Joint associations of accelerometer measured physical activity and sedentary time with all-cause mortality: a harmonised meta-analysis in more than 44 000 middle-aged and older individuals

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ABSTRACT
Objectives To examine the joint associations of accelerometer-measured physical activity and sedentary time with all-cause mortality.
Methods We conducted a harmonised meta-analysis including nine prospective cohort studies from four countries. 44 370 men and women were followed for 4.0 to 14.5 years during which 3451 participants died (7.8% mortality rate). Associations between different combinations of moderate-to-vigorous intensity physical activity (MVPA) and sedentary time were analysed at study level using Cox proportional hazards regression analysis and summarised using random effects meta-analysis.
Results Across cohorts, the average time spent sedentary ranged from 8.5 hours/day to 10.5 hours/day and 8 min/day to 35 min/day for MVPA. Compared with the referent group (highest physical activity/lowest sedentary time), the risk of death increased with lower levels of MVPA and greater amounts of sedentary time. Among those in the highest third of MVPA, the risk of death was not statistically different from the referent for those in the middle (16%; 95% CI 0.87% to 1.54%) and highest (40%; 95% CI 0.87% to 2.26%) thirds of sedentary time. Those in the lowest third of MVPA had a greater risk of death in all combinations with sedentary time; 65% (95% CI 1.25% to 2.19%), 65% (95% CI 1.24% to 2.21%) and 263% (95% CI 1.93% to 3.57%), respectively.
Conclusion Higher sedentary time is associated with higher mortality in less active individuals when measured by accelerometry. About 30–40 min of MVPA per day attenuate the association between sedentary time and risk of death, which is lower than previous estimates from self-reported data.

INTRODUCTION
Low levels of physical activity and high amounts of sedentary time are associated with higher risks for morbidity and mortality.1–3 Some previous meta-analyses concluded that the associations between sedentary behaviours and morbidity and mortality are independent of physical activity.2,3 In contrast, other large-scale, meta-analyses and cohort studies examining the joint associations between physical activity and sedentary behaviours suggest that high levels of physical activity attenuate or even eliminate the associations between sitting time with all-cause and cardiovascular disease mortality.4–6 However, the amount of time in moderate-to-vigorous-intensity physical activity (MVPA) that was needed to eliminate the risk of mortality associated with sitting time varied between studies.4–6

Previous studies relied on self-reported exposure data for assessing the joint associations between physical activity and sedentary behaviours with mortality.4–6 Self-reported assessment of physical activity and sedentary behaviours is prone to misclassification and social desirability bias, likely underestimates sedentary time, and has limited validity for estimating both light-intensity and total amount of physical activity.7,8 Furthermore, the potential impact of these biases may be compounded when combining information from two self-reported behaviours. For example, a previous meta-analysis comprising more than one million adults suggested that 60–75 min of daily MVPA was needed to eliminate the increased risk of death associated with sitting time,4 whereas others concluded that physical activity equivalent to meeting the current recommendations of 150–300 min of MVPA per week effectively attenuated the association between sitting and risk of death.6 Thus, the amount of physical activity needed to attenuate or even eliminate the higher risk of death associated with sedentary behaviours remains unclear.

The aim of this study was to examine the associations between different combinations (nine mutually exclusive groups) of physical activity and sedentary time with all-cause mortality using more precise accelerometer-derived measures. First, we examined the joint associations of total physical activity or time spent in MVPA (min/day) and different combinations of sedentary time with all-cause mortality. As a secondary aim, we examined whether the association between sedentary time and all-cause mortality differed across strata of total
physical activity or time spent in MVPA, to understand whether
the associations between sedentary time and mortality differ by
levels of physical activity. We used data from nine prospective
cohort studies from four countries that were harmonised at
study level and thereafter meta-analysed.

METHODS

Studies

Nine studies identified from a systematic review were included
(see online supplemental materials). Study selection, data
extraction and bias assessment are described in online supple-
mental materials. Details of participants, case ascertainment,
accelerometer device and covariates of the included studies are
described in online supplemental table 1.9–17 Three of the studies
were nationally representative samples of adults in Norway,17
Sweden12 and USA.15 Since our previous publication,1 where we
examined the associations between sedentary time and different
intensities of physical activity and mortality separately, we have
updated mortality data from the National Health and Nutrition
Examination Survey (NHANES) providing a median follow-up
period of 10.5 years, during which 1065 participants died
(previously, 6.5 years and 492 deaths). The sample weights
and the complex survey design of the NHANES were accounted
for prior to analyses.13

Harmonisation of exposure data

When combining data across different studies, data harmonisa-
tion enhances the validity of findings since different studies used
different research methods (eg, assessment of what constitutes
valid wear; determination of physical activity intensity, etc).
The harmonisation process included reprocessing all individual
accelerometer data and thereafter reanalysing individual study
data according to a standardised protocol (available on request)
by the participating study teams. Seven studies assessed phys-
ical activity and sedentary time with a version of the Actigraph
accelerometer9 10 12–14 17 18 and two with an Actical accelerom-
eter.10 16 We extracted data from the vertical axis in 60 s epochs
for harmonisation purposes. Non-wear time was defined as ≥90
consecutive minutes of zero counts per minute (CPM), allowing
for up to 2 min of non-zero counts if the interruption was
preceded or followed by ≥30 min of zero CPM.18 We included
all participants who recorded at least 10 hours of wear time per
day for four or more days. Total physical activity was defined
by total counts per day/wear time per day in minutes (CPM).
Sedentary time was defined as time spent at ≤100 CPM and
MVPA as ≥1952 CPM and ≥153522 for studies using the Acti-
graph and Actical accelerometers, respectively.

