Objectively measured total sedentary time and pattern of sedentary accumulation in older adults: associations with incident cardiovascular disease and all-cause mortality

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Abstract

Background: We examined associations of total duration and pattern of accumulation of objectively-measured sedentary behaviour (SB) with incident cardiovascular disease (CVD) and all-cause mortality among older adults.

Methods: Total sedentary time and eight sedentary accumulation pattern metrics were extracted from accelerometer data of 3991 Whitehall II study participants aged 60-83 years in 2012-2013. Incident CVD and all-cause mortality were ascertained up to March 2019.

Results: 299 CVD cases and 260 deaths were recorded over a mean (standard deviation) follow-up of 6.2 (1.3) and 6.4 (0.8) years, respectively. Adjusting for sociodemographic and behavioural factors, 1-SD (100.2 minutes) increase in total sedentary time was associated with 20% higher CVD risk (Hazard Ratio (95% confidence interval): 1.20 (1.05-1.37)). More fragmented SB was associated with reduced CVD risk (e.g. 0.86 (0.76-0.97) for 1-SD (6.2) increase in breaks per sedentary hour). Associations were not evident once health-related factors and moderate-to-vigorous physical activity (MVPA) were considered. For all-cause mortality, associations with more fragmented SB (e.g. 0.73 (0.59-0.91) for breaks per sedentary hour) were found only among the youngest older group (<74 years; p for interaction with age<0.01) independently from all covariates.

Conclusions: In this study, no associations of total sedentary time and sedentary accumulation patterns with incident CVD and all-cause mortality were found in the total sample once MVPA was considered. Our findings of reduced mortality risk with less total and more fragmented SB independent from MVPA among individuals <74 years need to be replicated to support the recent recommendations to reduce and fragment SB.

Keywords: Accelerometer; Prospective; Breaks in sedentary behaviour; Moderate-to-vigorous physical activity

Abbreviations

BMI: Body mass index

CHD: Coronary heart disease

CI: Confidence interval

CVD: Cardiovascular disease

ENMO: Euclidean Norm of raw accelerations Minus One

HES: Hospital Episode Statistics

HR: Hazard ratio

ICD: International Classification of Diseases

LDL: Low-density lipoprotein

LIPA: Light intensity physical activity

MVPA: Moderate to vigorous physical activity

NHS: National Health Service

OPACH: Objective Physical Activity and Cardiovascular Health

PA: Physical activity

SB: Sedentary behaviour

SD: Standard deviation

Introduction

Sedentary behaviours (SB) such as sitting is increasingly recognized as a risk factor for all-cause mortality[1] and cardiovascular disease (CVD),[2,3] and the extent to which its impact depends on the level of moderate-to-vigorous physical activity (MVPA) is raising research interest.[4] It is suggested that not just the total duration being sedentary but also the manner in which it accumulates throughout the day (for example in few long bouts or in several shorter bouts) might be important for health outcomes.[5,6]

Experimental studies have reported that interrupting sedentary time with physical activity (PA) has acute benefits on controlling postprandial glucose and insulin levels.[7,8] Such studies have shown that short PA breaks were slightly more effective for glycaemic control than a continuous PA bout of a similar level of energy expenditure.[8] Breaks in prolonged sitting have been shown to improve a wide range of cardiovascular parameters, especially blood pressure and vascular function.[9] Taken together, this has led to recent PA guideline to incorporate specific recommendation of limiting and frequently interrupting time in SB,[10,11] although evidence for these recommendations remain limited.[11,12] However, over the last century technological advances have been accompanied with a large increase in the prevalence of SB.[13,14] Identifying specific SB features, such as total duration or bout length,[5,15] detrimental for health is thus necessary to inform future tailored interventions to tackle the impact of SB on health. This is particularly important for older adults who spend almost 80% of their time being sedentary.[16]

Till date few prospective studies have investigated the pattern of sedentary accumulation, with inconsistent findings for both incident CVD[17,18] and all-cause mortality.[19,20] Only two studies on CVD risk that were sex-specific focused exclusively on older adults.[17,18] Additionally, baring a single study among older women,[18] the rest

emphasized on either sedentary breaks or length of sedentary bouts as accumulation pattern measures. However, concept such as breaks has been described as crude measure to quantify accrual patterns, limited by its dependence on accelerometer wear time and inability to provide precise information on nature of breaks in terms of length or intensity.[7,15] Use of measures that capture distribution of sedentary bout length and are sensitive to changes in SB has recently been recommended.[21,22]

This study aimed to assess the association of objectively-measured total sedentary time and the pattern of its accumulation with incident CVD and all-cause mortality among older adults. We also examined whether or not the associations were independent of MVPA. In the absence of a gold standard measure of sedentary accumulation patterns throughout the day, we used a comprehensive approach by investigating the association using eight measures of SB accumulation patterns.

