

Association of wearable-device-measured fragmented sedentary behavior with cardiovascular disease, mortality, and life expectancy

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ABSTRACT

Objective: It remains unclear whether the degree of fragmentation modifies the adverse health outcomes associated with prolonged sedentary behavior. This study aims to investigate the associations of objectively measured sedentary patterns with incident cardiovascular disease (CVD), mortality, and life expectancy.

Methods: This prospective cohort study included 89 010 UK Biobank participants (median age 63.5 years, 56.5% women) who provided 3 to 7 valid days of wrist accelerometer data. Daily sedentary time and number of sedentary breaks were the metrics of interest. Four overall sedentary behavior patterns were identified by joint classification of sedentary time and number of sedentary breaks. Outcomes were all-cause mortality, CVD incidence and mortality, CVD-free life expectancy, and total life expectancy. Multivariable Cox proportional hazards models were used to evaluate the associations of sedentary behavior metrics with all-cause mortality and CVD incidence, whereas Fine-Gray competing-risk models were used to evaluate their associations with cardiovascular mortality, with non-CVD death treated as a competing event. Restricted cubic splines were used to assess potential nonlinear associations. Multi-state survival analyses were performed to estimate CVD-free life expectancy. Isotemporal substitution models were used to estimate the

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effects of replacing sedentary time with moderate-to-vigorous physical activity (MVPA).

Results: During a median follow-up of 8.0 years, 3 730 deaths occurred, including 1 223 CVD deaths and 8 883 incident CVD cases. Total sedentary time showed J-shaped dose-response associations with all-cause and cardiovascular mortality and a linear association with increased CVD incidence. The number of sedentary breaks showed L-shaped associations with risks of all-cause mortality and CVD mortality. Compared to the least sedentary group, participants with prolonged sedentary time (≥ 10 h/d) and a low degree of fragmentation (sedentary break < 12 bouts/d) had a 51.5% higher risk of all-cause mortality [hazard ratio (HR)=1.515, 95% confidence interval (CI) 1.380 to 1.663], a 55.3% higher risk of cardiovascular mortality (subdistribution HR=1.553, 95% CI 1.325 to 1.820), and a 10.0% higher risk of incident CVD (HR=1.100, 95% CI 1.030 to 1.174). At age 50, the loss of life expectancy was primarily observed in CVD-free years (men: -2.770 years, 95% CI -3.392 to -2.148; women: -3.113 years, 95% CI -3.794 to -2.432). Notably, a higher frequency of sedentary breaks attenuated the increased mortality risk and the loss of CVD-free life expectancy associated with prolonged sedentary time. Nevertheless, replacing sedentary behavior with MVPA reduced the risk of mortality and CVD incidence among all sedentary participants, regardless of levels of fragmentation.

Conclusion: Prolonged sedentary time and its uninterrupted accumulation patterns are associated with greater risks of mortality and CVD, alongside reductions in CVD-free life expectancy. The increased mortality risk and the loss of CVD-free years may be mitigated by frequent interruptions to sedentary behavior.

KEY WORDS cardiovascular diseases; sedentary behavior; sedentary breaks; mortality; life expectancy; wearable devices

可穿戴设备测量的久坐行为间断与心血管病、死亡率和预期寿命的关系

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[摘要] 目的: 久坐间断频率是否能改变久坐行为与不良健康结局之间的关系尚不清楚。本研究旨在探讨客观测量的久坐行为模式对心血管病(cardiovascular disease, CVD)发病、病死率和预期寿命的影响。**方法:** 采用前瞻性队列研究设计, 纳入英国生物样本库 89 010 名佩戴加速计 3~7 个有效日的参与者(中位年龄为 63.5 岁, 女性占 56.5%)。每日总久坐时间和久坐中断次数为主要暴露因素。通过对总久坐时间和久坐中断次数进行交叉分类, 识别出 4 种整体久坐积累模式。结局指标为全因死亡、CVD 发病与死亡、无 CVD 预期寿命以及总预期寿命。采用多因素 Cox 比例风险模型评估久坐行为指标与全因死亡及 CVD 发病风险之间的关联; 采用 Fine-Gray 竞争风险模型评估久坐行为指标与 CVD 死亡风险之间的关联, 并将非 CVD 死亡视为竞争事件。采用限制性立方样条分析潜在的非线性关联, 多状态

