Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis

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ABSTRACT

OBJECTIVE
To examine the dose-response associations between accelerometer assessed total physical activity, different intensities of physical activity, and sedentary time and all cause mortality.

DESIGN
Systematic review and harmonised meta-analysis.

DATA SOURCES
PubMed, PsycINFO, Embase, Web of Science, Sport Discus from inception to 31 July 2018.

ELIGIBILITY CRITERIA
Prospective cohort studies assessing physical activity and sedentary time by accelerometry and associations with all cause mortality and reported effect estimates as hazard ratios, odds ratios, or relative risks with 95% confidence intervals.

DATA EXTRACTION AND ANALYSIS
Guidelines for meta-analyses and systematic reviews for observational studies and PRISMA guidelines were followed. Two authors independently screened the titles and abstracts. One author performed a full text review and another extracted the data. Two authors independently assessed the risk of bias. Individual level participant data were harmonised and analysed at study level. Data on physical activity were categorised by quarters at study level, and study specific associations with all cause mortality were analysed using Cox proportional hazards regression analyses. Study specific results were summarised using random effects meta-analysis.

MAIN OUTCOME MEASURE
All cause mortality.

RESULTS
39 studies were retrieved for full text review; 10 were eligible for inclusion, three were excluded owing to harmonisation challenges (eg, wrist placement of the accelerometer), and one study did not participate. Two additional studies with unpublished mortality data were also included. Thus, individual level data from eight studies (n=36 383; mean age 62.6 years; 72.8% women), with median follow-up of 5.8 years (range 3.0-14.5 years) and 2149 (5.9%) deaths were analysed. Any physical activity, regardless of intensity, was associated with lower risk of mortality, with a non-linear dose-response. Hazards ratios for mortality were 1.00 (referent) in the first quarter (least active), 0.48 (95% confidence interval 0.43 to 0.54) in the second quarter, 0.34 (0.26 to 0.45) in the third quarter, and 0.27 (0.23 to 0.32) in the fourth quarter (most active). Corresponding hazards ratios for light physical activity were 1.00, 0.60 (0.54 to 0.68), 0.44 (0.38 to 0.51), and 0.38 (0.28 to 0.51), and for moderate-to-vigorous physical activity were 1.00, 0.64 (0.55 to 0.74), 0.55 (0.40 to 0.74), and 0.52 (0.43 to 0.61). For sedentary time, hazards ratios were 1.00 (referent; least sedentary), 1.28 (1.09 to 1.51), 1.71 (1.36 to 2.15), and 2.63 (1.94 to 3.56).

CONCLUSION
Higher levels of total physical activity, at any intensity, and less time spent sedentary, are associated with substantially reduced risk for premature mortality, with evidence of a non-linear dose-response pattern in middle aged and older adults.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42018091808.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Physical inactivity is associated with many chronic diseases and premature mortality and increasing evidence also suggests that high levels of sedentary time may increase the risk of chronic diseases and mortality

Current physical activity guidelines are, however, informed primarily by self reported physical activity studies, which are susceptible to error

Thus the magnitude of associations is likely underestimated and the shape of dose-response relations, particularly for light intensity activity, is unclear

WHAT THIS STUDY ADDS

All intensities of physical activity, including light intensity, are associated with a substantially reduced risk of death in a dose-response manner

The observed effect sizes for the associations between physical activity and the risk of death are about twice as large compared with those previously reported in studies assessing physical activity by self report

A statistical significantly higher risk of death was observed for sedentary times of 9.5 or more hours daily

Introduction

Physical inactivity is associated with many chronic diseases,[1] premature mortality,[2] and substantial economic burden.[3] Increasing evidence also suggests that high levels of time spent sedentary might increase the risk of chronic diseases and mortality.[4 5]

The current evidence on the associations between physical activity or sedentary time and health outcomes

are primarily from studies that used participant self reported physical activity and sedentary time.[1] Self reports are, however, prone to recall and social desirability biases, which result in over-estimation of physical activity,[6 7] are usually restricted to a limited number of physical activity domains (eg, leisure time activity), underestimate sedentary time,[8] and rarely provide data on total physical activity and light physical activity.[7] Furthermore, the magnitude of the association between physical activity and mortality is likely underestimated, as a result of imprecision in exposure measurements, whereas the shape of the dose-response associations for light intensity physical activity is unclear. Indeed, the US Physical Activity Guidelines advisory committee recently indicated the impact of total physical activity and light intensity physical activity for reducing mortality risk as a priority for research.[1]

To reduce the biases associated with self report, several recent cohort studies have used device based methods (ie, accelerometry) when examining associations between physical activity or sedentary time and mortality.[9-13] However, the results are inconsistent, even when derived from the same dataset.[13 14] This is related to differences in analytical methods. Also, most of these studies are statistically underpowered to examine the associations between dose-response and intensity specific physical activity and mortality because of their relatively short follow-up time and few deaths.

