Device-measured physical activity, sedentary time, and risk of all-cause mortality: an individual participant data analysis of four prospective cohort studies

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ABSTRACT

Objectives To examine whether moderate-to-vigorous physical activity (MVPA) modifies the association between sedentary time and mortality and vice versa, and estimate the joint associations of MVPA and sedentary time on mortality risk.

Methods This study involved individual participant data analysis of four prospective cohort studies (Norway, Sweden, USA, baseline: 2003-2016, 11989 participants ≥50 years, 50.5% women) with hipaccelerometry-measured physical activity and sedentary time. Associations were examined using restricted cubic splines and fractional polynomials in Cox regressions adjusted for sex, education, body mass index, smoking, alcohol, study cohort, cardiovascular disease, cancer, and/ or diabetes, accelerometry wear time and age.

Results 6.7% (n=805) died during follow-up (median 5.2 years, IOR 4.2 years). More than 12 daily sedentary hours (reference 8 hours) was associated with mortality risk only among those accumulating <22 min of MVPA per day (HR 1.38, 95% CI 1.10 to 1.74). Higher MVPA levels were associated with lower mortality risk irrespective of sedentary time, for example, HR for 10 versus 0 daily min of MVPA was 0.85 (95% CI 0.74 to 0.96) in those accumulating <10.5 daily sedentary hours and 0.65 (95% CI 0.53 to 0.79) in those accumulating ≥10.5 daily sedentary hours. Joint association analyses confirmed that higher MVPA was superior to lower sedentary time in lowering mortality risk, for example, 10 versus 0 daily min of MVPA was associated with 28-55% lower mortality risk across the sedentary time spectrum (lowest risk, 10 daily sedentary hours: HR 0.45, 95% CI 0.31 to 0.65).

Conclusions Sedentary time was associated with higher mortality risk but only in individuals accumulating less than 22 min of MVPA per day. Higher MVPA levels were associated with lower mortality risk irrespective of the amount of sedentary time.

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INTRODUCTION

In western countries, adults spend an average of ~9 to 10 hours per day being sedentary, 1-3 mostly during working hours. 4-7 As higher sedentary time is associated with higher risk of non-communicable diseases and mortality, 8-11 preventive measures are important.

WHAT ARE THE FINDINGS

- ⇒ In this individual participant data analysis of four prospective cohort studies of adults aged 50 years and older with use of continuous data on physical activity, being sedentary more than 12 hours per day was associated with 38% higher mortality risk, but only among individuals accumulating less than 22 min per day of MVPA.
- ⇒ Higher levels of MVPA were associated with lower mortality risk irrespective of sedentary time, for example, 10 min higher MVPA per day were associated with 15% and 35% lower mortality risk in those being less and highly sedentary, respectively.

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FUTURE

⇒ Small amounts of MVPA may be an effective strategy to ameliorate the mortality risk from high sedentary time, where accumulating more than 22 min of MVPA eliminates the risk of high sedentary time.

Previous studies have shown that moderate-tovigorous physical activity (MVPA) and sedentary time can be combined differently to lower mortality risks. 12-16 Accumulating small amounts of MVPA may attenuate risks associated with high sedentary time, while higher amounts of MVPA (40-60 min per day) appear to eliminate risks from sedentary time. 12-16 Consequently, the recently updated World Health Organization (WHO) physical activity guidelines recommend individuals who are highly sedentary to engage in more than 300 min of MVPA per week. 17 Moreover, light physical activity and total volume of physical activity are also associated with lower mortality risk. 11 18

Previous meta-analyses examining associations between physical activity, sedentary time, and mortality are based on harmonised approaches, where individual data are harmonised at study level and aggregated data are thereafter metaanalysed. 12-15 In contrast, individual participant data analyses involve re-analysis of original data as one single study, ¹⁹ which offers high flexibility to detect





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exposure-outcome associations and their interactions. ¹⁹ ²⁰ This may also overcome limitations of arbitrary categorisations from aggregated summary data. ²¹ For example, in a recent harmonised meta-analysis, median MVPA ranged from 23 to 63 min per day in the most active category of the included cohorts. ¹¹ Such large variations between categories may lead to loss of information ²¹ and challenge translation to absolute physical activity targets for public health and clinical decision-making.

We pooled individual participant data from four prospective cohorts with device-measured physical activity in a one-step individual participant data analysis to allow the use of a continuous data form, and aimed to examine (1) whether the association between sedentary time and mortality is modified by physical activity and vice versa (whether the association between physical activity and mortality is modified by sedentary time), and (2) joint associations of MVPA and sedentary time on mortality risk.

METHODS

Individual participant data from four prospective cohorts from Norway, Sweden, and the USA were pooled. Baseline data were collected between 2003 and 2019: Tromsø Study 2015–2016²² 23; Healthy Ageing Initiative (HAI) 2012–2019²⁴; Norwegian National Physical Activity Survey (NNPAS) 2008-2009²⁵; and National Health and Nutrition Examination Survey (NHANES) 2003-2006.²⁶ These cohorts were included due to availability of individual participant data (NHANES data are freely available online), and hip-worn accelerometry, which enables harmonisation of data. Cohort descriptions are summarised in online supplemental file 1. We included individuals aged ≥ 50 years, with ≥ 4 days of 10 hours with valid accelerometry data, $^{28} \ge 2$ years follow-up time, and information on sex, educational level, weight, height, smoking, alcohol intake, and prevalent and/or previous cardiovascular disease (CVD), cancer and/or diabetes.

Mortality

Data on mortality was linked with the Norwegian and Swedish cause of death registries, and the United States National Death Index, through 31 December 2020 (Tromsø Study), 31 December 2017 (NNPAS), 31 December 2019 (HAI), and 31 December 2015 (NHANES), respectively.

Device-measured physical activity

All cohorts used ActiGraph accelerometers (ActiGraph, Pensacola, Florida, USA) placed at the hip (NHANES: AM-7164; NNPAS: GT1M; HAI: GT3X+; Tromsø Study: wGT3X-BT) (online supplemental file S2). We analysed accelerometry data using KineSoft version 3.3.80 (Kinesoft, Loughborough, UK). We removed data between 00:00 and 06:00 and, for harmonisation purposes, only considered data from the vertical axis. Nonwear time was defined as 60 consecutive min of zero counts with allowance for up to 2 min of non-zero counts over 100 counts per min.²⁹

Total physical activity was defined as counts per min divided by wear time, 30 and volume of intensity-specific physical activity as follows: sedentary <100 counts per min, 31 light physical activity 100–2019 counts per min, 25 and MVPA \geq 2020 counts per min. 29 The MVPA threshold was calibrated as an average from four validity protocols against indirect calorimetry during walking and running, $^{32-35}$ and the estimates of total physical activity and MVPA are reasonably well correlated with physical activity energy expenditure estimated using doubly labelled water during free-living conditions (ρ =0.37–0.51). 30 As wear

time differed across cohorts, we standardised all exposure variables to 16 hours wear time per day, for example (MVPA per day/wear time per day)×16.

Covariates

Covariates (sex, age, education (primary, high school, lower university, higher university), body mass index (BMI, <25, 25–29, ≥30 kg/m²), smoking (current, previous, never), alcohol intake (units per week), history of CVD, cancer and diabetes) were chosen a priori according to previous literature, ^{11 24 26 36–39} illustrated in a directed acyclic graph (online supplemental figure S1). History of CVD, cancer and diabetes were self-reported or obtained from national registries (HAI). Measurements and harmonisation of covariates are described in online supplemental file S3–S4 and table S1.

Statistical analyses

First, we performed Cox regressions to examine the association between physical activity and sedentary time with mortality using restricted cubic splines, adjusted for sex, education, BMI, smoking, alcohol intake, study cohort, CVD/cancer/diabetes, age (in years) as timescale, 40 and additional mutual adjustment of physical activity and sedentary time. 11 To avoid influence of extreme values, data outside the 1st and 99th percentile of exposure distributions were replaced with their respective 1st and 99th percentile values. The NHANES does not provide information on attendance or death date (only follow-up time to censoring, death or study end); therefore, we set the attendance date to 1 January 2004 (wave 2003-2004) and 1 January 2006 (wave 2005-2006), and calculated the death date, censoring (emigration) by addition of follow-up time. Participants' study entry was set 2 years after attendance (left-truncation) and followed to death, censoring (lost-to-follow-up) or study end.

We thereafter stratified analyses to examine dose-response associations between physical activity and mortality within strata of sedentary time, based on restricted cubic splines, and with sedentary time and mortality within strata of MVPA. We split sedentary time by full-sample median as 'low' $(<10.5 \text{ hours} \cdot \text{day}^{-1})$ and 'high' $(\ge 10.5 \text{ hours} \cdot \text{day}^{-1})$. Similarly, MVPA was split at median 22 min of MVPA per day. Knots in cubic splines were placed at the 10th, 50th and 90th percentiles of the analysis-specific distributions (eg, dose-response association for MVPA and knot placements estimated separately within low and high sedentary time). Changing knot locations or increasing knot numbers did not change the results. The reference of the spline was 0 min per day for MVPA¹¹ and 8 hours per day for sedentary time. 41 For light and total physical activity, we used the 10th percentile of the split sample-specific distribution because no quantitative thresholds are established for these variables.

To keep the continuous data form and to handle the non-linear associations observed in spline models in the joint analyses of MVPA and sedentary time with mortality, we used fractional polynomials to identify the best fit Cox regression model. As light physical activity and sedentary time were highly correlated (r=-0.96) and total physical activity includes sedentary time (<100 counts per min), we did not examine the joint associations of light or total physical activity with sedentary time.

We applied the following sensitivity analyses: (1) excluding the first 5 years of follow-up after study attendance to limit reverse causation bias; (2) median split sedentary time separately by the Norwegian and Swedish (Tromsø, HAI and NNPAS) and US (NHANES) cohorts to evaluate demographic region differences;

(3) accounting for non-identical output between AM-7164 and GT3X accelerometers by calibrating individual-level summary data in the NHANES⁴² (as described in online supplemental table S8).

Schoenfeld's residuals tests confirmed no violated proportional hazards for all covariates (all p≥0.08), except possibly education in low sedentary participants (p=0.02). However, loglog survival plots of education displayed reasonable parallel lines indicating no violated proportional hazards. Statistical analyses were performed using Stata version 17.0 (StataCorp LLC, TX, USA) with α set to 0.05.

Equity, diversity, and inclusion statement

Our study included cohort studies of high participation rates (Tromsø: 65% of all over 40 years in Tromsø municipality, Norway: HAI: 70% of all over 70 years in Västerbotten, Sweden) or national representative cohorts (NNPAS: randomly drawn by Statistics Norway, 36% participation; NHANES: oversampling of African American, Hispanics and those over 60 years), and sample-weights to yield national representative estimates (only used in the NHANES analysis due to the individual participant data approach). The Tromsø Study is situated above the Arctic Circle (ie, the Far North) and constitutes 40% of the total sample size (online supplemental file 1, table S2). The cohort studies recruited participants from all socioeconomic levels (online supplemental table S2, table 1). The author team includes both women and men, from multiple countries in Europe, and junior and senior researchers within physical activity, epidemiology, statistics, and medicine. Some of the authors have indigenous backgrounds, and many authors are affiliated with the northernmost university in the world (UiT The Arctic University of Norway). We did not consider equity, socioeconomic disadvantage, or inequities in marginalised communities in the analysis or interpretation of results as we considered this outside the scope of this study's aims. We examined geographical differences by performing separate analyses by the Norwegian and Swedish cohorts and the NHANES.

