Association of Accelerometer-Measured Sedentary Accumulation Patterns With Incident Cardiovascular Disease, Cancer, and All-Cause Mortality

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ORIGINAL RESEARCH

Association of Accelerometer-Measured Sedentary Accumulation Patterns With Incident Cardiovascular Disease, Cancer, and All-Cause Mortality

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BACKGROUND: Emerging evidence suggests accruing sedentary behavior (SB) in relatively more prolonged periods may convey additional cardiometabolic risks, but few studies have examined prospective outcomes. We examined the association of SB accumulation patterns with incident cardiovascular disease (CVD), cancer, and all-cause mortality (ACM).

METHODS AND RESULTS: Data were from 7671 EPIC-Norfolk (European Prospective Investigation Into Cancer and Nutrition–Norfolk) cohort middle- to older-aged adults who wore accelerometers on the right hip for 4 to 7 days. Cox proportional hazards regression modeled associations between 2 measures of SB accumulation and incident CVD, cancer, and ACM. These were usual SB bout duration (the midpoint of each individual's SB accumulation curve, fitted using nonlinear regression) and alpha (hybrid measure of bout frequency and duration, with higher values indicating relatively shorter bouts and fewer long bouts). Models were adjusted for potential confounders, then further for 24-hour time-use compositions. During mean follow-up time of 6.4 years, 339 ACM, 1106 CVD, and 516 cancer events occurred. Elevated rates of incident cancer and ACM were seen with more prolonged SB accumulation (lower alpha, higher usual SB bout duration) but not CVD. For usual SB bout duration and alpha, respectively, the confounder-adjusted hazard ratios per SD of the exposure were 1.12 (95% CI, 1.02–1.23) and 0.88 (95% CI, 0.79–0.98) with incident cancer and 1.16 (95% CI, 1.07–1.26) and 0.80 (95% CI, 0.72–0.89) with ACM (all $P<0.05$). Further adjustment for 24-hour time use weakened associations with ACM for usual bout duration (hazard ratio, 1.06; 95% CI, 0.97–1.16; $P=0.209$) and partially for alpha (hazard ratio, 0.87; 95% CI, 0.77–0.99; $P=0.029$).

CONCLUSIONS: Accruing SB in longer bout durations was associated with higher rates of incident cancer and ACM but not with incident CVD, with some evidence of direct SB accumulation effects independent of 24-hour time use. Findings provide some support for considering SB accumulation as an adjunct target of messaging to "sit less and move more."

Key Words: cancer ■ cardiovascular disease ■ compositional ■ mortality ■ patterns ■ physical activity ■ sedentary

Globally, cardiovascular disease (CVD) and cancer are leading causes of death and a major cause of disability and lost productivity in adults.[1,2] Being regularly physically active, particularly spending time in moderate- to vigorous-intensity physical activity (MVPA), is associated with significant reductions in both the risk of incident CVD and cancer (fatal and nonfatal). However, despite decades of promoting the benefits of MVPA to the general population, global physical activity levels remain insufficient.[3] Epidemiological evidence also shows that high volumes of sedentary behavior (SB)—defined as time spent sitting or reclining while

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CLINICAL PERSPECTIVE

What Is New?

- Middle-aged and older adults from the EPIC-Norfolk (European Prospective Investigation Into Cancer and Nutrition–Norfolk) cohort who displayed a pattern of being sedentary for long continuous periods had a higher risk of incident cancer and all-cause mortality over 6.4 years of follow-up, but not incident cardiovascular disease that has been seen in other studies.
- These elevated risks were present, after controlling for high amounts of sedentary behavior and low amounts of moderate and vigorous activity, which often co-occur with prolonged sedentary patterns.

What Are the Clinical Implications?

- In addition to promoting moderate and vigorous physical activity or "exercise," clinicians should consider supporting their patients to limit sedentary time and move more, including by breaking up long periods of sedentary behavior with more active alternatives.

Nonstandard Abbreviations and Acronyms

ACM	all-cause mortality
EPIC-Norfolk	European Prospective Investigation Into Cancer and Nutrition–Norfolk
HR_{90vs10}	hazard ratio for 90th versus 10th percentile
HRSD	hazard ratios per SD of the exposure
LPA	light-intensity physical activity
MVPA	moderate- to vigorous-intensity physical activity
SB	sedentary behavior

awake with low energy expenditure[4]—are associated with an elevated risk for all-cause mortality (ACM), CVD incidence and mortality, type 2 diabetes incidence, and some cancers, particularly among those who are not achieving recommended amounts of MVPA.[5–7] As such, most recent major national and global activity guidelines for adults now recognize the importance of also limiting SB and replacing it with more physical activity of any intensity—including light-intensity physical activity (LPA).[5,8–10] Some guidelines also advocate that adults both minimize and break up long periods of sitting.[9,11] While emerging evidence of health benefits has been deemed sufficient to develop these guidelines, it could be improved in ways to support nuanced aspects of message formation.

Information on SB bout accumulation patterns in relation to health outcomes may represent a promising and potentially powerful public health messaging tool,[5] particularly in middle and older aged adults with typically high volumes of SB and lower levels of MVPA.[12,13] Accumulating sedentary bouts a certain number of times (bout frequency), each for a certain period (bout duration), adds up to the total time spent in SB[14,15]—time that is not spent in physical activity. Ways to frame messages regarding these inextricably linked exposures[15] may be aided through more rigorous evaluation of the potential health consequences of SB bout accumulation patterns and how these may operate directly and indirectly through SB and physical activity. For example, it can help to guide whether messages should include an emphasis on breaking up prolonged SB or whether messages might include these, but more as a practical way to reduce large volumes of SB rather than as an additional risk factor.

To date, large-scale prospective studies linking both physical activity and SB to health outcomes have mostly relied on self-report methods,[16,17] which are more prone to recall and reporting bias and measurement error. Measurement of SB using accelerometers is generally recognized to have better accuracy, but importantly also allows for more detailed measures, including the quantification of SB accumulation patterns through bout durations. Indeed, preliminary evidence suggests that shorter bouts of SB and a higher frequency of breaks from SB may convey additional cardiometabolic benefit beyond reducing overall time spent in SB.[14,18] However, while cohort studies incorporating accelerometer assessments of physical activity and SB volume are emerging,[7,19,20] so far only a few have investigated the longitudinal associations of SB accumulation patterns (variously defined) with incident disease or mortality end points.[21–24] In particular, there remains a paucity of evidence on SB accumulation patterns for CVD risk in both men and women[22] as well as for both fatal and nonfatal cancers.[21] We addressed these combined knowledge gaps by evaluating the prospective associations of SB accumulation patterns with incident CVD, cancer, and ACM, testing both total effects and direct effects after excluding any effects occurring indirectly through time-use compositions (ie, SB and physical activity).

METHODS

Ethics Approval and Consent to Participate

The Norfolk District Local Research Ethics and East Norfolk and Waveney NHS Research Governance

Committee (05/Q0101/191) approved the study and signed informed consent was obtained from all participants.

Availability of Data and Materials

Individual-level data are available from the European Prospective Investigation Into Cancer and Nutrition–Norfolk Management Committee (contact via epic-norfolk@mrc-epid.cam.ac.uk) for researchers who meet the criteria for access to confidential data.

Study Population

Participants were from the EPIC-Norfolk (European Prospective Investigation Into Cancer and Nutrition–Norfolk) study,[25] a population-based cohort of 25 639 adults 40 to 79 years of age residing in Norfolk, United Kingdom. In brief, participants were recruited from general practices and invited for second, third, and fourth in-clinic assessments between 1998 and 2000, 2004 and 2011, and 2012 and 2016, respectively. Following the third and fourth assessments, a subsample of 7820 participants wore accelerometers (Actigraph, Pensacola, FL) on the right hip for 7 consecutive days, except during water activities (swimming, showering) or while sleeping. These assessments constitute the analytical baseline for this work and are henceforth referred to as "baseline." For participants who attended both the third and fourth in-clinic assessment visits between 2004 and 2016 and wore the accelerometer, data from their earliest visit (ie, third visit) were used as baseline for further analyses. The Norwich District Ethics Committee provided ethical approval, and all participants gave written informed consent.

Accelerometer Data Processing

Uniaxial (GT1M; data recorded in 5-second epochs) and triaxial (GT3X+; data recorded at 100 Hz) accelerometers were worn at the third and fourth assessments, respectively. Data were harmonized using previously described methods and integrated into 60-second epochs before processing.[26,27] Periods of nonwear time were defined as continuous 0 counts of ≥90 minutes[28] and excluded. Only adherent days with sufficient wear time (≥10 hours' wear) were included. Where ≥19 hours of wear time during a 24-hour period was observed (n=333 instances over all adherent days), indicating monitor wear during sleep, we ensured sleep was removed by overlaying self-reported usual get-up and go-to-bed times onto the time series and removing all time during these periods. Values reported by the individual were used when available; otherwise, the sample population median values were used. All the get-up and go-to-bed times used were verified to be reasonable by visual inspection of activity plots.

Sedentary Time and Sedentary Accumulation Patterns

To maximize comparability with existing literature, SB was identified as all time spent <100 cpm, a threshold that has previously been examined in this age group in terms of validity for the method used (vertical axis, 60-second epoch, hip worn).[12,28–30] Consensus is lacking at present on the best indicators of SB accumulation pattern. Studies[31,32] have quantified SB patterns as measures of mean (arithmetic and geometric) or median bout duration, and statistics that frame time in "prolonged" bouts of sitting (usually in bouts ≥30 minutes) or the number of "breaks" in SB (ie, how often a certain amount of SB is interrupted with activity) relative to amount of SB (percentage of SB in in prolonged bouts, breaks adjusted for SB, and breaks as a ratio of SB). Both the crude number of breaks and prolonged sitting time are sometimes considered, but these are not SB accumulation pattern measures unless framed in relation to total SB: ie, more crude breaks simply represent more SB bouts and higher SB time, and the amount of "prolonged" SB time is time spent in a subtype of total SB.

We extracted total SB and several measures of SB accumulation: alpha; usual SB bout duration (minutes); percentage of SB in "prolonged" bouts ≥30 minutes, fragmentation index, arithmetic and geometric mean SB bout duration (minutes), and median bout duration (minutes). The calculation and interpretation of these measures for this sample is outlined in Table S1, and several measures are plotted in Figure S1. To minimize multiple testing, we used both a data-driven and theoretically informed process to select the minimum number of measures (2) that ranked participants near identically to all the remaining SB accumulation measures (but not to each other) at around $|r_s|>0.8$ (see Table S2 and Figure S1). Of the potentially suitable choices meeting this criterion, alpha and usual bout duration were ultimately selected over alternatives (such as mean bout duration and percentage of SB in "prolonged" bouts ≥30 minutes) for theoretical reasons. Alpha and usual bout duration are summary statistics for the probability and cumulative distributions of SB bout duration,[15,32] with polar opposite approaches to the contribution of long bouts to the statistic (respectively, attenuate versus exacerbate) and, unlike percentage of SB in "prolonged" bouts, do not include any thresholds in the calculation. *Usual bout duration* (minutes) summarizes the midpoint of the cumulative distribution of SB bout durations, such that half of all SB time is accumulated in bouts of this duration or longer. This was calculated across all SB bouts on all

(computed over all adherent days using nonlinear regression). *Alpha* (unitless) summarizes the frequency distribution of SB bout duration (power-law probability distribution). Higher values of alpha and lower values of usual bout duration indicate a more broken-up (fragmented) pattern of SB bout accumulation.[15,32]

Physical Activity

Estimates of light-intensity (LPA) and moderate- to vigorous-intensity physical activity (MVPA) were also extracted, using 60-second epoch resolution and movement intensity thresholds of 100 to 2019 cpm and ≥2020 cpm, respectively.[7,12,28,29] Because time in physical activity and SB are compositional components of total time, these exposures were expressed as proportions of total time (SB, LPA, MVPA, and "other" time including in-bed time and nonwear) and then isometric log-ratio transformed[33,34] to a series of *z* parameters that can be used as covariates in analyses (Table S3).