We conducted a harmonised meta-analysis to examine the association between accelerometer measured physical activity and sedentary time and all cause mortality. Specifically, we examined the dose-response relations of total physical activity, different intensities of physical activity (light, low light, high light, moderate to vigorous, and vigorous) and sedentary time and all cause mortality.

Methods
We conducted a systematic review following the guidelines for Meta-Analyses and Systematic reviews for Observational Studies[15] and the PRISMA guidelines.[16] The review protocol is registered with the PROSPERO database (CRD42018091808).

Data sources
We performed a systematic search in five databases (PubMed, PsycINFO, Embase, Web of Science, Sport Discus) from inception of the database to 31 July 2018. When searching for eligible articles we used the search terms ("physical activity" *or* "physical activities" *or* "physically active" *or* "physical exercise" *or* "exercise" *or* "walk" *and* "mortality" *or* "mortalities" *or*" death "*or* "fatal" *or* "accelerometer" *or* "activity monitor" *or* "motion sensor" *or* "device-based" *or* "Actigraph" *or* "Actical" *or* "Sensewear" *or* "Actiband" *or* "Actiwatch"). Forward and backwards tracking was performed by examining the reference list of studies potentially eligible for inclusion.

Study selection
Two authors (UE, JSS) independently screened the 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 prospective cohort studies that assessed sedentary time and physical activity by accelerometry, had data on individual level exposure and all cause mortality, reported effect estimates as hazard ratios, odds ratios, or relative risks with 95% confidence intervals for all cause mortality, and were published in English or Scandinavian. Owing to the noticeable variations in output from accelerometers placed at different body sites,[17] which precludes harmonisation of physical activity data, we excluded three studies[18-20] in which physical activity was assessed by monitors placed on the upper arm, wrist, and thigh. On author request one eligible study was not included in the harmonised meta-analysis.[11]

Data extraction
One author (UE) extracted the following information from each eligible study: name of first author, study location, and number of participants, age of participants, number of each sex, 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. Another author (JSS) cross checked data extraction variables.

Risk of bias
Using the Newcastle Ottawa quality assessment scale,[21] two authors (UE, JT) independently assessed the studies and resolved disagreements by consensus. This semiquantitative scale uses a star system to assess the quality for eight items across three domains (selection, comparability, and exposure), with a maximum of one star for each item for high quality studies except for the comparability domain (two stars). Thus the total score ranges from 0 to 9. Supplementary table 2 provides further details of the quality rating.

Data synthesis and harmonisation of exposure variables
We contacted the corresponding author from each of the identified studies and asked whether he or she would be willing to contribute to a harmonised meta-analysis. To reduce heterogeneity in data cleaning and processing of accelerometer data among studies, authors of the studies reprocessed their individual participant data according to our standardised protocol. Data from the vertical acceleration axis in 60 second epochs were extracted, and we defined non-wear time as 90 consecutive minutes of 0 counts per minute (cpm), allowing up to a two minute interval of non-zero cpm if the interruption was accompanied by 30 consecutive minutes of 0 cpm either upstream or downstream.[22] We included all participants who recorded a wear time of 10 or more hours each day for four or more days.[23]

Each study computed several exposure variables from accelerometer measurements: total volume of physical activity (total counts/wear time in minutes, cpm); time (min/day) spent in six intensity specific variables (sedentary, ≤100 cpm,[24] light, 101-1951 cpm,[25] low light, 101-759 cpm,[13] high light, 760-1951 cpm,[13] moderate to vigorous, ≥1952 cpm,[25] vigorous, ≥5725cpm[25]; bouts of moderate-to-vigorous intensity physical activity, defined as 10 or more minutes of consecutive accelerometer readings ≥1952 cpm allowing for 1-2 minute drops below the threshold during each period of 10 or more minutes. For two studies[9 26] that assessed physical activity using the Actical accelerometer, the same wear time criteria as previously described were used and physical activity intensity thresholds computed according to previous validation studies[27 28]: sedentary, ≤100 cpm; light, 101-1534 cpm; low light, 101-599 cpm; high light, 600-1534 cpm; moderate to vigorous >1535 cpm; and vigorous ≥3960 cpm.

Analyses

Participating studies conducted several study specific analyses to examine the associations between exposure variables with all cause mortality using Cox proportional hazards regression analyses (hazard ratios and 95% confidence intervals) restricted to participants aged 40 or more years. Exposure data were categorised into quarters, with the first quarter (least active) as referent. Associations between physical activity variables with mortality were analysed with several levels of adjustment: model A (adjusting for wear time (except cpm, as wear time is included in this calculation), sex (if applicable), and age); model B (model A+adjustment for socioeconomic status and body mass index (BMI) and mutual adjustment of sedentary time and moderate-to-vigorous-intensity physical activity); and model C (model B+adjustment for covariates included in the study's final adjusted model, as listed in table 1). Mortality data from two studies[9 12] were updated from their publication follow-up before analyses. Owing to different data processing criteria the numbers of participants and deaths slightly differ from those previously published. Before the analyses, we accounted for the sample weights and complex survey design of the National Health and Nutrition Examination Survey (NHANES).[29]

Individual study summary data were meta-analysed with a random effects model yielding three pooled hazard ratios with 95% confidence intervals (first quarter as referent versus second to fourth quarters) in each model. We used model B as our primary model. For two variables, moderate-to-vigorous intensity physical activity in bouts and vigorous intensity physical activity, we included all participants who recorded zero minutes in the referent group, and we categorised the remaining participants into thirds.