RESULTS

In total, 805 (6.7%) of the 11 989 participants died during follow-up (median 5.2 years, IQR 4.2 years) (table 1). The NHANES cohort had the longest follow-up time and contributed with 65% of total deaths (online supplemental table S2). The ranges of physical activity and sedentary time were similar among cohorts (online supplemental figures S2-5). A flow chart of participant inclusion is found in online supplemental figure S6.

Wald tests confirmed departure from linearity in all models (all p<0.001). We observed two-way interactions between all physical activity estimates and sedentary time (p<0.001), but no interactions between physical activity or sedentary time and any covariates (all p>0.07). In analyses stratified by <10.5 (low) and ≥10.5 (high) sedentary hours per day, MVPA was curvilinearly associated with mortality risk with a steeper dose-response curve among participants with high compared with low sedentary time (figure 1A). For example, compared with 0 min per day, 10 min of MVPA were associated with 15% (HR 0.85, 95% CI 0.74 to 0.96) and 35% (HR 0.65, 95% CI 0.53 to 0.79) lower mortality risk among those with <10.5 and ≥ 10.5 sedentary hours per day, respectively.

Among participants accumulating ≥22 min of MVPA per day, sedentary time was not associated with mortality (12 hours·day⁻¹: HR 1.08, 95% CI 0.66 to 1.77) compared with

Table 1 Descriptive characteristics of the participants					
		Sedentary time			
	All	<10.5 hours·day ⁻¹	≥10.5 hours·day ⁻¹		
Total (N)	11 989	5943	6042		
Dead, n (%)	805 (6.7)	357 (6.0)	448 (7.4)		
Follow-up time (years)					
Median (25-75th percentile)	5.24 (4.66–8.85)	5.53 (4.70–9.25)	5.10 (4.64–5.94)		
Min-max	2.02-13.08	2.02-13.08	2.03-13.08		
Sex					
Women, n (%)	6057 (50.5)	3187 (53.6)	2870 (47.5)		
Men, n (%)	5932 (49.5)	2756 (46.4)	3176 (52.5)		
Age (mean±SD)	66.7±7.6	65.5±7.6	67.9±7.4		
50-59 years, n (%)	2595 (21.6)	1571 (26.4)	1024 (16.9)		
60-69 years, n (%)	3363 (28.1)	1691 (28.5)	1672 (27.7)		
70–79 years, n (%)	5607 (46.8)	2551 (42.9)	3056 (50.6)		
≥80 years, n (%)	424 (3.5)	130 (2.2)	294 (4.9)		
Birth year					
<1940, n (%)	1925 (16.1)	881 (14.8)	1044 (17.3)		
1940–49, n (%)	6591 (55.0)	3232 (54.4)	3359 (55.6)		
≥1950, n (%)	3473 (28.9)	1830 (30.8)	1643 (27.2)		
BMI (mean±SD)	27.0±4.5	26.6±4.4	27.4±4.7		
<25 kg/m², n (%)	4203 (35.1)	2254 (37.9)	1949 (32.2)		
25–29 kg/m², n (%)	5218 (43.5)	2600 (43.8)	2618 (43.3)		
≥30 kg/m², n (%)	2568 (21.4)	1089 (18.3)	1479 (24.5)		
Smoking					
Current smoker, n (%)	1434 (11.9)	696 (11.7)	738 (12.2)		
Previous smoker, n (%)	5584 (46.6)	2646 (44.5)	2938 (48.6)		
Never smoker, n (%)	4971 (41.5)	2601 (43.8)	2370 (39.2)		
Education					
Primary school, n (%)	3035 (25.3)	1506 (25.3)	1529 (25.3)		
High school, n (%)	3883 (32.4)	1941 (32.7)	1942 (32.1)		
University some, n (%)	2722 (22.7)	1443 (24.3)	1279 (21.2)		
University long, n (%)	2349 (19.6)	1053 (17.7)	1296 (21.4)		
Alcohol intake (mean±SD)	2.3±3.2	2.1±3.0	2.6±3.4		
Never, n (%)	1720 (14.3)	913 (15.4)	807 (13.4)		
<1.99 units·week ⁻¹ , n (%)	5921 (49.4)	3044 (51.2)	2877 (47.6)		
≥2 units·week ⁻¹ , n (%)	4348 (36.3)	1986 (33.4)	2362 (39.0)		
Disease, n (%)	6179 (51.5)	2757 (46.7)	3442 (57.1)		
CVD, n (%)	1858 (15.5)	710 (12.0)	1148 (19.0)		
Cancer, n (%)	1982 (16.5)	912 (15.4)	1070 (17.7)		
Diabetes, n (%)	1032 (8.6)	417 (7.0)	615 (10.2)		
Hypertension, n (%)	3722 (31.1)	1633 (27.7)	2089 (34.9)		
Physical activity					
Wear time (hours·days ⁻¹)* Mean±SD	14.00 : 1.60	14 00 , 1 50	14.02 , 1.62		
	14.90±1.60	14.88±1.58	14.92±1.63		
Total physical activity (cour Mean±SD		277 E . 121 7	224 9 : 102 4		
Sedentary time (hours-day	300.6±140.4	377.5±131.7	224.8±102.4		
· · · · · · · · · · · · · · · · · · ·		0.15+1.04	11 52±0 76		
Mean±SD	10.35±1.50	9.15±1.04	11.53±0.76		
Light physical activity (min Mean±SD		371 1±65 <i>/</i>	2/13 7±/13 E		
MVPA (min·day ⁻¹)	306.9±84.4	371.1±65.4	243.7±43.5		
Mean±SD	28.7±24.7	35.2±26.6	22.2±20.8		
Data are shown as mean±9			22.2120.0		

^{*}Wear time is displayed before standardising the physical activity and sedentary time estimates to 16 hours day

CVD, cardiovascular disease; MVPA, moderate and vigorous physical activity; BMI, body mass index.

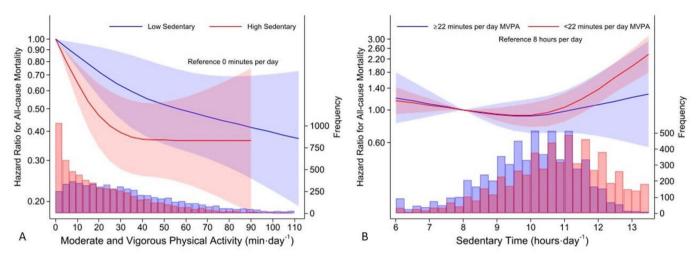


Figure 1 Restricted cubic spline regressions of HR (solid line) and 95% CI (transparent area) with higher (A) MVPA stratified by <10.5 (blue) and ≥10.5 (red) hours per day of sedentary time, and (B) sedentary time stratified by ≥22 (blue) and <22 (red) min of MVPA per day. Knots are placed at the 10th, 50th and 90th percentile of the distributions, separately (A) at <10.5 and ≥10.5 hours·day⁻¹ of sedentary time and (B) at ≥22 and <22 min of MVPA per day. Reference of both strata are set to (A) 0 min per day and (B) 8 hours per day. Data are adjusted for sex, education, BMI, smoking, alcohol intake, study cohort, history of CVD, cancer and/or diabetes, and age (in years) as timescale. Accelerometry wear time is adjusted by standardising all physical activity estimates to 16 hours wear time per day. MVPA and sedentary time are winsorized to the 1st and 99th percentile of their non-stratified distribution, BMI, body mass index; CVD, cardiovascular disease; MVPA, moderate-and-vigorous physical activity.

8 hours per day reference (figure 1B). Among participants accumulating <22 min of MVPA per day, sedentary time was curvilinearly associated with mortality. For example, more than 12 hours per day spent sedentary was associated with higher mortality risk (12 hours·day⁻¹, HR 1.38, 95% CI 1.10 to 1.74; 13 hours·day⁻¹, HR 1.98, 95% CI 1.53 to 2.57) compared with 8 hours per day (figure 1B).

For joint associations combining MVPA and sedentary time, the best fit fractional polynomial model included log(MVPA), sedentary time raised to power of 3 (sedentary time³), and 'log(sedentary time)*sedentary time3', and we included the main effect of these transformed variables along with two-way cross products of log(MVPA) with each transformed term of sedentary time. This model was different from a model including linear continuous interaction of 'MVPA*sedentary time' with their main effects (likelihood ratio p<0.001). Joint associations confirmed results from stratified analyses. Higher MVPA was associated with lower mortality risk irrespective of the amounts of sedentary time, whereas the association between sedentary time and mortality was largely influenced by MVPA levels (figure 2, online supplemental table S5). Compared with keeping MVPA constant at 0 min and 8 hours of daily sedentary time as reference, being sedentary 6 hours per day was associated with 56% higher mortality risk (HR 1.56, 95% CI 1.01 to 2.39), while more than 8 hours of sedentary time displayed overlapping CIs, even at 13 hours per day (HR 1.35, 95% CI 0.81 to 2.24) (figure 2, online supplemental table S5). Ten min of MVPA per day were associated with 32% (HR 0.68, 95% CI 0.49 to 0.95) lower mortality risk at 6 hours, 55% (HR 0.45, 95% CI 0.31 to 0.65) lower risk at 10 hours, and 28% (HR 0.72, 95%) CI 0.65 to 0.81) lower risk at 13 hours per day of sedentary time (figure 2, online supplemental table S3).

Light physical activity was curvilinearly associated with lower mortality risk but only in highly sedentary participants (figure 3A). Compared with 183 min per day as reference, 15 more min of light physical activity were associated with 11% (HR 0.89, 95% CI 0.85 to 0.95) lower mortality risk, and

maximal risk reduction was observed at 330 min per day (HR 0.61, 95% CI 0.43 to 0.86).

Total physical activity was inversely and curvilinearly associated with mortality risk in both low and high sedentary participants (figure 3B). The lowest mortality risk (HR 0.17, 95% CI 0.08 to 32) in those with low sedentary time was observed at

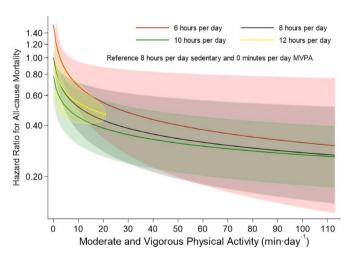


Figure 2 Combined associations modelled as fractional polynomials of sedentary time and MVPA on risk of mortality. HRs are based on a reference of 8 hours per day of sedentary time and 0 min per day of MVPA. Lines are arbitrary shown HR and 95% CI (transparent area): red line=6 hours of sedentary time, black line=8 hours of sedentary time, green line=10 hours of sedentary time, yellow line=12 hours of sedentary time. Data are adjusted for sex, education, BMI, smoking, alcohol intake, study cohort, history of CVD, cancer and/or diabetes, and age (in years) as timescale. Accelerometry wear time is adjusted by standardising all physical activity estimates to 16 hours wear time per day. MVPA and sedentary time are winsorized to the 1st and 99th percentile, BMI, body mass index; CVD, cardiovascular disease; MVPA, moderate-to-vigorous physical activity.