Analyses

All participating studies first categorised their participants into
thirds for total physical activity (CPM), time spent in MVPA and
sedentary time. To control for individual differences in wear
time, sedentary time and time spent in MVPA were expressed
as a percentage of total daily wear time before creating the
tertiles. Individual studies thereafter performed joint analyses
of total physical activity (CPM) combined with daily sedentary
time expressed as percentage of wear time, and daily MVPA (%
wear time) combined with daily sedentary time (% wear time) in
relation to all-cause mortality. Participants who were both most
physically active (ie, top third) and least sedentary (ie, bottom
third) formed the referent group. Effect sizes were estimated
using Cox proportional hazards regression analyses with 95% CI.
Analyses were restricted to those aged ≥40 years. Study
specific analyses were harmonised according to various levels
of adjustment. Model 1 (crude model) was adjusted for age
and sex (when applicable); model 2 (model 1 + adjustment for
socioeconomic status and body mass index (BMI)) and model 3
(model 2 + adjustment for covariates included in each study’s
published final multivariable-adjusted model (all cohorts, except
one,10 adjusted for smoking and presence of prevalent diseases
or self-reported poor health; see online supplemental table 1 for
details). In our final model (model 4), we excluded all deaths
within the first 2 years of follow-up and analysed the data with
the same adjustment as for model 3.

In stratified analyses (stratification by total physical activity
and MVPA), we assessed whether the dose–response association
between sedentary time and all-cause mortality differed between
groups with different levels of physical activity, always using
those least sedentary (bottom third) as the referent. These anal-
yses were performed using the same models (1–4) of adjustment
as described above for the joint association analyses.

Individual study summary data were meta-analysed with a
DerSimonian and Laird random effects model yielding eight
pooled HRs with 95% CIs for joint association analyses. We
assessed heterogeneity by I2 statistics.

Participant and study-level characteristics may modify associ-
ations between physical activity, sedentary time and mortality.
As analyses were performed separately for each study, we were
only able to examine study-level characteristics. To examine
the generalisability, we conducted subgroup analyses repeating
the multivariable adjusted, joint analyses by categorising indi-
vidual studies into studies based on national samples (Activity
Behaviour Change (ABC), Sweden; Norwegian National Phys-
ical Activity Survey (NNPAS), Norway; NHANES, USA) and
non-national samples (British Regional Heart Study, UK; Euro-
pean Prospective Investigation into Cancer and Nutrition,
Norfolk, UK; Framingham Heart Study, USA; The REasons for
Geographic and Racial Differences in Stroke, US; Walking Away
from Type 2 Diabetes, UK; Women’s Health Study, USA).

In sensitivity analysis, we excluded one study at a time and
repeated all analyses; the findings were unchanged (data not
shown). We also reanalysed our data and estimated summary HRs
across studies with the fixed effects inverse variance method,
and the main findings were unchanged (data not shown). Further,
we examined whether unmeasured or residual confounding may
have biased or ‘explained away’ our findings by estimating the
E-value for the joint association between sedentary time, MVPA
and mortality21 according to model 4.

RESULTS

In total, 44370 participants (69.7% women; mean age 65.8
years, SD 8.6 years) were available for meta-analysis of the
joint and stratified associations between physical activity and
sedentary time with all-cause mortality. They were followed for
4.0–14.5 years (median 6.0 years; 266 220 person years), during
which 3451 (7.8%) participants died.

Table 1 summarises the characteristics of the participants
by study. Participants from the three nationally representa-
tive samples (ABC, NHANES and NNPAS) were younger and

Patient and public involvement

No patients were involved in the planning, design or research
idea for this systematic review. Nor were they involved in the
analyses or data collection for the work. We did not evaluate
whether the individual studies included in the review had any
patient involvement.

Table 1 summarises the characteristics of the participants
by study. Participants from the three nationally representa-
tive samples (ABC, NHANES and NNPAS) were younger and
generally more active and spent less time sedentary compared with participants from the remaining studies. Across all cohorts, time spent sedentary, expressed as percentage of daily wear time varied fourfold between cohorts from 0.8% to 3.9%. Online supplemental table 2 shows the study specific medians (IQR) of total physical activity, sedentary time and MVPA by tertiles.

Joint associations: total physical activity and sedentary time
In multivariable-adjusted models (age, sex when applicable, socioeconomic position, BMI, smoking, presence of prevalent diseases or self-reported poor health, and other putative confounding factors displayed in online supplemental table 1) and excluding deaths within the first 2 years (figure 1) we observed that compared with the referent group (highest total physical activity/lowest sedentary time), the risk of all-cause mortality increased with lower levels of physical activity and greater amounts of sedentary time. Among those in the highest tertile of total activity, those in the middle and lowest tertiles of sedentary time experienced a 20% (95% CI 0.94% to 1.53%) and 88% (95% CI 0.92% to 3.84%) greater risk of death, compared with the referent group. However, these joint associations were not statistically different from the referent. As level of total physical activity decreased, the risk of death associated with greater amounts of sedentary time increased significantly. In the middle tertile of physical activity, the relative risks of mortality were 38% (95% CI 1.13% to 1.70%), 34% (95% CI 1.06% to 1.70%) and 44% (95% CI 0.99 to 2.10%) greater across increasing tertiles of sedentary time. In the least active third, the risks were 88% (95% CI 0.92% to 3.84%) greater, respectively, across increasing tertiles of sedentary time. Some effect estimates for extreme groups (eg, low total physical activity in combination with low sedentary time) had wide 95% CI due to small numbers. The HRs for the crude association and other less adjusted models (models 1–3) are shown in online supplemental figures 1–3.