Methods

Study population

The Whitehall II study is a prospective cohort established in 1985-1988 among 10,308 London-based civil servants (67% males) aged 35-55 years.[23] Since the inception of the study, sociodemographic, behavioural and health-related factors have been assessed using questionnaires and clinical examinations. Follow-up assessments have taken place approximately every 4-5 years, with the latest wave completed in 2015-2016. Participants provided written informed consent. Research ethics approval was obtained from the University College London ethics committee (reference number 85/0938), renewed at each contact.

Total sedentary time and sedentary accumulation pattern

The accelerometer sub-study was undertaken during the 2012-2013 wave of data collection for participants seen at the London clinic and for those living in the South-Eastern regions of England who underwent clinical examination at home. Participants were asked to wear a tri-axial accelerometer (GENEActiv Original; Activinsights Ltd, Kimbolton, UK) on their non-dominant wrist during 9 consecutive days over 24 hours. Data sampled at 85.7 Hz, with acceleration expressed relative to gravity (1 $g \approx 9.81$ m/second^2), were processed in R software using GGIR package[24] version 2.3-3 (https://rdrr.io/cran/GGIR/). Euclidean Norm of raw accelerations Minus one (ENMO) with negative numbers rounded to zero were calculated.[25] Sleep periods were then detected using a validated algorithm guided by sleep log.[26] Data from the first waking up (day 2) to waking up on the day before the last day (day 8) were used, corresponding to 7 full days. Waking period was defined as the period between waking and onset of sleep. Participants were included for analysis if they had daily wear time ≥2/3 of waking hours, for at least 2 weekdays and 2 weekend days.[27] Non-wear period among valid days was corrected based on a previously reported algorithm.[25]

Wrist-worn accelerometers have been reported to accurately classify movement behaviours based on metabolic intensity.[28] In absence of gold standard cut-points to classify movement behaviours in older adults, we used cut-points based on a study wherein adult participants undertook ten activities in laboratory in order to mimic free living posture/behaviours with the aim to elicit average accelerations that were similar to those observed in a free living situation.[29] These cut-points were in agreement with a recent study among older adults which derived cut-points using oxygen consumption when performing nine laboratory based activities of daily living and showed good classification accuracy.[30] Based on these studies, movement behaviour during waking period was classified as SB when average acceleration over a 60-second epoch was <40 milligravity (m*g*), 40-99 m*g* for

light intensity physical activity (LIPA) and ≥100 m*g* for MVPA.[29,31] Sedentary accumulation pattern was measured using 8 metrics: mean sedentary bout duration,[5] time in prolonged sedentary bouts, Gini index,[32,33] number of sedentary breaks,[32,33] breaks per sedentary hour,[34,35] Alpha,[32] and transition probability from sedentary to LIPA or MVPA states (Figure 1; see eMethods in the Supplement for description).[33]

Metrics (total time and accumulation pattern) were calculated for each day and averaged over 7 days. For those with <7 valid days (N = 95 (2.4%) participants), a weighted average was computed using data on weekend and week days.[27] Test-retest analysis conducted among 79 participants who wore the accelerometer for 7 days on average 26.5 (SD=4.6) days after the first measure suggests a good reliability of all the measures (correlations range: 0.62-0.82).

Ascertainment of CVD and All-Cause Mortality

CVD and mortality cases were ascertained by linkage to national registers up to the 31st of March 2019 using the unique National Health Service (NHS) identification number. *CVD* event was defined as occurrence of first fatal or non-fatal coronary heart disease (CHD), stroke or heart failure. Nonfatal events were traced from the Hospital Episode Statistics (HES) database based on the International Classification of Diseases (ICD) codes for CHD (ICD-10 codes I20–25), stroke (ICD-10 codes I60–I64) and heart failure (ICD-10 code I50). CHD and stroke cases were also determined using Whitehall II study-specific 12-lead resting electrocardiogram recording and MONICA-Augsburg stroke questionnaire, respectively. Further details of validation of CVD cases are provided in a separate publication.[36] CVD fatal events were drawn from the Office for National Statistics Mortality Register. *Death* from any cause was available from the UK Office for National Statistics Mortality Register.