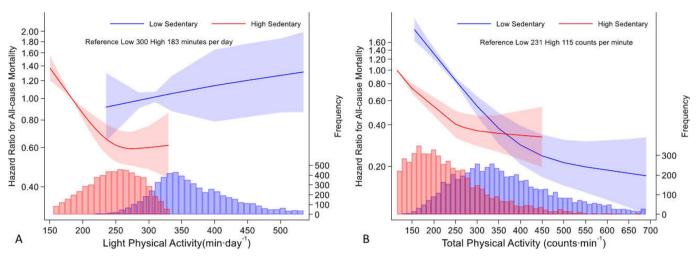


Figure 3 Restricted cubic spline regressions of HR (solid line) and 95% CI (transparent area) with higher (A) light physical activity and (B) total physical activity, stratified by sedentary time (<10.5 hours·day⁻¹ (blue) and ≥10.5 hours·day⁻¹ (red)). Knots are placed at the 10th, 50th and 90th percentile of the distributions. References are strata-specific 10th percentile: (A) low sedentary: 300 min per day, high sedentary: 183 min per day; (B) low sedentary: 231 counts per min per day, high sedentary: 115 counts per min per day. Data are adjusted for sex, education, BMI, smoking, alcohol intake, study cohort, history of CVD, cancer and/or diabetes, and age (in years) as timescale. Accelerometry wear time is adjusted by standardising all physical activity estimates to 16 hours wear time per day. Light and total physical activity are winsorized to the 1st and 99th percentile of their non-stratified distribution, BMI, body mass index; CVD, cardiovascular disease.

690 counts per min, and in those with high sedentary time at 450 counts per min (HR 0.33, 95% CI 0.20 to 54).

In the analyses with mutual adjustment of physical activity and sedentary time, higher physical activity of all intensities was associated with lower mortality risk (online supplemental table S4). Higher MVPA was curvilinearly associated with lower mortality risk; for example, mortality risk was 27% lower (HR 0.73, 95% CI 0.65 to 0.82) at 10 min of MVPA per day, and 61% lower (HR 0.39, 95% CI 0.30 to 0.51) at 50 min MVPA per day, compared with reference 0 min per day. There was no association between sedentary time and mortality below 11 hours per day; however, we observed a higher risk above 12 sedentary hours per day (12 hours.day⁻¹: HR 1.53, 95% CI 1.27 to 1.84; 13 hours.day⁻¹: HR 2.08, 95% CI 1.65 to 2.62) (online supplemental table S4).

Sensitivity analyses

When excluding the first 5 years of follow-up (n=7266, deaths=463), associations between physical activity and mortality were generally attenuated although in the expected direction (online supplemental table S5). In contrast, the association between sedentary time and mortality was unchanged (online supplemental table S5). In analyses split by Norwegian and Swedish (Tromsø, HAI and NNPAS) and US (NHANES) cohorts, results remained unchanged (online supplemental tables S6 and S7), except among those with <22 min of MVPA per day in the Norwegian and Swedish cohorts, where 9–11 hours per day of sedentary time was associated with lower mortality risk, but with higher risk at 12–13 hours per day (online supplemental table S6). When calibrating NHANES estimates to newer Acti-Graph accelerometers, results were unchanged compared with the main analyses (online supplemental table S8).

DISCUSSION

In this individual participant data analysis from four prospective cohort studies with device-measured physical activity, higher levels of MVPA were associated with lower mortality risk irrespective of the amounts of sedentary time. In contrast, higher

sedentary time was only associated with mortality risk in participants with low levels of MVPA. Accumulating at least 22 min per day of MVPA eliminated the association between sedentary time and mortality. Total physical activity was associated with lower mortality risk both in individuals below and above median sedentary time, while light intensity physical activity was only associated with mortality risk in highly sedentary individuals.

These results suggest that although many adults spend most of the day being sedentary, ¹⁻³ performing low amounts of MVPA and even light physical activity may lower their risk of mortality. The recent updated WHO guidelines suggest aiming for the upper limit of 300 min per week of MVPA for those who are highly sedentary, ¹⁷ while this study suggests accumulating 22 min per day of MVPA; this can be regarded as equivalent to meeting the lower limit physical activity guideline (>150 min per week, equivalent to 22 min per day over 7 days). However, this interpretation depends on the definitions of MVPA thresholds in accelerometry data.

In non-stratified analyses, higher physical activity was associated with lower mortality risk, and higher sedentary time was associated with higher mortality risk. This is consistent with previous studies examining associations between device-measured physical activity¹¹ ²⁴ ²⁶ ³⁶ ³⁸ and sedentary time¹¹ ²⁴ ²⁶ ³⁶ ⁴³ with mortality. However, we observed effect modifications by sedentary time, which have been indicated by previous meta-analyses examining joint associations of physical activity and sedentary time with mortality, ¹² ¹⁶ ⁴⁴ but not formally tested. Although those with higher sedentary time yielded greater relative benefits from an equivalent amount of MVPA compared with less sedentary participants in our study, small amounts of MVPA were also associated with lower mortality risk among those with low sedentary time.

Higher amounts of light physical activity were associated with lower mortality risk. This is consistent with previous studies. The studies of However, light physical activity was not associated with mortality in those with low sedentary time. For total physical activity, the lowest mortality risk was observed among those with low sedentary time. Consequently, although high total

physical activity levels are possible to achieve in combination with high sedentary time, accumulating such large volumes of total physical activity and thus maximise risk reduction appears more easily achievable in combination with low sedentary time (ie, more light physical activity).

Nevertheless, combined with the result that light physical activity was only associated with lower mortality risk in the highly sedentary, this may indicate that maximal risk reduction for total physical activity in the least sedentary also included a fair amount of MVPA. This interpretation aligns with two recent studies, where the lowest mortality risks were observed in those with the greatest proportion of physical activity energy expenditure deriving from MVPA. This means that for the highly sedentary, engagement in either light physical activity or MVPA are effective options for reducing mortality risk. However, for the least sedentary, a higher intensity (ie, MVPA) may be needed to obtain additional benefits. Moreover, we observed no excess risk at higher ends of total physical activity, which is consistent with previous studies. It is a factority to the no harmful mortality risks for those engaging in high amounts of physical activity.

In joint analyses of MVPA and sedentary time, higher MVPA was associated with lower mortality risk at any given amount of sedentary time. Interestingly, this association was U-shaped with the lowest mortality risk observed at 10 hours of sedentary time. This is partly inconsistent with our analyses stratified by sedentary time (figure 1A), suggesting a J-shaped pattern. We speculate this may be explained by a cohort effect, as a U-shaped pattern of lower mortality risk with higher sedentary time was also observed in the analysis restricted to the Norwegian and Swedish cohorts. Both wear time and sedentary time were higher in these cohorts compared with the NHANES. While we excluded all data between 00:00 and 06:00 for harmonisation purposes, it is plausible that some sleep may have been misclassified as sedentary time.

Previous meta-analyses examining joint associations with device-measured physical activity and sedentary time have reported high mortality risks with high sedentary time. 14 15 One study reported that ~10-11 daily sedentary hours in combination with low MVPA (~2 min) were associated with a 140% higher mortality risk compared with the referent combining ~8 hours of sedentary time and 30–40 min of MVPA. 14 Others reported that ~8 hours of sedentary time in combination with ~2 min of MVPA was associated with a 60% lower mortality risk compared with ~12 hours of sedentary time. 15 We observed no higher mortality risk with higher sedentary time in our joint analysis. This may be attributed to our individual participant data analysis, which overcomes limitations of aggregated studylevel data¹⁹ 20 used by others. 14 15 However, we cannot exclude the possibility that this observation is attributed to our participants being mostly older adults.

Strengths

Our individual participant data analysis allowed us to examine exposure-interaction associations with higher certainty, ¹⁹ ²⁰ including preserving continuous physical activity data, which likely minimised loss of information and statistical power. ²¹ Moreover, although our sensitivity analyses excluding the first 5 years of follow-up suggested attenuated magnitudes of associations, the dose–response patterns were similar.

Limitations

We lacked repeated measures of exposures and covariates during follow-up, which makes our analyses susceptive to changes in physical activity and confounders. A recent study reported lower mortality risk of long-term exposure of physical activity compared with a single baseline measure. However, other studies have reported that high baseline physical activity yields similar lower mortality risk as increasing physical activity from low to high levels. Moreover, a 7 day accelerometry recording appears reasonably stable over time. S1 52

Statistical adjustments were limited to covariates that could be harmonised, leaving potential residual confounding from variables such as mobility limitations, diet, and general health status. Putative sources such as education, smoking and disease, which are associated with diet quality, ⁵³ may to some degree act as proxies for non-included confounding sources. Follow-up time was short in some cohorts, which may influence our results as excluding follow-up years is likely insufficient to minimise the influence of reverse causation bias, particularly for sedentary time. ⁵⁴ Larger studies of device-measured physical activity with longer follow-up are warranted to validate our findings.

Accelerometry-measured physical activity may not correctly classify all activity types and their corresponding intensity (eg, cycling, resistance-type exercises, garden work). Thus, we cannot exclude the possibility of some misclassification of the different intensities, such as sedentary time and light intensity physical activity, but also between light physical activity and MVPA. Our MVPA threshold was calibrated as an average from four validity protocols against indirect calorimetry during walking and running, 32–35 indicating the lower threshold of moderate-intensity physical activity for these activity types. However, other activity types (eg, cycling, resistance-type exercises, garden work) that correspond to MVPA may be misclassified as light physical activity.

Similarly, our chosen sedentary time threshold may also introduce misclassification. For example, in one study, a threshold of <100 counts per min was found to be slightly more accurate (80% sensitivity; 67% specificity) than <150 counts per min (70% sensitivity; 67% specificity) in classifying sitting from standing, using thigh-worn monitors as the reference. As there is no consensus on sedentary time thresholds, we used a commonly used threshold previously shown to provide sedentary time estimates associated with higher mortality risk. Turthermore, we used an absolute intensity classification, which does not account for individual variation in age, cardiorespiratory fitness, body weight, or pre-existing conditions, which may all influence the relationship between absolute and relative physical activity.

This study includes mostly older adults, and whether the observed dose–response associations are generalisable to younger adults is unknown. Finally, due to the individual participant data approach, we were unable to use the sample weights provided by the NHANES to yield nationally representative estimates. However, sample-weighted NHANES analyses were used in the sensitivity analysis by the NHANES cohort, and were consistent with our main analyses.

CONCLUSION

Sedentary time was associated with higher mortality risk only in individuals accumulating less than 22 min of MVPA per day. MVPA levels were associated with lower mortality risk irrespective of the amount of sedentary time. Efforts to promote physical activity may have substantial health benefits for individuals, and small amounts of MVPA may be an effective strategy to ameliorate mortality risk associated with high sedentary time.

