease incidence

Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension), sleep duration. Shaded area represents 95% CI
Supplemental Figure 5: Stratified dose-response association of steps, all-cause mortality, and cardiovascular disease incidence by sedentary time. Adjustment for biomarkers

Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension), sleep duration, waist circumference, glycated hemoglobin A1C, high-density and low-density lipoprotein, blood pressure, and triglycerides. Shaded area represents 95%CI
**Supplemental Figure 6:** Stratified dose-response association of steps, all cause mortality, and cardiovascular disease incidence by sedentary time. Exclusion of participants with fair or poor self-rated health, underweight, or had an event within the first two years of follow up

**All-cause mortality**

**Cardiovascular disease incidence**

Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension) and sleep duration. Shaded area represents 95%CI
**Supplemental Figure 7: Stratified dose-response association of all-cause mortality and steps by sedentary time; highest quartile and lowest three quartile grouping.**

**All-cause mortality**

![Graph showing the association between sedentary time and all-cause mortality.](image)

- **Sedentary time per day**
  - 11.5 or more hours
  - Less than 11.5 hours

**Steps per day**

Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension) and sleep duration. Shaded area represents 95%CI.

7
Supplemental Figure 8: Stratified dose-response association of cardiovascular disease incidence and steps by sedentary time; highest quartile and lowest three quartile grouping.

Cardiovascular disease incidence

Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension) and sleep duration. Shaded area represents 95% CI.
Supplemental Figure 9: Stratified dose-response association of cardiovascular disease incidence and steps by sedentary time; cause-specific analysis.

Cardiovascular disease incidence

Adjusted for age, sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension) and sleep duration. Shaded area represents 95%CI. Square= minimum dose (ED50); circle= optimum dose (nadir of curve)
Supplemental Figure 10: Stratified dose-response association of cardiovascular disease incidence and steps by sedentary time; age subgroups.

Cardiovascular disease incidence

Adjusted for sex, ethnicity, education, smoking status, alcohol consumption, diet, parental history of CVD and cancer, medication use (cholesterol, insulin, and hypertension) and sleep duration. Shaded area represents 95%CI. Square= minimum dose (ED50); circle= optimum dose (nadir of curve)
### Supplemental Table 1: Assessment of CVD and cancer incidence* and definition of diseases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient hospitalisation</td>
<td>The inpatient hospitalization data were provided by either the Hospital Episode Statistics for England, the Patient Episode Database for Wales, or the Scottish Morbidity Record for Scotland</td>
</tr>
<tr>
<td>Cardiovascular disease definition</td>
<td>CVD was defined as diseases of the circulatory system, excluding hypertension, diseases of arteries, and lymph. The ICD-10 codes included were: I0, I11, I13, I20-I51, I60-169.</td>
</tr>
</tbody>
</table>

*Incident events included fatal and nonfatal events
**Supplemental Table 2: Covariate definitions**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>UK Biobank field ID (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous (years)</td>
<td>34, 52, accelerometer date-timestamp</td>
</tr>
<tr>
<td>Sex</td>
<td>Female/Male</td>
<td>31</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Asian, Black, Mixed, Other, White</td>
<td>21000</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never, past, current</td>
<td>20116</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Units/week; 1 unit = 8g of pure ethanol</td>
<td>20117, 1558</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>Hours spent sleeping</td>
<td>Derived from accelerometer data</td>
</tr>
<tr>
<td>Diet</td>
<td>Fruits and vegetables servings/day</td>
<td>1309, 1319, 1289, 1299</td>
</tr>
<tr>
<td>Education</td>
<td>College/University; A/AS level; O levels; CSE; NVQ/HND/HNC; other</td>
<td>6138</td>
</tr>
<tr>
<td>Parental history of CVD</td>
<td>Self-reported mother or father diagnosed with heart disease or stroke</td>
<td>20107, 20110</td>
</tr>
<tr>
<td>Parental history of cancer</td>
<td>Self-reported mother or father diagnosed with prostate cancer, breast cancer, bowel cancer, or lung cancer</td>
<td>20107, 20110</td>
</tr>
<tr>
<td>Use of cholesterol medication</td>
<td>Yes/No</td>
<td>6177, 6153</td>
</tr>
<tr>
<td>Use of blood pressure medication</td>
<td>Yes/No</td>
<td>6177, 6153</td>
</tr>
<tr>
<td>Use of diabetes medication</td>
<td>Yes/No</td>
<td>6177, 6153</td>
</tr>
<tr>
<td>Glycated hemoglobin A1C</td>
<td>Continuous; mmol/mol</td>
<td>30750</td>
</tr>
<tr>
<td>High density lipoprotein</td>
<td>Continuous; mmol/mol</td>
<td>30760</td>
</tr>
<tr>
<td>Low density lipoprotein</td>
<td>Continuous; mmol/mol</td>
<td>30780</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>Continuous; mmHg</td>
<td>4079</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Continuous; mmHg</td>
<td>4080</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Continuous; mmol/L</td>
<td>30870</td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>Continuous; cm</td>
<td>48</td>
</tr>
</tbody>
</table>
Supplemental Table 3: Crude absolute risk stratified by steps and sedentary behaviour groups