Based on the individual studies log transformed hazard ratios for each of the quarters in model B, we described the underlying dose-response associations with sedentary time, total physical activity, and intensity specific activity using a restricted cubic spline model to allow for potential non-linearity.[30] We prespecified three knots at the 25th, 50th, and 75th centiles of the exposure variable distributions using the medians of the quarters to define the exposure levels (supplementary table 8, and see fig 2). We accounted for non-zero referent groups by centring the exposure levels.[31] Departure from linearity was assessed by a Wald test examining the null hypothesis that the coefficient of the second spline was equal to zero.[32] Model fit was examined visually using de-correlated residuals-versus-exposure plots and by the coefficient of determination.[33] Data from two studies that assessed physical activity by the Actical accelerometer[9 26] were only included for time spent in moderate-to-vigorous intensity physical activity for the dose-response analyses because of the noticeable difference in absolute output for the other exposure variables compared with the Actigraph accelerometer.[34]

In sensitivity analyses, we excluded deaths within the first two years of follow-up and reanalysed the data according to model B. We reanalysed data for total physical activity (cpm) excluding the two studies[9 26] in which physical activity was measured by a different type of accelerometer than used in the other studies. We also reanalysed the data excluding the two studies in which data on the association between physical activity and mortality had not been previously published.[26 35] We reanalysed our data and estimated summary hazard ratios across studies with fixed effects inverse variance method, and the main findings were unchanged (data not shown). We assessed heterogeneity by I[2] statistics. Finally, to assess possible publication bias we created funnel plots for the individual study hazard ratios, comparing extreme exposure quarters and calculated the Egger's test for funnel plot symmetry. Meta-analyses were performed using Matlab (R2014a, Mathworks, Natick, MA).

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. The results from the present study will be disseminated through the institutional websites and press releases.

Results

Overall, 39 of 518 identified articles were retrieved for full text review. Ten were eligible for inclusion, three were excluded owing to harmonisation challenges (ie. monitor placements), and one study did not participate, leaving six for inclusion (fig 1).[9 10 12 13 36 37] Data were publicly available from one of the identified studies[13] and data were obtained from a further two studies with pertinent data available.[26 35]

Thus individual level data from eight studies, of which three were from nationally representative

Table 1 | Characteristics of studies included in the meta-analysis

Publication	Study; location; No of participants; No of cases	Year of baseline assessment; mean follow-up	Case ascertainment	Accelerometer type (location)	Covariates	Quality assessment*
Bakrania et al[36]	Walking Away from Type 2 Diabetes (WAT2D), England; n=654 (411 men, 243 women); 26 cases	2010-11; 5.7 years	Office for National Statistics	Actigraph GT3X+ (right hip)	Age, sex, BMI, socioeconomic status	8
Diaz et al[9]	Reasons for Geographic and Racial Differences in Stroke (REGARDS); US; n=7862 (3580 men; 4282 women); 590 cases	2003-07; 5.3 years	Review of death certificates, medical records, and administrative databases	Actical (right hip)	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	9
Dohrn et al[10]	Sweden Attitude Behaviour and Change study (ABC), Sweden; n=834 (371 men, 463 women); 79 cases	2001-02; 14.5 years	National death register	Actigraph 7164 (lower back)	Age, sex, education, BMI, smoking, history of hypertension, heart disease, cancer, and diabetes	9
Jefferis et al[37]	British Regional Heart Study (BRHS), UK; n=1412 men; 250 cases	2010-12; 6.0 years	National Health Service central registers	Actigraph GT3X+ (right hip)	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	9
Lee et al[12]	Women's Health Study (WHS), US; n=16738, women; n=504	2011-17; 4.3 years	Medical records, death certificates, or National Death Index	Actigraph GT3X+ (right hip)	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	9
Unpublished data (Murabito et al[26])	Framingham Heart Study (FHS), US; n=2621 (1225 men, 1396 women); 77 cases	2008-11; 4.0 years	Medical records, death certificates	Actical (right hip)	Age, sex, education, BMI, ethnicity, smoking, self reported health	9
NHANES[13] (data downloaded from wwwn.cdc.gov/nchs/nhanes/Default.aspx and Public-use Linked Mortality data†	National Health and Nutrition Examination Survey (NHANES), US;(n=3978 (1977 men, 2001 women); 492 cases	2003-06; 6.5 years	National Death Index, National Center for Health Statistics	Actigraph 7164 (right hip)	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)	9
Unpublished data (Hansen et al[35])	Norwegian National Physical Activity Survey 1 (NNPAS), Norway; n=2284; 131 cases	2008-09; 8.9 years	Death certificates, Norwegian death register	Actigraph GT1M (right hip)	Age, sex, education, BMI, wear time, smoking, alcohol, number of medical conditions	9

BMI=body mass index.