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Patient and public involvement statement The Tromsø Study advisory board includes patient and public representatives. Some participants acted as ambassadors in The Tromsø Study and HAI Study during data collection, and actively contributed to recruitment of participants. There was no patient or public involvement in the NNPAS or NHANES. There was no public involvement when designing and conducting this study.

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Data availability statement Tromsø Study, HAI and NNPAS: The data underlying this article were provided by third parties (described below) under licence. Data can be shared on request to the third parties. NHANES data are available online at: https://wwwn.cdc.gov/nchs/nhanes/. Access to data: Tromsø Study upon application to the Data and Publication Committee for the Tromsø Study: https://uit.no/research/tromsostudy. HAI upon request to principal investigator Professor Anna Nordström, mail: anna.h.nordstrom@umu.se. NNPAS upon request to principal investigator Professor Sigmund Alfred Anderssen, mail: sigmundaa@nih.no.

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REFERENCES

- 1 Loyen A, Clarke-Cornwell AM, Anderssen SA, et al. Sedentary time and physical activity surveillance through accelerometer pooling in four European countries. Sports Med 2017:47:1421–35.
- 2 Matthews CE, Carlson SA, Saint-Maurice PF, et al. Sedentary behavior in U.S. adults: fall 2019. Med Sci Sports Exerc 2021;53:2512–9.
- 3 Hansen BH, Kolle E, Steene-Johannessen J, et al. Monitoring population levels of physical activity and sedentary time in Norway across the LifeSpan. Scand J Med Sci Sports 2019;29:105–12.
- 4 Thorp AA, Healy GN, Winkler E, et al. Prolonged sedentary time and physical activity in workplace and non-work contexts: a cross-sectional study of office, customer service and call centre employees. Int J Behav Nutr Phys Act 2012;9:128.
- 5 Kazi A, Haslam C, Duncan M, et al. Sedentary behaviour and health at work: an investigation of industrial sector, job role, gender and geographical differences. Ergonomics 2019;62:21–30.
- 6 Kurita S, Shibata A, Ishii K, et al. Patterns of objectively assessed sedentary time and physical activity among Japanese workers: a cross-sectional observational study. BMJ Open 2019;9:e021690.
- 7 Koh D. Sedentary behaviour at work—an underappreciated occupational hazard Occup Med 2018;68:350–1.
- 8 Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 2015;162:123–32.
- 9 Patterson R, McNamara E, Tainio M, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol 2018;33:811–29.
- 10 Dempsey PC, Biddle SJH, Buman MP, et al. New global guidelines on sedentary behaviour and health for adults: broadening the behavioural targets. Int J Behav Nutr Phys Act 2020;17:151.
- 11 Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. BMJ 2019;366:14570.
- 12 Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet 2016;388:1302–10.
- 13 Ekelund U, Brown WJ, Steene-Johannessen J, et al. Do the associations of sedentary behaviour with cardiovascular disease mortality and cancer mortality differ by physical activity level? A systematic review and harmonised meta-analysis of data from 850 060 participants. Br J Sports Med 2019;53:886–94.
- 14 Ekelund U, Tarp J, Fagerland MW, et al. Joint associations of accelero-meter measured physical activity and sedentary time with all-cause mortality: a harmonised metaanalysis in more than 44 000 middle-aged and older individuals. Br J Sports Med 2020:54:1499–506.
- 15 Chastin S, McGregor D, Palarea-Albaladejo J, et al. Joint association between accelerometry-measured daily combination of time spent in physical activity, sedentary behaviour and sleep and all-cause mortality: a pooled analysis of six prospective cohorts using compositional analysis. Br J Sports Med 2021;55:1277–85.
- 16 Stamatakis E, Gale J, Bauman A, et al. Sitting time, physical activity, and risk of mortality in adults. J Am Coll Cardiol 2019;73:2062–72.
- 17 Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451–62.
- 18 Chastin SFM, De Craemer M, De Cocker K, et al. How does light-intensity physical activity associate with adult cardiometabolic health and mortality? Systematic review with meta-analysis of experimental and observational studies. Br J Sports Med 2019;53:370–6.
- 19 Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:bmj.c221.
- 20 Riley RD, Debray TPA, Fisher D, et al. Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: statistical recommendations for conduct and planning. Stat Med 2020;39:2115–37.
- 21 Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006;25:127–41.
- 22 Sagelv EH, Ekelund U, Pedersen S, et al. Physical activity levels in adults and elderly from triaxial and uniaxial accelerometry. The Tromsø study. PLoS One 2019;14:e0225670.
- 23 Hopstock LA, Grimsgaard S, Johansen H, et al. The seventh survey of the Tromsø study (Tromsø7) 2015-2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. Scand J Public Health 2022;50:919–29.
- 24 Ballin M, Nordström P, Niklasson J, et al. Associations of objectively measured physical activity and sedentary time with the risk of stroke, myocardial infarction or all-cause mortality in 70-year-old men and women: a prospective cohort study. Sports Med 2021;51:339–49.

Review

- 25 Hansen BH, Kolle E, Dyrstad SM, et al. Accelerometer-determined physical activity in adults and older people. Med Sci Sports Exerc 2012;44:266–72.
- 26 Matthews CE, Keadle SK, Troiano RP, et al. Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults. Am J Clin Nutr 2016:104:1424–32.
- 27 Evenson KR, Wen F, Herring AH. Associations of accelerometry-assessed and self-reported physical activity and sedentary behavior with all-cause and cardiovascular mortality among US adults. Am J Epidemiol 2016;184:621–32.
- 28 Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. *Med Sci Sports Exerc* 2005;37:S531–43.
- 29 Troiano RP, Berrigan D, Dodd KW, et al. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–8.
- 30 Chomistek AK, Yuan C, Matthews CE, et al. Physical activity assessment with the Actigraph GT3X and doubly labeled water. Med Sci Sports Exerc 2017;49:1935–44.
- 31 Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the United States, 2003–2004. Am J Epidemiol 2008;167:875–81.
- 32 Leenders NY, Sherman WM, Nagaraja HN, et al. Evaluation of methods to assess physical activity in free-living conditions. Med Sci Sports Exerc 2001;33:1233–40.
- 33 Freedson PS, Melanson E, Sirard J. Calibration of the computer science and applications. Med Sci Sports Exerc 1998;30:777–81.
- 34 Brage S, Wedderkopp N, Franks PW, et al. Reexamination of validity and reliability of the CSA monitor in walking and running. Med Sci Sports Exerc 2003;35:1447–54.
- 35 Yngve A, Nilsson A, Sjostrom M, et al. Effect of monitor placement and of activity setting on the MTI accelerometer output. *Med Sci Sports Exerc* 2003;35:320–6.
- 36 Dempsey PC, Strain T, Khaw K-T, et al. Prospective associations of accelerometer-measured physical activity and sedentary time with incident cardiovascular disease, cancer, and all-cause mortality. Circulation 2020;141:1113–5.
- 37 Del Pozo Cruz B, Ahmadi M, İnan-Eroglu E, et al. Prospective associations of accelerometer assessed physical activity with mortality and incidence of cardiovascular disease among adults with hypertension: the UK Biobank study. J Am Heart Assoc 2022:11:e023290
- 38 Strain T, Wijndaele K, Dempsey PC, et al. Wearable-device-measured physical activity and future health risk. Nat Med 2020;26:1385–91.
- 39 Yang Y, Dixon-Suen SC, Dugué P-A, et al. Physical activity and sedentary behaviour over adulthood in relation to all-cause and cause-specific mortality: a systematic review of analytic strategies and study findings. Int J Epidemiol 2022;51:641–67.
- 40 Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med 2004;23:3803–20.
- 41 Ross R, Chaput J-P, Giangregorio LM, et al. Canadian 24-hour movement guidelines for adults aged 18-64 years and adults aged 65 years or older: an integration of physical activity, sedentary behaviour, and sleep. Appl Physiol Nutr Metab 2020;45:S57–102.

- 42 Ried-Larsen M, Brønd JC, Brage S, et al. Mechanical and free living comparisons of four generations of the Actigraph activity monitor. Int J Behav Nutr Phys Act 2012;9:113
- 43 Diaz KM, Howard VJ, Hutto B, et al. Patterns of sedentary behavior and mortality in U.S. middle-aged and older adults: a national cohort study. Ann Intern Med 2017:167:465–75.
- 44 Migueles JH, Lee I-M, Sanchez CC, et al. Revisiting the association of sedentary behavior and physical activity with all-cause mortality using a compositional approach: the women's health study. Int J Behav Nutr Phys Act 2021;18.
- 45 Saint-Maurice PF, Troiano RP, Berrigan D, et al. Volume of light versus moderate-tovigorous physical activity: similar benefits for all-cause mortality J Am Heart Assoc 2018:7:e008815
- 46 Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med 2015:175:959–67.
- 47 Martinez-Gomez D, Cabanas-Sanchez V, Yu T, et al. Long-term leisure-time physical activity and risk of all-cause and cardiovascular mortality: dose-response associations in a prospective cohort study of 210 327 Taiwanese adults. Br J Sports Med 2022;56:919–26.
- 48 Mok A, Khaw K-T, Luben R, et al. Physical activity trajectories and mortality: population based cohort study. BMJ 2019;365:12323.
- 49 Saint-Maurice PF, Coughlan D, Kelly SP, et al. Association of leisure-time physical activity across the adult life course with all-cause and cause-specific mortality. JAMA Netw Open 2019;2:e190355.
- 50 Byberg L, Melhus H, Gedeborg R, et al. Total mortality after changes in leisure time physical activity in 50 year old men: 35 year follow-up of population based cohort. BMJ 2009;338:b688.
- 51 Keadle SK, Shiroma EJ, Kamada M, et al. Reproducibility of accelerometer-assessed physical activity and sedentary time. Am J Prev Med 2017;52:541–8.
- 52 Saint-Maurice PF, Sampson JN, Keadle SK, et al. Reproducibility of accelerometer and posture-derived measures of physical activity. Med Sci Sports Exerc 2020;52:876–83.
- 53 Darmon N, Drewnowski A. Does social class predict diet quality? Am J Clin Nutr 2008;87:1107–17.
- 54 Tarp J, Hansen BH, Fagerland MW, et al. Accelerometer-measured physical activity and sedentary time in a cohort of US adults followed for up to 13 years: the influence of removing early follow-up on associations with mortality. Int J Behav Nutr Phys Act 2020:17:39.
- 55 Kozey-Keadle S, Libertine A, Staudenmayer J, et al. The feasibility of reducing and measuring sedentary time among overweight, non-exercising office workers. J Obes 2012;2012;282303.
- 56 Johnson CL, Paulose-Ram R, Ogden CL, et al. National health and nutrition examination survey: analytic guidelines. Vital Health Stat 2013:1–24.