<table>
<thead>
<tr>
<th>Steps and sedentary time</th>
<th>Total Mortality</th>
<th>Cardiovascular disease incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High ST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4,000 steps</td>
<td>5.41 (5.32, 5.50)</td>
<td>19.85 (19.53, 20.18)</td>
</tr>
<tr>
<td>4,000 to 8,000 steps</td>
<td>3.40 (3.34, 3.45)</td>
<td>15.58 (15.35, 15.80)</td>
</tr>
<tr>
<td>&gt;8,000 steps</td>
<td>3.05 (2.96, 3.13)</td>
<td>13.51 (13.18, 13.84)</td>
</tr>
<tr>
<td><strong>Low ST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4,000 steps</td>
<td>3.74 (3.62, 3.86)</td>
<td>16.54 (15.93, 17.15)</td>
</tr>
<tr>
<td>4,000 to 8,000 steps</td>
<td>2.43 (2.39, 2.47)</td>
<td>11.70 (11.50, 11.90)</td>
</tr>
<tr>
<td>&gt;8,000 steps</td>
<td>2.27 (2.24, 2.30)</td>
<td>10.95 (10.79, 11.11)</td>
</tr>
</tbody>
</table>

Values represent percent and (95% CI’s); High ST ≥10.5 hours/day; Low ST <10.5 hours/day; stepping categories are based on tertiles.
Supplemental Table 4: E-values for optimal and minimal steps/day for all-cause mortality and cardiovascular disease incidence by sedentary time

<table>
<thead>
<tr>
<th>Steps/day</th>
<th>Total Mortality</th>
<th>Cardiovascular disease incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High ST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal dose</td>
<td>4,100</td>
<td>1.81 (1.56)</td>
</tr>
<tr>
<td>Optimal dose</td>
<td>9,000</td>
<td>2.66 (2.08)</td>
</tr>
<tr>
<td><strong>Low ST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal dose</td>
<td>4,400</td>
<td>1.67 (1.21)</td>
</tr>
<tr>
<td>Optimal dose</td>
<td>10,300</td>
<td>2.26 (1.39)</td>
</tr>
</tbody>
</table>
Supplemental Text 1: Physical activity, sedentary behaviour, and step classification

Physical activity was classified using a previously validated Random Forest (RF) activity classifier. RF is an ensemble of multiple decision trees. Each tree is learned on a bootstrap sample of training data and each node in the tree is split using the best among a randomly selected set of acceleration features. The decisions from each tree are aggregated and a final model prediction is based on majority vote. The RF model requires very little pre-processing of the data, as the features do not need to be normalized. Additionally, the model is resistant to over fitting the training data because each tree within the forest is independently grown to maximum depth using a randomly selected subset of features.