Covariates

The sociodemographic information collected during clinic visits and used in these analyses were age, sex, education level (none, General Certificate of Education (GCE) ordinary level, General Certificate of Education advanced level, bachelor's degree, and above), social class (unemployed, nonskilled workers, semiskilled workers, skilled workers, managers, and professionals), smoking status (current, former, and never), and alcohol intake (units/week). All these were assessed via self-completed questionnaire. Baseline medical history of diabetes or taking diabetes medications; taking medication for hypertension/dyslipidemia/depression; and family history of CVD (stroke/myocardial infarction), diabetes, or cancer were also self-reported using a detailed health and lifestyle questionnaire. Additionally, updated information on prevalent heart disease, stroke, and cancer was collected up until the third clinical assessment via either self-report or record linkage with hospital episode statistics. Dietary intake was assessed using a 130-item semiquantitative food frequency questionnaire and adherence to the Mediterranean diet pyramid (derived on the basis of 15 components on the pyramid for which continuous scores from 0 to 1 were assigned for each component) was used as an overall measure of diet quality.[35,36] Trained research staff measured each participant's weight, height, and waist circumference following standard operating procedures. They also measured physical function measures of hand grip strength (dynamometer; kg), usual walking speed (timed 4-meter walk test; m/sec), and a timed chair stand speed (5 sit-to-stands; stand/min) following standardized protocols.[37] A continuously distributed physical function *z* score was then derived using all 3 variables (PF_1+PF_2+PF_3/3), which were standardized (*z*=[value-mean]/SD) in sex-specific strata, for later sensitivity analyses.

Clinical and Mortality Outcomes

Outcomes assessed were total (nonfatal or fatal) incident CVD (*International Classification of Diseases, Ninth Revision* [*ICD-9*] 401–448 or *International Classification of Diseases, Tenth Revision* [*ICD-10*] I10–I79), total (nonfatal or fatal) incident cancer (*ICD-9* 140-280 or *ICD-10* C00-C97) and ACM. Outcome status was ascertained via hospital admissions and death certificates by ending the follow-up at the date of death or by March 31, 2018, for all outcomes.

Data Inclusion

Only participants with ≥4 adherent days were included. After the exclusion of participants with invalid accelerometer data (n=139) or missing covariate data (n=10), 7671 participants were available for analysis. Data were treated as complete case and the 10 participants with missing covariate data were excluded. From this sample of 7671, those with a baseline history of stroke/myocardial infarction (n=2180) or cancer (n=1219) were excluded from the incident CVD or cancer analyses, respectively, and we further excluded outcomes of interest within 2 years of follow-up (CVD, n=474; cancer, n=1268; ACM, n=108) to minimize the risk of reverse causality bias.

Statistical Analysis

The associations of SB accumulation with incident CVD, cancer, and ACM were examined using Cox proportional hazard regression models (using age as the underlying time scale), which were also stratified by sex in secondary analyses. These models used age as the underlying time scale and modeled exposures using restricted cubic splines with 3-evenly spaced knots. Given our SB pattern exposure measures (some of which are almost nonlinear functions of each other; see Table S1), we allowed for nonlinear relationships a priori by modeling our exposures using restricted cubic splines with 3 evenly spaced knots. Likelihood ratio significance tests were used to compare the spline model to the linear model and test for nonlinearity. Results from the spline models are reported graphically, as hazard ratios (HRs) with 95% CIs, with HR (95% CI) and *P* values from the linear model also reported when likelihood ratio tests indicated no evidence of nonlinearity. Figure S2 shows the conceptual approach guiding the statistical modeling through directed acyclic graphs.[38] This posits that a prolonged pattern of SB accumulation (measured as lower alpha and higher usual bout duration) causes a large volume

of SB and, concurrently, less physical activity to be accumulated (measured as time-use compositions), and that this may cause adverse health sequelae (incident CVD, cancer, and ACM) directly and/or indirectly, with other a priori identified variables that may form part of the causal pathway or act as confounders.

An overview of all the statistical models with relevant adjustments and exclusions is provided in Table S4. Model 1 was adjusted for sex and accelerometer device type only (with age as underlying time scale), while model 2a additionally adjusted for demographic and lifestyle covariates (see Figure S2) and constitute the main results regarding whether the SB accumulation pattern is associated with clinical outcomes (ie, total effects). Model 3a then examined the degree to which effects of SB accumulation pattern are independent of the total amount of SB and physical activity arising from the pattern of behavior (ie, direct effects), by adjusting for 24-hour time use in terms of the isometric log-ratio transformed z parameters (see Table S2 and Figure S3). Due to collinearity (variance inflation factor >10), isometric log-ratio parameter z3 was dropped. As such, models accounted for amount of nonwear/in-bed versus waking wear time (z1), and the balance of waking hours between SB and physical activity (z2), but not for relative balance of LPA versus MVPA within physical activity (z3). Relationships of the isometric log-ratio parameters with SB accumulation (Figure S3) indicated the omission of z3 was not likely important, as it had very limited relationships with alpha (r_s=−0.03) and usual bout duration (r_s=0.11). By contrast, z2 and z1 were important in relation to SB accumulation (r_s with alpha and usual bout duration, respectively: −0.50, 0.51 [z2] and −0.31, 0.34 [z1]). That is, both alpha and usual bout duration were more correlated with %SB and %LPA than with the remaining time uses (Figure S4).

Sensitivity Analyses

A range of sensitivity analyses were performed. Sex-stratified models were examined to ensure that an effect specific to one sex was not missed in overall models. Separate models additionally adjusted for body mass index (models 2b and 3b), diet quality (models 2c and 3c), and physical function (models 2d and 3d), which in previous studies have been considered as potential confounders and/or as causal intermediates. Additional rationale for separate adjustment for diet quality and physical function was that they had some missing data (both ≤10% of the sample; detailed in Table S4). Diet quality was also very poorly correlated with alpha (r_s=0.06) and usual bout duration (r_s=−0.07); thus, its role as a potential confounder was questionable together with unnecessary reductions to sample size. Finally, to further investigate potential reverse causality bias in the ACM outcomes, we excluded participants with prevalent chronic disease (history of stroke/myocardial infarction or cancer) at baseline in models 2e and 3e. Based on the strong rank-order correlations (Table S2), we expect our 2 x SB accumulation exposures should broadly reflect the findings from all SB accumulation measures. However, to provide directly comparable findings with some previous studies,[21–23] we have also reported supplementary results based on arithmetic mean SB bout duration. All data processing and analyses were conducted using Stata v15.1 (StataCorp, College Station, TX) and statistical significance set at P<0.05 (2-tailed). Results are reported with 95% CIs and according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[39]

RESULTS

Descriptive Characteristics of the Sample

A total of 1081 incident CVD, 440 incident cancer, and 612 ACM events occurred for 5017, 6234, and 7563 participants, respectively, in the final analytical samples. As previously reported,[28] participants with valid accelerometer data did not differ significantly from those who did not wear the accelerometer in terms of age, sex, body mass index, education level, and self-rated health. Mean follow-up time for incident CVD and cancer was 6.1 and 6.3 years (30 424 and 39 232 person-years), respectively, and 6.4 years (48 323 person-years) for ACM. Table 1 summarizes the baseline characteristics of the cases and noncases in the analysis samples for each outcome (Table S5 stratified by sex). Mean age at baseline for the ACM sample was 70.2 years (SD, 7.5 years), mean body mass index was 26.9 kg/m^2 (SD, 4.3 kg/m^2); and 55.4% were women. On average, cases for all outcomes were older, more overweight, of higher education level, and were more likely to take medications and have a history of diabetes. They also tended to be less physically active and spend more time in SB, with longer usual SB bout durations.

Association of SB Accumulation Patterns With Health Outcomes

Likelihood ratio tests did not detect any significant nonlinearity (all P≥0.05; range, P=0.1–0.9). The shape of associations of SB accumulation patterns with incident CVD, incident cancer, and ACM (Figure) mostly also supported a lack of nonlinearity, except for some possible (nonsignificant) flattening out of relationships with incident cancer at alpha of ≈1.9 (60th percentile) and usual SB bout duration of ≈30 to 35 minutes (≈90th percentile).

Table 1. Descriptive Characteristics of Sample at Baseline by Incident CVD, Cancer, and All-Cause Mortality Status

Characteristics	Incident CVD		Incident cancer		All-cause mortality	
	Noncases (n=3936)	Cases (n=1081)	Noncases (n=5794)	Cases (n=440)	Noncases (n=6951)	Cases (n=612)
Follow-up time, y, mean±SD	6.3±2.8	5.1±2.3	6.4±2.8	5.1±2.3	6.5±2.8	5.6±2.4
Women, n (%)	2403 (61.1)	593 (54.9)	3214 (55.5)	175 (39.8)	3931 (56.6)	258 (42.2)
Age, y, mean±SD	67.8±6.8	71.1±7.2	69.7±7.5	71.4±7.4	69.7±7.3	76.2±7.7
Education level, n (%)						
None	850 (21.6)	297 (27.5)	1443 (24.9)	106 (24.1)	1688 (24.3)	174 (28.4)
General Certificate of Education ordinary level	524 (13.3)	124 (11.5)	728 (12.6)	44 (10.0)	844 (12.1)	63 (10.3)
General Certificate of Education advanced level	1775 (45.1)	486 (45.0)	2564 (44.3)	213 (48.4)	3123 (44.9)	279 (45.6)
Bachelor's degree and above	787 (20.0)	174 (16.1)	1059 (18.3)	77 (17.5)	1296 (18.6)	96 (15.7)
Social class, n (%)						
Unemployed	40 (1.0)	6 (0.6)	57 (1.0)	2 (0.5)	65 (0.9)	3 (0.5)
Professional	363 (9.2)	94 (8.7)	488 (8.4)	42 (9.5)	609 (8.8)	53 (8.7)
Managerial/Technical	1610 (40.9)	426 (39.4)	2295 (39.6)	208 (47.3)	2809 (40.4)	251 (41.0)
Skilled nonmanual	617 (15.7)	172 (15.9)	912 (15.7)	57 (13.0)	1059 (15.2)	109 (17.8)
Skilled manual	807 (20.5)	230 (21.3)	1245 (21.5)	75 (17.0)	1477 (21.2)	112 (18.3)
Semiskilled	424 (10.8)	129 (11.9)	674 (11.6)	47 (10.7)	786 (11.3)	67 (10.9)
Nonskilled	75 (1.9)	24 (2.2)	123 (2.1)	9 (2.0)	146 (2.1)	17 (2.8)
Smoking status, n (%)						
Current	203 (5.2)	60 (5.6)	290 (5.0)	29 (6.6)	356 (5.1)	35 (5.7)
Former	1612 (41.0)	467 (43.2)	2554 (44.1)	208 (47.3)	3019 (43.4)	322 (52.6)
Never	2121 (53.9)	554 (51.2)	2950 (50.9)	203 (46.1)	3576 (51.4)	255 (41.7)
Alcohol intake, units/wk, median (IQR)	4.0 (1.0–9.0)	3.0 (0.0–8.0)	4.0 (0.5–9.0)	4.0 (1.0–8.0)	4.0 (0.5–9.0)	3.0 (0.0–8.0)
Baseline history of diabetes or taking diabetes medications, n (%)	78 (2.0)	48 (4.4)	222 (3.8)	33 (7.5)	268 (3.9)	48 (7.8)
Antihypertensive medication, n (%)	426 (10.8)	371 (34.3)	1632 (28.2)	161 (36.6)	1938 (27.9)	293 (47.9)
Lipid-lowering medication, n (%)	342 (8.7)	199 (18.4)	998 (17.2)	120 (27.3)	1206 (17.4)	188 (30.7)
Antidepressant medication, n (%)	216 (5.5)	90 (8.3)	379 (6.5)	33 (7.5)	444 (6.4)	64 (10.5)
Family history of CVD (stroke, myocardial infarction), n (%)	1732 (44.0)	573 (53.0)	2823 (48.7)	231 (52.5)	3384 (48.7)	332 (54.2)
Family history of cancer, n (%)	1527 (38.8)	454 (42.0)	2250 (38.8)	177 (40.2)	2771 (39.9)	244 (39.9)
Family history of diabetes, n (%)	497 (12.6)	138 (12.8)	804 (13.9)	55 (12.5)	942 (13.6)	91 (14.9)
Body mass index, kg/m^2, mean±SD	26.2±4.0	27.0±4.1	26.9±4.3	27.3±4.0	26.9±4.3	27.0±4.3
Maximum handgrip, kg, mean±SD	30.9±10.2	30.4±9.9	30.8±10.3	32.0±10.1	30.7±10.3	28.7±9.6
Usual walking speed, m/s, mean±SD	1.2±0.2	1.1±0.2	1.1±0.2	1.1±0.3	1.1±0.2	1.0±0.3
Chair stand speed, stands/min, mean±SD	28.3±8.1	25.9±7.9	27.3±8.0	26.0±8.0	27.3±8.0	23.6±7.2
Physical function, *z* score, mean±SD *	0.2±0.7	0.0±0.7	0.1±0.7	0.0±0.7	0.1±0.7	0.0±0.7
Accelerometer results†						
Valid wear days, mean±SD	6.6±0.6	6.7±0.6	6.6±0.6	6.7±0.6	6.6±0.6	6.7±0.6
Valid wear time, min/d, mean±SD	868.4±57.5	862.7±59.2	864.1±59.8	862.6±58.4	864.1±59.1	849.2±60.2
Moderate- to vigorous-intensity physical activity (cpm ≥2020), min/d, median (IQR)	20.1 (9.4–34.7)	14.3 (6.1–27.7)	16.6 (6.7–31.3)	14.3 (4.7–29.5)	16.4 (6.7–30.9)	6.2 (1.2–17.1)
Light-intensity physical activity (cpm 100–2019, h/d, mean±SD)	4.8±1.3	4.6±1.3	4.6±1.3	4.4±1.3	4.6±1.3	3.9±1.4
Sedentary behavior (cpm <100), h/d, mean±SD‡	9.2±1.4	9.4±1.4	9.4±1.4	9.7±1.4	9.4±1.4	10.1±1.5
Usual SB bout duration, min, median (IQR)§	16.0 (12.6–20.7)	17.0 (13.2–22.4)	16.9 (13.1–22.3)	19.0 (14.3–24.5)	17.0 (13.1–22.3)	20.6 (15.4–27.9)