生存分析模型用于评估无CVD预期寿命, 等时替代模型用于估计以中高强度运动替代久坐时间的效应。**结果:** 在中位随访时间8.0年期间, 全因死亡3 730例, 其中CVD死亡1 223例, CVD发病8 883例。久坐总时间与全因和心血管死亡风险均呈J型剂量反应关系, 与心血管发病风险增加呈线性关系。久坐中断次数与全因死亡和CVD死亡风险呈L型关联。与久坐最少者相比, 久坐时间长(≥ 10 h/d)且间断频率低(久坐中断次数 < 12 回合/天)者全因死亡风险增加51.5% [风险比(hazard ratio, *HR*)=1.515, 95% 置信区间(confidence interval, *CI*)1.380~1.663], 心血管死亡风险增加55.3% (亚分布 *HR*=1.553, 95% *CI* 1.325~1.820), CVD发病风险增加10.0% (*HR*=1.100, 95% *CI* 1.030~1.174)。50岁时的预期寿命损失主要为无CVD预期寿命(男性减少2.770年, 95% *CI* -3.392~-2.148; 女性减少3.113年, 95% *CI* -3.794~-2.432)。较多的久坐中断次数可减轻与长时间久坐相关的死亡风险增加及无CVD预期寿命损失。无论间断频率如何, 用中高强度运动替代久坐时间仍有更多获益。**结论:** 长时间久坐及其不间断的积累模式与全因死亡、CVD死亡及发病风险增加密切相关, 并会导致无CVD预期寿命缩短。通过频繁打断久坐行为, 可有效缓解长时间久坐带来的死亡风险及无CVD预期寿命损失。

[关键词] 心血管疾病; 久坐行为; 久坐间断; 死亡率; 预期寿命; 可穿戴设备

Over half of adults in developed countries spend more than nine hours per day in sedentary behavior (SB)^[1-2]. Accumulating evidence indicates that higher sedentary time (ST) is associated with detrimental health outcomes, including incident cardiovascular disease (CVD) and mortality^[2-5]. Although the current guidelines emphasize the importance of minimizing ST^[6-10], reducing the harms of high amounts of ST may require engagement in more than recommended levels of moderate-to-vigorous intensity physical activity (MVPA)^[6]. In fact, global physical activity (PA) remains insufficient^[11]. Recent Meta-analyses^[12-13] have shown that protocols involving frequent, brief SB breaks improve glycemic control more effectively than those with fewer, longer breaks of comparable energy expenditure. This suggests that modifying the manner of SB accumulation throughout the day (i.e., shifting to a fragmented pattern) might be an alternative behavioral strategy. However, the relationship between SB patterns and long-term health outcomes remains incompletely understood.

Emerging studies^[14-21] using accelerometer data have found that prolonged and uninterrupted SB is associated with a higher risk of all-cause mortality and CVD. Nevertheless, it remains unclear whether the health risks associated with prolonged sitting can be mitigated by a fragmented SB pattern. As there is no standardized measure for describing SB patterns^[18, 22], most studies^[16-19] characterized them using multiple distinct metrics. The limitation of these metrics lies in their insufficient interpretability (e.g., Alpha or Gini index) or their inability to reflect the variability of SB accumulation (e.g., mean SB bout duration)^[21]. Although

2 studies^[14-15] examined the joint association of total ST and mean SB bout duration, the intrinsic correlation between these 2 metrics ($r=0.61$ ^[14] and $r=0.76$ ^[15]) made it difficult to clarify the interplay between ST and its accumulation pattern. To address these limitations, a more intuitive and feasible approach is needed that can present the SB pattern from different dimensions.