The classifier categorized physical activity in 10 second windows into 1 of 4 activity classes: sedentary, standing utilitarian movements (ironing a shirt, washing dishes), walking activities (gardening, active commuting, mopping floors), running/high energetic activities (active playing with children). For the 2-level step detection, these activities were further assigned as non-ambulatory and ambulatory activities. The diagram below depicts how activity was classified at both activity levels. For ambulatory activities, a previously validated signal peak detection step count algorithm was applied. The algorithm detects peaks in the acceleration signal and applies a series of parameters (peak magnitude, periodicity, and continuity) to identify peaks that represent steps. These peaks are then summed within each ambulatory window.

Activity, sedentary behaviour, and stepping differentiation from sleep and non-wear was identified using the change in tilt angle and acceleration standard deviation. Monitors were calibrated and corrected for orientation using previously published methods.

Physical activity type and ambulatory classification

Although previously validated, to assess the robustness and generalizability of the sedentary behaviour and ambulatory classification, performance was evaluated in an independent sample of 211 participants (Age range = 18 to 91; 60.6% female) performing structured and free-living activities from the US (University of California Irvine Center for Machine Learning and Intelligent Systems Physical Activity Monitoring for Aging People study [published data], accessible at https://archive.ics.uci.edu/ml/datasets and Clemson University Shimmer3 Pedometer Dataset.)
[published data], accessible at https://sites.google.com/view/rmattfeld/pedometer-dataset?authuser=0), Australia (University of Sydney Intermittent Lifestyle Physical Activity Study [unpublished data]) and UK (University of Oxford Capture 24 study [published data], accessible at https://ora.ox.ac.uk/objects/uuid:99d7c092-d865-4a19-b096-cc16440cd001). Because of the picture-based ground truth provided in the Capture 24 dataset, a ground-truth label had to be consistent for at least 5 minutes to be extracted. A total of 139,944 activity samples (23,324 minutes) were collected. For free-living activities participant-worn body-cameras, or researcher-held Go-Pro video-recordings were used to attain ground-truth physical activity. The activity coding procedures have been previously described. Classification performance was evaluated using overall accuracy, kappa statistic, recall, precision, and F1-score.

Step detection was evaluated in 60 of the participants who had ground-truth step counts using video direct observation or a thigh-worn monitor that has a 99% accuracy with directly observed steps. Step detection performance was evaluated using Pearson Correlation, intraclass correlation coefficient (two-way fixed mixed effects model), mean absolute percent error, and mean bias. To assess the accuracy under a variety of walking conditions, in a subsample of 30 participants with available data, we further evaluated performance by separating different walking speeds (treadmill-based), walking under free-living conditions, and walking very fast/running under free-living conditions.

### Activity classification performance in the four datasets:

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Precision</th>
<th>F1-score</th>
<th>Kappa statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulation</td>
<td>86.2 (82.2, 90.2)</td>
<td>96.0 (93.4, 98.6)</td>
<td>90.8 (86.3, 95.3)</td>
<td>0.84 (0.79, 0.89)</td>
</tr>
<tr>
<td>Sedentary</td>
<td>91.5 (86.2, 96.8)</td>
<td>72.5 (66.1, 78.9)</td>
<td>80.9 (73.1, 88.7)</td>
<td>0.72 (0.66, 0.78)</td>
</tr>
</tbody>
</table>

### Step detection in the 60 participants with ground-truth step data:

<table>
<thead>
<tr>
<th></th>
<th>Correlation (95% CI)</th>
<th>Intraclass correlation coefficient (95% CI)</th>
<th>Mean absolute percent error (SD)</th>
<th>Steps mean bias (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steps</td>
<td>0.96 (0.93, 0.98)</td>
<td>0.86 (0.77, 0.92)</td>
<td>10.6% (9.2%)</td>
<td>103 (±152)</td>
</tr>
</tbody>
</table>

Ground-truth step total: mean (SD)= 1,254 (±545) median [IQR]= 1,219 [907, 1,658]
Slow, comfortable, and fast paced walking were based on treadmill speeds and participant preferences that corresponded to <3 km/h, 3-5 km/h, and >6 km/h, respectively. Error bars = 95% CI.