Joint associations: MVPA and sedentary time
In multivariable-adjusted models (age, sex when applicable, socioeconomic position, BMI, smoking, presence of prevalent diseases or self-reported poor health and other putative confounding factors displayed in online supplemental table 1) and excluding deaths within the first 2 years (figure 1) we observed that compared with the referent group (highest total physical activity/lowest sedentary time), the risk of all-cause mortality increased with lower levels of physical activity and greater amounts of sedentary time. Among those in the highest tertile of total activity, those in the middle and lowest tertiles of sedentary time experienced a 20% (95% CI 0.94% to 1.53%) and 88% (95% CI 0.92% to 3.84%) greater risk of death, compared with the referent group. However, these joint associations were not statistically different from the referent. As level of total physical activity decreased, the risk of death associated with greater amounts of sedentary time increased significantly. In the middle tertile of physical activity, the relative risks of mortality were 38% (95% CI 1.13% to 1.70%), 34% (95% CI 1.06% to 1.70%) and 44% (95% CI 0.99 to 2.10%) greater across increasing tertiles of sedentary time. In the least active third, the risks were 88% (95% CI 0.92% to 3.84%) greater, respectively, across increasing tertiles of sedentary time. Some effect estimates for extreme groups (eg, low total physical activity in combination with low sedentary time) had wide 95% CI due to small numbers. The HRs for the crude association and other less adjusted models (models 1–3) are shown in online supplemental figures 1–3.

Table 1  Descriptive characteristics of participants

<table>
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<tr>
<th>Study</th>
<th>WAT2D</th>
<th>REGARDS</th>
<th>ABC</th>
<th>BRHS</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
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<tr>
<td>Men (n=411)</td>
<td>64.4</td>
<td>62.3</td>
<td>69.9</td>
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<td>68.2</td>
<td>68.7</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>88.4</td>
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<td>1.78</td>
<td>1.79</td>
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<tr>
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<td>0.06</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Women (n=4282)</td>
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<td></td>
<td></td>
<td>0.07</td>
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<td>87.0</td>
<td>89.6</td>
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<tr>
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<td>17.0</td>
<td>16.5</td>
<td>10.6</td>
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<tr>
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<td></td>
<td>11.7</td>
</tr>
<tr>
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<td>34.0</td>
<td>28.3</td>
<td>25.9</td>
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<td>3.0</td>
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<td>3.9</td>
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<td>Obese (%)</td>
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<td>74.9</td>
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<td>Wear time (min/day)</td>
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<td>843</td>
<td>850</td>
<td>809</td>
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<td>(n=463)</td>
<td>(216)</td>
<td>(209)</td>
<td>(282)</td>
<td>(211)</td>
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<tr>
<td>Sedentary (hours/day)</td>
<td>9.6</td>
<td>8.7</td>
<td>11.5</td>
<td>8.7</td>
</tr>
<tr>
<td>(n=3580)</td>
<td>(1.5)</td>
<td>(1.5)</td>
<td>(1.4)</td>
<td>(1.7)</td>
</tr>
<tr>
<td>Sedentary (%)</td>
<td>63.2</td>
<td>62.1</td>
<td>81.2</td>
<td>57.6</td>
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<tr>
<td>MVPA (min/day)</td>
<td>32.0</td>
<td>19.1</td>
<td>9.8</td>
<td>35.5</td>
</tr>
<tr>
<td>(n=3580)</td>
<td>(26.6)</td>
<td>(17.3)</td>
<td>(14.9)</td>
<td>(30.0)</td>
</tr>
<tr>
<td>MVPA (%)</td>
<td>3.8</td>
<td>2.2</td>
<td>1.1</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>3.5</td>
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<td></td>
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<td>1.8</td>
</tr>
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</table>

Data are mean (SD).

BMI, body mass index; BRHS, British Regional Heart Study; CPM, counts per minute; EPIC, European Prospective Investigation into Cancer; FHS, Framingham Heart Study; MVPA, moderate-to-vigorous intensity physical activity; NHANES, National Health and Nutrition Examination Survey; NNPAS, Norwegian National Physical Activity Survey; REGARDS, The Reasons for Geographic and Racial Differences in Stroke; WAT2D, Walking Away from Type 2 Diabetes; WHS, Women’s Health Study.
and excluding deaths within the first 2 years (model 4; figure 2) we observed similar patterns of associations as for total physical activity. Among those in the highest tertile of MVPA, the risk of death was not statistically different from the referent for those in the middle (16%; 95% CI 0.87% to 1.54%) and highest (40%; 95% CI 0.87% to 2.26%) tertiles of sedentary time. Similarly, as levels of MVPA decreased the risk of death increased. In the middle tertile of MVPA, the relative risks of death were 5% (95% CI 0.83% to 1.33%), 31% (95% CI 1.02% to 1.67%) and 68% (95% CI 1.22% to 2.30%) greater across increasing tertiles of sedentary time compared with the referent. Those in the lowest third of MVPA had an increased risk of death in all combinations with sedentary time; 65% (95% CI 1.25% to 2.19%), 65% (95% CI 1.24% to 2.21%) and 263% (95% CI 1.93% to 3.57%), respectively. The HRs for the crude association and other less adjusted models (models 1–3) are shown in online supplemental figures 4–6.

In subgroup analyses, we examined the joint associations between time in MVPA and sedentary time with all-cause mortality separately in the nationally representative samples (n=5977, 933 deaths) and in the remaining non-national cohorts (n=36,226, 2141 deaths) (figure 3A,B). In both subgroups, the shape of the dose–response patterns was similar to our primary analyses. However, in the nationally representative cohorts, the
that physical activity and sedentary time can be combined differently, although not completely eliminated, in those in the highest third of time spent in MVPA. In contrast, those with low physical activity (lowest third) had a higher risk of premature death, with the greatest risk of death occurring in those with the highest sedentary time. In stratified analyses, the risk of death was higher by increasing levels of time spent sedentary across strata for time in MVPA, whereas the role of total physical activity in modulating risk of death with high sedentary time was less clear.