Since SB and PA are mutually exclusive behaviors during waking hours^[23], a greater number of PA bouts means that SB is interrupted more frequently for a given ST. Hence, a joint classification that characterizes both the total amount of SB and frequency of SB breaks may better reflect the overall structure of SB accumulation. Few studies have examined the joint associations of total ST and the number of SB breaks with mortality and incident CVD. Moreover, a previous study^[24] has reported hazard ratios (*HRs*) for the association between SB and incident CVD and mortality. CVD-free life expectancy (LE) provides a more intuitive measure of the benefits of primary prevention by considering both morbidity and mortality^[25-26]. Despite this, the relationship between objectively-measured SB and CVD-free LE remained unexplored.

Using accelerometer data from a large-scale cohort of middle-aged and older adults in the UK Biobank, this study derives 5 specific pattern metrics to evaluate SB from 2 dimensions: Accumulation (total ST, mean sedentary bout length, and maximum sedentary bout length) and breaks (number of SB breaks and mean sedentary break length). This study aims to investigate the associations of objectively measured sedentary patterns with incident CVD, mortality, and LE.

1 Subjects and methods

1.1 Ethics statements

The UK Biobank is a large prospective cohort study that recruited over 500 000 participants aged 40–69 years in the UK between 2006 and 2010^[27]. Participants provided written informed consent, and ethical approval for the UK Biobank was granted by the North West Multicenter Research Ethics Committee (Reference number: 16/NW/0274). Additionally, this study was registered in the Chinese Clinical Trial Registry (Registered number: ChiCTR2400083272) and approved by the Ethics Committee of Xiangya Hospital of Central South University (Approval number: 202307141).

1.2 Study design and participants

Within the accelerometer substudy conducted from 2013 to 2015, 103 684 participants wore a wrist-based triaxial accelerometer (AX3; Axivity Ltd) for 7 consecutive days (wear period) to record their daily body movements. Participants who provided 3 to 7 valid wear days (>16 h/d^[28]) of wrist accelerometer data were included in the current analysis. The exclusion criteria were as follows: 1) Withdrawal of informed consent; 2) insufficient accelerometer data (accelerometer data with poor calibration, non-physiological data, unreliable data size, poor quality data, or the daily wear time of less than 16 h/d); 3) missing data for analytical covariates; 4) implausibly high ST (>18 h/d); 5) no follow-up data. Additionally, for analyses evaluating CVD incidence and LE, participants with prevalent CVD at baseline were excluded. A flowchart detailing the participant inclusion and exclusion process is provided in Supplementary Figure 1 (<https://doi.org/10.57760/sciencedb.xbyxb.00165>).

1.3 Accelerometer-derived patterns of SB

Raw accelerometer signals were segmented into 30-second epochs, and each epoch was then classified as SB, MVPA, light physical activity (LPA), or sleep using a validated machine-learning algorithm developed for the UK Biobank^[29]. This algorithm provides a more accurate classification than the traditional threshold-based method (mean accuracy=88%; kappa=0.80)^[29]. Based on this classification, a sedentary bout was

defined as a continuous period of SB lasting at least 60 s during waking time^[28], and a sedentary break was defined as at least 60 s of waking PA following a sedentary bout^[14]. Using these definitions, SB patterns were summarized in 2 dimensions: SB accumulation and SB breaks. SB accumulation metrics included total ST (total hours of daily SB accumulation), mean sedentary bout length (determined for each day separately), and maximum sedentary bout length (determined for each day). SB break metrics included the number of SB breaks (the daily frequency of transitions from SB bout to waking PA bout^[15, 17]) and mean SB break length (the average duration of SB breaks, determined for each day separately). Total ST and the number of SB breaks were included in the primary analysis. The other metrics were included in the secondary analysis. Detailed information on each metric and data processing is provided in Supplementary Table 1 (<https://doi.org/10.57760/sciencedb.xbyxb.00165>).

