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

Edvard H Sagelv[1]*, Laila A Hopstock[2], Bente Morseth[1], Bjørge H Hansen[3,4], Jostein Steene-Johannessen[4], Jonas Johansson[5], Anna Nordström[6,1], Pedro F Saint-Maurice[7], Ola Løvsletten[5], Tom Wilsgaard[5], Ulf Ekelund[4,8], Jakob Tarp[9]

Affiliations:

[1]School of Sport Sciences, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[2]Department of Health and Care Sciences, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[3]Department of Sport and Physical Education, Faculty of Health and Sport Sciences, University of Agder, Kristiansand, Norway

[4]Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway

[5]Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[6]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

[7]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, United States

[8]Department of Chronic Diseases and Ageing, the Norwegian Institute for Public Health, Oslo, Norway

[9]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

***Correspondence:**

Edvard H Sagelv

E-mail: edvard.h.sagelv@uit.no

Phone: +47 77660236

Twitter: @edvardhsagelv

Address: UiT The Arctic University of Norway, Postboks 6050 Langnes, 9037 Tromsø, Troms, Norway

Word count: 3794

ABSTRACT

Objectives: 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: Individual participant data analysis of four prospective cohort studies (Norway, Sweden, United States, baseline: 2003-2016, 11989 participants ≥50 years, 50.5% women) with hip-accelerometry-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, interquartile range: 4.2 years). More than 12 daily sedentary hours (reference: 8 hours) was associated with mortality risk only among those accumulating <22 minutes of MVPA per day (HR:1.38,95%CI:1.10-1.74). Higher MVPA levels were associated with lower mortality risk irrespective of sedentary time, *e.g.*, HR for 10 versus 0 daily minutes of MVPA was 0.85 (95%CI:0.74-0.96) in those accumulating <10.5 daily sedentary hours and 0.65 (95%CI:0.53-0.79) in those accumulating ≥10.5 daily sedentary hours (HR:0.65,95%CI:0.53-0.79). Joint association analyses confirmed that higher MVPA was superior to lower sedentary time in lowering mortality risk, *e.g.*, 10 versus 0 daily minutes 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:0.31-0.65).

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

Summary box

What is already known about this topic

- The World Health Organization suggest adults with high levels of sedentary time should aim for the upper-limit of the moderate-to-vigorous physical activity (MVPA) guideline of 150-300 minutes per week to reduce the detrimental health effects of sedentary time.

What are the new 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 minutes per day of MVPA.
- Higher levels of MVPA were associated with lower mortality risk irrespective of sedentary time, *e.g.*, 10 minutes higher MVPA per day were associated with 15% and 35% lower mortality risk in those being less and highly sedentary, respectively.
- Small amounts of MVPA may be an effective strategy to ameliorate the mortality risk from high sedentary time.

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 is important.

Previous studies have shown that moderate-to-vigorous 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 minutes 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 minutes 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 harmonized approaches, where individual data are harmonized at study level and aggregated data are thereafter meta-analysed (12-15). In contrast, individual participant data analyses involve reanalysis of original data as one single study (19), which offers high flexibility to detect 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 harmonized meta-analysis, median MVPA ranged from 23 to 63 minutes 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 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 United States were pooled. Baseline data were collected between 2003 and 2019: Tromsø Study 2015-2016 (22, 23); Healthy Ageing Initiative (HAI) 2012-2019 (24); Norwegian National Physical Activity Survey (NNPAS) 2008-2009 (25); and National Health and Nutrition Examination Survey (NHANES) 2003-2006 (26, 27). These cohorts were included due to availability of individual participant data (NHANES data are freely available online), and hip-worn accelerometry, which enables harmonization of data. Cohort descriptions are summarised in Supplementary File S1. We included individuals aged ≥50 years, with ≥4 days of 10 hours with valid accelerometry data (28), ≥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.

Patient and public involvement

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.

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, United States) placed at the hip (NHANES: AM-7164; NNPAS: GT1M; HAI: GT3X+; Tromsø Study: wGT3X-BT) (Supplementary File S2). We analyzed accelerometry data using KineSoft version 3.3.80 (Kinesoft, Loughborough, United Kingdom). We removed data between 00:00-06:00 am and, for harmonization purposes, only considered data from the vertical axis. Non-wear time was defined as 60 consecutive minutes of zero counts with allowance for up to 2 minutes of non-zero counts over 100 counts per minute(29).