**Comparison with previous studies**

These results provide a unique contribution because previous studies examining the joint associations between physical activity and sedentary time and mortality have assessed physical activity and sedentary behaviours by self-report. A previous meta-analysis suggested that between 60 and 75 min per day of leisure time physical activity of moderate intensity was needed to eliminate the risk of mortality associated with sitting time. While the pattern of associations is generally similar when comparing our findings with self-report, we were able to quantify the amount of time spent in MVPA needed to attenuate the risk of premature death associated with sedentary time.

Our joint analysis results suggest that about 30–40 min (median of medians=34 min; IQR: 26–48 min) of MVPA per day (online supplemental table 2) attenuated the risk of death in our most conservative model. Those with as little as 11 min per day of MVPA in combination with ‘low’ sedentary time (ie, <8.5 hours per day) did not differ in risk compared with the referent group (ie, highest third of MVPA in combination with lowest third for sedentary time). This finding may suggest that relatively low levels of MVPA, lower than the current recommendations, reduces the risk of death if combined with low levels of sedentary time. In contrast, in the lowest third of MVPA comprising those who accumulated about 2 min of MVPA per day on average, all combinations with sedentary time (ie, 8.5–10.7 hours per day) were associated with a higher risk of premature death with point estimates all higher than all combinations of sedentary time in the high MVPA category.

Subgroup analyses that categorised studies into national (ABC, NHANES, NNPPAS) and non-national samples indicated that sedentary time was associated with higher risk of death in the low active third, (average MVPA of about 11 min per day of MVPA) in the national cohorts only. Compared with the
non-national cohorts that accumulated about 2 min of MVPA in the least active third, the national cohorts included younger and more active individuals with a longer period of follow-up. How these characteristics may modulate the association between sedentary time and mortality requires further scrutiny when longer follow-up data are available.

Our results also indicate that the amount of MVPA needed to attenuate the risk associated with sedentary time may be lower than previously suggested using self-reported data. However, this is likely explained in part by differences between self-reported and accelerometer measured physical activity and sedentary behaviour. Self-reported physical activity usually only assesses specific domains, such as leisure time and recreational physical activity accumulated in bouts or categorised into specific time blocks (self-report studies typically ask about activities that last at least 10 min in duration, in keeping with previous physical activity guidelines; this 10 min minimum duration has now been removed in the most recent guidelines, whereas accelerometers capture more movement across multiple domains.

The recently updated physical activity guidelines from the USA and WHO recommend that adults should participate in physical activity for 150–300 minutes of at least moderate intensity every week. They also state that people should move more and sit less throughout the day and that any activity is better than none. The new guidelines from WHO also acknowledge the emerging evidence on the interaction between sedentary behaviour and MVPA and states that adults should aim to do more than recommended levels of MVPA to reduce the detrimental effects of high sedentary time. The results from this study, where physical activity and sedentary time were

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**Table 2** Meta-analysis for the associations between sedentary time (% of daily wear time) and all-cause mortality by levels of total physical activity (CPM) and time spent in moderate-to-vigorous-intensity physical activity (MVPA; % of daily wear time) (n=44,370; 3451 (model 1); n=42,420; 3137 (model 2); n=42,203; 3074 (model 3); n=42,303; 2508 (model 4)) (n in each cell refers to number of participants and deaths)

<table>
<thead>
<tr>
<th></th>
<th>Low sedentary</th>
<th>Medium sedentary</th>
<th>High sedentary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total PA (CPM)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low PA</td>
<td>1 (Ref)</td>
<td>0.65 (0.36 to 1.18)</td>
<td>1.02 (0.58 to 1.78)</td>
</tr>
<tr>
<td>Medium PA</td>
<td>1 (Ref)</td>
<td>0.97 (0.95 to 1.26)</td>
<td>1.10 (0.71 to 1.70)</td>
</tr>
<tr>
<td>High PA</td>
<td>1 (Ref)</td>
<td>1.13 (0.90 to 1.41)</td>
<td>1.55 (0.86 to 2.77)</td>
</tr>
<tr>
<td><strong>MVPA</strong></td>
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<tr>
<td>Low PA</td>
<td>1 (Ref)</td>
<td>0.91 (0.73 to 1.14)</td>
<td>1.73 (1.32 to 2.27)</td>
</tr>
<tr>
<td>Medium PA</td>
<td>1 (Ref)</td>
<td>1.08 (0.90 to 1.29)</td>
<td>1.50 (1.24 to 1.82)</td>
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<tr>
<td>High PA</td>
<td>1 (Ref)</td>
<td>1.18 (0.90 to 1.56)</td>
<td>1.61 (1.05 to 2.46)</td>
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<tr>
<td><strong>Model 2</strong></td>
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<tr>
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<td>1 (Ref)</td>
<td>0.65 (0.36 to 1.18)</td>
<td>1.04 (0.58 to 1.85)</td>
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<tr>
<td>Medium PA</td>
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<td>1.00 (0.74 to 1.34)</td>
<td>1.08 (0.84 to 1.38)</td>
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<td>1.20 (0.94 to 1.53)</td>
<td>1.71 (0.94 to 3.10)</td>
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<td><strong>Model 3</strong></td>
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<tr>
<td>Low PA</td>
<td>1 (Ref)</td>
<td>0.98 (0.78 to 1.23)</td>
<td>1.86 (1.44 to 2.39)</td>
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<td>Medium PA</td>
<td>1 (Ref)</td>
<td>1.18 (0.95 to 1.45)</td>
<td>1.57 (1.28 to 1.91)</td>
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<td>1 (Ref)</td>
<td>1.31 (1.03 to 1.65)</td>
<td>1.71 (1.14 to 2.59)</td>
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<tr>
<td><strong>Model 4</strong></td>
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<tr>
<td>Low PA</td>
<td>1 (Ref)</td>
<td>0.69 (0.37 to 1.26)</td>
<td>1.01 (0.56 to 1.85)</td>
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<td>Medium PA</td>
<td>1 (Ref)</td>
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<td>1.21 (0.86 to 1.72)</td>
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<td>1 (Ref)</td>
<td>1.19 (0.94 to 1.52)</td>
<td>1.80 (0.87 to 3.74)</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex (when applicable).
†Adjusted for age, sex (when applicable), socioeconomic status and BMI.
‡Adjusted for age and sex (when applicable), socioeconomic status and BMI and additional covariates described in online supplemental table 1.
§Model three and excluding deaths within 2 years; boldface indicates significant association (p<0.05).