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Supplementary Files

Supplementary File S1. Descriptions of the study cohorts

The Tromsø Study 2015-16

The Tromsø Study is an ongoing population-based cohort study in Tromsø Municipality in Northern Norway. It includes seven surveys (1974, 1979-80, 1986-87, 1994-95, 2001, 2007-08, 2015-16), of which the seventh survey in 2015-16 included accelerometry measurements of 6778 participants in a sub-sample of the 21083 (participation 65%) attending participants. The ActiGraph wGT3X-BT (ActiGraph, LLC, Pensacola, United States) accelerometer was handed out at attendance and used on the right hip for eight consecutive days and mailed back in a pre-paid envelope, and the age-span of participants was 40-84 years (2). The Tromsø Study was approved by the Regional Ethics Committee for Medical and Health Research (reference 2014/940). The Tromsø Study data was linked to the Norwegian Cause of Death Registry through 2020, which is consistently found to provide 100% completeness of registered deaths compared with global vital statistics (3-5). In total, 4836 participants had valid accelerometry data and information on all covariates (alcohol, body mass index, cohort, smoking, education, sex, prevalent cardiovascular disease (myocardial infarction, stroke, angina pectoris, atrial fibrillation), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥2 years follow-up time.

Healthy Ageing Initiative (HAI) 2012-2019

The HAI study is an ongoing population-based cohort study in Umeå, Sweden. It invites all adults aged >70 years every year from inception in 2012. The primary aim is to identify risk factors for cardiovascular disease, falls and fractures. Participation is 70%. The ActiGraph GT3X+ (ActiGraph, LLC, Pensacola, United States) accelerometer was handed out in the clinic and used on the right hip and worn for seven consecutive days (6, 7). The HAI study was approved by the Regional Ethical Review Board in Umeå, Sweden (reference number: 07-031M). We extracted data from inception in 2012 through 2019, which was linked to the Swedish Cause of Death Registry (8) through 2019, which is consistently proved to provide 100% completeness of registered deaths compared with global vital statistics (3-5). In total, 4312 participants had valid accelerometry data and information on all covariates (alcohol, body mass index, cohort, smoking, education, sex, prevalent cardiovascular disease (myocardial infarction, stroke), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥2 years follow-up time.

The Norwegian National Physical Activity Survey (NNPAS) 2008-09

The NNPAS is an ongoing national representative cohort study aimed at monitoring physical activity levels of Norwegians with 2 completed (2008-09 and 2014-15) and one ongoing data collection (2021-22). We extracted data from the first wave conducted in 2008-09 (9). Of the 11248 invited participants, 3485 (34%) accepted the invitation. The ActiGraph GT1M (ActiGraph, LLC, Pensacola, FL) accelerometer was used on the right hip, and were sent by mail to participants with order to wear it for worn for seven consecutive days. The age-span of the participants was 20-85 years (9). The REK region South-East B approved the study (Reference number: S-08046b). Data on mortality was linked with the Norwegian Cause of Death Registry through 2017. In total, 1465 participants had valid accelerometry data and information on all covariates (alcohol, body mass index, cohort,

smoking, education, sex, prevalent and previous cardiovascular disease (myocardial infarction, stroke, angina pectoris), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥ 2 years follow-up time.

The National Health and Nutrition Examination Survey (NHANES) 2003-06

The NHANES is an ongoing national representative survey in the United States with 19 complete surveys since inception in 1959-62. We downloaded data from the 2003-04 and 2005-06 survey (available at https://wwwn.cdc.gov/nchs/nhanes/), as they used the ActiGraph 7164 (ActiGraph, LLC, Pensacola, FL) accelerometer on the right hip and worn for seven consecutive days. The NHANES is approved by the National Centre for Health Statistics Research Ethics Review Board. Mortality was linked with the United States National Death Index through 2015 (10), which is previously found to provide 100% completeness of deaths compared with global vital statistics (3). Of the 5147 who wore an accelerometer, 2221 (43%) participants provided valid accelerometry data and information on all confounders (alcohol, body mass index, cohort, smoking, education, sex, prevalent cardiovascular disease (myocardial infarction, stroke, angina pectoris), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥2 years follow-up time.

Supplementary File S2. Harmonization of the exposure

Participants from all studies used ActiGraph accelerometers (ActiGraph, LLC, Pensacola, FL United States) on their hip, but used different generations of the device; AM-7164 (NHANES), GT1M (NNPAS), GT3X+ (HAI), wGT3X-BT (Tromsø Study). As the AM-7164 and GT1M records per 60-seconds epochs (acceleration counts, proprietary) from the vertical axis, we reduced raw vertical acceleration units (gravitational force) from the GT3X+ (HAI, sampled at 30 Hz) and wGT3X-BT (Tromsø Study, sampled at 100 Hz) to 60 second epochs using the ActiLife Software (ActiGraph, LLC, Pensacola, FL United States). The HAI, NNPAS and NHANES used a seven-day wear protocol and participants were instructed to wear the device while being awake and remove it for sleeping and water activities (6, 7, 9, 11-13), while the Tromsø Study used a 24-hour wear protocol (also while sleeping but not water activities) (2). Therefore, all accelerometer data between 0 and 6am from all study cohorts were removed from further analyses, as also previously applied in the NNPAS sample (9). The data were further analyzed using the KineSoft software (KineSoft version 3.3.80, Loughborough, United Kingdom). Non-wear time was defined as 60 consecutive minutes of zero acceleration with 2 min spike-allowance (14). Wear time was defined as 4 days of at least 10 hours (15).

Supplementary File S3. Harmonization of covariates

Body weight and height were measured in at study visit in the Tromsø Study, HAI and NHANES, while this was self-reported in the NNPAS. BMI was calculated as kg/m^2 and classified as normal weight ($<25 \ kg/m^2$), overweight ($25-29 \ kg/m^2$) and obese ($\ge 30 \ kg/m^2$). Smoking, alcohol, education, and disease were retrieved from questionnaires, except for education in the HAI study, which was retrieved from Statistics Sweden (6). Smoking was grouped as current, previous, and never smoker. Similar questions on alcohol intake were used in all cohorts but the Tromsø Study, HAI and NNPAS had similar categorical answer alternatives, while the NHANES reported their alcohol intake by number of days over a year. To harmonize alcohol intake, we calculated units of alcohol per week for all cohorts by multiplying frequency with usual number of drinks (Supplementary Table S3). Education in The Tromsø Study and NNPAS was grouped as primary school (≤ 10 years school), high

school (11-13 years school), university <4 years and university ≥4 years, while education in the HAI was grouped as primary school, high school, and university <3 years and ≥3 years, and NHANES data were grouped as primary school, high school, and university (any year). To harmonize education, we grouped education as primary school, high school, university short (Tromsø and NNPAS: <4 years, HAI: <3 years, NHANAS: university any degree), and university long (Tromsø and NNPAS: ≥4 years, HAI: ≥3 year, NHANES: N/A).

Supplementary File S4. Disease information

Information on diseases were retrieved from questionnaires in the Tromsø Study, NNPAS and NHANES with participants answering the following question, "Have your doctor ever told you had X (disease)" (NNPAS, NHANES and HAI) and "Do you have or have you had X (cancer, diabetes)" and "Have you had X (cardiovascular diseases)" in The Tromsø Study, which was dichotomized as yes/no. In the HAI data, we combined Swedish national registry data of myocardial infarction, stroke and cancer with self-reported disease as self-reported disease appeared to be underreported. Diseases was dichotomized as yes (1) and no (0).

References for supplementary files

- 1. Hopstock LA, Grimsgaard S, Johansen H, Kanstad K, Wilsgaard T, Eggen AE. The seventh survey of the Tromsø Study (Tromsø7) 2015-2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. Scand J Public Health. 2022:14034948221092294.
- 2. Sagelv EH, Ekelund U, Pedersen S, Brage S, Hansen BH, Johansson J, et al. Physical activity levels in adults and elderly from triaxial and uniaxial accelerometry. The Tromsø Study. PLoS One. 2019;14(12):e0225670.
- 2. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ. 2005;83(3):171-7.
- 3. Mahapatra P, Shibuya K, Lopez AD, Coullare F, Notzon FC, Rao C, et al. Civil registration systems and vital statistics: successes and missed opportunities. Lancet. 2007;370(9599):1653-63.
- 4. Phillips DE, Lozano R, Naghavi M, Atkinson C, Gonzalez-Medina D, Mikkelsen L, et al. A composite metric for assessing data on mortality and causes of death: the vital statistics performance index. Popul Health Metr. 2014;12:14.
- 5. Ballin M, Nordström P, Niklasson J, Nordström A. Associations of Objectively Measured Physical Activity and Sedentary Time with the Risk of Stroke, Myocardial Infarction or All-Cause Mortality in 70-Year-Old Men and Women: A Prospective Cohort Study. Sports Med. 2021;51(2):339-49.
- 6. Johansson J, Nordström A, Nordström P. Objectively measured physical activity is associated with parameters of bone in 70-year-old men and women. Bone. 2015;81:72-9.
- 7. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765-73.
- 8. Hansen BH, Kolle E, Dyrstad SM, Holme I, Anderssen SA. Accelerometer-determined physical activity in adults and older people. Med Sci Sports Exerc. 2012;44(2):266-72.

- 9. Epidemiology. NCfHSOoAa. Public-use Linked Mortality File Hyattsville, Maryland: Centers for Disease Control and Prevention; 2015 [cited 2021 23.06]. Available from: https://www.cdc.gov/nchs/data-linkage/mortality-public.htm.
- 10. Matthews CE, Keadle SK, Troiano RP, Kahle L, Koster A, Brychta R, et al. Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults. Am J Clin Nutr. 2016;104(5):1424-32.
- 11. Evenson KR, Wen F, Herring AH. Associations of Accelerometry-Assessed and Self-Reported Physical Activity and Sedentary Behavior With All-Cause and Cardiovascular Mortality Among US Adults. Am J Epidemiol. 2016;184(9):621-32.
- 12. Tarp J, Hansen BH, Fagerland MW, Steene-Johannessen J, Anderssen SA, Ekelund U. Accelerometer-measured physical activity and sedentary time in a cohort of US adults followed for up to 13 years: the influence of removing early follow-up on associations with mortality. Int J Behav Nutr Phys Act. 2020;17(1):39.
- 13. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008;40(1):181-8.
- 14. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. Med Sci Sports Exerc. 2005;37(11 Suppl):S531-43.

Supplementary Tables

Supplementary Table S1. Alcohol questionnaire in the cohorts and the processing of the data

	Tromsø, HAI	and NNPAS	NHANES		
	Question		Question		
Answer alternatives	How often do you usually drink alcohol? (times per week)	How many units of alcohol do you usually drink? (usual drinks per time)	In the past 12 months, how often did drink any type of alcoholic beverage? Reported in days 0-365 (times per week)	In the past 12 months, on those days that you drank alcoholic beverages, on the average, how many drinks did you have? Reported in units, 1-50 (usual drinks per time)	
1	Never (0)	1-2 (1.5)	0 =never (0)	1-2 (1.5)	
2	Monthly or less frequently (0.25)	3-4 (3.5)	1-12 days =Monthly or less frequently (0.25)	3-4 (3.5)	
3	2-4 times a month (0.75)	5-6 (5.5)	13-48 days =2-4 times a month (0.75)	5-6 (5.5)	
4	2-3 times a week (2.5)	7-9 (8)	49-156=2-3 times a week (2.5)	7-9 (8)	
5	4 or more times a week (4)	10 or more (10)	157 to highest=4 or more times a week (4)	>10 (10)	
Units per week =	Times per week x	•	Times per week	k usual drinks per time	

Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=National Norwegian Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey.