Total physical activity was defined as counts per minute divided by wear time(30), and volume of intensity-specific physical activity as follows: Sedentary: <100 counts per minute (31), light physical activity: 100-2019 counts per minute(25), and MVPA: ≥2020 counts per minute(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 standardized all exposure variables to 16 hours wear time per day: *e.g.* (MVPA per day/wear time per day) x 16.

Covariates

Covariates (sex, age, education (primary, high school, lower university, higher university), body mass index (BMI, <25, 25-29, ≥30 kg/m^2), 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 (Supplementary Figure S1). History of CVD, cancer and diabetes were self-reported or obtained from national registries (HAI). Measurements and harmonization of covariates are described in Supplementary File S3-4, and Supplementary 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, adjustment 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 attendance date to 01.01.2004 (wave 2003-2004) and 01.01.2006 (wave 2005-2006), and calculated death date, censoring (emigration) by addition of follow-up time. Participants´ study entry was set two 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 hours·day^{-1}) and “high” (≥10.5 hours·day^{-1}). Similarly, MVPA was split at median 22 minutes of MVPA per day. Knots in cubic splines were placed at the 10th, 50th and 90th percentiles of the analysis-specific distributions (*e.g.*, 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 minutes per day for MVPA(11) 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 minute), 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 United States (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 NHANES(42) (as described in Supplementary Table S8).

Schoenfeld´s residuals tests confirmed no violated proportional hazards for all covariates (all $p \geq 0.08$), except possibly education in low sedentary participants ($p=0.02$). However, log-log survival plots of education displayed reasonable parallel lines indicating no violated proportional hazards. Statistical analyses were performed using Stata version 17.0 (StataCorp LLC, Texas, United States) with alpha 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 (*i.e.*, the Far North) and constitutes 40% of the total sample size (Supplementary File S1, Supplementary Table S2). The cohort studies recruited participants from all socioeconomic levels (Supplementary Table S2, Table 1). The Author team includes both women and men, 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 marginalized 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, interquartile range 4.2 years) (Table 1). The NHANES cohort had longest follow-up time and contributed with 65% of total deaths (Supplementary Table S2). The ranges of physical activity and sedentary time were similar among cohorts (Supplementary Figure S2-5). A flow chart of participant inclusion is found in Supplementary Figure S6.

Table 1. Descriptive characteristics of the participants.

	All	**Sedentary Time**	
		<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/m^2, n (%)	4203 (35.1)	2254 (37.9)	1949 (32.2)
25-29 kg/m^2, n (%)	5218 (43.5)	2600 (43.8)	2618 (43.3)
≥30 kg/m^2, 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 $units \cdot week^{-1}$, n (%)	5921 (49.4)	3044 (51.2)	2877 (47.6)
≥2 $units \cdot week^{-1}$, 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)[a]			
Mean ± SD	14.90 ± 1.60	14.88 ± 1.58	14.92 ± 1.63
Total physical activity (counts·min⁻¹)			
Mean ± SD	300.6 ± 140.4	377.5 ± 131.7	224.8 ± 102.4
Sedentary Time (hours·day⁻¹)			
Mean ± SD	10.35 ± 1.50	9.15 ± 1.04	11.53 ± 0.76
Light Physical Activity (min·day⁻¹)			
Mean ± SD	306.9 ± 84.4	371.1 ± 65.4	243.7 ± 43.5
MVPA (min·day⁻¹)			
Mean ± SD	28.7 ± 24.7	35.2 ± 26.6	22.2 ± 20.8

Data are shown as mean ± SD, or as frequency (percentage). [a]Wear time is displayed prior to standardizing the physical activity and sedentary time estimates to 16 $hours \cdot day^{-1}$. CVD=cardiovascular disease, MVPA=moderate and vigorous physical activity, BMI=body mass index, SD=standard deviation.

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 minutes per day, 10 minutes of MVPA were associated with 15% (HR:0.85, 95%CI:0.74-0.96) and 35% (HR: 0.65, 95%CI:0.53-0.79) lower mortality among those with <10.5 and ≥10.5 sedentary hours per day, respectively.