Ascertainment of Covariates

Covariates were assessed using questionnaire or during the clinical examination at 2012-2013 wave, as well as data from electronic health records including HES and the Mental Health Services Data Set. Sociodemographic variables consisted of sex, ethnicity (white, non-white), marital status (married/cohabitating, divorced/widowed/single), education (≤primary school, lower secondary, higher secondary school, university, higher degree; treated as continuous variable), last known occupational position (administrative, professional/executive, clerical/support). Behavioural factors included alcohol consumption (0, 1-14, >14 units per week), smoking status (current and recent ex-(less than 5 years) smokers, long-term ex-smokers, never smokers), fruits and vegetables consumption (< once daily, once daily, > once daily). Health-related factors consisted of prevalent diabetes (fasting glucose ≥7.0 mmol/l or self-reported doctor diagnosed diabetes or use of diabetes medication or hospitalizations ascertained through record linkage to the HES (ICD-9 codes 250 or ICD-10 code E11)), body mass index (BMI; categorized as <24.9, 25-29.9, and ≥30 kg/m²), hypertension (systolic/diastolic blood pressure ≥140/90 mmHg or use of antihypertensive drugs), hyperlipidaemia (low-density lipoproteins (LDL) >4.1 mmol/l or use of lipid-lowering drugs) assessed at the clinical examination, and morbidity index. For analysis on incident CVD, the morbidity index was calculated as the count of the following chronic conditions: cancer, arthritis, chronic obstructive pulmonary disease, depression, Parkinson disease, and dementia. For all-cause mortality the index additionally included CHD, stroke and heart failure as chronic ailments.

Statistical analysis

For analysis on incident CVD, participants were censored at date of CVD, non-CVD related death to account for competing risks, or 31st March 2019 (end of follow-up), whichever came first. For all-cause mortality, censoring date was either date of death or end of follow-up (31st March 2019), whichever came first. Four models were constructed. First model was adjusted for sociodemographic variables and total day duration (between awaking and sleep onset). Then additionally adjusted for behavioural factors, followed by further adjustment for health-related factors. The final model included MVPA recommendation (<150 vs ≥150 minutes per week).

Potential non-linear associations of total sedentary time and sedentary accumulation pattern metrics at 2012-2013 wave with incident CVD and all-cause mortality risk was tested using likelihood ratio test comparing fully adjusted Cox regression models with only linear term against models with cubic spline terms.[37] When associations were deemed linear, exposures were treated as continuous variables in analyses. For ease of interpretability and comparability, exposures were standardized (mean=0, standard deviation (SD)=1) using mean and SD from the largest analytical sample, one with mortality as outcome. All analyses were conducted using Cox regression with age as timescale. Proportionality assumption was verified using Schoenfeld's test.

Owing to substantial correlations between total sedentary time and sedentary accumulation pattern metrics, they could not be mutually adjusted. Alternatively, we tested the interaction between total sedentary time (categorized using median split) and each sedentary accumulation pattern metric. We also tested interactions with age (continuous), sex, obesity (<30 kg/m^2 and ≥30 kg/m^2) and morbidity (0 and ≥1 prevalent chronic ailment). When interactions were found, analyses were repeated separately in each group (for age,

groups were split as <74 years and ≥74 years to allow enough cases in each group). All analyses were undertaken using STATA statistical software version 15 (StataCorp, College Station, Texas) and R version 3.6.3 (http://www.r-project.org) with a two-sided P<0.05 considered statistically significant.

Sensitivity analysis

Three sets of sensitivity analyses were conducted. First, to examine potential for reverse causation, main analysis was repeated by excluding CVD events and death occurring within first two years of follow-up for incident CVD and all-cause mortality outcomes, respectively. Second, the stratified analysis on age for all-cause mortality was repeated using an alternative age cut-point based on median age split. Third, the main analyses were repeated by adjusting for MVPA as a continuous instead of as a dichotomous variable.

Results

Participant characteristics

Among the 6308 participants in the 2012-2013 wave, 4880 were invited to participate in the accelerometer sub-study, with 4492 agreeing and 4008 returning the devices successfully with valid data (eFigure 1 in the Supplement). Excluding those with pre-existing CVD (for incident CVD outcome) or missing covariates led to an analytical sample of 3321 participants for analysis on incident CVD and 3991 for all-cause mortality. Compared with participants invited to the accelerometer sub-study (n = 4880) and subsequently included (n = 3991) in the analyses, participants not included (n = 889) were on average younger (excluded vs included participants: 68.9 vs 69.4 years, P=0.03), more likely to be women (33.5% vs 25.8%, P<0.001), non-white (10.5% vs 7.4%, P<0.01), and had higher education level (36.6 vs 31.0, P<0.01) (eTable 1 in the Supplement). During a mean follow-up of 6.2 (SD=1.3) years, there

were a total of 299 incident CVD events (CHD (62.9%), stroke (17.7%) and heart failure (19.4%)). A total of 260 all-cause deaths were recorded over a mean follow-up of 6.4 (SD=0.8) years.