1.4 Outcome ascertainment

The primary outcome was all-cause mortality. The secondary outcomes included cardiovascular mortality, CVD incidence, CVD-free LE, and total LE. Fatal or non-fatal CVD was defined as circulatory system disease excluding hypertension, arterial, or lymphatic disease^[30]. Mortality data were collected from the death registry. CVD incidence was identified from self-report, primary care, or hospital admission sources. Follow-up began on the date each participant's accelerometry monitoring period ended (between June 8, 2013 and December 30, 2015) and ended upon the occurrence of an outcome event or data censoring (October 31, 2022). Detailed information on outcome ascertainment is described in Supplementary Table 2 (<https://doi.org/10.57760/sciencedb.xbyxb.00165>).

1.5 Covariates

In the primary analysis, covariates included age, gender, ethnicity, educational attainment, employment status, Townsend deprivation index (TDI), smoking status, alcohol consumption, diet, self-reported health, family history of CVD, and daily MVPA time. Covariates were selected a priori based on known associations with SB and mortality and CVD from the literature, along with previous studies of the UK

Biobank^[2, 29, 31]. Full covariate descriptions are provided in Supplementary Table 3 (<https://doi.org/10.57760/sciencedb.xbyxb.00165>).

1.6 Statistical analysis

All analyses were performed using R Version 4.3.2 (R Foundation). Data are presented as frequency (constituent ratio) for categorical variables and median (25th percentile, 75th percentile) for continuous variables. Cox proportional hazard regression models were used to assess the *HRs* and 95% confidence intervals (*CI*s) for all-cause mortality and CVD incidence associated with quartiles of each SB pattern metric. Fine-Gray subdistribution method was used for cardiovascular mortality, with non-CVD deaths considered as a competing risk. As there are no universally accepted clinical cut-off points for SB pattern metrics, these variables were categorized into quartiles according to their distributions. This approach allowed comparisons across increasing exposure levels, ensured relatively balanced numbers of participants in each group, and reduced the influence of extreme values. The lowest quartile was used as the reference group. The models were adjusted for a series of covariates. Model 1 was adjusted for age and gender. Model 2 was further adjusted for ethnicity, education level, employment status, TDI, smoking status, alcohol consumption, diet, self-reported health, and family history of CVD. Model 3 was additionally adjusted for daily MVPA time. To evaluate the independent effects of total ST and the number of sedentary breaks, each was further mutually adjusted for the other in their respective models in the secondary analyses. Spearman's rank correlation was used to assess collinearity among SB metrics. To avoid multicollinearity, the significantly correlated metrics were not included in the same model (Supplementary Figure 2, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). Schoenfeld residual method was used to test the proportionality of hazards assumption, and no evidence of violation of the assumption was found. Restricted cubic spline functions (RCS) were used to examine the continuous dose-response relationship between each SB pattern metric and all-cause mortality, cardiovascular mortality, and CVD incidence. Knots were set at the 10th, 50th, and 90th percentiles^[2, 28]. The reference was the median of

each SB pattern metric. Likelihood ratio tests were used to assess the nonlinearity.

Multi-state survival analysis was performed to estimate LE with and without CVD^[32]. Total LE was the sum of all state-specific LE. Three states were set in the multi-state survival models: 1) Free of CVD; 2) presence of CVD; 3) death. Individuals could only enter one state at each transition, and reversals were not allowed. The possible transitions between these states are presented in Supplementary Figure 3 (<https://doi.org/10.57760/sciencedb.xbyxb.00165>). For each SB pattern metric, a separate multi-state survival model was fitted with age as the timescale, and strata were set as gender and quartiles of the corresponding metric. The Gompertz distribution was selected for all models because it yields the lowest Akaike information criterion (AIC). Total and specific-state LE were estimated using the method used by Andreas Höhn, et al^[33]. This study focused on LE at age 50 years and assumed a maximum lifespan of age 100 years. The 95% *CI*s of LE estimation were calculated using the Bootstrap method with 1 000 repeated sampling.