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

†National Center for Health Statistics. Office of Analysis and Epidemiology, Public-use Linked Mortality File, 2015. Hyattsville, MD, USA (www.cdc.gov/nchs/data_access/data_linkage/mortality.htm).

surveillance systems[10][13][35] including 36 383 participants (mean age 62.6 years; 72.8% women) with a median follow-up time of 5.8 years (mean 6.7 years, range 3.0-14.5 years, 243 766 person years) were included in the meta-analyses. During follow-up, 2149 (5.9%) participants died. Table 1 summarises the characteristics of studies (participant characteristics by study are presented in supplementary table 1). The quality scores were high, at 8 or 9 (table 1 and supplementary table 2).

Compared with the referent, any level of physical activity regardless of intensity was associated with a substantially lower risk of mortality (table 2, supplementary figs 1a-f). The magnitude of lowered risk was most pronounced for total physical activity; hazard ratios (95% confidence intervals) for increasing

quarter were: 1.00 (referent, least active), 0.48 (0.43 to 0.54), 0.34 (0.26 to 0.45), and 0.27 (0.23 to 0.32) (table 2, model B, supplementary fig 1a). Higher levels of light intensity physical activity, as well as low and high light intensity physical activity were also associated with substantially reduced risks of death during follow-up. The risk reductions were most pronounced when the second quarter was compared against the referent for all levels of adjustment (table 2, fig 2). For example, the risk was reduced to 0.55 (0.49 to 0.63) in the second quarter for high light intensity physical activity and additionally reduced in the third (0.38, 0.30 to 0.48) and fourth (0.37, 0.32 to 0.46) quarters compared with the referent (table 2, model B). Higher levels of moderate-to-vigorous intensity physical activity were also associated with a reduced risk of death even after
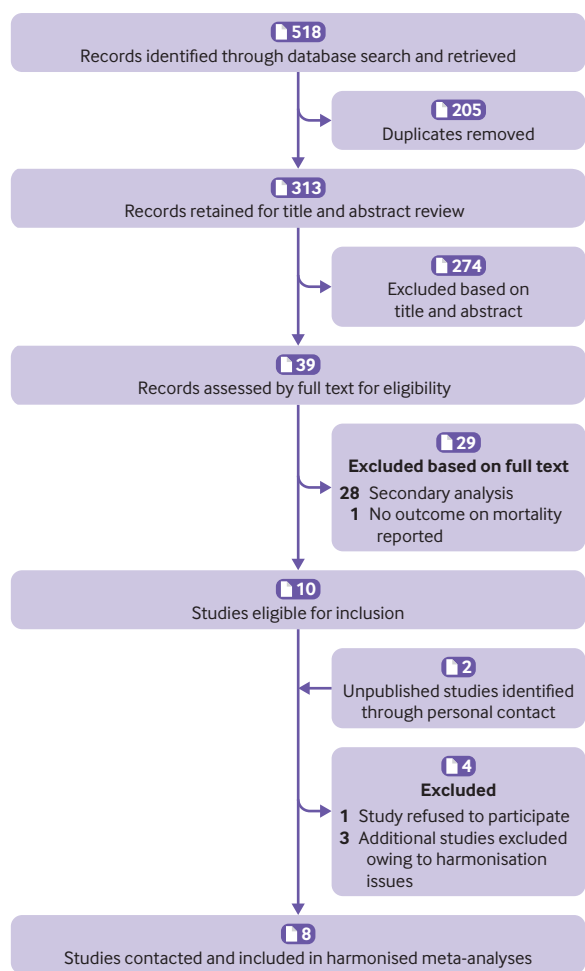
Fig 1 | Study selection

adjustment for sedentary time (table 2, models B and C; fig 2). The risk of death increased with increasing time spent sedentary; hazard ratios for increasing quarters were: 1.00 (referent), 1.28 (1.09 to 1.51), 1.71 (1.36 to 2.15), and 2.63 (1.94 to 3.56) after adjustment for age, sex, BMI, socioeconomic status, wear time, and time spent in moderate-to-vigorous intensity physical activity (table 2, models B and C; fig 2).

The differences in physical activity and sedentary time (min/day) between the referent and the second quarter were broadly equal to 60 min/day of light intensity physical activity, 35 min/day of low light intensity physical activity, 25 min/day of high light intensity physical activity, 5 min/day of moderate-to-vigorous intensity physical activity, and 70 min/day of sedentary time (supplementary table 3).

Higher levels of bouts of moderate-to-vigorous intensity physical activity and any vigorous intensity physical activity were also associated with reduced risk of mortality (supplementary table 4). However, low numbers of participants undertook physical activity in bouts of moderate-to-vigorous physical activity or in any vigorous physical activity (supplementary table 4), potentially making these estimates less reliable.