Participants with incident CVD events were more likely to be older, men, non-white, less educated, smokers and have worse cardiometabolic profile compared to those who did not develop CVD over the follow-up (Table 1). Those who died were more likely to be older, married/cohabitating, less educated, have poorer diet, worse cardiometabolic profile, and more comorbidities than surviving participants (Table 1). Participants with incident CVD or all-cause death were likely to spend more time in SB, accumulate sedentary time in longer bouts and with fewer interruptions, and were less likely to switch from sedentary to LIPA and MVPA states compared to those without the event of interest (Table 1). The correlations of total sedentary time with the 8 sedentary accumulation metrics ranged from 0.45 (Gini index) to 0.88 (Time in prolonged (≥30 min) sedentary bouts) in absolute term (eTable 2 in the Supplement). Time in MVPA was moderately correlated with most variables (r=0.27 to 0.67 in absolute term).

There was no evidence of a non-linear relationship of total sedentary time and sedentary accumulation metrics with incident CVD (*P* nonlinearity range: 0.06-0.72) and all-cause mortality (*P* nonlinearity range: 0.14-0.94) so all variables were examined as continuous variables in the models. All SB measures were standardized so that 1-SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Association of sedentary time and its accumulation pattern with incident CVD

Table 2 shows the associations of total sedentary time and sedentary accumulation pattern metrics with incident CVD. In analysis adjusted for sociodemographic factors, 1-SD higher total sedentary time was associated with higher risk of incident CVD (Hazard Ratio (HR) 1.20, 95% confidence interval 1.06-1.37). All accumulation measures, except Gini Index were significantly associated with CVD risk. A 1-SD increase in mean sedentary bout duration (HR 1.18, 1.08-1.30) and in prolonged sedentary bout duration (HR 1.18, 1.06-1.33) were associated with 18% increase in CVD risk while 1-SD increase in transition probability from sedentary to MVPA state (HR 0.81, 0.70-0.94) was associated with the largest decrease in CVD risk. No changes were observed in risk estimates when adjusting for behavioural factors. After additional adjustment for health-related factors, the association remained only for mean sedentary bout duration (HR 1.14, 1.03-1.26) and was no longer significant on further adjustment for MVPA (HR 1.09, 0.98-1.23). In models adjusted for MVPA but not health-related factors, associations were no more evident either, except for mean duration bout sedentary which had borderline significance (HR 1.12, 1.00-1.24, P=0.045; eTable 3 in the Supplement). As a comparison, the HR for meeting the MVPA recommendation of 150 minutes per week was 0.69 (0.52-0.92, P=0.01) in a model adjusted for sociodemographic, behavioural and health-related factors (eTable 4 in the Supplement). Associations of sedentary accumulation metrics with CVD risk did not vary by total sedentary time (*P* interaction: 0.07-0.57). There was no evidence that age, sex, obesity or morbidity status modified the association of total sedentary time and metrics of sedentary accumulation pattern with incident CVD (all P interaction >0.07).

Association of sedentary time and its accumulation pattern with mortality

The association of sedentary time and its accumulation pattern with all-cause mortality is shown in Table 3. In analysis adjusted for sociodemographic factors, a 1-SD increase in total sedentary time (HR 1.35, 1.17-1.56), mean sedentary bout duration (HR 1.10, 1.03-1.17) and prolonged sedentary bout duration (HR 1.27, 1.13-1.43) were associated with higher mortality risk. More fragmented SB pattern as shown by 1-SD increase in number of sedentary breaks (HR 0.83, 0.74-0.94), breaks per sedentary hour (HR 0.80, 0.70-0.91), Alpha (HR 0.81, 0.72-0.92), transition probability from sedentary to LIPA (HR 0.82, 0.72-0.93) and MVPA (HR 0.69, 0.57-0.84) states were associated with lower mortality risk. Additional adjustment for behavioural and health-related factors slightly attenuated the associations. On further adjustment for MVPA, none of the associations remained significant. Meeting the recommended MVPA duration was associated with a 41% reduction in mortality risk in the fully adjusted model (HR 0.59, 0.44-0.78; eTable 4 in the Supplement). There was no evidence that the associations between sedentary accumulation metrics and mortality vary by sedentary time (*P* interaction: 0.42-0.75).