BMI, body mass index; CPM, counts per minute; MVPA, moderate-to-vigorous intensity physical activity; PA, physical activity.
measured by accelerometer, suggest that accumulating time in MVPA equivalent to the upper level of the 150–300 min per week recommendation may be sufficient to attenuate the detrimental association between sedentary time and risk of premature death. Evidence is also accumulating on the beneficial effect of total physical activity and light intensity physical activity for longevity. In joint analyses of sedentary time and total physical activity (which includes light, moderate and vigorous intensities), we observed a higher risk of death for higher amounts of time spent sedentary in all combinations with total physical activity. However, the risk was not statistically different from the referent in the most active third of total physical activity (figure 1). In line with current physical activity recommendations, reducing sedentary time must increase total physical activity (since time in a day is finite) and thus likely reduce the risk of premature death. However, because of uncertainty in effect estimates for some cross-combinations of total activity and sedentary time, more work is needed to determine the interplay between total activity and sedentary time in relation to mortality. The cohorts included in our meta-analyses accumulated approximately 16 min in MVPA per day. Although not directly comparable, this is lower than population-based estimates in Swedish and Norwegian men and women aged 60–85 years and comparable to US men, but higher than in US women aged 60–75 years. Further, time spent sedentary was almost 10 hours per day and considerably higher than comparable population-based estimates from the USA with a younger age structure. Thus, the associations observed between combinations of physical activity and sedentary time with mortality may not be generalisable to younger and more active populations, nor to low-income and middle-income countries.

Strengths and limitations

To our knowledge, this is the first meta-analysis examining the joint associations between physical activity, sedentary time and all-cause mortality using accelerometer measured exposure variables. Accelerometer measured physical activity has higher precision which reduces random error as compared with self-report and, importantly, minimises bias due to correlated cognitive biases in self-reported physical activity and sedentary behaviours. Additional strengths of this study include harmonisation of exposure data and study specific analyses according to a standardised protocol reducing heterogeneity due to different data reduction and data cleaning procedures. We were able to control for many potential confounders in our final model and estimated the E-value as an indicator of the potential impact of unmeasured or residual confounding. An uncontrolled confounder must be associated with both the exposure combination (physical activity and sedentary time) and mortality in the order of at least two to bias or negate the observed associations for those combinations including either the lowest third of MVPA or highest third of sedentary time (E-values between 2.1 and 4.63; lower CI 1.61 to 3.2; online supplemental table 3). To put this in context, the HR for all-cause mortality comparing never vs current smokers was 2.26 and 1.34 in the NHANES and NNPAS data sets, respectively. While we cannot rule out residual confounding, uncontrolled confounding would have to be as large in magnitude as smoking to distort our results. Finally, in our most conservative model, we excluded deaths within the first 2 years to reduce the risk of reverse causation bias. However, follow-up time was short (median 5.5 years) in some of the cohorts which may have a substantial impact on observed associations.

Limitations of our study include its observational design. We cannot rule out reverse causation bias from prevalent medical conditions or subclinical disease despite the results excluding deaths within the first 2 years supporting our conclusion. We adjusted our analyses for several covariates including smoking and pre-existing illness or self-reported poor health in our final model but cannot exclude the possibility of residual or unmeasured confounding or other biases. Our sample included middle-aged and older individuals who were at least 40 years at baseline, and it is unclear if the results are generalisable to younger populations. Some of the groups in our analyses had low numbers of individuals and deaths making the point estimates uncertain. Low number of individuals and cases in some of the referent groups in our stratified analyses for total physical activity also makes these associations less reliable. Two different accelerometers were used by the included cohorts and these have only moderate agreement on total sedentary time for the applied cut-points, suggesting they assess sedentary time slightly differently. We reanalysed our data excluding one study at a time to examine if the results were influenced by a specific study and the results were not materially altered. Sedentary time estimated from movement-based cut-points may include non-sedentary behaviours such as standing. However, in the older participants, when movement was not registered over long periods, they were likely to be sedentary rather than standing with little movement. Errors in estimating MVPA and sedentary time are not completely uncorrelated as they are measured from the same device, for instance, failure to correctly identify non-wear time would increase sedentary time and subsequently lower our measure of total physical activity and MVPA in percent of wear-time. Finally, exposure variables were only measured once and change in behaviours between baseline and follow-up may have affected our results. However, accelerometer measured physical activity and sedentary time show good stability (Intra-class correlation 0.70–0.83) over two to 3 years in a 70-year-old women.

CONCLUSION

Higher sedentary time is associated with higher mortality in less active individuals when measured by accelerometer. About
30–40 min of MVPA per day attenuate the association between sedentary time and risk of death, which is lower than previous estimates from self-reported data.

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Contributors UE led the work of the writing group (JT, MWF, JSI, BHH, SAA and I-ML) and wrote the manuscript. MWF and JT analysed the data. MWF, JT and UE had full access to study level data from all contributing studies. All authors contributed to the design of the study, interpreted the data and critically reviewed the report.

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Patient consent for publication Not required.