Joint association analyses of total ST and the number of SB breaks were conducted to assess the association between overall SB patterns and the outcomes. Participants were categorized into 4 mutually exclusive groups using the cut-points of total ST (10 h/d) and number of SB breaks (12 bouts/d), which were selected based on the method used in previous studies^[14, 34]: Low ST and high interruptions (reference group), low ST and low interruptions, high ST and high interruptions, and high ST and low interruptions. The *HRs* for each group associated with the outcomes were estimated using Model 3. The multiplicative interactions between total ST and the number of SB breaks were evaluated using likelihood ratio tests comparing models with and without the cross-product term. The additive interactions were assessed using the relative excess risk due to interaction (*RERI*) and the corresponding 95% *CI*s^[35]. Stratified analyses of overall SB patterns according to ST levels were subsequently conducted to evaluate the effects of interruption levels on the outcomes. A post hoc examination of effect modification was performed by repeating the joint association analyses of total ST and number of SB breaks using median splits.

Isotemporal substitution models (ISMs) were used to estimate the effects of reallocating ST to MVPA or LPA on all-cause mortality, cardiovascular mortality, and CVD incidence among individuals with high ST but distinct interruption levels^[29, 36]. Furthermore, multiple secondary and sensitivity analyses were conducted to verify the robustness of the results (Supplementary Methods, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). A two-sided $P < 0.05$ was considered statistically significant.

2 Results

2.1 Demographic characteristics

A total of 89 010 participants were included in the

analyses (Supplementary Figure 1, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). The median age was 63.5 (56.4, 68.6) years, and 56.5% were female. The median number of valid wear days was 7 (7, 7) days. The median daily wear time was 23.8 (23.5, 24.0) h/d. The median total ST was 9.1 (7.8, 10.4) h/d. The median number of SB breaks was 13 (11, 15) bouts/d. Table 1 summarizes participants' characteristics across quartiles of total ST. Over the median follow-up time of 8.0 (7.5, 8.5) years, corresponding to 705 256 person-years, 3 730 (4.2%) participants died from all causes and 1 223 (1.4%) from CVD. For CVD incidence and LE analyses, the participants with prevalent CVD were further excluded, resulting in 75 889 participants with 8 883 (11.7%) incident CVD events.