For all-cause mortality, a consistent interaction was observed between age and SB measures (*P* interaction: 0.001-0.009, except for transition probability from sedentary to MVPA state where P=0.18). In fully adjusted analyses stratified by age (Figure 2), total sedentary time and most SB accumulation metrics were significantly associated with all-cause mortality among those aged <74 years (N=3001, N death=114; eTable 5 in the Supplement) whereas there was no association among the oldest group (age ≥74 years, N= 990, N death= 146; eTable 6 in the Supplement). While causes of death did not differ in both age groups, SB measures were on average better among younger group (eTable 7 in the Supplement).

Sensitivity analysis

Excluding 88 CVD events within the first 2 years of follow-up (eTable 8 in the Supplement) completely attenuated associations, including in model adjusted only for sociodemographic factors except for mean sedentary bout duration. Removing 45 all-cause mortality events within the first 2 years of follow-up either in the full population (eTable 9 in the Supplement) or by age group (eTable 10 in the Supplement) did not affect the findings. Using a median age split in analysis for all-cause mortality showed similar findings as in the main analyses with associations evident only in the youngest age group (<68.4 years) (eFigure 2 in the Supplement). Adjusting for MVPA as a continuous instead of dichotomous variable in the final adjustment model did not change the findings (eTable 11 and 12 in the Supplement).

Discussion

This prospective study based on objective measures of SB and PA in older adults with a mean follow-up of over 6 years presents three key findings. First, total sedentary time and all SB accumulation metrics, apart from the Gini index, were associated with incident CVD and death independently from sociodemographic and behavioural factors. Secondly, the observed association of total sedentary time and pattern of sedentary accumulation with incident CVD was explained by health-related factors and MVPA duration. Thirdly, among the youngest older adults, total sedentary time and most sedentary accumulation pattern measures remained associated with all-cause mortality even after accounting for health-related factors and MVPA, while no association was found irrespective of the metrics in oldest old.

Studies based on self-reported measures[38,39] have found higher sedentary time to be associated with increased risk of CVD incidence, while conclusions are mixed for the limited number of studies using objective measures.[17,18,40-42] A pooled analysis of 9 prospective studies, mean age of 54.4 years and median follow-up of 11 years, reported a non-linear

association of questionnaire assessed sedentary time with CVD incidence, with the increase in risk observed only at a duration greater than 10 hours/day, when adjusted for PA.[38] In contrast using objectively-assessed SB, the Objective Physical Activity and Cardiovascular Health (OPACH) study of older women found a linear dose-response relationship where each 1 additional hour of sedentary time was associated with 12% higher CVD risk[18] in model accounting for multiple risk factors and MVPA. In other studies the associations were attenuated on adjustment with higher intensity PA,[17] health-related factors[41,42] or both,[40] as also found in our study.

Till date two prospective studies have examined the association of sedentary accumulation pattern with incident CVD.[17,18] A study based on older men did not find any association between sedentary breaks or bouts and CVD risk.[17] In the OPACH study, longer mean sedentary bout duration, less breaks in sedentary time, and accumulating sedentary time in a prolonged manner was associated with higher CVD risk among older women.[18] These associations persisted for mean sedentary bout duration and Alpha, on further adjustment for CVD risk factors and MVPA, albeit not mutually adjusted. In our study, adjustment for wide range of health-related factors including CVD risk markers attenuated the association apart for mean sedentary bout duration. This suggests a potential role of CVD risk markers in the association between SB metrics and CVD risk, which is in accordance with previous findings showing SB metrics associated with cardiometabolic risk factors in adults.[43,44] In our case, this association was no more significant on either mutual or separate adjustment for MVPA. Findings might differ owing to metric utilized, adjustment level and use of self-reported data for morbidity prevalence[18] unlike in our study which uses health-records linkage data.