Ethics approval Ethical approval was obtained for all individual studies but was not required for this meta-analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The study-specific summary data included in the meta-analyses can be obtained from the corresponding author; ulf.ekelund@nhi.no.

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REFERENCES


SUPPLEMENTARY MATERIALS

Systematic search

We conducted a systematic review following the guidelines for Meta-Analyses and Systematic reviews for Observational Studies (1) and the PRISMA guidelines (2). The review protocol is registered with the PROSPERO database (PROSPERO 2018 CRD42018091808).

Data sources

We performed a systematic search in five databases (PubMed, PsycINFO, Embase, Web of Science, Sport Discus) from database inception until July 31st 2018 and updated the search until March 31st 2020. The following list of search terms was used when searching for eligible articles; (#1"physical activity" OR "physical activities" OR "physically active" OR "physical exercise" OR "exercise" OR "walk" AND #2 "mortality" OR "mortalities" OR "death" OR "fatal" AND #3 "accelerometer" OR "activity monitor" OR "motion sensor" OR "device-based" OR "Actigraph" OR "Actical" OR "Sensewear" OR "Actiband" OR "Actiwatch"). We performed forward and backward tracking by examining the reference list of studies potentially eligible for inclusion.

Study selection

Two authors (UE, JSS) independently screened all titles and abstracts. After exclusion of duplicates, one author (JSS) performed a full-text review and the final list of studies was discussed among the writing group. Inclusion criteria were; 1) prospective cohort studies that assessed sedentary time and physical activity by accelerometry; 2) had data on individual level exposure and outcome (all-cause mortality); 3) reported effect estimates as hazard ratios (HR), odds ratios (OR) or relative risk (RR) with 95% confidence intervals (95% CI) for all-cause mortality; 4) were published in English or Scandinavian language. Due to the marked difference in output from accelerometers placed at different body sites (3), which precludes harmonisation of physical activity data, we excluded three studies (4-6) in which physical activity was assessed by monitors placed on the upper arm, wrist and thigh, respectively. One eligible study did not wish to participate in the harmonised meta-analysis (7). We have previously published the results for the separate dose-response associations between different
intensities of physical activity and sedentary time with all-cause mortality comprising eight of the studies included in this meta-analysis. The updated search identified one additional study eligible for inclusion (8).

Data Extraction
One author (UE) extracted the following information from each eligible study: name of the first author; study location; source and number of participants; age of participants; number of men and women; years of follow-up; number of deaths from all causes; methods of case ascertainment; assessment details for physical activity and sedentary time; and covariates included in final, adjusted models. Data extraction variables were cross-checked by another author (JSS).

Risk of Bias
Using the Newcastle-Ottawa quality assessment scale (9), two authors (UE, JT) independently assessed the studies, and any disagreements were resolved by consensus. This semi-quantitative scale assesses the quality for eight items across three domains (selection, comparability and exposure) using a star system, with a maximum of one star per item for high quality studies except for the comparability domain (two stars). Thus, the total score ranges from zero to nine. Further details of the quality rating are found below (Supplementary Table 4).
## Supplementary tables

### Supplementary Table 1. Description of studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants; number of cases; year of baseline assessment and follow-up years (median)</th>
<th>Case ascertainment</th>
<th>Accelerometer Device and Method</th>
<th>Covariates adjusted for in final model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking Away from Type 2 Diabetes (WAT2D), England (10)</td>
<td>654; 26; 2010-11; 5.7 y</td>
<td>Office for National Statistics</td>
<td>Actigraph GT3X+ (right hip)</td>
<td>Age, sex, BMI, socioeconomic status</td>
</tr>
<tr>
<td>Reasons for Geographic and Racial Differences in Stroke (REGARDS); US (11)</td>
<td>7866; 590; 2003-07; 5.3 y</td>
<td>Review of death certificates, medical records, and administrative databases</td>
<td>Actical (right hip)</td>
<td>Age, sex, BMI, education, race, region of residence, season the accelerometer was worn, current smoking, alcohol use, diabetes, hypertension, dyslipidemia, estimated glomerular filtration rate, atrial fibrillation, history of coronary heart disease, and history of stroke</td>
</tr>
<tr>
<td>Sweden Attitude Behaviour and Change study (ABC), Sweden (12)</td>
<td>834; 79; 2001-02; 14.5 y</td>
<td>National death register</td>
<td>Actigraph 7164 (lower back)</td>
<td>Age, sex, education, BMI, smoking, history of hypertension, heart disease, cancer, and diabetes</td>
</tr>
<tr>
<td>British Regional Heart Study (BRHS), UK (13)</td>
<td>1412; 250; 2010-12; 6.0 y</td>
<td>National Health Service central registers</td>
<td>Actigraph GT3X+ (right hip)</td>
<td>Age, BMI, Social class, season of accelerometer wear, region of residence, lives alone / with others, alcohol, smoking, sleep, locomotor disability, previous MI, stroke or heart failure</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Follow-up</td>
<td>Measurements</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------------------------------------</td>
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<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Women's Health Study (WHS), US (14)</td>
<td>16738; 504; 2011-17; 4.3 y</td>
<td>Medical records, death certificates or the National Death Index</td>
<td>Actigraph GT3X+ (right hip)</td>
<td>Age, income, BMI, smoking, alcohol, intakes of saturated fat, fibre, fruits, and vegetables, hormone therapy, parental history of myocardial infarction, family history of cancer, general health, history of cardiovascular disease, history of cancer, and cancer screening</td>
</tr>
<tr>
<td>Framingham Heart Study (FHS), US (16)</td>
<td>2621; 77; 2008-11; 4.0 y</td>
<td>Medical records, death certificates</td>
<td>Actical (right hip)</td>
<td>Age, sex, education, BMI, ethnicity, smoking, self-reported health</td>
</tr>
<tr>
<td>National Health and Nutrition Examination Survey (NHANES), US (18)</td>
<td>4319; 1065; 2003-06; 10.5 y</td>
<td>National Death Index, National Center for Health Statistics</td>
<td>Actigraph 7164 (right hip)</td>
<td>Age, socioeconomic status, BMI, ethnicity, smoking, alcohol, mobility limitations, number of medical conditions (diabetes, congestive heart failure, coronary heart disease, angina pectoris, heart attack, stroke, cancer)</td>
</tr>
<tr>
<td>Norwegian National Physical Activity Survey 1 (NNPAS) (17)</td>
<td>2284; 131; 2008-09; 8.9 y</td>
<td>Death certificates, Norwegian death register</td>
<td>Actigraph GT1M (right hip)</td>
<td>Age, sex, education, BMI, smoking, alcohol, number of medical conditions (diabetes, coronary heart disease, angina pectoris, heart attack, stroke, cancer)</td>
</tr>
<tr>
<td>The European Prospective Investigation into Cancer and Nutrition (EPIC) Norfolk, UK (9)</td>
<td>7657; 721; 2004-16; 5.4 y</td>
<td>Death certificates, Office for National Statistics</td>
<td>Actigraph GT1M and GT3X+ (harmonised; right hip)</td>
<td>Age, sex, education, BMI, social class, smoking, alcohol, diabetes, antihypertensive drugs, lipid lowering drugs, anti-depression drugs, cardiovascular disease, cancer, family history of disease (heart attack, stroke, diabetes, cancer)</td>
</tr>
</tbody>
</table>