Among participants accumulating ≥22 minutes of MVPA per day, sedentary time was not associated with mortality (12 hours·day^{-1}: HR:1.08, 95%CI:0.66-1.77) compared with 8 hours per day reference (Figure 1B). Among participants accumulating <22 minutes 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:1.10-1.74; 13 hours·day^{-1}, HR: 1.98, 95%CI:1.53-2.57) 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 time^3), "log(sedentary time)*sedentary time^3", 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 amounts of sedentary time whereas the association between sedentary time and mortality was largely influenced by MVPA levels (Figure 2, Supplementary Table S5). Compared with keeping MVPA constant at 0 minutes 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:1.01-2.39), while more than 8 hours of sedentary time displayed overlapping CIs, even at 13 hours per day (HR:1.35, 95%CI:0.81-2.24) (Figure 2, Supplementary Table S5). Ten minutes of MVPA per day were associated with 32% (HR:0.68, 95%CI:0.49-0.95) lower mortality risk at 6 hours, 55% (HR:0.45, 95%CI:0.31-0.65) lower risk at 10 hours, and 28% (HR:0.72, 95%CI:0.65-0.81) lower risk at 13 hours per day of sedentary time (Figure 2, Supplementary Table S3).

Light physical activity was curvilinearly associated with lower mortality risk but only in highly sedentary participants (Figure 3A). Compared with 183 minutes per day as reference, 15 more minutes of light physical activity were associated with 11% (HR:0.89, 95%CI:0.85-0.95) lower mortality risk, and maximal risk reduction was observed at 330 minutes per day (HR:0.61, 95%CI:0.43-0.86).

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:0.08-32) in those with low sedentary time was observed at 690 counts per minute, and in those with high sedentary time at 450 counts per minute (HR:0.33, 95%CI:0.20-54).

In the analyses with mutual adjustment of physical activity and sedentary time, higher physical activity of all intensities was associated with lower mortality risk (Supplementary Table S4). Higher MVPA was curvilinearly associated with lower mortality risk; for example, mortality risk was 27% lower (HR:0.73, 95%CI:0.65-0.82) at 10 minutes of MVPA per day and 61% lower (HR:0.39, 95%CI:0.30-0.51) at 50 minutes MVPA per day, compared to reference 0 minutes 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:1.27-1.84; 13 hours·day^{-1}: HR:2.08, 95%CI:1.65-2.62) (Supplementary Table S4).

Sensitivity analyses

When excluding the first five years of follow-up (n=7266, deaths=463), associations between physical activity and mortality were generally attenuated although in the expected direction (Supplementary Table S5). In contrast, the association between sedentary time and mortality was unchanged (Supplementary Table S5). In analyses split by Norwegian and Swedish (Tromsø, HAI and NNPAS) and United States (NHANES) cohorts, results remained unchanged (Supplementary Table 6-7), except among those with <22 minutes 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 associated with higher risk at 12-13 hours per day (Supplementary Table S6). When calibrating NHANES estimates to newer ActiGraph accelerometers, results were unchanged compared with the main analyses (Supplementary 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 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 minutes 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 minutes per week of MVPA for those who are highly sedentary (17), while this study suggests accumulating 22 minutes 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 minutes per day over seven 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 associated with higher mortality risk. This is consistent with previous studies examining associations between device-measured physical activity (11, 24, 26, 36-38) and sedentary time (11, 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 (11, 27, 36). 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 (*i.e.*, 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(38, 45). 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 (*i.e.*, 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 (11, 38, 46). Thus, there appears to be 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 (~2min) were associated with a 140% higher mortality risk compared with the referent combining ~8 hours of sedentary time and 30-40 minutes of MVPA(14). Others reported that ~8 hours of sedentary time in combination with ~2min 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 overcome limitations of aggregated study-level data (19, 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 minimized loss of information and statistical power(21). Moreover, although our sensitivity analyses excluding the first five 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(47). However, other studies have reported that high baseline physical activity yield similar lower mortality risk as increasing physical activity from low to high levels(48-50). Moreover, a seven-day accelerometry recording appears reasonably stable over time(51, 52).

Statistical adjustments were limited to covariates that could be harmonized, leaving potential residual confounding from variables such as mobility limitations, diet, and general health status. Putative sources like 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 minimize 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 (*e.g.*, 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 (29). However, other activity types (*e.g.*, cycling, resistance type exercises, garden work) that corresponds 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 minute was found be slightly more accurate (80% sensitivity; 67% specificity) than <150 counts per minute (70% sensitivity; 67% specificity) in classifying sitting from standing, using thigh-worn monitors as the reference(55). 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(11). Furthermore, 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 generalizable 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(56). 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 minutes of MVPA per day. MVPA levels was 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.