A meta-analysis of 8 prospective studies found that longer accelerometer-assessed sedentary time was associated with increased all-cause mortality risk even after adjustment for MVPA.[1] Only few observational studies have examined the associations between patterns

of sedentary accumulation and all-cause mortality,[19,20] but findings reported were inconsistent. In the present study, associations of total sedentary time and most SB accumulation pattern metrics with all-cause mortality differed as a function of age and were evident only among the youngest older adults even when accounting for a large set of confounders including MVPA. This could explain differences in findings between previous studies where a study based on adults with mean age of 63.5 years found higher number of breaks to be associated with lower mortality risk,[19] while another study among older men with mean age of 78.4 years did not report any association using same measure.[20] Another study based on the sample used in the former study (mean age=63.5) found replacing prolonged sedentary bouts with shorter sedentary bouts not to be associated with reduced mortality risk, although it was the case for replacement with LIPA or MVPA.[45] This is in line with our finding that increase in switching from sedentary to either LIPA or MVPA states is associated with reducing mortality risk in youngest older adults.

A potential explanation of the differential associations observed by age group is the better overall level of SB measures seen in the younger compared to the oldest group. Another possible reason could be due to the change in functional capacity over the life course, also termed as "fitness gap".[46] Among the oldest old population, as the capacity itself is lacking we would not expect to see association of SB with all-cause mortality.

Our study has several strengths. It is longitudinal, based on both men and women as compared to the earlier notable studies based only on men[20] or women,[18] with exclusive focus on older adults. We controlled analyses for a wide range of factors such as CVD biological risk factors and diabetes prevalence which were ascertained using multiple objective sources including clinical examinations rather than being self-reported. Additionally, in the absence of a gold standard measure of accumulation of sedentary time, we used a large and comprehensive range of metrics as exposures on the same outcomes.

The limitations should also be noted. First, the Whitehall II study is an occupational cohort wherein participants are healthier than the general population, but it has been shown previously that the associations between cardiovascular risk factors, including physical activity, and CVD risk are similar to that in the general population.[47] Second, we adjusted for a broad range of confounders, but a possibility of an unmeasured factor to further explain the association still exists.

Conclusion

The 2018 United States of America Physical Activity guidelines and the 2020 WHO guidelines on physical activity and sedentary behaviour concluded that there is insufficient evidence to indicate that sedentary breaks are important factors for incident CVD and all-cause mortality.[11,12] In this study we examined associations of multiple sedentary accumulation pattern measures with both outcomes, given that different metrics might be indicative of distinct features of SB. Based on our findings, we reiterate the importance of MVPA for CVD prevention,[42] as associations of total sedentary time and accumulation patterns with CVD risk were no more evident once MVPA was considered. In addition, there was evidence of higher all-cause mortality risk with increased total and less fragmented sedentary time independently from MVPA in the younger older adults. If these later findings are replicated in future studies, this would support the current Canadian recommendations[10] on limiting and interrupting long periods of sedentary time. Why such associations are not seen in the oldest group requires further investigation.

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Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

MSY and SS developed the research question and study design. MSY and VTVH performed the statistical analysis. MSY wrote the first and successive drafts of the manuscript. All authors conceived and designed the study, analysed and interpreted the data, and drafted or critically revised the manuscript for important intellectual content, or, in addition, acquired data. MSY had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. MSY is the guarantor. The corresponding author attests that all listed authors meet authorship criteria.

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Table 1 Baseline characteristics of study participants

	Incident CVD (N=3321)			All-cause mortality (N=3991)		
Characteristics	**No**	**Yes**	**P value**	**No**	**Yes**	**P value**
N (row %)	3022 (91.0)	299 (9.0)		3731 (93.5)	260 (6.5)	
Age (years), M (SD)	68.6 (5.5)	71.5 (5.9)	<0.001	69.1 (6.0)	73.7 (5.4)	<0.001
Women	830 (27.5)	55 (18.4)	0.001	967 (25.9)	63 (24.2)	0.55
Non-white	173 (5.7)	33 (11.0)	<0.001	272 (7.3)	23 (8.9)	0.35
Married/cohabitating	2264 (74.9)	226 (75.6)	0.80	2802 (75.1)	179 (68.9)	0.03
University or higher degree	995 (32.9)	76 (25.4)	0.01	1175 (31.5)	63 (24.2)	0.01
Low occupational position	1495 (49.5)	155 (51.8)	0.42	1885 (50.5)	146 (56.2)	0.08
Recent-ex/current smokers	152 (5.0)	23 (7.7)	0.05	205 (5.5)	16 (6.2)	0.65
>14 units of alcohol per week	716 (23.7)	72 (24.1)	0.88	875 (23.5)	50 (19.2)	0.12
Daily intake of fruits & vegetable	2424 (80.2)	227 (75.9)	0.08	2972 (79.7)	193 (74.2)	0.04
BMI ≥30 kg/m^2	496 (16.4)	62 (20.7)	0.06	678 (18.2)	45 (17.3)	0.73