Supplementary Table S2. D	escriptive charac	teristics by cohort
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T	Tromsø	HAI	NNPAS	NHANES
Total (N)	4836	3467	1465	2221
Dead (n (%))	94 (1.9)	91 (2.6)	100 (6.8)	520 (23.4)
Follow up time (years)	F 00 (4 70 F 07)	4 40 (0 00	0.05 (0.00	10.50 (0.50
Median (25-75th percentile)	5.03 (4.72-5.27)	4.40 (3.20-	9.05 (8.88-	10.58 (9.50-
NA:	0.05.5.70	5.71)	9.18)	11.67)
Min-max	2.05-5.70	2.02-7.58	2.41-9.63	2.08-13.08
Sex (n (%))	0550 (50.0)	4740 (50.4)	700 (50.4)	1010 (15.0)
Women	2552 (52.8)	1748 (50.4)	738 (50.4)	1019 (45.9)
Men	2284 (47.2)	1719 (49.6)	727 (49.6)	1202 (54.1)
Age (mean ± SD)	65.9 ± 7.6	70.4 ± 0.2	61.9 ± 8.5	65.7 ± 9.7
50-59 years (n (%))	1185 (24.5)	N/A	715 (48.8)	695 (31.3)
60-69 years (n (%))	2130 (44.0)	N/A	470 (32.1)	763 (34.4)
70-79 years (n (%))	1370 (28.3)	3467 (100)	239 (16.3)	531 (23.9)
≥80 years (n (%))	151 (3.1)	N/A	41 (2.8)	232 (10.4)
Birth year (n (%))				
<1940	528 (10.9)	N/A	301 (20.5)	1096 (49.3)
1940-1949	1862 (38.5)	3467 (100)	543 (37.1)	719 (32.4)
≥1950	2446 (50.6)	N/A	621 (42.4)	406 (18.3)
BMI (mean ± SD)	27.2 ± 4.3	26.5 ± 4.2	25.6 ± 3.7	28.5 ± 5.6
<25 kg/m² (n (%))	1529 (31.6)	1357 (39.1)	700 (47.8)	617 (27.8)
25-29 kg/m ² (n (%))	2234 (46.2)	1500 (43.3)	597 (40.7)	887 (39.9)
≥30 kg/m² (n (%))	1073 (22.2)	610 (17.6)	168 (11.5)	717 (32.3)
Smoking (n (%))				
Current smoker	561 (11.6)	243 (7.0)	242 (16.5)	388 (17.5)
Previous smoker	2448 (50.6)	1589 (45.8)	593 (40.5)	954 (42.9)
Never smoker	1827 (37.8)	1635 (47.2)	630 (43.0)	879 (39.6)
Education (n (%))				
Primary school	1502 (31.1)	577 (16.6)	321 (21.9)	635 (28.6)
High school	1371 (28.3)	1406 (40.6)	542 (37.0)	564 (25.4)
University some	899 (18.6)	486 (14.0)	315 (21.5)	1022 (46.0)
University long	1064 (22.0)	998 (28.8)	287 (19.6)	N/A
Alcohol intake (mean ± SD)	2.8 ± 3.0	2.7 ± 3.4	2.9 ± 3.5	0.5 ± 1.4
Never (n (%))	422 (8.7)	410 (11.8)	149 (10.2)	739 (33.3)
<1.99 units week-1 (n (%))	2265 (46.8)	1597 (46.1)	635 (43.3)	1424 (64.3)
≥2 units·week-1 (n (%))	2149 (44.5)	1460 (42.1)	681 (46.5)	58 (2.6)
Disease (n (%))	2212 (45.7)	2456 (71.5)	388 (26.5)	1123 (50.6)
CVD ``	867 (17.9)	380 (11.0)	188 (12.8)	423 (19.1)
Cancer	552 (11.4)	969 (28.0)	130 (8.9)	331 (14.9)
Diabetes	319 (6.6)	285 (8.2)	83 (5.7)	345 (15.5)
Hypertension	1272 (26.7)	1871 (54.5)	44 (3.0)	535 (24.1)
Physical activity	, ,	,	, ,	, ,
Meeting physical activity guidelir	nes (n (%))			
<150 min·week ⁻¹	2452 (50.7)	1425 (41.1)	561 (38.3)	1724 (77.6)
≥150 min·week ⁻¹	2384 (49.3)	2042 (58.9)	904 (61.7)	497 (22.4)
Wear time (hours-days-1)*	==== ()	_== (===)	(•)	()
Mean ± SD	16.20 ± 1.15	14.00 ± 1.15	14.56 ± 1.09	13.68 ± 1.27
Total physical activity (counts mi			1.00	
Mean ± SD	253.2 ± 112.1	340.7 ± 146.7	354.0 ± 147.6	305.8 ± 147.6
Sedentary time (hours·day-1)	200.2 2 112.1	3.0.7 - 1.10.7	30 2 1 17.0	300.0 = 117.0
Mean ± SD	10.77 ± 1.30	10.38 ± 1.35	10.11 ± 1.45	9.53 ± 1.76
Light physical activity (min·day-1		10.00 ± 1.00	10.11 ± 1.40	J.JJ ± 1.70
Mean ± SD	286.7 ± 71.3	289.8 ± 71.9	316.5 ± 81.0	371.0 ± 97.4
MVPA (min·day⁻¹)	200.7 ± 7 1.0	200.0 ± 11.0	310.5 ± 01.0	07 1.0 ± 37. 4
Mean ± SD	26.5 ± 22.0	36.2 ± 27.1	36.1 ± 26.2	16.7 ± 19.2
IVICALI ± 3D	20.0 ± 22.0	JU.2 I 21.1	30.1 ± 20.2	10.1 ± 13.4

Data are shown as mean ± SD, or as frequency (percentage). *wear time is displayed prior to standardizing the physical activity and sedentary time estimates to 16 hours day 1. CVD=cardiovascular disease, MVPA=moderate and vigorous physical activity, SD=standard deviation, Tromsø=The Tromsø Study 2015-16, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey.

Supplementary Table S3. Hazard ratio of combined moderate and vigorous physical activity, and sedentary time using fractional polynomials.

HR	(95%0	CI)			Seden	tary Time (hou	urs·day⁻¹)		
		6	7	8	9	10	11	12	13
	0	1.56 (1.01-2.39	1.24 (1.00-1.53)	Ref.	0.85 (0.70-1.03)	0.78 (0.55-1.11)	0.80 (0.50-1.26)	0.95 (0.57-1.56)	1.35 (0.81-2.24)
1y-1	10	0.68 (0.49-0.95	0.59 (0.43-0.81)	0.51 (0.37-0.72)	0.47 (0.32-0.67)	0.45 (0.31-0.65)	0.47 (0.33-0.67)	0.54 (0.41-0.72)	0.72 (0.65-0.81)
nin·da	20	0.55 (0.34-0.88	0.48 (0.31-0.75)	0.43 (0.28-0.65)	0.40 (0.26-0.60)	0.39 (0.26-0.57)		0.47 (0.43-0.52)	N/A
vity (r	30	0.48 (0.27-0.85	0.42 (0.25-0.71)	0.38 (0.24-0.62)		0.35 (0.24-0.52)	0.37 (0.28-0.49)	N/A	N/A
Moderate and Vigorous Physical Activity (min·day⁻¹)	40	0.43 (0.23-0.83	0.39 (0.22-0.69)	0.36 (0.21-0.60)	0.34 (0.21-0.54)	0.33 (0.22-0.49)	0.35 (0.27-0.45)	N/A	N/A
nysica	50	0.40 (0.20-0.81	0.36 (0.20-0.67)	0.33 (0.19-0.58)	0.32 (0.19-0.52)	0.31 (0.21-0.47)	0.33 (0.27-0.42)	N/A	N/A
us Pł	60	0.38 (0.18-0.80)	0.34 (0.18-0.65)	0.32 (0.18-0.56)	0.30 (0.18-0.50)	0.30 (0.20-0.46)	0.32 (0.26-0.39)	N/A	N/A
/igoro	70	0.36 (0.16-0.79)	0.33 (0.17-0.65)	0.31 (0.17-0.55)	0.29 (0.17-0.49)	0.29 (0.19-0.44)	0.31 (0.26-0.37)	N/A	N/A
and \	80	0.34 (0.15-0.78)	0.31 (0.16-0.64)	0.29 (0.16-0.54)	0.28 (0.17-0.48)	0.28 (0.19-0.43)	0.30 (0.26-0.35)	N/A	N/A
lerate	90	0.33 (0.14-0.77)	0.30 (0.15-0.63)	0.29 (0.15-0.53)	0.27 (0.16-0.47)	0.28	0.29	N/A	N/A
Mod	100	0.32 (0.13-0.77)	0.29 (0.14-0.62)	0.28 (0.15-0.53)	0.27 (0.15-0.46)	0.27 (0.18-0.41)	0.29 (0.26-0.32)	N/A	N/A
	110	0.31 (0.12-0.76)	0.29 (0.13-0.62)	0.27 (0.14-0.52)	0.26 (0.15-0.45)	0.26	0.28 (0.26-0.30)	N/A	N/A

Data are shown as HR with 95%Cl, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours day wear time). Hazard ratios are displayed at arbitrary values of the fractional polynomials cox regression, references are set to 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data.

|--|

Total Physical Activity (counts·min ⁻¹)*			
	HR (95%CI)		
100 counts·min⁻¹	1.20 (1.14-1.26)		
150 counts⋅min⁻¹	Ref.		
200 counts⋅min-1	0.77 (0.71-0.82)		
250 counts·min⁻¹	0.63 (0.56-0.71)		
300 counts·min⁻¹	0.54 (0.46-0.63)		
350 counts⋅min-1	0.49 (0.41-0.58)		
400 counts·min⁻¹	0.46 (0.39-0.55)		
450 counts⋅min-1	0.45 (0.37-0.55)		
500 counts⋅min ⁻¹	0.45 (0.36-0.56)		
550 counts⋅min ⁻¹	0.45 (0.35-0.57)		
600 counts·min⁻¹	0.44 (0.34-0.59)		
	ctivity (min·day ⁻¹)*		
150 min·day⁻¹	1.30 (1.19-1.42)		
180 min⋅day ⁻¹	1.11 (1.07-1.15)		
200 min∙day⁻¹	Ref.		
210 min·day⁻¹	0.95 (0.93-0.97)		
240 min·day⁻¹	0.81 (0.76-0.87)		
270 min⋅day⁻¹	0.71 (0.63-0.80)		
300 min⋅day-1	0.64 (0.55-0.74)		
330 min·day⁻¹	0.60 (0.51-0.71)		
360 min·day⁻¹	0.59 (0.50-0.70)		
390 min⋅day-1	0.59 (0.50-0.70)		
420 min·day⁻¹	0.61 (0.51-0.73)		
450 min·day-1	0.63 (0.52-0.77)		
480 min·day⁻¹	0.65 (0.52-0.82)		
510 min⋅day⁻¹	0.68 (0.52-0.88)		
	nysical Activity (min·day ⁻¹)*		
0 min·day⁻¹	Ref.		
10 min⋅day⁻¹	0.73 (0.65-0.82)		
20 min·day⁻¹	0.55 (0.45-0.68)		
30 min⋅day⁻¹	0.46 (0.36-0.59)		
40 min·day⁻¹	0.41 (0.32-0.53)		
50 min·day ⁻¹	0.39 (0.30-0.51)		
60 min⋅day-¹	0.37 (0.28-0.50)		
70 min⋅day⁻¹	0.36 (0.26-0.51)		
80 min⋅day⁻¹	0.35 (0.23-0.52)		
90 min⋅day ⁻¹	0.34 (0.21-0.55)		
100 min·day⁻¹	0.33 (0.19-0.57)		
	e (hours·day ⁻¹)¤		
6 hours·day⁻¹	1.14 (0.94-1.38)		
7 hours·day-¹	1.07 (0.97-1.18)		
8 hours·day ⁻¹	Ref.		
9 hours·day ⁻¹	0.95 (0.87-1.04)		
10 hours·day⁻¹	0.97 (0.83-1.13)		
11 hours·day⁻¹	1.15 (0.97-1.37)		
12 hours·day⁻¹	1.53 (1.27-1.84)		
13 hours·day⁻¹	2.08 (1.65-2.62)		
own on UD with 050/CL adjusted for ago (in timesee	la) alaahal PMI amaking advantion aay CVD dia		

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours·day⁻¹ wear time), and additionally adjusted for:

*sedentary time moderate-and-vigorous physical activity. Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data.