Table 1. Continued

Characteristics	Incident CVD		Incident cancer		All-cause mortality	
	Noncases (n=3936)	Cases (n=1081)	Noncases (n=5794)	Cases (n=440)	Noncases (n=6951)	Cases (n=612)
Alpha, mean±SD‖	1.9±0.1	1.9±0.1	1.9±0.1	1.8±0.1	1.9±0.1	1.8±0.1

cpm indicates counts per minute; CVD, cardiovascular disease; IQR, interquartile range, and SB, sedentary behavior.

*An overall *z* score derived from hand grip strength (kg), usual walking speed (m/sec), and a timed chair stand speed (stand/min).

†Valid wear days are days with ≥10 hours of valid wear time (convention for compliant wear). Data from the Actigraph GT1M and GT3X+ accelerometers were harmonized using standard approaches to produce virtually identical results during standardized movements (ie, activity volume and intensity) and making them suitable for combined analyses. For participants who attended both the third and fourth in-clinic assessment visits (baseline) between 2004 and 2016 and wore an accelerometer, data from their earliest visit (ie, third visit) were used as baseline.

‡Estimates for SB volume similar to those reported in Dempsey et al (2020),[7] differing slightly because of small differences in inclusion criteria.

§Usual SB bout duration (also known as w50 or x50) is the midpoint of the cumulative distribution of SB bout durations. Half of all SB time is accumulated in bouts longer than the usual SB bout duration.

‖Alpha is a unitless measure ranging from 1.4 to 2.6 that characterizes the frequency distribution of SB bout durations. Higher values indicate SB accumulation patterns with relatively more short bouts (ie, more interrupted) and relatively fewer short bouts.

Confounder-adjusted models (model 2a) showed no large or statistically significant association of SB pattern with incident CVD, with all HRs per SD of the exposure (HR_{SD}) and their CIs very close to 1 (Table 2). For incident cancer, confounder-adjusted models showed higher rates with more prolonged SB accumulation ($P<0.05$); however, associations were modest, with HR_{SD} ≈1.1 for usual SB bout duration and HR_{SD} ≈0.9 for alpha. For ACM, confounder-adjusted models showed higher rates with more prolonged SB accumulation (Table 2) that were statistically significant ($P<0.001$); however, associations were again modest, with HR_{SD} slightly over 1.1 for usual SB bout duration and slightly stronger (HR_{SD} ≈0.8) for alpha.

Table 3 shows the extent of risk across percentiles of the population, including comparing those with the most extreme differences in SB pattern. These comparisons (HR for 90th versus 10th percentile, HR_{90vs10}) indicated modest but not trivial differences in incident cancer rates favoring a less prolonged SB accumulation, based on both usual SB bout duration (HR_{90vs10}, 1.47; 95% CI, 1.07–2.02) and alpha (HR_{90vs10}, 0.68; 95% CI, 0.51–0.91). Similarly, ACM rates were modestly in favor of a less prolonged SB pattern based on alpha (HR_{90vs10}, 0.63; 95% CI, 0.48–0.84) and to a lesser and not statistically significant degree based on usual SB bout duration (HR_{90vs10}, 1.32; 95% CI, 0.98–1.79).

Role of Time-Use in Associations of SB Accumulation Pattern

The SB pattern, only when measured by alpha, showed significant associations with incident cancer and ACM rates that were independent of time use (Table 2; model 3a). However, there also was limited evidence to support that associations seen for SB patterns operated through time use, with only modest attenuation of HR. For incident cancer, the small HR_{SD} was 0.88 (95% CI, 0.79–0.98) for alpha was nearly identical at 0.87 (95% CI, 0.76–0.99) after adjustment, as was the small HR_{SD} for usual SB bout duration (1.12; 95% CI, 1.02–1.23), which became 1.10 (95% CI, 0.98–1.23) and showed loss of significance due to because of widening of CIs. Confounder-adjusted associations with ACM were HR_{SD} of 1.16 (95% CI, 1.07–1.26) for usual SB bout duration and HR_{SD} of 0.80 (95% CI, 0.72–0.89) for alpha, while their SB volume-adjusted counterparts were weaker, with HR_{SD} of 1.06 (95% CI, 0.97–1.16) and HR_{SD} of 0.87 (95% CI, 0.77–0.99), respectively.

Sensitivity Analyses

Sex-stratified analyses were broadly similar to the overall results in that rates of incident cancer and ACM, but not incident CVD, tended to be somewhat higher with more prolonged SB accumulation. However, the associations were weak in women and only reached statistical significance in men (Table S6; model 2a).

The associations of SB accumulation patterns with incident CVD, cancer, and ACM, having adjusted for confounders (model 2a) and 24-hour time use (models 3a), were for the most part not materially altered in sensitivity analyses (see Table S7) further adjusting for body mass index (models 2b and 3b), diet quality (models 2c and 3c), and physical function (models 2d and 3d). The tendency was mostly for the magnitude of associations to move slightly closer toward the null upon additional adjustment (eg, HR_{SD}, 0.88 [95% CI, 0.79–0.98] to 0.90 [95% CI, 0.81–1.01]) for alpha and incident cancer after adjustment for body mass index, or for CIs to widen slightly (higher *P* values for the linear model). However, associations were strengthened slightly after adjustment for physical function but only for incident cancer (eg, HR_{SD}, 0.88 [95% CI, 0.79–0.98] to 0.84 [95% CI, 0.75–0.95] for alpha). Further sensitivity analyses that excluded those with prevalent disease in ACM-specific models (models 2d and 3d) slightly reduced the precision of HR estimates overall because of the drop in sample size (widened the 95% CIs), marginally weakened the nonsignificant positive effect sizes for usual SB bout duration, and slightly

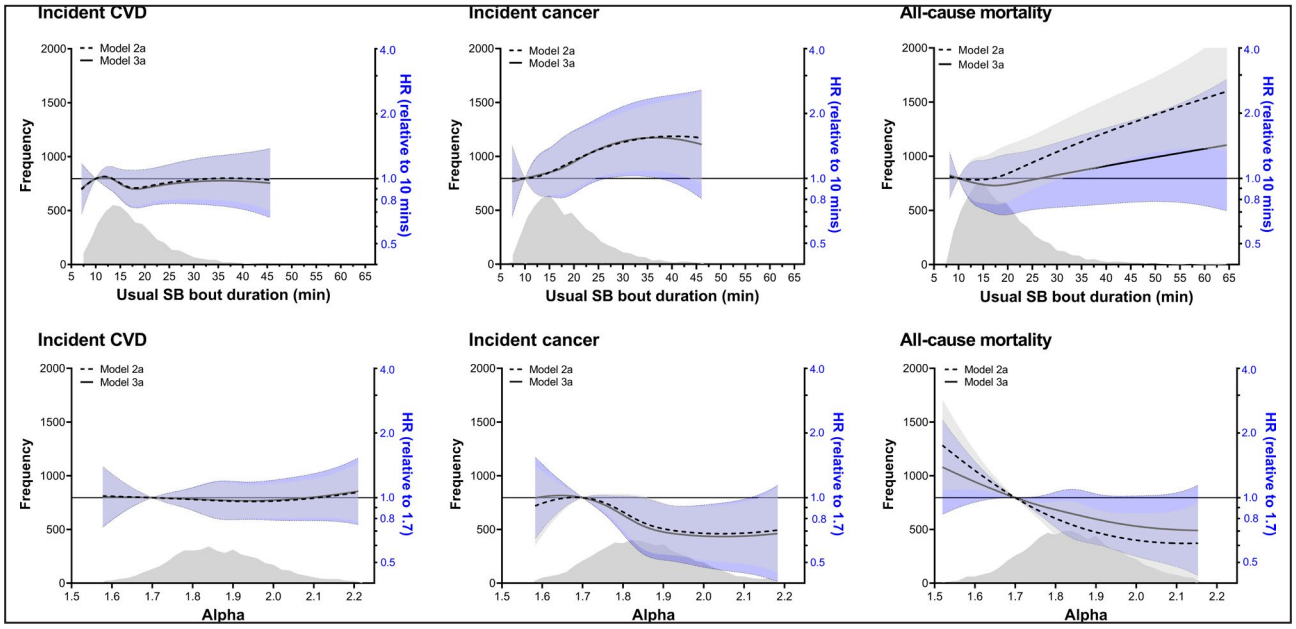

Figure. Baseline exposure distribution and hazard ratios (HR; 95% CIs) for incident CVD, incident cancer, and all-cause mortality with SB bout accumulation patterns.
Models were fitted with the use of restricted cubic splines (3 evenly spaced knots), and results are shown between 1st and 99th percentiles of the relevant exposure. Reference values chosen for each exposure approximated the 10th percentile (usual SB bout duration=10 minutes and alpha=1.7 [unitless; higher values indicate accumulation patterns with relatively more interrupted SB time than prolonged SB time]). Likelihood ratio tests for nonlinearity were all nonsignificant (P>0.05), indicating linear models were reasonable (presented in Table 2). Covariates that violated the proportional hazard assumptions (education level; social class, family history of diabetes and CVD) were included as baseline strata. Model 1 is adjusted for sex and device type (with age as the underlying time scale). Model 2a is adjusted as for model 1 plus education level; social class; smoking status; alcohol intake; baseline history of diabetes or taking diabetes medications (not for cancer); taking medication for hypertension/dyslipidemia (not for cancer outcome), or depression; and family history of CVD (stroke/myocardial infarction), diabetes, or cancer (not CVD or diabetes for cancer outcome). Model 3a includes the same covariates as model 2a and further adjusts for the composition of 24-hour time use (z1 and z2; with z3 dropped because of collinearity). Participants with a history of stroke/myocardial infarction or cancer were excluded for all incident CVD or cancer outcome models, respectively. For all-cause mortality, history of stroke/myocardial infarction or cancer was statistically adjusted for. CVD indicates cardiovascular disease; and SB, sedentary behavior.

strengthened the inverse effect sizes (lower HR) for alpha (Table S7).

Further models for arithmetic mean SB bout duration, which were reported in Table S8 to harmonize with studies that focused on this indicator,[21–23] had similar results to those reported in our main findings (confounder adjusted, model 2a), that is, no large or significant association with incident CVD and significant associations with incident cancer and ACM with more prolonged patterns. Examining this risk exposure across the population, the associations (comparing most versus least extreme patterns) were in the range of what was seen for alpha and usual SB bout duration.