We observed non-linear, dose-response associations (P values from the second spline <0.02 for each exposure variable) for the associations between all exposure variables and mortality (fig 2, supplementary table 5). The maximal risk reduction for total physical activity (hazard ratio 0.34, 95% confidence interval 0.27 to 0.43) was observed at about 300 cpm. Maximal risk reductions for light intensity physical activity (0.48, 0.38 to 0.63), low light intensity physical activity (0.45, 0.34 to 0.60), high light intensity physical activity (0.40, 0.31 to 0.52), and moderate-to-vigorous intensity physical activity (0.39, 0.26 to 0.59) were observed at about 375 min/day, 325 min/day, 80 min/day, and 24 min/day, respectively. No further risk reductions occurred with higher levels of activity except for low light intensity physical activity where the risk appeared to decrease further (supplementary table 5).

The dose-response relations between sedentary time and mortality increased gradually from about 7.5 to 9 hours and were more pronounced at greater than 9.5 hours (fig 2, supplementary table 5). Ten and 12 hours each day spent sedentary were associated with 1.48 (1.22 to 1.79) and 2.92 (2.24 to 3.83) higher risk of death, respectively.

The results did not appreciably change when excluding deaths within the first two years of follow-up, except for a small attenuation for the association between sedentary time and mortality (supplementary table 6). Similarly, sensitivity analyses excluding the two studies in which physical activity was assessed by a different monitor did not change the results (supplementary table 7). There was no evidence of publication bias; however, the plots should be interpreted cautiously owing to the small number of studies (supplementary figs 2 and 3).

Discussion

Higher levels of total physical activity at any intensity and less time spent sedentary are associated with a substantially reduced risk for premature mortality, with evidence of a non-linear dose-response pattern in middle aged and older adults. Our observations on the associations between accelerometry measured physical activity or sedentary time and all cause mortality provide important data for informing public health recommendations. Firstly, they reinforce the non-linear, dose-response relation but with considerably larger effect sizes than in studies using self reports. Secondly, the total volume of physical activity, irrespective of intensity, is associated with a substantially reduced risk of death during follow-up. Thirdly, the greatest risk reduction for mortality was observed when the second quarter was compared with the referent, for all activity intensities. Fourthly, maximal risk reductions were seen at about 375 min/day of light intensity physical activity or 24 min/day of moderate-to-vigorous intensity physical activity. Fifthly, a statistically significantly higher risk of death was observed from 9.5 or more hours per day for time spent sedentary.

Strengths and limitations of this study

Our meta-analysis has several strengths. Physical activity and sedentary time were measured using accelerometry, and all individual participant data were reanalysed in a harmonised manner. Device based measures of sedentary time and physical activity are less prone to biases usually associated with self report. However, interpreting associations with physical activity assessed by devices across studies is challenging because of variations in processing data collected from devices. Our harmonised approach substantially reduced heterogeneity among studies by applying a common and standardised definition of wear time, inclusion criteria, and definitions of thresholds for physical activity intensity and sedentary time. Furthermore, the large sample size allowed meta-analyses of the dose-response relations between various intensities of physical activity, including low and high light, and all cause mortality, as well as providing more precise results with narrower confidence intervals than in previous studies. Finally, we defined the absolute amount of time associated with maximal risk reduction for all cause mortality for different levels of physical activity intensity and identified a threshold for sedentary time where the risk of death increased more rapidly, based on the shape of the curve for the dose-response association.

This study also has some limitations. All studies were conducted in the US and western Europe limiting generalisability beyond these populations.

All study data were analysed with men and women combined and after adjustment for sex. Thus we cannot exclude different associations between sexes; however, the results from the two studies of men and women separately[12 37] are in agreement, suggesting the observed associations are similar. Residual confounding might exist, although the studies adjusted their analyses for several covariates (often including pre-existing illness, mobility limitations; all studies adjusted for smoking) in the final model and results were similar to those from the primary model, including sex, age, BMI, socioeconomic status, and wear time. We attempted to minimise bias from reverse causation by excluding all deaths within the first two years in sensitivity analyses. The hazard ratios were materially unchanged for the associations of total physical activity and light intensity or moderate-to-vigorous intensity physical activity with mortality, and slightly attenuated for sedentary time. However, bias from reverse causation might persist.[38] All studies in our analysis included middle aged and older adults who were at least 40 years old; it is unclear whether the estimates of the absolute physical activity levels associated with maximal risk reduction apply to younger people. For the purposes of harmonisation, only data recorded from a single (vertical) axis were analysed; this tends to detect less time in light and moderate intensity activity and more time being sedentary compared with data recorded from three axes of newer generation devices.[39]

Table 2 | Meta-analysis for associations between total physical activity, intensities of physical activity or sedentary time by quarters and all cause mortality