Hypertension[a]	1347 (44.6)	183 (61.2)	<0.001	1899 (50.9)	167 (64.2)	<0.001
Hyperlipidaemia[b]	1365 (45.2)	150 (50.2)	0.10	1885 (50.5)	136 (52.3)	0.58
Diabetes	311 (10.3)	58 (19.4)	<0.001	461 (12.4)	53 (20.4)	<0.001
Morbidity index,[c] M (SD)	0.33 (0.6)	0.36 (0.6)	0.36	0.52 (0.7)	0.89 (1.0)	<0.001
Following recommendations of 150 min/day of MVPA	2592 (85.8)	216 (72.2)	<0.001	3116 (83.5)	154 (59.2)	<0.001
Sedentary time variables, M (SD)						
Daily sedentary time, min/d	709.5 (98.2)	741.3 (110.0)	<0.001	714.9 (99.1)	760.5 (105.6)	<0.001
Mean sedentary bout duration	11.0 (5.2)	12.9 (9.5)	<0.001	11.3 (5.8)	13.9 (8.8)	<0.001
Time in prolonged (≥30 min) sedentary bouts, min/d	372.5 (138.1)	417.5 (162.4)	<0.001	380.1 (140.5)	452.3 (164.0)	<0.001
Gini index	0.67 (0.04)	0.68 (0.03)	0.004	0.68 (0.04)	0.69 (0.04)	<0.001
Number of sedentary breaks	71.7 (15.4)	68.8 (18.1)	0.002	71.2 (15.7)	65.8 (18.4)	<0.001
Breaks per sedentary hour	6.4 (1.9)	5.9 (2.1)	<0.001	6.3 (1.9)	5.5 (2.0)	<0.001
Alpha	1.76 (0.13)	1.73 (0.14)	<0.001	1.76 (0.13)	1.71 (0.14)	<0.001
Transition probability (%) from						
sedentary to LIPA state	9.9 (3.0)	8.8 (3.3)	0.001	10.0 (3.0)	9.4 (3.3)	<0.001

sedentary to MVPA state	0.55 (0.48)	0.32 (0.36)	<0.001	0.57 (0.49)	0.43 (0.41)	<0.001

Abbreviations: M, mean; SD, standard deviation; PA, physical activity; LIPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity; BMI, body mass index.

Values are N (col %) unless otherwise stated.

[a]Systolic/diastolic blood pressure ≥140/90mmHg or use of antihypertensive drugs.

[b]Low-density lipoprotein ≥4.1 mmol/l or use of lipid lowering drugs.

[c]Number of chronic conditions among: cancer, arthritis, chronic obstructive pulmonary disease, depression, Parkinson disease, and dementia for incident CVD. Addition of coronary heart disease, stroke and heart failure for all-cause mortality.

Table 2 Associations of total sedentary time and sedentary accumulation patterns with incident CVD (N total = 3321, N events = 299, mean follow-up (SD) = 6.2 (1.3) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors[a]	**Additionally adjusted for behavioural factors[b]**	**Additionally adjusted for health-related factors[c]**	**Additionally adjusted for MVPA[d]**
Total sedentary time	1.20 (1.06-1.37)	1.20 (1.05-1.37)	1.11 (0.97-1.27)	1.02 (0.88-1.19)
Sedentary accumulation pattern metrics[e]				
(1) Mean sedentary bout duration	1.18 (1.08-1.30)	1.19 (1.08-1.30)	1.14 (1.03-1.26)	1.09 (0.98-1.23)
(2) Time in prolonged (≥30 min) sedentary bouts	1.18 (1.06-1.33)	1.19 (1.06-1.33)	1.11 (0.99-1.26)	1.05 (0.92-1.20)
(3) Gini index	1.06 (0.94-1.19)	1.07 (0.95-1.21)	1.03 (0.91-1.16)	0.99 (0.88-1.12)
(4) Number of sedentary breaks	0.87 (0.77-0.97)	0.86 (0.77-0.97)	0.91 (0.81-1.02)	0.94 (0.84-1.07)
(5) Breaks per sedentary hour	0.86 (0.76-0.97)	0.86 (0.76-0.97)	0.92 (0.81-1.04)	0.97 (0.85-1.10)
(6) Alpha	0.84 (0.75-0.95)	0.85 (0.75-0.95)	0.90 (0.79-1.01)	0.94 (0.82-1.07)

Transition probability from				
(7) sedentary to LIPA state	0.88 (0.78-0.99)	0.87 (0.78-0.99)	0.93 (0.82-1.05)	0.98 (0.86-1.11)
(8) sedentary to MVPA state	0.81 (0.70-0.94)	0.82 (0.70-0.95)	0.87 (0.75-1.01)	0.92 (0.79-1.08)

Abbreviations: CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; PA, physical activity; LIPA, light intensity physical activity;

MVPA, moderate-to-vigorous physical activity; SD, standard deviation.