DISCUSSION

A growing body of literature suggests that higher volumes of SB are associated with an elevated risk of CVD, cancer, and ACM.[5–7] Previously in EPIC-Norfolk,[7] we showed that higher SB volumes are associated with ACM and incident cancer, with less evidence for incident CVD, particularly after adjustment for MVPA. We build upon this work here by examining whether, and how, these outcomes were related to a behavioral pattern of accumulating SB for long periods at a time in middle- and older-aged adults. After adjusting for potential confounders, a more prolonged SB bout accumulation pattern was associated with higher rates of incident cancer and ACM, but such associations were not observed with incident CVD. Based on alpha as the indicator, all of the total effect of SB accumulation on incident cancer and most of the effect on ACM appeared to occur directly, remaining present at a similar or only slightly reduced magnitude after removing any effects that may occur because a pattern of prolonged SB accumulation results in accruing more SB and less physical activity. Based on usual SB bout duration as the indicator, associations with ACM were almost entirely indirect (attenuated completely with

Table 2. Linear Association of Incident CVD and Cancer Events and All-Cause Mortality With SB Bout Accumulation Patterns

	Incident CVD		Incident cancer		All-cause mortality			Incident CVD		Incident cancer		All-cause mortality	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Usual SB bout duration, min							Alpha						
Model 1	1.02 (0.96–1.08)	0.542	1.08 (0.98–1.19)	0.102	1.14 (1.06–1.22)	<0.001	Model 1	0.96 (0.90–1.02)	0.187	0.90 (0.81–1.00)	0.049	0.82 (0.75–0.90)	<0.001
Model 2a	1.00 (0.94–1.06)	0.914	1.12 (1.02–1.23)	0.023	1.16 (1.07–1.26)	<0.001	Model 2a	1.00 (0.93–1.07)	0.968	0.88 (0.79–0.98)	0.024	0.80 (0.72–0.89)	<0.001
Model 3a	0.99 (0.92–1.07)	0.795	1.10 (0.98–1.23)	0.099	1.06 (0.97–1.16)	0.209	Model 3a	1.00 (0.92–1.09)	0.932	0.87 (0.76–0.99)	0.038	0.87 (0.77–0.99)	0.029

Hazard ratios and 95% CIs depicting the linear association (per 1 SD change) between usual SB bout duration and alpha with incident CVD, incident cancer and all-cause mortality. CVD indicates cardiovascular disease; HR, hazard ratio; and SB, sedentary behavior.

Model 1 is adjusted for sex and device type (with age as the underlying time scale). Model 2a is adjusted as for model 1 plus education level; social class; smoking status; alcohol intake; baseline history of diabetes or taking diabetes medications (not for cancer); taking medication for hypertension/dyslipidemia (not for cancer outcome), or depression; and family history of CVD (stroke/myocardial infarction), diabetes, or cancer (not CVD or diabetes for cancer outcome). Model 3a includes the same covariates as Model 2a and further adjusts for the composition of 24-hour time use (z1 and z2; with z3 dropped because of collinearity).

Participants with a history of stroke/myocardial infarction or cancer were excluded all for incident CVD or cancer outcome models, respectively. For all-cause mortality, history of stroke/myocardial infarction or cancer was statistically adjusted for in models 2 and 3 (a-d). Models 2e and 3e include the same covariates as Models 2a and 3a, but exclude participants with a history of stroke/myocardial infarction or cancer.

adjustment), while the results for incident cancer were somewhat equivocal (there was a loss of significance but no change in hazard ratio). Previous literature has supported associations of SB accumulation on various health end points, mostly independently of volume of SB or MVPA.[14,18,40]

The present findings suggest that "breaking up SB" may serve as a useful and pragmatic adjunct to messages to be more physically active and limit SB, such as in public health guidelines in Australia and the United Kingdom.[9,11] The total effects that were observed supported a message that adults should break up SB with more LPA or MVPA. A message that long SB bouts should be replaced with shorter bouts of SB (not altering the amount of SB and physical activity) had only equivocal support, in that the direct effects were only sometimes seen. No clear dose-response or threshold of bout duration can be recommended with any rigor, since each individual's SB accumulation pattern is composed of a distribution of bout durations rather than a single duration.

Our findings extend upon previous cross-sectional evidence suggesting that more prolonged SB accumulation patterns may be deleteriously associated with cardiometabolic risk factors[14,18,40] and recent prospective evidence indicating higher risk of either incident CVD,[22] cancer mortality,[21] or ACM.[23,24] Several factors make it difficult to compare our findings to these previous studies, which notably all had fewer clinical/ACM events and shorter follow-up times compared with ours. Most of these studies[21–24] have examined both "total" and "direct" effects to some degree, usually reporting models with and without adjustment for total SB and/or MVPA. However, our study is better placed to estimate direct effects that do not operate through time use, as many of these studies did not fully capture nonlinear relationships or did not account for SB, LPA, and MVPA simultaneously, for example, via compositional data analysis or other isotemporal substitution modeling.

Interestingly, we observed little evidence of an association for incident CVD, with CIs ruling out a substantial (≥50%) elevation or reduction in HR as unlikely. This contrasts with previous literature related to cardiometabolic risk factors[14,18,40] and with the prospective findings of Bellettiere and colleagues,[22] which showed strong and consistent (dose-related) associations of more prolonged SB accumulation with higher CVD risk (n=545 CVD events) in older US women. These differences potentially could be related to variations in the population studied (who were older, women only, and had a different mix of ethnicities) or study methods; such as the extent to which prevalent CVD cases or early CVD events were removed, as well as some potential measurement error in the accelerometer methods for our uniaxial accelerometry. Sex alone is unlikely

Table 3. Association of Incident CVD and Cancer Events and All-Cause Mortality With SB Bout Accumulation Patterns Across Percentiles of the Population

	Incident CVD (n=5017; no. of events=1081; person years=30 425)				Incident cancer (n=6234; no. of events=440; person years=39 234)				All-cause mortality (n=7563; no. of events=612; person years=48 303)			
Percentile	p10	p30	p60	p90	p10	p30	p60	p90	p10	p30	p60	p90
Usual SB bout duration, min												
	10	15	20	30	10	15	20	30	10	15	20	30
Model 1	1	0.98 (0.85–1.13)	0.95 (0.80–1.13)	1.05 (0.86–1.27)	1	1.02 (0.80–1.29)	1.15 (0.85–1.55)	1.37 (1.01–1.87)	1	0.94 (0.74–1.18)	1.00 (0.76–1.32)	1.18 (0.90–1.55)
Model 2a	1	0.95 (0.82–1.11)	0.92 (0.76–1.10)	0.99 (0.80–1.22)	1	1.07 (0.84–1.36)	1.21 (0.89–1.64)	1.47 (1.07–2.02)	1	0.99 (0.77–1.26)	1.05 (0.78–1.42)	1.32 (0.98–1.79)
Model 3a	1	0.95 (0.81–1.11)	0.90 (0.74–1.10)	0.97 (0.76–1.23)	1	1.07 (0.82–1.38)	1.19 (0.85–1.67)	1.49 (1.02–2.16)	1	0.94 (0.72–1.21)	0.94 (0.68–1.29)	1.04 (0.73–1.46)
Alpha												
	1.7	1.8	1.9	2	1.7	1.8	1.9	2	1.7	1.8	1.9	2
Model 1	1	0.95 (0.85–1.06)	0.91 (0.76–1.08)	0.87 (0.73–1.04)	1	0.85 (0.71–1.02)	0.71 (0.55–0.93)	0.70 (0.53–0.92)	1	0.81 (0.70–0.95)	0.71 (0.57–0.88)	0.67 (0.52–0.86)
Model 2a	1	0.98 (0.88–1.10)	0.96 (0.80–1.16)	0.96 (0.80–1.16)	1	0.86 (0.71–1.04)	0.72 (0.54–0.94)	0.68 (0.51–0.91)	1	0.80 (0.67–0.96)	0.69 (0.54–0.88)	0.63 (0.48–0.84)
Model 3a	1	0.99 (0.87–1.11)	0.97 (0.79–1.19)	0.97 (0.79–1.21)	1	0.83 (0.68–1.02)	0.69 (0.51–0.94)	0.66 (0.47–0.92)	1	0.88 (0.73–1.06)	0.79 (0.61–1.04)	0.74 (0.53–1.02)

Data are hazard ratios and 95% CIs and were fitted with the use of restricted cubic splines (3 evenly spaced knots). Results presented approximate the 10th (reference), 30th, 60th and 90th percentiles across all 3 outcomes for usual SB bout duration=10, 15, 20, 30 minutes and alpha= 1.7, 1.8, 1.9, 2 (unitless; higher values indicate accumulation patterns with relatively more interrupted ST than prolonged ST). Covariates that violated the proportional hazard assumptions (education level; social class, family history of diabetes and CVD) were included as baseline strata. CVD indicates cardiovascular disease; and SB, sedentary behavior.

Model 1 is adjusted for sex and device type (with age as the underlying time scale). Model 2a is adjusted as for model 1 plus education level; social class; smoking status; alcohol intake; baseline history of diabetes or taking diabetes medications (not for cancer); taking medication for hypertension/dyslipidemia (not for cancer outcome), or depression; and family history of CVD (stroke/myocardial infarction), diabetes, or cancer (not CVD or diabetes for cancer outcome). Model 3a includes the same covariates as model 2a and further adjusts for the composition of 24-hour time use (z1 and z2; with z3 dropped because of collinearity).

Participants with a history of stroke/myocardial infarction or cancer were excluded for all incident CVD or cancer outcome models, respectively. For all-cause mortality, history of stroke/myocardial infarction or cancer was statistically adjusted for in models 2a and 3a.

to explain the different findings, as our sex-stratified analysis did not detect sizeable or significant effects within women. Our findings for ACM and incident cancer were more consistent with previous literature[23,24] and provide further context and supporting evidence for both fatal and nonfatal cancer risk in relation to SB bout accumulation patterns. Consistent with our findings, Gilchrist and colleagues[21] also recently showed a borderline association of more prolonged SB accumulation with increased risk of cancer mortality in confounder- and MVPA-adjusted models (HR, 1.01 per 1 min/bout increase in [arithmetic] mean SB bout duration; 95% CI, 1.00–1.02; *P*=0.06).

The choice of metric for SB accumulation may be important in the examination of associations with CVD, cancer, and ACM. Indeed, a "scattergun" approach increases problems with multiple testing, while a single poorly chosen indicator risks missing associations. Previous prospective studies of clinical end points[21–23] have focused primarily on arithmetic mean SB bout duration as their main SB accumulation pattern metric, while Di and colleagues[24] also explored several additional fragmentation metrics with ACM. Two studies have included alpha and usual SB bout duration, tested in relation to incident CVD[22] and ACM (alpha only).[24] We used both a data-driven and theoretically informed process to select 2 indicators that were not highly correlated with each other, but that collectively correlated, often nonlinearly, at r_s>0.8 with all the other SB accumulation indicators. These 2 indicators (alpha and usual bout duration) should therefore capture any effects detectable through the other indicators, so long as nonlinearity is addressed. Both in our work and in Bellettiere and colleagues'[14] recent studies of cardiometabolic risk biomarkers and CVD risk,[22] there were distinct tendencies for alpha to be most sensitive to detecting associations with health outcomes, usual bout duration to be least sensitive, and arithmetic mean to be somewhere in between. Notably, this directly parallels the degree to which each statistic is robust to the very long bouts in the heavy-tailed SB bout duration distribution (ie, alpha most and usual bout duration least). This observation may be coincidental or could highlight something important about very long bouts. For example, these very long bouts might be comparatively sporadic or have limited repeatability (alpha has shown more repeatability than usual but duration[15]), might be most subject to misclassification (eg, most prone to confusion with nonwear or sleep), or might reflect a dimension of SB that has not been considered, such as the type or context of SB performed.[41]

Our findings, and the literature in general, have mostly considered SB accumulation patterns in terms of bout duration, with limited exploration of other facets of behavioral patterns. Knowing how long bouts of SB last does not necessarily indicate whether prolonged bouts of SB are separated by a small or large amount of physical activity. Indeed, the requisite amount, type, and/or intensity of physical activity that should interrupt SB is not fully established.[5] Time of day, including relative to food intake,[42–44] could also be important. In addition, we accounted for extent of time use but not the accumulation pattern of active time uses, which is highly intertwined with the pattern of SB accumulation. That is, the results indicate that the manner of accumulating sedentary (versus active) behaviors shows importance beyond volume of sedentary and more active time uses. However, they are not able to show whether these effects are produced through the avoidance of long bouts, the presence of repeated shorter bouts (meaning repeated active bouts are also occurring), or what the prolonged SB accumulation implies for the how fragmented or prolonged the active bouts between each sedentary bout would be. A more complete consideration of patterns may also help elucidate causal pathways or underlying mechanisms that may help to refine appropriate SB guidelines[5,9,45,46] and intervention messaging. Future research could also evaluate further aspects of behavioral patterns to provide evidence-based guidance regarding any particularly "risky" times of the day to be sedentary, how long people should engage in prolonged SB before needing to interrupt it, and, importantly, for how long and with what type or intensity of activity they should aim to interrupt their SB (ie, the most effective and pragmatic countermeasures).