References to original studies within brackets (see reference list in main document)
**Supplementary Table 2.** Study specific medians (Interquartile range) of total physical activity, sedentary time and MVPA by tertiles.

<table>
<thead>
<tr>
<th></th>
<th>WAT2D</th>
<th>REGARDS*</th>
<th>ABC</th>
<th>BRHS</th>
<th>WHS</th>
<th>FHS*</th>
<th>NHANES</th>
<th>NNPAS</th>
<th>EPIC-NORFOLK</th>
<th>Median of medians**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Physical Activity (CPM)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Medium PA</td>
<td>272 (248-304)</td>
<td>74 (50-98)</td>
<td>316 (296-346)</td>
<td>166 (142-188)</td>
<td>205 (185-226)</td>
<td>115 (86-144)</td>
<td>251 (223-277)</td>
<td>309 (286-338)</td>
<td>225</td>
<td>251</td>
</tr>
<tr>
<td>High PA</td>
<td>439 (373-503)</td>
<td>147 (77-217)</td>
<td>465 (413-546)</td>
<td>287 (244-356)</td>
<td>313 (277-371)</td>
<td>200 (111-289)</td>
<td>396 (347-478)</td>
<td>444 (401-523)</td>
<td>345</td>
<td>396</td>
</tr>
<tr>
<td><strong>Sedentary (hours/d)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Low sedentary</td>
<td>7.6 (6.8-8.1)</td>
<td>10.6 (9.0-12.1)</td>
<td>7.1 (6.4-7.6)</td>
<td>9.1 (8.4-9.6)</td>
<td>8.7 (8.1-9.6)</td>
<td>10.4 (9.4-11.4)</td>
<td>6.5 (5.7-7.3)</td>
<td>8.5 (7.6-9.4)</td>
<td>8.2</td>
<td>8.5</td>
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<tr>
<td>Medium sedentary</td>
<td>8.9 (8.4-9.5)</td>
<td>11.8 (10.2-13.2)</td>
<td>8.6 (8.1-9.2)</td>
<td>10.3 (9.8-10.9)</td>
<td>9.9 (9.6-10.2)</td>
<td>11.6 (11.0-12.9)</td>
<td>8.6 (7.9-9.2)</td>
<td>9.3 (8.6-10.1)</td>
<td>9.4</td>
<td>9.4</td>
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<tr>
<td>High sedentary</td>
<td>10.2 (9.4-10.8)</td>
<td>12.4 (10.8-14.0)</td>
<td>10.0 (9.3-10.8)</td>
<td>11.3 (10.6-12.0)</td>
<td>11.2 (10.8-11.8)</td>
<td>12.9 (12.2-13.5)</td>
<td>10.2 (9.3-11.2)</td>
<td>10.3 (9.4-11.1)</td>
<td>10.7</td>
<td>10.7</td>
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<tr>
<td><strong>Sedentary (% time)</strong></td>
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<tr>
<td>Low sedentary</td>
<td>54 (50-57)</td>
<td>75 (64-86)</td>
<td>48 (43-51)</td>
<td>64 (60-68)</td>
<td>58 (54-64)</td>
<td>71 (64-78)</td>
<td>47 (42-51)</td>
<td>57 (51-62)</td>
<td>58 (54-61)</td>
<td>58</td>
</tr>
<tr>
<td>Medium sedentary</td>
<td>63 (61-65)</td>
<td>83 (73-94)</td>
<td>58 (54-62)</td>
<td>73 (70-77)</td>
<td>66 (64-68)</td>
<td>79 (75-82)</td>
<td>60 (58-63)</td>
<td>63 (58-67)</td>
<td>67 (65-69)</td>
<td>66</td>
</tr>
<tr>
<td>High sedentary</td>
<td>72 (69-75)</td>
<td>88 (76-99)</td>
<td>67 (63-73)</td>
<td>81 (76-85)</td>
<td>75 (72-79)</td>
<td>88 (83-92)</td>
<td>72 (68-77)</td>
<td>70 (67-75)</td>
<td>76 (73-79)</td>
<td>75</td>
</tr>
<tr>
<td><strong>MVPA (min/d)</strong></td>
<td></td>
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</tr>
<tr>
<td>Low PA</td>
<td>6.4 (3.1-10.1)</td>
<td>0 (0-0.3)</td>
<td>10.6 (5.3-14.8)</td>
<td>1.1 (0.4-2.3)</td>
<td>1.8 (0.1-2.7)</td>
<td>0.9 (0.3-5)</td>
<td>2.3 (1.1-3.7)</td>
<td>12.4 (6.1-20.6)</td>
<td>7.7</td>
<td>4.2 (4.1-12.1)</td>
</tr>
<tr>
<td>Medium PA</td>
<td>20.8 (16.4-24.6)</td>
<td>2.2 (0-4.7)</td>
<td>27.0 (22.4-32.6)</td>
<td>9.3 (6.7-13.0)</td>
<td>9.0 (0.6-11.7)</td>
<td>9.7 (4.4-14.1)</td>
<td>11.2 (8.3-15.3)</td>
<td>31.0 (23.4-39.1)</td>
<td>24.8</td>
<td>11.2</td>
</tr>
<tr>
<td>High PA</td>
<td>48.1 (37.3-64.1)</td>
<td>16.4 (0-33)</td>
<td>52.2 (43.2-65.6)</td>
<td>30.6 (22.9-43.0)</td>
<td>28.8 (19.8-39.6)</td>
<td>28.1 (8.8-38.7)</td>
<td>34.3 (26.1-48.4)</td>
<td>56.3 (43.4-71.9)</td>
<td>51.6</td>
<td>34.3</td>
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<tr>
<td><strong>MVPA (% time)</strong></td>
<td></td>
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<tr>
<td>Activity Level</td>
<td>MAU</td>
<td>(90x-200x)</td>
<td>MAU</td>
<td>(90x-200x)</td>
<td>MAU</td>
<td>(90x-200x)</td>
<td>MAU</td>
<td>(90x-200x)</td>
<td>MAU</td>
<td>(90x-200x)</td>
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</tr>
<tr>
<td>Low PA</td>
<td>0.8</td>
<td>(0.4-1.2)</td>
<td>0.0</td>
<td>(0-0.003)</td>
<td>1.2</td>
<td>(0.6-1.6)</td>
<td>0.1</td>
<td>(0-0.027)</td>
<td>0.2</td>
<td>(0-0.3)</td>
</tr>
<tr>
<td>Medium PA</td>
<td>2.4</td>
<td>(2.0-2.90)</td>
<td>0.3</td>
<td>(0-0.6)</td>
<td>3.0</td>
<td>(2.5-3.6)</td>
<td>1.1</td>
<td>(0.8-1.5)</td>
<td>1.0</td>
<td>(0.7-1.3)</td>
</tr>
<tr>
<td>High PA</td>
<td>5.8</td>
<td>(4.5-7.4)</td>
<td>1.9</td>
<td>(0.3-9)</td>
<td>5.8</td>
<td>(4.8-7.3)</td>
<td>3.6</td>
<td>(2.7-5.1)</td>
<td>3.2</td>
<td>(2.2-4.4)</td>
</tr>
</tbody>
</table>