Table 1 Baseline characteristics of participants by quartiles of total ST

Characteristics	Overall	Total ST/(h·d ⁻¹)			
		Quartile 1 (<7.8)	Quartile 2 (7.8 to 9.1)	Quartile 3 (9.1 to 10.4)	Quartile 4 (≥10.4)
<i>n</i>	89 010	22 242	22 264	22 237	22 267
Age/years	63.5 (56.4, 68.6)	62.7 (55.8, 67.9)	64.0 (57.1, 68.7)	63.8 (56.7, 68.8)	63.4 (56.0, 68.9)
Gender/[No.(%)]					
Female	50 328 (56.5)	14 580 (65.6)	13 729 (61.7)	12 364 (55.6)	9 655 (43.4)
Male	38 682 (43.5)	7 662 (34.4)	8 535 (38.3)	9 873 (44.4)	12 612 (56.6)
White ethnicity/[No.(%)]	86 424 (97.1)	21 530 (96.8)	21 678 (97.4)	21 616 (97.2)	21 600 (97.0)
Education/[No.(%)]					
College or university degree	39 085 (43.9)	8 469 (38.1)	9 512 (42.7)	10 221 (46.0)	10 883 (48.9)
Other qualifications	49 925 (56.1)	13 773 (61.9)	12 752 (57.3)	12 016 (54.0)	11 384 (51.1)
Employment/[No.(%)]					
Employed	53 764 (60.4)	13 519 (60.8)	12 876 (57.8)	13 400 (60.3)	13 969 (62.7)
Unemployed or retired	35 246 (39.6)	8 723 (39.2)	9 388 (42.2)	8 837 (39.7)	8 298 (37.3)
TDI	-2.5 (-3.8, -0.2)	-2.5 (-3.9, -0.4)	-2.6 (-3.9, -0.5)	-2.5 (-3.8, -0.3)	-2.3 (-3.7, 0.2)
Smoking status/[No.(%)]					
Current	5 792 (6.5)	1 370 (6.2)	1 345 (6.0)	1 396 (6.3)	1 681 (7.5)
Never	51 250 (57.6)	13 112 (58.9)	12 810 (57.6)	12 793 (57.5)	12 535 (56.3)
Previous	31 968 (35.9)	7 760 (34.9)	8 109 (36.4)	8 048 (36.2)	8 051 (36.2)
Alcohol consumption/(g·week ⁻¹)	84.0 (24.5, 140.0)	70.0 (17.5, 140.0)	84.0 (28.0, 154.0)	84.0 (28.0, 154.0)	84.0 (21.0, 168.0)
Diet/[No.(%)]					
Healthy	24 396 (27.4)	6 700 (30.1)	6 406 (28.8)	6 061 (27.3)	5 229 (23.5)
Intermediate	42 228 (47.4)	10 618 (47.8)	10 658 (47.9)	10 500 (47.2)	10 452 (46.9)
Unhealthy	22 386 (25.2)	4 924 (22.1)	5 200 (23.3)	5 676 (25.5)	6 586 (29.6)
BMI/(kg·m ⁻²)	26.0 (23.6, 29.0)	25.2 (22.9, 27.9)	25.7 (23.3, 28.5)	26.1 (23.8, 29.0)	27.2 (24.5, 30.5)
Hypertension/[No.(%)]	25 209 (28.3)	5 290 (23.8)	5 953 (26.7)	6 385 (28.7)	7 581 (34.1)

Table 1 (continued)

Characteristics	Overall	Total ST/(h·d ⁻¹)			
		Quartile 1 (<7.8)	Quartile 2 (7.8 to 9.1)	Quartile 3 (9.1 to 10.4)	Quartile 4 (≥10.4)
Diabetes/[No.(%)]	21 326 (24.0)	4 477 (20.1)	5 055 (22.7)	5 320 (23.9)	6 474 (29.1)
Hyperlipidemia/[No.(%)]	12 296 (13.8)	2 472 (11.1)	2 926 (13.1)	3 092 (13.9)	3 806 (17.1)
CVD/[No.(%)]	13 121 (14.7)	2 828 (12.7)	3 044 (13.7)	3 327 (15.0)	3 922 (17.6)
Self-reported health/[No.(%)]					
Excellent	19 353 (21.7)	5 074 (22.8)	5 038 (22.6)	4 942 (22.2)	4 299 (19.3)
Good	53 453 (60.1)	13 618 (61.2)	13 627 (61.2)	13 458 (60.5)	12 750 (57.2)
Fair	13 939 (15.7)	3 095 (13.9)	3 185 (14.3)	3 347 (15.1)	4 312 (19.4)
Poor	2 265 (2.5)	455 (2.1)	414 (1.9)	490 (2.2)	906 (4.1)
Family history of CVD/ [No.(%)]	65 832 (74.0)	16 393 (73.7)	16 624 (74.7)	16 548 (74.4)	16 267 (73.1)
Mean sedentary bout length/ (min·bout ⁻¹)	33.9 (28.4, 40.6)	25.8 (22.8, 29.2)	31.4 (28.5, 34.9)	36.2 (32.8, 40.3)	44.5 (39.4, 51.0)
Maximum sedentary bout length/(h·bout ⁻¹)	2.1 (1.7, 2.6)	1.5 (1.3, 1.8)	1.9 (1.7, 2.2)	2.3 (2.0, 2.6)	2.8 (2.4, 3.2)
Number of sedentary breaks/(bouts·d ⁻¹)	13 (11, 15)	12 (10, 14)	13 (12, 15)	13 (12, 15)	12 (10, 14)
Mean sedentary break length/ (min·bout ⁻¹)	25.2 (20.9, 30.4)	32.3 (26.4, 38.4)	27.5 (24.1, 31.1)	24.1 (21.4, 27.2)	20.2 (17.7, 23.0)
Daily MVPA time/(min·d ⁻¹)	31.9 (15.4, 55.6)	36.4 (18.1, 64.1)	35.4 (18.0, 60.4)	32.1 (16.1, 54.6)	24.8 (11.0, 44.2)
Valid wear days	7 (7, 7)	7 (6, 7)	7 (7, 7)	7 (7, 7)	7 (7, 7)
Valid wear time/(h·d ⁻¹)	23.8 (23.5, 24.0)	23.7 (23.2, 24.0)	23.8 (23.4, 24.0)	23.8 (23.5, 24.0)	23.8 (23.6, 24.0)