Strengths, Limitations, and Future Directions

The prospectively collected data on 3 important clinical end points, in both men and women, alongside accelerometer-derived measures of activity are important strengths of this study. The study population, middle- to older-aged adults, are notably also an appropriate population for targeting messages and interventions regarding SB, given their typically high volumes of SB and poorer adherence to current MVPA guidelines. However, less error in measuring SB accumulation, and potentially less bias of estimates toward the null, might have been achieved with either a thigh-mounted accelerometer[47,48] or a waist-worn triaxial monitor with algorithms[49] that can better separate sitting from standing posture, and ideally with 24-hour monitoring to minimize unobserved behaviors.[50] A further strength was the carefully selected conceptual model underpinning the range of statistical models presented. These considered the total effect of SB accumulation patterns, how it may operate by shifting time use toward SB (and therefore away from LPA and MVPA), potential confounding variables, and reverse causality bias. Although models were adjusted for a range of important confounding variables, further confounding

may also have occurred via some unmeasured factors or included variables measured with substantial error such as diet quality. The study was also mostly well powered, as indicated by CIs, with sufficient precision to rule out large HR (CVD) or exclude the null (incident cancer, ACM), except when modeling the highly overlapping exposures of SB accumulation and time use, which resulted in some widening of CIs around HR for alpha with ACM. We were also not powered to examine associations of SB patterns with specific cancer or CVD subtypes, which may have provided further insights. Smaller sample sizes for secondary sex-stratified models may have also limited comparisons. Finally, while we minimized the issue of multiple testing through our exposure selection procedures, there were still several tests conducted.

Future larger studies or pooled analyses of prospective end points using high-quality measures of SB accumulation would be highly informative. Additional study of the combined associations of sedentary time and sedentary accumulation patterns with incident disease outcomes in older adults may be warranted in larger/pooled cohort samples.[19] Larger samples would also permit exploration of further important topics, such as potentially differential associations of sedentary patterns at specific high or low levels of sedentary behavior and physical activity. More specific advice would also need to be informed by future research that can quantify "dose" in relation to both how long at a time people engage in SB, as well as any requirements concerning the duration, type, timing, and intensity of physical activity used to interrupt prolonged SB.[5] Ideally, such research should allocate dose and behavioral substitutions experimentally.[51,52] Longer accelerometer measurement protocols and repeated measures of the accelerometer exposures could also add further insights.[46]

CONCLUSIONS

This study suggests that accruing SB in a prolonged manner is associated with higher rates of incident cancer and ACM, adding to a growing body of literature linking insufficient MVPA and excessive volumes of SB to premature mortality through cancer and CVD.[5,8,10,45] In contrast with previous research in older women,[22] our study did not support an association of SB accumulation with incident CVD. Prolonged SB accumulation patterns might not solely lead to increased risk through how they shift time use toward more SB and less physical activity, with direct contribution of the SB pattern itself to incident cancer and ACM, at least when measured by alpha. These findings provide useful implications for how messaging for interventions and guidelines might be framed. For example, a message to "break up" prolonged periods of SB[9,11] with more active alternatives could be pragmatic in promoting a shift in behavior away from SB towards more physical activity, while acknowledging that adults still need to sit, as well as focusing on less prolonged accumulation of SB. There was some support (but weaker) for associations of SB accumulation on incident cancer and ACM independent of time uses, and accordingly there is some basis (but less) for messaging around accumulating SB in a less consolidated manner, and in specifically emphasizing prolonged SB as a target for sedentary reduction (ie, shifting both SB time and accumulation).

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1: Description of indicators of SB bout accumulation patterns

SB accumulation measures	Estimation method *	Description with pros (✓) and cons (×)
Arithmetic mean SB bout duration	$\frac{\sum \text{time in SB bouts}}{\text{n SB bouts}}$	● Summary statistic for normal distributions ● Higher values indicate a more prolonged pattern of SB bout accumulation ✓ Well known statistic, easy to calculate × Higher than the midpoint of midpoint of the distribution of bout duration (log-normal or power-law) × Not a robust statistic for presence of very long bouts
Geometric mean SB bout duration	$e^{\frac{\sum ln(time\ in\ SB\ bouts)}{n\ SB\ bouts}}$	● Summary statistic for lognormal distribution † ● Midpoint that is between the median and arithmetic mean ● Higher values indicate a more prolonged pattern of SB bout accumulation durations: could be power-law or lognormal). ✓ Somewhat simple to calculate as mean of log-transformed variable, exponentiated ✓ Robust statistic for presence of very long bouts
Median SB bout duration	For odd number of SB bouts $X^{\frac{n}{2}}$ For even number of SB bouts $\frac{(X^{[\frac{n-1}{2}]} + X^{[\frac{n+1}{2}]})}{2}$ X = SB bouts ordered by duration n = n SB bouts	● Summary statistic for the midpoint (50%) of the SB bout duration distribution ● Half of all **SB bouts** are longer and half are shorter than the median ● Higher values indicate a more prolonged pattern of SB bout accumulation ✓ Well known statistic, simple to calculate ✓ No distribution assumed × Order statistic, ignores information from the durations of the long bouts that contribute most per bout to total SB time
Fragmentation index	$\frac{n\ breaks}{\sum time\ in\ SB\ bouts}$ *or alternatively* $\frac{n\ SB\ bouts}{\sum time\ in\ SB\ bouts}$	● Intended to indicate how often SB is interrupted relative to the amount of SB ● Almost or exactly the inverse of arithmetic mean SB bout duration ● Lower values indicate a more prolonged pattern of SB bout accumulation ✓ Simple to calculate ✓ One of the first and most commonly reported SB pattern measures x Can be confused with crude n breaks
% of SB hours in bouts ≥30 min	$100\ x\ \frac{\sum \text{time in SB bouts} \geq 30\ \text{min}}{\sum \text{time in SB bouts}}$	● Intended to indicate the extent to which total SB is comprised of the prolonged type, defined commonly as for 30 min or longer at a time ● Higher values indicate a more prolonged pattern of SB bout accumulation ✓ Simple to calculate × Specific to the threshold selected (here, ≥30 min)
Alpha, $\hat{\alpha}$	Estimated by maximum likelihood methods as: $\hat{\alpha} = 1 + n\left[\sum_{i=1}^{n} ln\frac{t_i}{t_{min}}\right]^{-1}$ *n* = number of SB bouts *t* = bout duration (min) and t_{min} = shortest bout recorded / recordable by the monitor	● Summary statistic for power-law distribution [b] ● Lower values indicate a more prolonged pattern of SB bout accumulation (higher a more broken up or fragmented pattern) ✓ Robust statistic for the presence of very long bouts ('outliers') – these are expected in power-law distribution / its summary statistics × Unfamiliar statistic / calculation × Only sometimes interpretable in relation to the midpoint

Usual SB bout duration (also referred to as *w50* or *x50*)	Calculated (in this study) by non-linear regression estimating the following sigmoidal curve function: $$y = \frac{t^n}{t^n + x50^n}$$ where *t* = SB bout duration (min), *n* = a free parameter, x50 = usual SB bout duration (min), and *y* = the proportion of SB time accumulated in bouts ≤ *t*	● Summary statistic for the midpoint (50%) of the cumulative distribution of SB bout duration. ● Half of all SB **time** is accumulated in bouts of this duration or longer ● Effect of each SB bout on the statistic is proportional to how much it contributes to total SB time ● Higher values indicate a more prolonged pattern of SB bout accumulation × Unfamiliar calculation with some computational effort required × Not a robust statistic for the presence of very long bouts

SB = sedentary behavior.

* In this study, SB accumulation statistics were calculated over all SB bouts on all adherent days rather than calculated per day and averaged. This maximizes the sample of bouts to calculate each statistic and avoids any issues for days with no or too few SB bouts to calculate valid statistics.
† The distribution of SB bout duration is highly skewed (with numerous very short bouts and fewer long bouts) and is arguably approximated by a lognormal or power-law distribution.

Table S2: Spearman's rank order correlation coefficients (r_s) between indicators of SB bout accumulation patterns in middle aged to older adults (n=7563, EPIC-Norfolk).

	Alpha †	**Usual SB bout duration**	**Arithmetic mean**	**Geometric mean**	**Median**	**Fragmentation Index †**	**% of SB in bouts ≥30 min**
Alpha †	**1.00**						
Usual SB bout duration, min	0.74	**1.00**					
Arithmetic mean SB bout duration, min	0.91*	0.95*	**1.00**				
Geometric mean SB bout duration, min	1.00*‡	0.74	0.91*	**1.00**			
Median SB bout duration, min	0.84*	0.47	0.67	0.84*	**1.00**		
Fragmentation index (n SB bouts/SB hours) †	0.91*	0.95*	1.00*§	0.91*	0.67	**1.00**	
% of SB hours in bouts ≥30 min	0.63	0.97*	0.87*	0.63	0.37	0.87*	**1.00**

SB = sedentary behavior.

* r >0.8
† Sign of correlations are reversed as required to reflect correlations across increasingly prolonged SB accumulation pattern by both metrics.
‡ alpha and geometric mean SB bout duration are perfect non-linear transforms of each other.
§ fragmentation index and arithmetic mean SB bout duration are perfect inverse of each other.

Table S3: Isometric log-ratio (ilr) parameterization of the 4-part composition of 24-hour time use (non-wear/in-bed, SB, LPA, MVPA).

Parameter	Calculation	Parameter interpretation
z1	$\sqrt{\frac{3}{4}}\ \ln \frac{Other}{\sqrt[3]{SB\ \times LPA\ \times MVPA}}$	- Extent of waking wear time ↓ - More in-bed & non-wear time, less waking wear time (SB + LPA + MVPA)
z2	$\sqrt{\frac{2}{3}}\ \ln \frac{SB}{\sqrt[2]{LPA\ \times MVPA}}$	- Sedentariness of waking wear time ↑ - More SB, less physical activity (MVPA + LPA)
z3	$\sqrt{\frac{1}{2}}\ \ln \frac{LPA}{MVPA}$	- Intensity of physical activity ↓ - More LPA, less MVPA

SB = sedentary behavior; LPA = light intensity physical activity; MVPA = moderate-to-vigorous physical activity

Table S4: Overview of statistical models with relevant adjustments and exclusions for each outcome

Model	Outcomes	Covariate adjustments *	Exclusions †,‡,§
1	ACM, CVD, Cancer	*Gender*	
2a	ACM, CVD, Cancer	*ACM: Gender;* device type; *education level; social class; smoking status; alcohol intake; baseline history of diabetes mellitus or taking diabetes mellitus medications; taking medication for hypertension, taking medication for dyslipidemia, taking medication for depression; family history of CVD (stroke/myocardial infarction), diabetes mellitus, or cancer; and baseline history of stroke/myocardial infarction or cancer.* *CVD: Gender;* device type; *education level; social class; smoking status; alcohol intake; baseline history of diabetes mellitus or taking diabetes mellitus medications; taking medication for hypertension, taking medication for dyslipidemia, taking medication for depression; family history of CVD (stroke/myocardial infarction) or diabetes mellitus.* *Cancer: Gender;* device type; *education level; social class; smoking status; alcohol intake; baseline history of diabetes mellitus or taking diabetes mellitus medications; taking medication for depression; family history of cancer.*	
2b	ACM, CVD, Cancer	Model 2a covariates + additional adjustment for *BMI*	
2c	ACM, CVD, Cancer	Model 2a covariates + additional adjustment for *diet quality*	Missing diet quality data ACM, n=659 CVD, n=374 Cancer, n=540
2d	ACM, CVD, Cancer	Model 2a covariates + additional adjustment for *physical function*	Missing physical function data ACM, n=811 CVD, n=353 Cancer, n=621
2e	ACM only	Same covariates as model 2a (minus adjustment for history of stroke/myocardial infarction and cancer)	Participants with a history of stroke/myocardial infarction or cancer
3a	ACM, CVD, Cancer	Model 2a covariates + additional adjustment for the *composition of 24-hour time use* (z1 and z2; with z3 dropped due to collinearity)	
3b	ACM, CVD, Cancer	Model 3a covariates + additional adjustment for *BMI*	
3c	ACM, CVD, Cancer	Model 3a covariates + additional adjustment for *diet quality*	Same exclusions as Model 2c
3d	ACM, CVD, Cancer	Model 3a covariates + additional adjustment for *physical function*	Same exclusions as Model 2d
3e	ACM only	Same covariates as model 3a (minus adjustment for history of stroke/myocardial infarction or cancer)	Same exclusions as model 2e

SB = sedentary behavior; CVD = cardiovascular disease; ACM = all-cause mortality.