Variables	Hazard ratios (95% CI) for all cause mortality*; No of participants; No of deaths			
	First quarter (least active)	Second quarter	Third quarter	Fourth quarter (most active)
Model A				
Total physical activity (cpm)	1 (ref) (n=9189; 1301)	0.47 (0.42 to 0.53) (n=9225; 506)	0.35 (0.26 to 0.47) (n=9207; 277)	0.28 (0.22 to 0.34) (n=9231; 220)
Physical activity intensity:				
Light (min/d)	1 (ref) (n=9191; 1188)	0.58 (0.52 to 0.64) (n=9214; 547)	0.42 (0.36 to 0.43) (n=9212; 332)	0.36 (0.28 to 0.46) (n=9235; 237)
Low light (min/d)	1 (ref) (n=9182; 1100)	0.64 (0.57 to 0.72) (n=9224; 552)	0.46 (0.38 to 0.56) (n=9229; 376)	0.41 (0.35 to 0.50) (n=9217; 276)
High light (min/d)	1 (ref) (n=9166; 1261)	0.53 (0.47 to 0.60) (n=9241; 517)	0.36 (0.31 to 0.42) (n=9207; 290)	0.36 (0.25 to 0.51) (n=9227; 236)
Moderate to vigorous (min/d)	1 (ref) (n=9095; 1221)	0.54 (0.48 to 0.60) (n=9296; 525)	0.40 (0.29 to 0.56) (n=9235; 311)	0.35 (0.28 to 0.44) (n=9226; 247)
Sedentary (min/d)	1 (ref) (n=9219; 339)	1.32 (1.14 to 1.54) (n=9223; 432)	1.97 (1.69 to 2.30) (n=9201; 598)	3.22 (2.49 to 4.15) (n=9190; 935)
Model B†				
Total physical activity (cpm)	1 (ref) (n=9096; 1187)	0.48 (0.43 to 0.54) (n=9105; 483)	0.34 (0.26 to 0.45) (n=9096; 265)	0.27 (0.23 to 0.32) (n=9086, 214)
Physical activity intensity:				
Light (min/d)	1 (ref) (n=9073; 1089)	0.60 (0.54 to 0.68) (n=9101; 511)	0.44 (0.38 to 0.51) (n=9090; 320)	0.38 (0.28 to 0.51) (n=9119; 229)
Low light (min/d)	1 (ref) (n=9066; 1010)	0.66 (0.56 to 0.77) (n=9106; 518)	0.47 (0.38 to 0.58) (n=9112; 353)	0.42 (0.34 to 0.52) (n=9099; 268)
High light (min/d)	1 (ref) (n=9054; 1159)	0.55 (0.49 to 0.63) (n=9120; 483)	0.38 (0.30 to 0.48) (n=9088; 278)	0.37 (0.32 to 0.46) (n=9113; 229)
Moderate to vigorous (min/d)	1 (ref) (n=9002; 1139)	0.64 (0.55 to 0.74) (n=9153; 468)	0.55 (0.40 to 0.74) (n=9123; 305)	0.52 (0.43 to 0.61) (n=9105; 237)
Sedentary (min/d)	1 (ref) (n=9102; 327)	1.28 (1.09 to 1.51) (n=9105; 417)	1.71 (1.36 to 2.15) (n=9096; 562)	2.63 (1.94 to 3.56) (n=9080; 843)
Model C†				
Total physical activity (cpm)	1 (ref) (n=8971; 1122)	0.54 (0.48 to 0.61) (n=9004; 458)	0.41 (0.32 to 0.51) (n=8972; 259)	0.34 (0.29 to 0.41) (n=8985; 208)
Physical activity intensity:				
Light (min/d)	1 (ref) (n=8944; 1030)	0.66 (0.58 to 0.74) (n=8979; 485)	0.51 (0.44 to 0.57) (n=8992; 308)	0.44 (0.34 to 0.59) (n=9017; 224)
Low light (min/d)	1 (ref) (n=8939; 959)	0.70 (0.62 to 0.79) (n=8997; 490)	0.54 (0.48 to 0.63) (n=8999; 338)	0.48 (0.40 to 0.57) (n=8997; 260)
High light (min/d)	1 (ref) (n=8919; 1086)	0.63 (0.56 to 0.71) (n=8990; 467)	0.46 (0.39 to 0.54) (n=8985; 269)	0.45 (0.31 to 0.65) (n=9028; 225)
Moderate to vigorous (min/d)	1 (ref) (n=8875; 1077)	0.69 (0.58 to 0.81) (n=9041; 441)	0.62 (0.48 to 0.80) (n=9009; 297)	0.61 (0.50 to 0.75) (n=9007; 232)
Sedentary (min/d)	1 (ref) (n=9001; 317)	1.21 (1.02 to 1.42) (n=9006; 403)	1.56 (1.24 to 1.98) (n=8969; 536)	2.18 (1.61 to 2.95) (n=8956; 791)