Supplementary Table S5. Hazard ratio of mortality with higher physical activity stratified by median sedentary time and excluding first 5 years follow-up time

	Sedentary Time	
	<10.5 hours∙day⁻¹	≥10.5 hours·day ⁻¹
n (dead)	3947(231)	3319(232)
Total Physical Activity (counts·min ⁻¹)	HR (95%ĆI)	HR (95%ĆI)
120 counts·min ⁻¹	N/A	Ref.
150 counts⋅min⁻¹	N/A	0.82 (0.73-0.91)
200 counts⋅min⁻¹	1.11 (0.99-1.26)	0.61 (0.48-0.78)
250 counts⋅min⁻¹	Ref.	0.51 (0.38-0.70)
300 counts·min⁻¹	0.90 (0.80-1.00)	0.47 (0.35-0.62)
350 counts·min⁻¹	0.83 (0.67-1.02)	0.46 (0.29-0.71)
400 counts min⁻¹	0.78 (0.60-1.01)	N/A
450 counts⋅min ⁻¹	0.76 (0.57-1.01)	N/A
Light Physical Activity (min·day ⁻¹)		•
150 min·day ⁻¹	N/A	0.99 (0.82-1.20)
180 min·day ⁻¹	N/A	Ref.
210 min·day ⁻¹	N/A	1.00 (0.83-1.19)
240 min·day ⁻¹	N/A	0.94 (0.70-1.25)
270 min·day ⁻¹	N/A	0.79 (0.58-1.06)
300 min·day ⁻¹	Ref.	0.61 (0.43-0.86)
330 min·day ⁻¹	0.96 (0.78-1.20)	0.47 (0.29-0.76)
360 min·day ⁻¹	0.94 (0.63-1.39)	N/A
390 min·day ⁻¹	0.93 (0.57-1.53)	N/A
420 min·day ⁻¹	0.95 (0.56-1.61)	N/A
450 min·day ⁻¹	0.98 (0.59-1.64)	N/A
480 min·day ⁻¹	1.02 (0.62-1.68)	N/A
510 min·day ⁻¹	1.06 (0.64-1.75)	N/A
Moderate and Vigorous Physical Activity		74,71
0 min·day-1	Ref.	Ref.
10 min·day⁻¹	0.94 (0.80-1.11)	0.70 (0.53-0.94)
20 min·day ⁻¹	0.89 (0.65-1.22)	0.54 (0.33-0.88)
30 min·day ⁻¹	0.84 (0.55-1.28)	0.48 (0.28-0.82)
40 min·day ⁻¹	0.79 (0.50-1.27)	0.46 (0.27-0.81)
50 min·day⁻¹	0.75 (0.46-1.21)	0.47 (0.27-0.84)
60 min·day⁻¹	0.70 (0.43-1.15)	0.48 (0.25-0.93)
70 min·day⁻¹	0.66 (0.39-1.13)	0.50 (0.23-1.07)
80 min·day⁻¹	0.62 (0.34-1.14)	0.51 (0.20-1.27)
90 min·day ⁻¹	0.59 (0.29-1.19)	0.52 (0.18-1.52)
100 min·day ⁻¹	0.55 (0.24-1.25)	N/A
110 min·day ⁻¹	0.52 (0.20-1.34)	N/A
		prous Physical Activity
	<22 min·week ⁻¹	≥22 min·week ⁻¹
n (dead)	3674 (372)	3592 (91)
Sedentary Time	001.1(012)	000= (0.7)
6 hours·day⁻¹	1.01 (0.77-1.33)	1.42 (0.87-2.32)
7 hours day ¹	1.01 (0.88-1.15)	1.19 (0.93-1.52)
8 hours·day⁻¹	Ref.	Ref.
9 hours day ¹	1.00 (0.87-1.14)	0.86 (0.70-1.07)
10 hours day	1.02 (0.80-1.30)	0.81 (0.58-1.13)
11 hours day	1.14 (0.86-1.52)	0.87 (0.56-1.36)
12 hours day	1.41 (1.05-1.89)	1.00 (0.49-2.04)
13 hours day	1.83 (1.29-2.59)	1.15 (0.40-3.28)
ota are shown as HP with 95% CL adjusted for age (in time		

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours day⁻¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data.

Supplementary Table S6. Hazard ratio of mortality with higher physical activity stratified by median <10.9 and ≥10.9 hours per day of sedentary time in the Norwegian and Swedish cohorts (Tromsø Study, HAI, NNPAS).

	Sedentary Time	
	<10.6 hours·day⁻¹	≥10.6 hours·day ⁻¹
n (dead)	4814 (108)	4954 (177)
otal Physical Activity (counts·min⁻¹)	HR (95%CI)	HR (95%CI)
100 counts·min⁻¹	N/A	Ref.
150 counts·min⁻¹	N/A	0.60 (0.50-0.72)
200 counts·min⁻¹	N/A	0.38 (0.27-0.53)
250 counts·min⁻¹	ref	0.20 (0.10-0.49)
300 counts·min⁻¹	0.84 (0.70-1.02)	0.24 (0.16-0.37)
350 counts·min⁻¹	0.72 (0.52-1.00)	0.23 (0.14-0.36)
400 counts·min⁻¹	0.63 (0.43-0.94)	0.21 (0.12-0.38)
450 counts·min⁻¹	0.57 (0.37-0.87)	0.20 (0.11-0.39)
500 counts·min⁻¹	0.49 (0.30-0.79)	N/A
550 counts·min⁻¹	0.47 (0.28-0.79)	N/A
600 counts·min⁻¹	0.45 (0.25-0.79)	N/A
650 counts·min⁻¹	0.40 (0.19-0.82)	N/A
ight Physical Activity (min·day ⁻¹)	,	
160 min·day ⁻¹	N/A	1.58 (1.31-1.92)
190 min⋅day ⁻¹	N/A	Ref.
220 min∙day⁻¹	N/A	0.68 (0.59-0.79)
250 min⋅day ⁻¹	N/A	0.60 (0.49-0.74)
280 min⋅day⁻¹	Ref.	0.70 (0.51-0.95)
310 min⋅day⁻¹	1.10 (0.84-1.44)	0.88 (0.51-1.51)
340 min⋅day⁻¹	1.20 (0.75-1.92)	N/A
370 min⋅day ⁻¹	1.29 (0.74-2.38)	N/A
400 min·day⁻¹	1.37 (0.79-2.38)	N/A
430 min·day ⁻¹	1.42 (0.82-2.47)	N/A
Moderate and Vigorous Physical Activity		
0 min·day ⁻¹	Ref.	Ref.
10 min·day⁻¹	0.81 (0.66-1.00)	0.68 (0.53-0.87)
20 min·day⁻¹	0.66 (0.44-0.99)	0.49 (0.32-0.75)
30 min·day⁻¹	0.55 (0.31-0.96)	0.40 (0.24-0.65)
40 min·day ⁻¹	0.47 (0.24-0.90)	0.35 (0.22-0.57)
50 min·day ⁻¹	0.41 (0.21-0.81)	0.33 (0.20-0.54)
60 min·day ⁻¹	0.37 (0.19-0.72)	0.30 (0.17-0.53)
70 min·day ⁻¹	0.34 (0.17-0.65)	0.28 (0.15-0.55)
80 min·day ⁻¹	0.31 (0.16-0.62)	0.27 (0.12-0.59)
90 min·day⁻¹	0.28 (0.13-0.60)	N/A
100 min·day ⁻¹	0.26 (0.11-0.61)	N/A
110 min·day ⁻¹	0.24 (0.09-0.63)	N/A
110 mm day	Moderate and Vigo	orous Physical Activity
Sedentary Time	<22 min·week ⁻¹	≥22 min·week ⁻¹
n (dead)	4249 (180)	5519 (105)
6 hours·day⁻¹	2.15 (1.38-3.35)	0.69 (0.35-1.37)
7 hours·day ⁻¹	1.47 (1.18-1.83)	0.83 (0.59-1.17)
8 hours·day ⁻¹	Ref.	Ref.
9 hours·day ⁻¹	0.68 (0.55-0.85)	1.20 (0.86-1.68)
10 hours·day ⁻¹	0.48 (0.31-0.74)	1.36 (0.78-2.36)
11 hours day	0.43 (0.25-0.76)	1.37 (0.77-2.42)
12 hours day 1	0.65 (0.37-1.15)	1.27 (0.67-2.43)
13 hours day	1.29 (0.74-2.24)	1.18 (0.49-2.86)

Data are shown as HR with 95%Cl, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours day⁻¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data.

Supplementary Table S7. Hazard ratio of mortality with higher physical activity stratified by median <9.6 and ≥9.6 hours per day of sedentary time in the NHANES*.