* age as the underlying time scale in all models
† all participants with a history of stroke/myocardial infarction or cancer were excluded from the incident CVD or cancer analyses, respectively.
‡ all participants with early cases (CVD or cancer) and/or deaths within 2 years of follow-up were excluded for all outcomes.
§ all participants with missing data for diet quality or physical function were excluded from those specific models.

Table S5. Descriptive characteristics of sample at baseline for incident CVD, cancer, and all-cause mortality, stratified by gender.

Characteristics	Incident CVD		Incident Cancer		All-Cause Mortality	
	Men (n=2021)	Women (n=2996)	Men (n=2845)	Women (n=3389)	Men (n=3374)	Women (n=4189)
Follow-up time (years), mean±SD	5.9 ± 2.7	6.2 ± 2.7	6.2 ± 2.7	6.4 ± 2.8	6.3 ± 2.7	6.5 ± 2.8
Age (years), mean±SD	69.0 ± 7.0	68.2 ± 7.0	70.4 ± 7.4	69.3 ± 7.5	70.9 ± 7.5	69.7 ± 7.5
Education level, n (%)						
None	377 (18.7)	770 (25.7)	588 (20.7)	961 (28.4)	678 (20.1)	1,184 (28.3)
General Certificate of Education (GCE) Ordinary Level	211 (10.4)	437 (14.6)	272 (9.6)	500 (14.8)	319 (9.5)	588 (14.0)
GCE Advanced Level	980 (48.5)	1,281 (42.8)	1,375 (48.3)	1,402 (41.4)	1,653 (49.0)	1,749 (41.8)
Bachelor's degree, and above	453 (22.4)	508 (17.0)	610 (21.4)	526 (15.5)	724 (21.5)	668 (15.9)
Social class, n (%)						
Unemployed	15 (0.7)	31 (1.0)	23 (0.8)	36 (1.1)	24 (0.7)	44 (1.1)
Professional	208 (10.3)	249 (8.3)	262 (9.2)	268 (7.9)	327 (9.7)	335 (8.0)
Managerial/Technical	838 (41.5)	1,198 (40.0)	1,196 (42.0)	1,307 (38.6)	1,409 (41.8)	1,651 (39.4)
Skilled non-manual	236 (11.7)	553 (18.5)	319 (11.2)	650 (19.2)	387 (11.5)	781 (18.6)
Skilled manual	457 (22.6)	580 (19.4)	654 (23.0)	666 (19.7)	773 (22.9)	816 (19.5)
Semi-skilled	228 (11.3)	325 (10.8)	337 (11.8)	384 (11.3)	389 (11.5)	464 (11.1)
Non-skilled	39 (1.9)	60 (2.0)	54 (1.9)	78 (2.3)	65 (1.9)	98 (2.3)
Smoking status, n (%)						
Current	97 (4.8)	166 (5.5)	138 (4.9)	181 (5.3)	158 (4.7)	233 (5.6)
Former	1,027 (50.8)	1,052 (35.1)	1,538 (54.1)	1,224 (36.1)	1,841 (54.6)	1,500 (35.8)
Never	897 (44.4)	1,778 (59.3)	1,169 (41.1)	1,984 (58.5)	1,375 (40.8)	2,456 (58.6)
Alcohol intake (units/week), median (IQR)	6.0 (2.0-13.0)	3.0 (0.0-7.0)	6.0 (2.0-13.0)	2.5 (0.0-7.0)	6.0 (2.0-13.0)	2.5 (0.0-7.0)
Baseline history of diabetes or taking diabetes medications, n (%)	71 (3.5)	55 (1.8)	152 (5.3)	103 (3.0)	184 (5.5)	132 (3.2)
Anti-hypertensive medication, n (%)	329 (16.3)	468 (15.6)	883 (31.0)	910 (26.9)	1,081 (32.0)	1,150 (27.5)
Lipid-lowering medication, n (%)	256 (12.7)	285 (9.5)	633 (22.2)	485 (14.3)	768 (22.8)	626 (14.9)
Anti-depressant medication, n (%)	72 (3.6)	234 (7.8)	121 (4.3)	291 (8.6)	144 (4.3)	364 (8.7)
Family history of CVD (stroke, myocardial infarction), n (%)	874 (43.2)	1,431 (47.8)	1,337 (47.0)	1,717 (50.7)	1,589 (47.1)	2,127 (50.8)

Family history of cancer, n (%)	780 (38.6)	1,201 (40.1)	1,098 (38.6)	1,329 (39.2)	1,327 (39.3)	1,688 (40.3)
Family history of diabetes, n (%)	228 (11.3)	407 (13.6)	381 (13.4)	478 (14.1)	438 (13.0)	595 (14.2)
Body mass index (kg/m^2), mean±SD	99.4 ± 9.8	88.6 ± 11.2	100.9 ± 10.2	90.0 ± 11.9	100.8 ± 10.2	90.1 ± 11.9
Maximum handgrip (kg), mean±SD	40.1 ± 8.0	24.5 ± 5.5	39.0 ± 8.3	23.9 ± 5.8	38.8 ± 8.2	23.8 ± 5.8
Usual walking speed (m/s), mean±SD	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.3
Chair stand speed (stands/min), mean±SD	28.6 ± 8.2	27.2 ± 8.0	27.9 ± 8.0	26.7 ± 8.0	27.7 ± 8.1	26.5 ± 8.0
Physical function (z-score), mean±SD *	0.2 ± 0.7	0.2 ± 0.7	0.1 ± 0.7	0.1 ± 0.7	0.1 ± 0.7	0.1 ± 0.7
Accelerometer results						
Valid wear days, mean±SD	6.7 ± 0.6	6.7 ± 0.6	6.7 ± 0.6	6.6 ± 0.6	6.7 ± 0.6	6.6 ± 0.6
Valid wear-time, min/day, mean±SD	877.8 ± 59.1	860.0 ± 56.0	872.7 ± 60.3	856.7 ± 58.2	871.1 ± 60.0	856.2 ± 57.8
Moderate-to-vigorous-intensity physical activity (cpm ≥2020), min/day, median (IQR)	22.3 (10.8-38.0)	16.5 (7.3-30.0)	19.6 (8.0-35.3)	14.3 (5.7-27.6)	18.9 (7.4-34.6)	13.5 (5.1-26.6)
Light-intensity physical activity (cpm 100-2019, hr/day, mean±SD	4.5 ± 1.3	4.9 ± 1.2	4.4 ± 1.3	4.8 ± 1.3	4.3 ± 1.3	4.8 ± 1.3
Sedentary behaviour (cpm <100), hr/day, mean±SD	9.6 ± 1.4	9.0 ± 1.3	9.8 ± 1.4	9.2 ± 1.4	9.8 ± 1.4	9.2 ± 1.4
Usual SB bout duration, min, median (IQR)	18.1 (14.1-23.1)	15.1 (11.8-19.3)	19.1 (14.5-24.4)	15.6 (12.2-20.4)	19.3 (14.7-24.8)	15.8 (12.4-20.7)
Alpha, mean±SD	1.8 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.9 ± 0.1

SB = sedentary behavior; CVD = cardiovascular disease; cpm = counts per minute.

* An overall z-score derived from hand grip strength (kg), usual walking speed (m/sec), and a timed chair stand speed (stand/min).

Table S6: Linear association of incident CVD and cancer events and all-cause mortality with SB bout accumulation patterns – stratified by gender.

	Incident CVD		Incident Cancer		All-Cause Mortality	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Usual SB bout duration, min						
Men						
Model 2a	1.04 (0.95-1.15)	0.397	1.19 (1.05-1.35)	0.007	1.24 (1.12-1.38)	<0.001
Model 3a	1.02 (0.91-1.14)	0.709	1.14 (0.99-1.32)	0.063	1.12 (0.99-1.27)	0.061
Women						
Model 2a	0.97 (0.89-1.06)	0.529	1.01 (0.86-1.19)	0.922	1.04 (0.92-1.19)	0.510
Model 3a	0.98 (0.89-1.08)	0.727	1.03 (0.85-1.25)	0.741	0.96 (0.83-1.12)	0.625
Alpha						
Men						
Model 2a	0.96 (0.87-1.07)	0.488	0.84 (0.73-0.97)	0.016	0.72 (0.63-0.83)	<0.001
Model 3a	0.98 (0.87-1.11)	0.749	0.85 (0.72-1.00)	0.057	0.77 (0.65-0.90)	0.002
Women						
Model 2a	1.00 (0.92-1.10)	0.963	0.95 (0.81-1.12)	0.528	0.92 (0.80-1.07)	0.280
Model 3a	0.98 (0.87-1.10)	0.717	0.90 (0.74-1.11)	0.321	1.02 (0.85-1.23)	0.820

Hazard Ratios and 95% confidence intervals (CIs) depicting the association (per 1 standard deviation change) between mean SB bout duration and incident CVD, incident cancer and all-cause mortality. SB = sedentary behavior; CVD = cardiovascular disease.

Model 2a (age as the underlying time scale) is adjusted for device type; education level; social class; smoking status; alcohol intake; baseline history of diabetes mellitus or taking diabetes mellitus medications (not for cancer); taking medication for hypertension/dyslipidemia (not for cancer outcome), or depression; and family history of CVD (stroke/myocardial infarction), diabetes mellitus, or cancer (not CVD or diabetes for cancer outcome). Model 3a includes the same covariates as Model 2a and further adjusts for the composition of 24-hour time use (z1 and z2; with z3 dropped due to collinearity). Further details on specific covariate adjustments per outcome are detailed in Table S4.

Participants with a history of stroke/myocardial infarction or cancer were excluded for all incident CVD or cancer outcome models, respectively. For all-cause mortality, history of stroke/myocardial infarction or cancer was statistically adjusted for.

- **Incident CVD:** Men (n=2,021, events=488, person years=11,876); Women (n=2,996, events=593, person years=18,549).
- **Incident Cancer:** Men (n=2,845, events=265, person years=17,560); Women (n=3,389, events=175, person years=21,674).
- **All-Cause Mortality:** Men (n=3,374, events=354, person years=21,144); Women (n=4,189, events=258, person years=27,160).

Table S7: Linear association of incident CVD and cancer events and all-cause mortality with SB bout accumulation patterns – sensitivity analyses with additional adjustment for BMI, diet quality, or physical function, and exclusion of prevalent disease for all-cause mortality models.