cpm=counts per minute.
Model A adjusted for sex (when applicable), age, and wear time (n=36852, 2304 deaths). Model B adjusted for sex (when applicable), age, body mass index, socioeconomic position, and wear time (n=36383, 2149 deaths). Model C additionally adjusted for covariates listed in table 1 (n=35 932, 2047 deaths).
*By Cox regression.
†Moderate-to-vigorous physical activity and sedentary time are mutually adjusted.
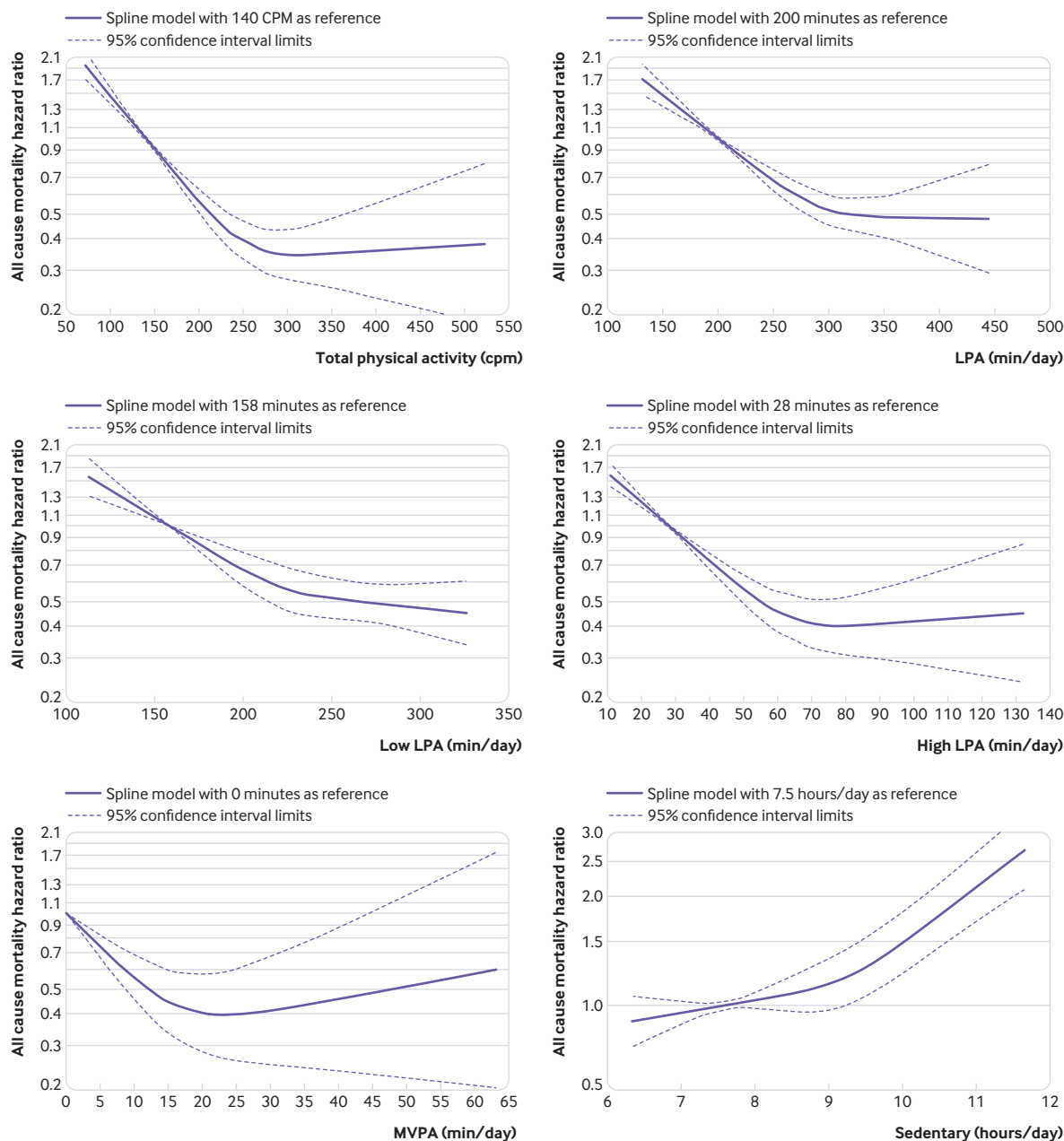
Fig 2 | Dose-response associations between total physical activity (top left), light intensity physical activity (LPA) (top right), low LPA (middle left), high LPA (middle right), moderate-to-vigorous intensity physical activity (MVPA) (bottom left), and sedentary time (bottom right, data from REGARDS (Reasons for Geographic and Racial Differences in Stroke)[9] and FHS (Women's Health Study)[12] are only included for MVPA) and all cause mortality. Modelling performed using restricted cubic splines with knots at 25th, 50th, and 75th centiles of exposure specific distribution from medians of quarters (least to most active). The exposure reference is set as the median of the medians in the reference group (least active) (see supplementary table 3). Knot locations are available in supplementary table 8. cpm=counts per minute

Intensity thresholds are influenced by participant age and activities included in any calibration study and there is currently no consensus about standard intensity thresholds. We used thresholds derived during locomotor activities (ie, walking and jogging) in young adults when defining time spent in light, moderate, and vigorous physical activity,[25] that are higher than those derived in older women in a range of activities, including sitting and standing.[40] This could affect the absolute time spent in vigorous physical activity and in prolonged bouts of moderate-

to-vigorous physical activity. Furthermore, results were combined from studies using two different brands of accelerometers; however, when we restricted analyses to the six studies using the same accelerometer brand, similar findings were observed. Risk of bias was assessed using the Newcastle-Ottawa scale suggested as an alternative to the Risk of Bias in Non-randomised Studies of Interventions.[41] Finally, physical activity and sedentary time were only measured once, therefore changes in these behaviours might affect the observed associations.