*Data based on Actical accelerometer; **median of medians based on Actigraph accelerometer (excluding REGARDS and FHS)
Supplementary Table 3. E-values (upper or lower 95% CI within brackets) for different combinations of time spent in MVPA and sedentary time with all-cause mortality. Data are from the multivariate adjusted model (Figure 2d) (N=42303, 2508 deaths)

<table>
<thead>
<tr>
<th></th>
<th>Low sedentary</th>
<th>Medium Sedentary</th>
<th>High Sedentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>High MVPA</td>
<td>REF</td>
<td>1.62 (1.51)</td>
<td>2.10 (1.68)</td>
</tr>
<tr>
<td>Medium MVPA</td>
<td>1.27 (1.80)</td>
<td>1.91 (1.01)</td>
<td>2.67 (1.61)</td>
</tr>
<tr>
<td>Low MVPA</td>
<td>2.62 (1.75)</td>
<td>2.60 (1.72)</td>
<td>4.63 (3.20)</td>
</tr>
</tbody>
</table>
### Supplementary Table 4. Quality assessment of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Representativeness</th>
<th>Selection</th>
<th>Ascertainment Exposure</th>
<th>Outcome</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Follow Up</th>
<th>Adequacy</th>
</tr>
</thead>
</table>

For full details of the coding system (A to D) see http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf

References to original studies within brackets (see reference list in main document)
### Supplementary Figures

**Supplementary figure 1.** The joint association between total physical activity and sedentary time and all-cause mortality. Analyses are adjusted for age and sex (n=44,370; 3451 deaths).
Supplementary figure 2. The joint association between total physical activity and sedentary time and all-cause mortality. Analyses are adjusted for age, sex, BMI and socio-economic position (n=42,420; 3137 deaths).
Supplementary figure 3. The joint association between between total physical activity and sedentary time and all-cause mortality. Analyses are adjusted for age, sex, BMI, socio-economic position, smoking, presence of prevalent diseases or self-reported poor health, other putative confounding factors displayed in Supplementary Table 1 (n=42,203; 3074 deaths).
**Supplementary figure 4.** The joint association between moderate-to-vigorous-intensity physical activity and sedentary time and all-cause mortality. Analyses are adjusted for age and sex (n=44,370; 3451 deaths).
**Supplementary figure 5.** The joint association between moderate-to-vigorous-intensity physical activity and sedentary time and all-cause mortality. Analyses are adjusted for age, sex, BMI and socio-economic position (n=42,420; 3137 deaths).
Supplementary figure 6. The joint association between between moderate-to-vigorous-intensity physical activity and sedentary time and all-cause mortality. Analyses are adjusted for age, sex, BMI, socio-economic position, smoking, presence of prevalent diseases or self-reported poor health, other putative confounding factors displayed in Supplementary Table 1 (n=42,203; 3074 deaths).
Supplementary References