	Incident CVD		Incident Cancer		All-Cause Mortality	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Usual SB bout duration, min						
Model 2b	0.97 (0.91-1.03)	0.328	1.10 (0.99-1.21)	0.074	1.16 (1.07-1.27)	<0.001
Model 2c	1.00 (0.93-1.07)	0.951	1.09 (0.98-1.21)	0.097	1.15 (1.05-1.25)	0.002
Model 2d	1.00 (0.93-1.07)	0.980	1.17 (1.06-1.30)	0.002	1.09 (0.99-1.20)	0.090
Model 2e					1.16 (1.03-1.31)	0.017
Model 3b	0.98 (0.91-1.05)	0.501	1.09 (0.97-1.22)	0.152	1.08 (0.98-1.18)	0.127
Model 3c	0.99 (0.92-1.07)	0.776	1.10 (0.98-1.24)	0.121	1.06 (0.96-1.17)	0.279
Model 3d	1.00 (0.92-1.07)	0.909	1.16 (1.03-1.30)	0.015	1.02 (0.92-1.14)	0.682
Model 3e					1.07 (0.93-1.24)	0.343

	Incident CVD		Incident Cancer		All-Cause Mortality	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Alpha						
Model 2b	1.03 (0.96-1.10)	0.407	0.90 (0.81-1.01)	0.065	0.81 (0.73-0.90)	<0.001
Model 2c	0.99 (0.92-1.06)	0.787	0.91 (0.82-1.02)	0.106	0.84 (0.75-0.93)	0.001
Model 2d	1.01 (0.94-1.09)	0.715	0.84 (0.75-0.95)	0.004	0.84 (0.75-0.95)	0.006
Model 2e					0.80 (0.67-0.95)	0.010
Model 3b	1.02 (0.94-1.11)	0.626	0.88 (0.77-1.00)	0.057	0.87 (0.77-0.99)	0.030
Model 3c	1.00 (0.91-1.09)	0.950	0.88 (0.76-1.00)	0.058	0.91 (0.79-1.04)	0.150
Model 3d	1.02 (0.94-1.11)	0.628	0.85 (0.74-0.98)	0.021	0.88 (0.76-1.01)	0.077
Model 3e					0.88 (0.72-1.08)	0.235

Hazard Ratios and 95% confidence intervals (CIs) depicting the linear association (per 1 standard deviation change) between usual SB bout duration and alpha with incident CVD, incident cancer and all-cause mortality. SB = sedentary behavior; CVD = cardiovascular disease.

For reference, Model 1 was adjusted for gender and device type (with age as the underlying time scale). Model 2a was adjusted as for model 1 plus education level; social class; smoking status; alcohol intake; baseline history of diabetes mellitus or taking diabetes mellitus medications (not for cancer); taking medication for hypertension/dyslipidemia (not for cancer outcome), or depression; and family history of CVD (stroke/myocardial infarction), diabetes mellitus, or cancer (not CVD or diabetes for cancer outcome). Model 3a includes the same covariates as Model 2a and further adjusts for the composition of 24-hour time use (z1 and z2; with z3 dropped due to collinearity).

Models 2b, 2c and 2d include the same covariates as Model 2a and further adjust for BMI, diet quality or physical function, respectively. Models 3b, 3c and 3d include the same covariates as Model 3a and further adjust for BMI, diet quality or physical function, respectively. Further details on specific covariate adjustments per outcome are detailed in Table S4.

Participants with a history of stroke/myocardial infarction or cancer were excluded all for incident CVD or cancer outcome models, respectively. For all-cause mortality, history of stroke/myocardial infarction or cancer was statistically adjusted for in models 2 and 3 (a-d). Models 2e and 3e include the same covariates as Models 2a and 3a, but exclude participants with a history of stroke/myocardial infarction or cancer.

- Incident CVD: Model 2b & 3b (n=5016, events=1081); Models 2c & 3c (n=4643, events=1010); Models 2d & 3d (n=4664, events=962).
- Incident Cancer: Model 2b & 3b (n=6231, events=440); Models 2c & 3c (n=5694, events=402); Models 2d & 3d (n=5613, events=381).
- **All-Cause Mortality:** Model 2b & 3b (n=7557, events=610); Models 2c & 3c (n=6904, events=547); Models 2d & 3d (n=6752, events=455); Models 2e & 3e (n=4709, events=238).

Table S8: Association of incident CVD and cancer events and all-cause mortality with (arithmetic) mean SB bout duration across percentiles of the population.

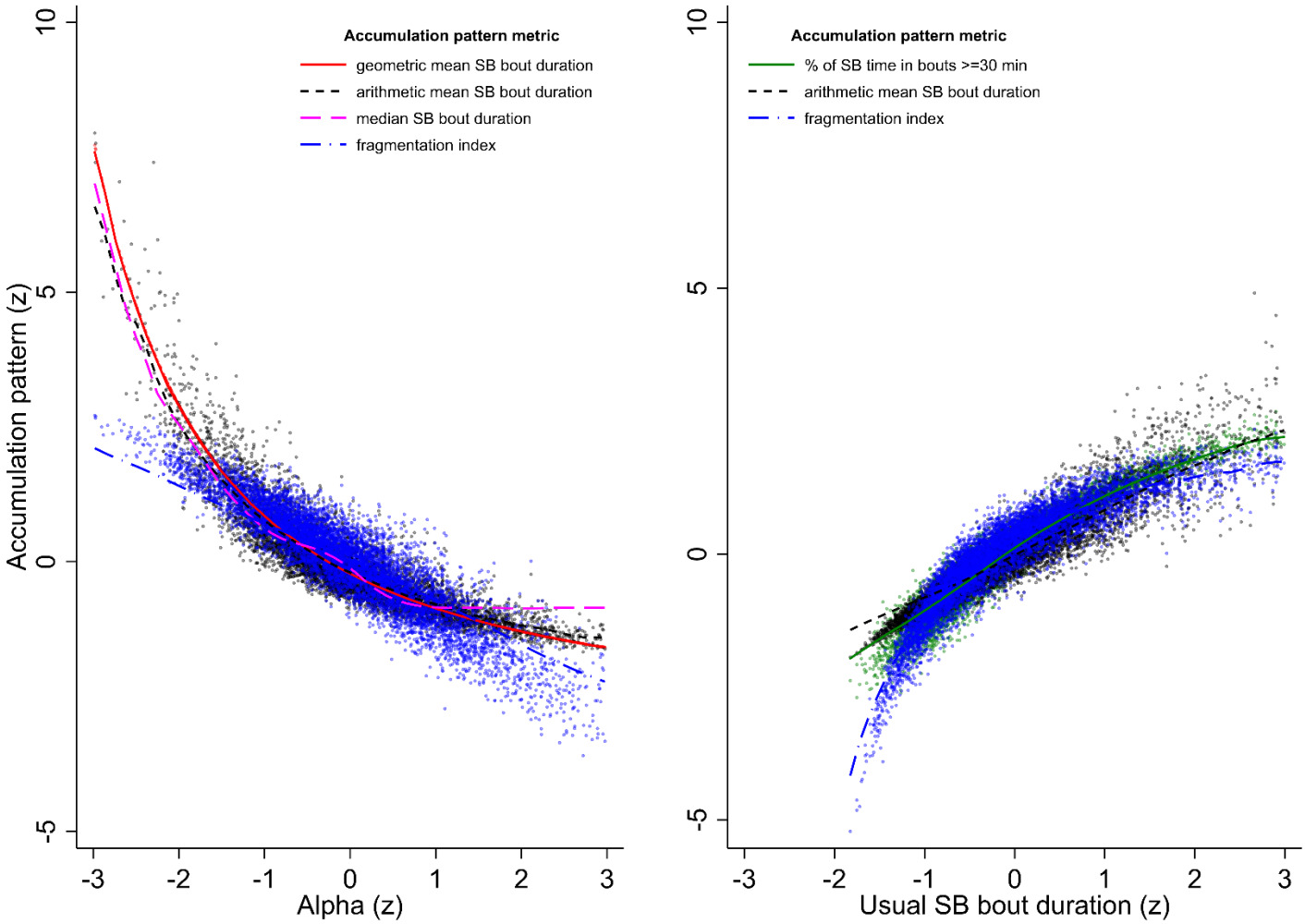
	Incident CVD (n=5,017; no. of events=1,081; person years=30,425)				Incident Cancer (n=6,234; no. of events=440; person years=39,234)				All-Cause Mortality (n=7,563; no. of events=612; person years=48,303)			
Percentile	**p10**	**p30**	**p60**	**p90**	**p10**	**p30**	**p60**	**p90**	**p10**	**p30**	**p60**	**p90**
Mean SB duration, min												
	5	6	8	10	5	6	8	10	5	6	8	10
Model 1	1	1.01 (0.91-1.12)	1.00 (0.84-1.20)	1.08 (0.90-1.29)	1	0.98 (0.82-1.18)	1.22 (0.90-1.63)	1.41 (1.06-1.88)	1	0.96 (0.80-1.17)	1.11 (0.84-1.47)	1.29 (0.99-1.67)
Model 2a	1	0.98 (0.88-1.10)	0.95 (0.79-1.14)	0.99 (0.82-1.20)	1	1.02 (0.85-1.23)	1.27 (0.94-1.72)	1.48 (1.11-1.99)	1	1.02 (0.83-1.25)	1.19 (0.88-1.61)	1.42 (1.06-1.90)
Model 3a	1	0.98 (0.87-1.10)	0.94 (0.77-1.15)	0.97 (0.77-1.23)	1	1.03 (0.85-1.26)	1.31 (0.93-1.83)	1.57 (1.10-2.25)	1	1.00 (0.81-1.24)	1.09 (0.78-1.51)	1.17 (0.84-1.65)

Data are Hazard Ratios and 95% confidence intervals (CIs) and were fitted with the use of restricted cubic splines (3 evenly spaced knots). Results presented approximate the 10th (reference), 30th, 60th and 90th percentiles across all three outcomes for mean SB bout duration= 5, 6, 8, 10 (min). Covariates that violated the proportional hazard assumptions (education level; social class, family history of diabetes mellitus and CVD) were included as baseline strata. SB = sedentary behavior; CVD = cardiovascular disease.

Model 1 is adjusted for gender and device type (with age as the underlying time scale). Model 2a is adjusted as for model 1 plus education level; social class; smoking status; alcohol intake; baseline history of diabetes mellitus or taking diabetes mellitus medications (not for cancer); taking medication for hypertension/dyslipidemia (not for cancer outcome), or depression; and family history of CVD (stroke/myocardial infarction), diabetes mellitus, or cancer (not CVD or diabetes for cancer outcome). Model 3a includes the same covariates as Model 2a and further adjusts for the composition of 24-hour time use (z1 and z2; with z3 dropped due to collinearity). Further details on specific covariate adjustments per outcome are detailed in Table S4.

Participants with a history of stroke/myocardial infarction or cancer were excluded for all incident CVD or cancer outcome models, respectively. For all-cause mortality, history of stroke/myocardial infarction or cancer was statistically adjusted for in models 2a and 3a.

Figure S1: Fractional polynomial curves showing relationships of alpha (left) and usual SB bout duration (right) with their highly correlated SB pattern measures (r_s > 0.8) in middle aged to older adults (n=7563, EPIC-Norfolk).