[a]Models adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

[b]Models additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

[c]Models additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and morbidity index.

[d]Models additionally adjusted for MVPA recommendation.

[e]Metrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Table 3 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality (N total = 3991, N events = 260, mean follow-up (SD) = 6.4 (0.8) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors[a]	**Additionally adjusted for behavioural factors[b]**	**Additionally adjusted for health-related factors[c]**	**Additionally adjusted for MVPA[d]**
Total sedentary time	1.35 (1.17-1.56)	1.32 (1.15-1.53)	1.29 (1.11-1.49)	1.16 (0.98-1.38)
Sedentary accumulation pattern metrics[e]				
(1) Mean sedentary bout duration	1.10 (1.03-1.17)	1.08 (1.01-1.15)	1.07 (1.00-1.15)	1.03 (0.95-1.11)
(2) Time in prolonged (≥30 min) sedentary	1.27 (1.13-1.43)	1.25 (1.11-1.40)	1.22 (1.08-1.38)	1.12 (0.98-1.29)

bouts				
(3) Gini index	1.13 (1.00-1.29)	1.13 (0.99-1.28)	1.11 (0.97-1.26)	1.06 (0.93-1.20)
(4) Number of sedentary breaks	0.83 (0.74-0.94)	0.85 (0.75-0.95)	0.86 (0.77-0.97)	0.92 (0.81-1.05)
(5) Breaks per sedentary hour	0.80 (0.70-0.91)	0.81 (0.72-0.93)	0.83 (0.73-0.95)	0.90 (0.78-1.04)
(6) Alpha	0.81 (0.72-0.92)	0.83 (0.73-0.94)	0.84 (0.75-0.96)	0.92 (0.80-1.05)
Transition probability from				
(7) sedentary to LIPA state	0.82 (0.72-0.93)	0.83 (0.73-0.95)	0.85 (0.75-0.97)	0.92 (0.80-1.06)
(8) sedentary to MVPA state	0.69 (0.57-0.84)	0.71 (0.58-0.86)	0.74 (0.61-0.90)	0.82 (0.67-1.01)

Abbreviations: CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; PA, physical activity; LIPA, light intensity physical activity;

MVPA, moderate-to-vigorous physical activity; SD, standard deviation.

[a]Models adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

[b]Models additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

[c]Models additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and morbidity index.

[d]Models additionally adjusted for MVPA recommendation.

[e]Metrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Titles and legends to figures

Figure 1 Description of metrics of sedentary accumulation pattern.

Abbreviations: LIPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity; SB, standard behaviour.

Figure 2 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality stratified by age.

Abbreviations: PA, physical activity; LIPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity; SD, standard deviation.

Models adjusted for age (as timescale), sociodemographic, behavioural, health-related risk factors, and MVPA recommendation. Metrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Figure1

Metric	Description	Interpretation of higher values
(1) Mean sedentary bout duration	Average length of a sedentary bout	Less fragmentation of sedentary time → *unfavorable*
(2) Time in prolonged sedentary bouts	Total duration of sedentary bouts lasting ≥30 minutes	Greater number and/or lengthier long sedentary bouts → *unfavorable*
(3) Gini index	Nonparametric summary of variability in length of sedentary bouts normalized by average duration	Range from 0 to 1; value towards 1 indicative that small proportion of longer sedentary bouts compose total sedentary time → *unfavorable*
(4) Number of sedentary breaks	Number of interruptions of sedentary bouts	More fragmented SB → *favorable*
(5) Breaks per sedentary hour	Number of sedentary breaks per hour of SB	Greater number of interruptions per hour of SB → *favorable*
(6) Alpha	Parametric summary of the distribution of length of sedentary bouts	Sedentary time composed of larger proportion of short length sedentary bouts → *favorable*
Transition probability from (7) sedentary to LIPA state (8) sedentary to MVPA state	Probability of transitioning from sedentary to a physically active (either LIPA or MVPA) state	Range from 0 to 1; value towards 1 indicate frequent switching from sedentary to LIPA or MVPA state → *favorable*

Figure2