	Sedentary Time		
	<9.6 hours·day⁻¹	≥9.6 hours·day⁻¹	
n (dead)	1104 (165)	1117 (335)	
Total Physical Activity (counts·min ⁻¹)	HR (95%CI)	HR (95%CI)	
160 counts·min⁻¹	N/A	Ref.	
280 counts·min ⁻¹	Ref.	N/A	
305 counts·min⁻¹	N/A	0.56 (0.42-0.75)	
380 counts·min⁻¹	0.94 (0.70-1.25)	N/A	
480 counts·min⁻¹	0.93 (0.63-1.37)	N/A	
580 counts·min⁻¹	0.96 (0.63-1.48)	N/A	
Light Physical Activity (min·day ⁻¹)			
230 min·day⁻¹	N/A	Ref.	
260 min·day⁻¹	N/A	0.83 (0.73-0.96)	
290 min·day⁻¹	N/A	0.74 (0.59-0.93)	
350 min⋅day ⁻¹	N/A	0.74 (0.53-1.05)	
380 min⋅day ⁻¹	Ref.	N/A	
410 min⋅day ⁻¹	1.23 (0.91-1.68)	N/A	
440 min⋅day ⁻¹	1.45 (0.86-2.47)	N/A	
470 min·day⁻¹	1.56 (0.86-2.84)	N/A	
500 min·day ⁻¹	1.54 (0.88-2.68)	N/A	
Moderate and Vigorous Physical Activity	(min·day ⁻¹)		
0 min·day⁻¹	Ref.	Ref.	
10 min·day⁻¹	1.03 (0.80-1.35)	0.45 (0.33-0.61)	
20 min·day⁻¹	1.05 (0.65-1.70)	0.35 (0.24-0.51)	
30 min⋅day ⁻¹	1.04 (0.57-1.89)	0.36 (0.25-0.53)	
	•	rous Physical Activity	
Sedentary Time	<22 min·week⁻¹	≥22 min·week ⁻¹	
n (dead)	1617 (455)	604 (65)	
6 hours·day⁻¹	0.99 (0.68-1.44)	1.54 (0.60-3.94)	
7 hours·day⁻¹	1.00 (0.83-1.20)	1.22 (0.82-1.81)	
8 hours·day⁻¹	Ref.	Ref.	
9 hours⋅day⁻¹	1.03 (0.88-1.21)	0.87 (0.71-1.07)	
10 hours·day⁻¹	1.13 (0.89-1.44)	0.79 (0.50-1.26)	
11 hours day⁻¹	1.38 (1.08-1.76)	0.73 (0.33-1.64)	
12 hours·day⁻¹	1.80 (1.37-2.38)	N/A	
13 hours day 1	2.41 (1.61-3.61)	N/A	

Data are shown as HR with 95%Cl, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours-day¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, Cl=confidence interval, N/A=not applicable due to unobserved data, NHANES=National Health and Nutrition Examination Survey.*NHANES estimates are sample-weighted to provide nationally representative estimates.

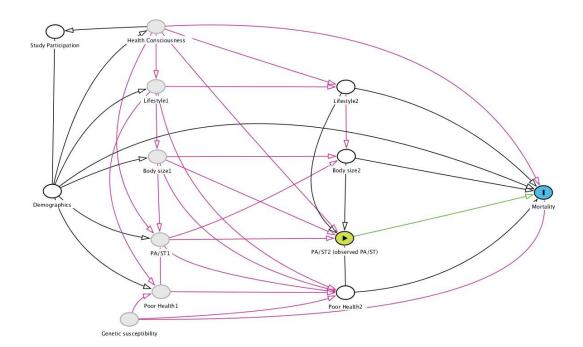
Supplementary Table S8. Hazard ratio of mortality with higher physical activity stratified by median sedentary time and adjusted NHANES estimates of physical activity and sedentary time.

	Seden	itary Time
	<10.5 hours⋅day⁻¹	≥10.5 hours·day ⁻¹
n (dead)	5848(331)	6141 (474)
Total Physical Activity (counts min-1)	HR (95%CI)	HR (95%CI)
100 counts·min ⁻¹	N/A	Ref.
150 counts · min⁻¹	N/A	0.67 (0.59-0.75)
200 counts·min⁻¹	N/A	0.47 (0.38-0.59)
250 counts·min⁻¹	Ref.	0.38 (0.30-0.49)
300 counts·min⁻¹	0.89 (0.81-0.99)	0.34 (0.26-0.45)
350 counts·min⁻¹	0.81 (0.68-0.96)	0.32 (0.23-0.45)
400 counts·min⁻¹	0.76 (0.61-0.94)	N/A
450 counts·min ⁻¹	0.72 (0.57-0.91)	0.30 (0.18-0.50)
Light Physical Activity (min·day ⁻¹)		
150 min⋅day ⁻¹	N/A	1.35 (1.20-1.52)
180 min⋅day ⁻¹	N/A	Ref.
210 min·day⁻¹	N/A	0.76 (0.68-0.84)
240 min⋅day ⁻¹	N/A	0.64 (0.55-0.75)
270 min⋅day ⁻¹	N/A	0.65 (0.55-0.77)
300 min·day⁻¹	Ref.	0.73 (0.55-0.97)
330 min⋅day ⁻¹	1.11 (0.95-1.30)	N/A
360 min⋅day ⁻¹	1.22 (0.94-1.58)	N/A
390 min⋅day ⁻¹	1.29 (0.96-1.73)	N/A
420 min⋅day ⁻¹	1.33 (0.98-1.79)	N/A
450 min⋅day ⁻¹	1.36 (1.00-1.85)	N/A
Moderate and Vigorous Physical Activity	(min·day ⁻¹)	
0 min·day⁻¹	Ref.	Ref.
10 min·day⁻¹	0.84 (0.72-0.97)	0.65 (0.53-0.80)
20 min⋅day ⁻¹	0.71 (0.54-0.94)	0.47 (0.34-0.66)
30 min·day⁻¹	0.62 (0.43-0.89)	0.40 (0.28-0.58)
40 min·day⁻¹	0.55 (0.37-0.83)	0.37 (0.26-0.54)
50 min·day⁻¹	0.51 (0.33-0.77)	0.36 (0.24-0.55)
60 min⋅day ⁻¹	0.47 (0.31-0.73)	0.35 (0.21-0.58)
70 min⋅day ⁻¹	0.44 (0.28-0.71)	0.34 (0.18-0.63)
80 min·day⁻¹	0.42 (0.25-0.71)	N/A
90 min·day⁻¹	0.39 (0.21-0.72)	N/A
100 min·day ⁻¹	0.37 (0.18-0.75)	N/A
	Moderate and Vigo	rous Physical Activity
n (dead)	6162 (652)	5827(153)
Sedentary Time	<22 min∙week⁻¹	≥22 min·week ⁻¹
6 hours·day⁻¹	1.17 (0.94-1.45)	1.23 (0.81-1.88)
7 hours·day ⁻¹	1.08 (0.97-1.20)	1.11 (0.90-1.37)
8 hours·day ⁻¹	Ref.	Ref.
9 hours·day⁻¹	0.93 (0.83-1.03)	0.92 (0.76-1.10)
10 hours day⁻¹	0.91 (0.75-1.10)	0.90 (0.68-1.20)
11 hours∙day⁻¹	1.01 (0.80-1.27)	0.99 (0.70-1.38)
12 hours day⁻¹	1.32 (1.05-1.66)	1.13 (0.69-1.87)
13 hours⋅day ^{₋1}	1.86 (1.44-2.39)	1.30 (0.63-2.70)

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours day¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, Cl=confidence interval, N/A=not applicable due to unobserved data. NHANES data are calibrated by individual-level summary data in the NHANES, accounting for non-identical output between AM-7164 and GT3X accelerometers (CPM x 0.92, light physical activity (min·day¹) x 0.88, and sedentary time (hours·day¹) x 1.02), while MVPA appears comparable between ActiGraph generations (Ried-Larsen M, Brønd JC, Brage S, Hansen BH, Grydeland M, Andersen LB, et al. Mechanical and free living comparisons of four generations of the Actigraph activity monitor. Int J Behav Nutr Phys Act. 2012;9:113.)

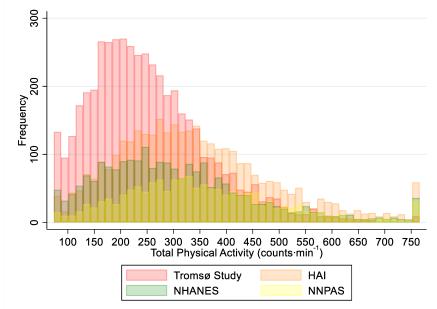
Supplementary Figures

Supplementary Figure S1. Directed acyclic graph for the association between physical activity and mortality.



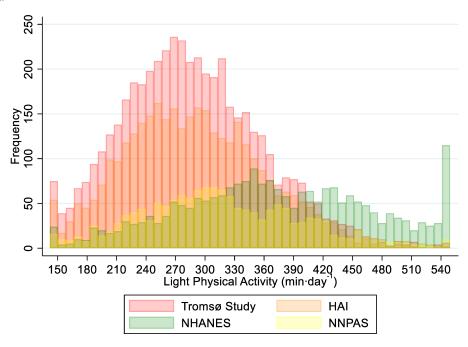
Green circle (with arrow)=exposure, Green circle=ancestor of exposure, Blue circle (I)=outcome, Red circle=ancestor of both exposure and outcome, White circle=adjusted variable, Grey circle=unobserved/latent variable, Blue circle= ancestor of outcome, Green line=causal path, Purple line=biasing path. PA=physical activity, ST=sedentary time, lifestyle=non-PA/ST lifestyle factors, *e.g.*, diet quality, smoking and alcohol intake. Poor health=health-related factors, comorbidities and disease. Genetic susceptibility=genetic disposition to poor health that could manifest in many different forms. The directed acyclic graph was inspired by Yang *et al.*, 2021, *Int J Epidemiol*, doi: https://doi.org/10.1093/ije/dyab181.

Supplementary Figure S2. Histogram of total physical activity measured as counts per minute by cohort.



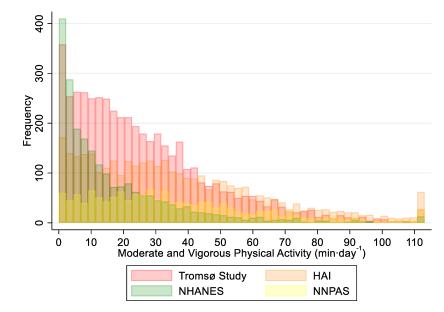
Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

Supplementary Figure S3. Histogram of minutes per day of light physical activity by cohort.



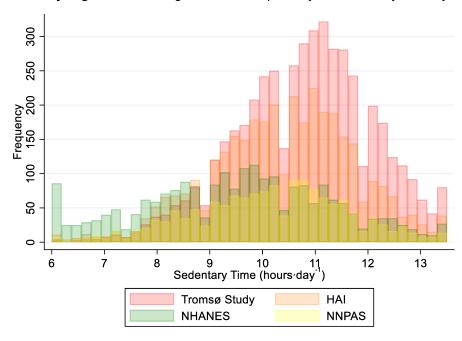
Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

Supplementary Figure S4. Histogram of minutes per day of moderate-vigorous physical activity by cohort.



Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

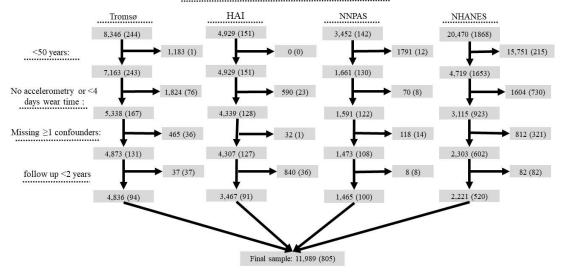
Supplementary Figure S5. Histogram of hours per day of sedentary time by cohort.



Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

Supplementary Figure S6. Flow chart of included participants.

Flow chart of included participants: N(dead)



Tromsø = The Tromsø Study 2015-16, HAI=Healthy Ageing initiative, NNPAS=Norwegian National Physical Activity Survey 2008-09, NHANES=National Health and Nutrition Examination Survey 2003-0