Figure legends

Figure 1. Restricted cubic spline regressions of hazard ratio (solid line) and 95% confidence intervals (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 minutes of MVPA per day. Knots are placed at the 10^{th}, 50^{th} and 90^{th} percentile of the distributions, separately (A) at <10.5 and ≥10.5 hours·day^{-1} of sedentary time and (B) at ≥22 and <22 minutes of MVPA per day. Reference of both strata are set to (A) 0 minutes 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 standardizing all physical activity estimates to 16 hours wear time per day. MVPA and sedentary time are winsorized to the 1^{st} and 99^{th} percentile of their non-stratified distribution, MVPA=moderate-and-vigorous physical activity, CVD=cardiovascular disease, BMI=body mass index.

Figure 2. Combined associations modelled as fractional polynomials of sedentary time and MVPA on risk of mortality. Hazard ratios are based on a reference of 8 hours per day of sedentary time and 0 minutes per day of MVPA. Lines are arbitrary shown hazard ratios and 95% confidence intervals (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 standardizing 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, MVPA=moderate-and-vigorous physical activity, CVD=cardiovascular disease, BMI=body mass index.

Figure 3. Restricted cubic spline regressions of hazard ratio (solid line) and 95% confidence intervals (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 minutes per day, high sedentary: 183 minutes per day; (B) low sedentary: 231 counts per minute per day, high sedentary: 115 counts per minute 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 standardizing 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, CVD=cardiovascular disease, BMI=body mass index.

DECLERATIONS

Disclaimer

The National Center for Health Statistics was not involved in analyzing, interpreting, nor necessarily endorses any of the conclusions of the present study. The content is solely the responsibility of the authors.

Ethics approval

All cohort studies were conducted according to the Declaration of Helsinki for Medical Research and all participants in all studies provided written informed consent. The Regional Ethics Committee for Medical and Health Research (REK) North approved the present study (reference 2016/1792), and the Tromsø Study (reference 2014/940). The Regional Ethical Review Board in Umeå, Sweden, approved the HAI study (reference 07-031M). The REK region South-East B approved the NNPAS study (reference S-08046b). The National Centre for Health Statistics Research Ethics Review Board approved the NHANES (available at: https://www.cdc.gov/nchs/nhanes/irba98.htm).

Author contributions

EHS, BM, UE and LAH designed the study. LAH, BM, JJ, AN, JSJ, and BHH contributed to acquisition and processing of raw data. EHS act as guarantor for the study. EHS processed the Tromsø Study and HAI accelerometry data, BHH processed the NNPAS accelerometry data, and JT processed the NHANES accelerometry data. EHS merged and harmonized data. EHS and TW performed statistical analyses. TW, OL, and JT provided statistical expertise. EHS wrote the initial draft of the manuscript. All authors critically reviewed the study´s results, contributed to revisions and approved the final version of the manuscript.

Data availability

Tromsø Study, HAI and NNPAS: The data underlying this article were provided by third parties (described below) under license. 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.

Funding

This work was funded by High North Population studies, an internally funded research project at UiT The Arctic University of Norway to EHS and JJ (no grant number), and The Danish Diabetes Association to JT (no grant number). The remaining authors are funded through their respective positions/tenures.

Acknowledgments

We would like to acknowledge all research technicians and researchers involved in the planning, data collection and data storage for the respective cohort studies. We also thank all research participants for their contributions with data. We also acknowledge principal investigator Professor Sigmund Alfred Anderssen for providing data access to the NNPAS, and PhD Jonathan Bergman for inputs on statistical analyses.

Supplementary data

Supplementary File S1. Descriptions of the study cohorts.

Supplementary File S2. Harmonization of the exposure.

Supplementary File S3. Harmonization of covariates.

Supplementary File S4. Disease information.

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

Supplementary Table S2. Descriptive characteristics by cohorts.

Supplementary Table S3. Hazard ratio of mortality by physical activity and sedentary time.

Supplementary Table S4. Hazard ratio of mortality with higher physical activity stratified by median sedentary time and excluding first 5 years follow-up time.

Supplementary Table S5. 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).

Supplementary Table S6. 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.

Supplementary Table S7. Hazard ratio of mortality with higher physical activity stratified by median sedentary time and adjusted NHANES estimates of physical activity and sedentary time.

Supplementary Figure S1. Histogram of total physical activity by cohorts.

Supplementary Figure S2. Histogram of light physical activity by cohorts.

Supplementary Figure S3. Histogram of moderate and vigorous physical activity by cohorts.

Supplementary Figure S4. Histogram of sedentary time by cohorts.

Supplementary Figure S5. Flow chart of included participants.

Competing interests

None declared.

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