Comparison with other studies

Higher levels of total physical activity, which combine the frequency, duration, and intensity of activity, were associated with a substantially reduced risk of death in a dose-response fashion. In spline analyses, the maximal risk reduction was observed at about 300 counts per minutes (cpm, fig 2, supplementary table 5). This value mirrors the median total physical activity for the third quarter across studies (supplementary table 3). It is also similar to the mean value observed in US men, between 10-15% higher than in US women and about 10-15% lower than in the population based samples from Norway and Sweden (supplementary table 1). The amount of total physical activity required for maximal risk reduction thus seems achievable for large segments of the population. For those unable to accumulate this amount, it is encouraging to note that the largest risk reduction was observed between the second quarter and the referent (least active). The observed magnitude of risk reduction (about 60-70%) is more than twice as large as previously reported from studies assessing total physical activity by self report.[42] Our findings extend previous observations from individual studies on device assessed total physical activity[10 12] and those reported for total physical activity in community dwelling elderly people,[43 44] by reducing the uncertainty in the effect estimates in a much larger and more heterogeneous sample.

Our results also suggest substantial risk reductions from light intensity physical activity, in a dose-response fashion. A recent meta-analysis[45] that combined self reported and device based measures of light intensity physical activity observed a pooled risk reduction of 29% when extreme groups were compared, smaller in magnitude than the estimate reported here (about 60% when the fourth quarter was compared with the referent). Time accumulated in moderate-to-vigorous intensity physical activity was also associated with reduced mortality risk in a dose-response manner. It should be noted, however, that the definition of intensity[1 46] is based on absolute intensity (ie, as customary, light intensity=1.5-2.9 metabolic equivalents of task (METs); moderate-to-vigorous intensity ≥3 METs). In older people, who constitute most of the participants in our meta-analysis, maximal cardiorespiratory fitness may not exceed 6 or 7 METs.[47] Thus high light intensity physical activity as defined in the present analyses might actually represent moderate-to-vigorous intensity physical activity, relative to the fitness level of these older adults. Future calibration studies aimed at identifying intensity thresholds for light and moderate intensity physical activity from tri-axial accelerometry based on relative intensity (ie, % maximal cardiorespiratory fitness) are needed, especially for use in older populations. Owing to the low numbers of people with high levels of time spent in moderate-to-vigorous intensity physical activity, wide confidence intervals were observed at this part of the dose-response curve warranting cautious interpretation. The maximal risk reduction was seen at about 24 min/day, congruent with the minimum recommended level of physical activity for Americans[46] and the proposed draft of the new UK physical activity guidelines[48] of at least 150 minutes of moderate intensity physical activity each week. Similar to total physical activity and light intensity physical activity, the maximal risk reduction observed for moderate-to-vigorous physical activity (about 60%), is about twice the magnitude as previously reported in a meta-analysis, where physical activity was assessed by self report.[49] We observed smaller magnitudes of risk reduction for bouts of moderate-to-vigorous intensity physical activity and vigorous intensity physical activity compared with the other physical activity exposure variables. Most participants, however, did not record any minutes at these intensity levels, limiting the interpretation of these observations.

Higher sedentary time was positively associated with higher risk of death, and the risk increased at levels greater than 9.5 hours each day. This estimate is higher than a proposed threshold of 6 to 8 hours each day identified in a recent meta-analysis examining the association between primarily self reported sitting time and mortality.[5] Given the strong association between total physical activity and mortality, it is plausible that findings for sedentary time reflect the "flip side" of a coin.[50]

Implications and future research

Recent national[51] and international[52] strategies to improve public health through physical activity in populations are supported by our results. Additionally, these results reinforce the new physical activity recommendations for Americans to limit sedentary time and that moderate-to-vigorous intensity physical activity need not occur in 10 minute bouts.[46] Furthermore, the findings are important for policymakers and can inform future guideline development by also recognising the role of light intensity physical activity and hence total physical activity for reducing the risk of premature death. Thus, the public health message might simply be "sit less and move more and more often."

We only investigated associations with all cause mortality. Thus more work is needed to determine the associations between physical activity and sedentary time with cause specific mortality and for other chronic morbidities such as type 2 diabetes, which may manifest at a younger age than the age of our cohorts. Future studies using repeated measures of physical activity with device based methods such as acclerometry are also needed to examining the associations between changes in physical activity and sedentary time with clinical health outcomes. Finally, data on the association between device based assessment of physical activity and mortality from low and middle income countries are currently unavailable.

Conclusion

Our findings provide clear scientific evidence that higher levels of total physical activity—regardless of intensity level—and lesser amounts of sedentary time are associated with lower risk for premature mortality,

with evidence of non-linear, dose-response patterns in middle aged and older people.

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Supplementary information: additional tables and figures