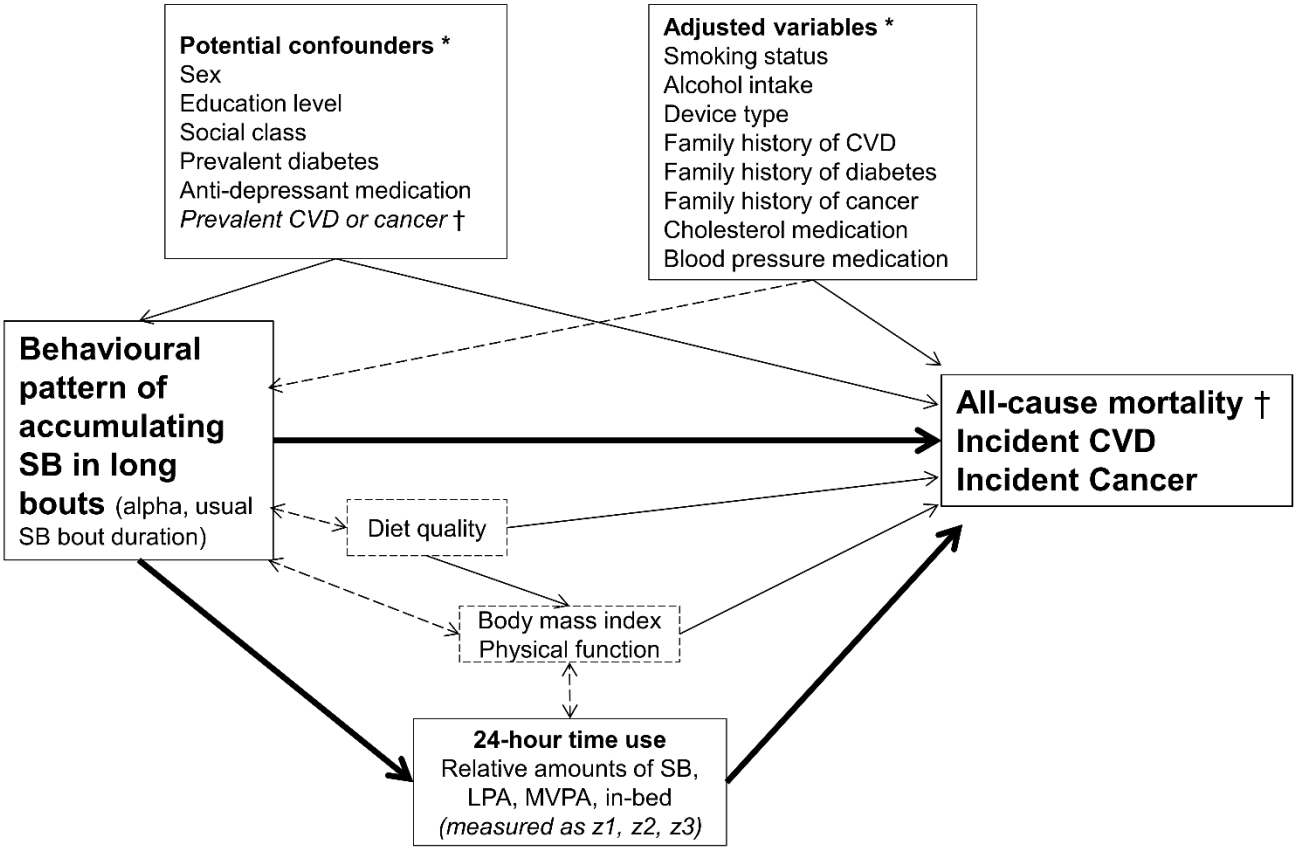


Values are converted to z-scores (by subtracting the population-level mean and dividing by population-level standard deviation, resulting in values that correspond to one standard deviation change; z = (x-μ)/σ) to aid interpretation.

Graph displays -3 to +3 z for alpha and usual SB bout duration.

y-axis = -z for fragmentation index. For clarity, only the line is displayed for median SB bout duration.

Figure S2: Directed acyclic graphs (DAG) of causal assumptions and potential confounder / adjusted variables.



SB = sedentary behavior; CVD = cardiovascular disease.

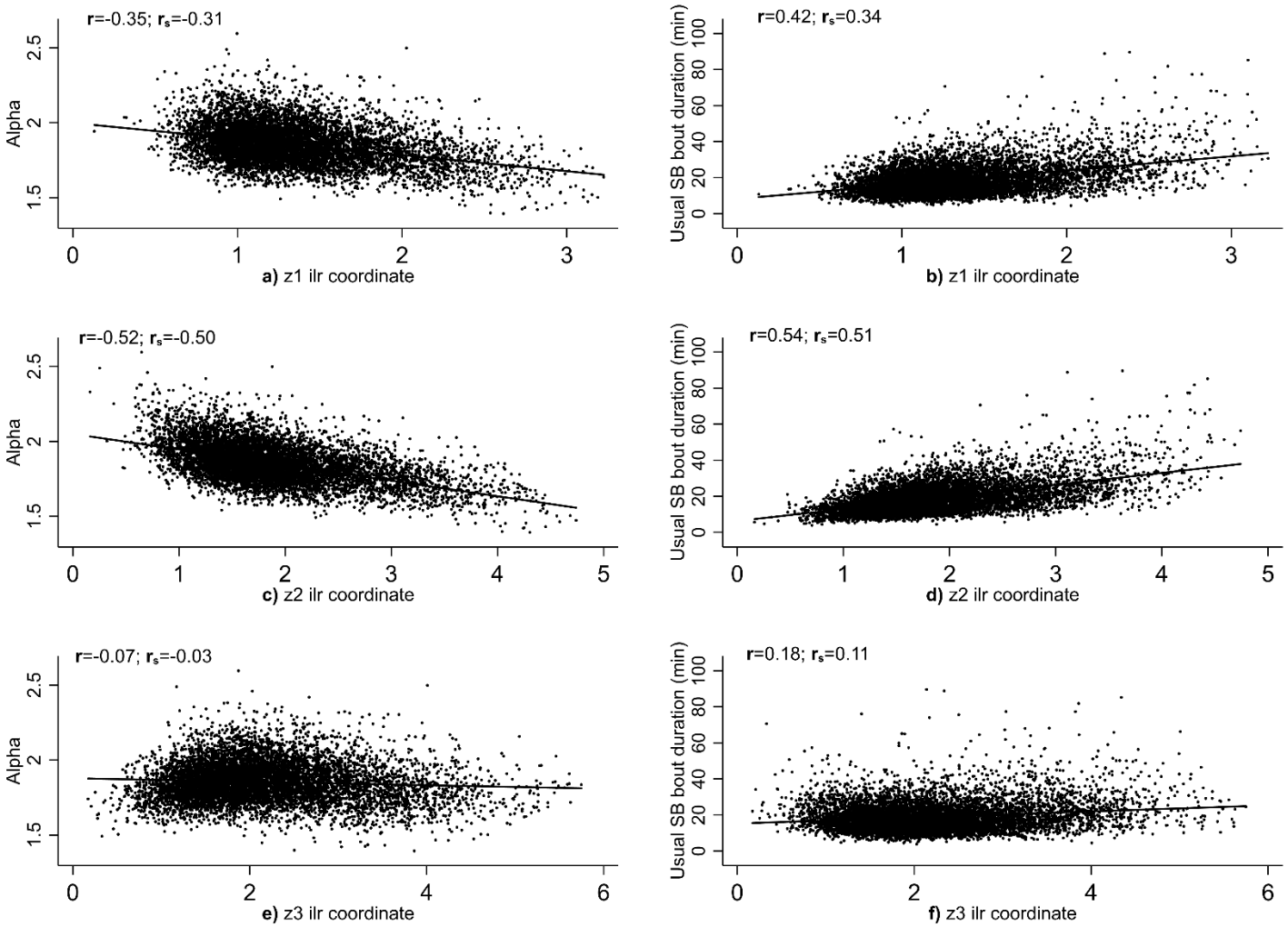
* For purposes of clarity in this DAG, covariate adjustment variables here are based on the most comprehensively adjusted all-cause mortality models only, but specific covariate adjustments for incident CVD and cancer (i.e. some differences in adjustment for family history of disease and medications) are detailed in Table S4.

† For all-cause mortality only, an additional sensitivity analysis excluded prevalent CVD or cancer (as opposed to only adjusting for them as potential confounders) to examine potential for reverse causality bias (also see Table S4).

Age included as the underlying timescale in all cox models. *Potential confounders* are assumed ancestors of both the exposure and the outcome (or 'true' confounders). *Adjusted variables* are adjusted similarly to potential confounders (i.e., total effects), but labelled as such here given it is debatable whether they are also true ancestors of the exposure (dashed arrows). A separate additional model (model 3a) adjusted for 24-hour time use in terms of the ilr transformed z parameters (see Table S3 and Figure S4) to examine the degree to which effects of SB accumulation pattern are independent of the total amount of SB and physical activity arising from the pattern of behavior (i.e., direct effects).

Body mass index, physical function and *diet quality* have been considered as potential confounders and/or as causal intermediates in previous studies, thus were modelled separately in additional sensitivity analyses. Diet quality was additionally considered separately due to some missing data [n=659 (8.7%) missing] and given its very low correlations with alpha (r_s=0.06) and usual SB bout duration (r_s=0.07).

Figure S3: Scatterplots of alpha (left) and usual SB bout duration (right) over ilr z coordinates.

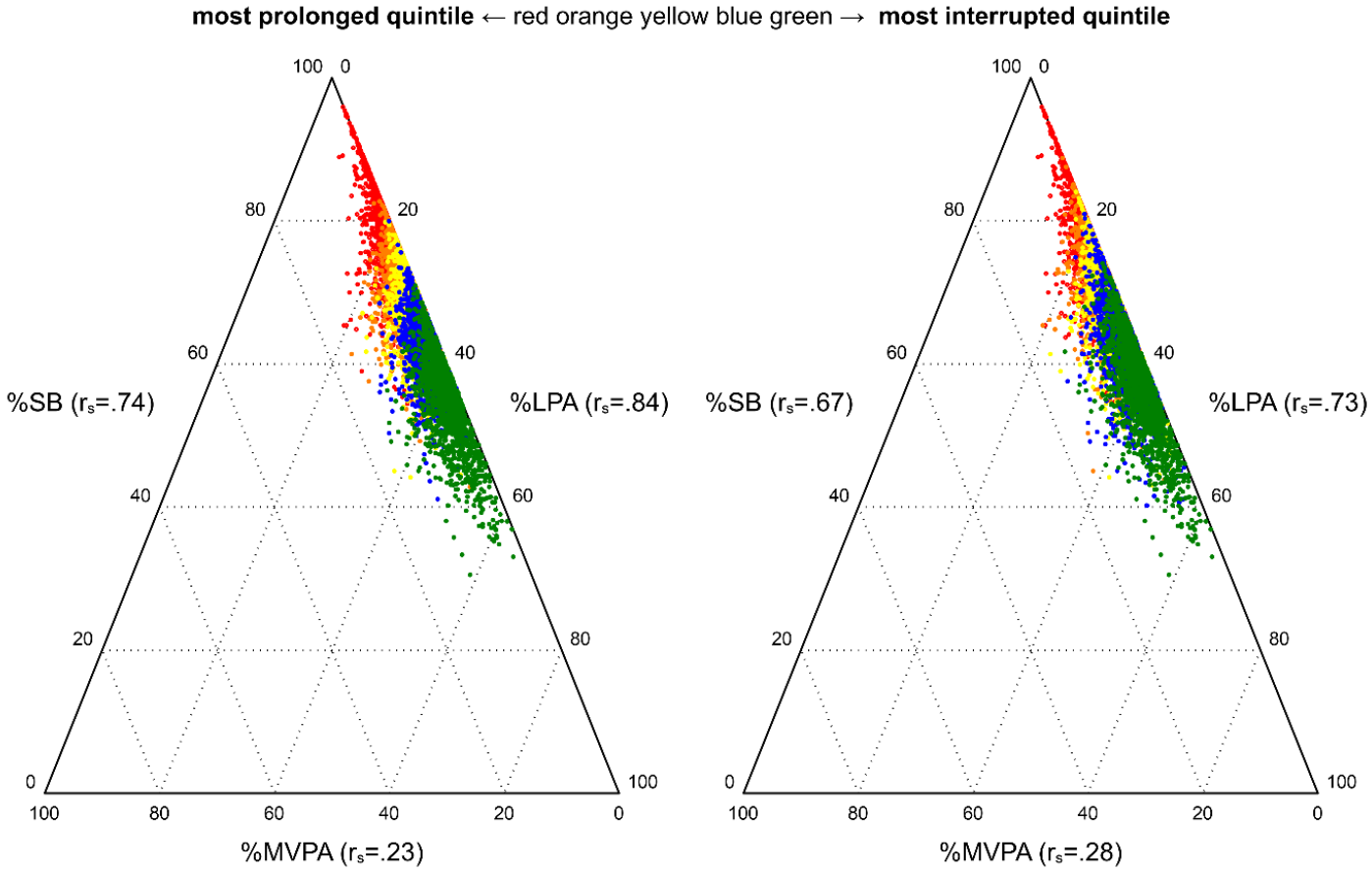


SB = sedentary behavior.

r=pearson; r_s=spearman

z1 (panels a and b) = less waking wear time; z2 (panels c and d) = more SB waking hours; z3 (panels e and f) = less intense physical activity

Figure S4: Tri-plot showing alpha (left) and usual SB bout duration (right) across the composition of 24-hour time use (sub-composition %SB, %LPA, %MVPA displayed)



SB = sedentary behavior; LPA = light intensity physical activity; MVPA = moderate-to-vigorous physical activity

r_s=spearman with alpha (left) and usual bout duration (right).