Data are presented as frequency (constituent ratio) for categorical variables and median (25th percentile, 75th percentile) for continuous variables. ST: Sedentary time; BMI: Body mass index; CVD: Cardiovascular disease; MVPA: Moderate-to-vigorous physical activity; TDI: Townsend deprivation index.

2.2 Associations of total ST with all-cause mortality, CVD morbidity and mortality, CVD-free LE, and total LE

Adjusted for potential confounders and MVPA, participants in the highest quartile of total ST (≥10.4 h/d) had significantly increased risks of all-cause and cardiovascular mortality, the *HRs* (95% *CI*s) were 1.247 (1.135 to 1.370) and 1.389 (1.174 to 1.644) compared with the lowest quartile (<7.8 h/d) (Table 2). Compared with the lowest quartile, higher quartiles of total ST were associated with an increased risk of CVD incidence; the *HRs* (95% *CI*s) for the second, third, and highest quartiles were 1.087 (1.023 to 1.156), 1.073 (1.009 to 1.142), and 1.159 (1.089 to 1.233), respectively (all *P*<0.05). The results persist after

adjustment for the number of SB breaks (Supplementary Table 4, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). Dose-response relationships between total ST and all-cause mortality and cardiovascular mortality were both J-shaped (both *P* nonlinear <0.001, Figure 1). The association between total ST and CVD incidence appeared linear (*P* nonlinear=0.419).

At 50 years of age, men in the highest quartile lived on average -2.228 (95% *CI* -2.805 to -1.652) fewer years free of CVD and -2.566 (95% *CI* -3.741 to -1.390) years shorter in total LE, compared with men in the lowest quartile. The corresponding reductions in women were -2.475 (95% *CI* -3.107 to -1.843) years for CVD-free LE and -2.254 (95% *CI* -3.241 to -1.267) years for total LE (all *P*<0.05, Figure 2).

Table 2 Risks of mortality and CVD incidence according to total ST and number of sedentary breaks quartiles

Exposure/Outcome	Events/ total number	Event rate (per 1 000 person- years, 95% <i>CI</i>)	Model 1		Model 2		Model 3	
			<i>HR</i> (95% <i>CI</i>)	<i>P</i>	<i>HR</i> (95% <i>CI</i>)	<i>P</i>	<i>HR</i> (95% <i>CI</i>)	<i>P</i>
Total ST*								
All-cause mortality								
Q1	730/ 22 242	4.123 (3.829 to 4.433)	1 (Reference)		1 (Reference)		1 (Reference)	
Q2	767/ 22 264	4.336 (4.034 to 4.654)	0.938 (0.847 to 1.038)	0.214	0.934 (0.844 to 1.034)	0.188	0.921 (0.832 to 1.019)	0.111
Q3	921/ 22 237	5.227 (4.895 to 5.576)	1.103 (1.000 to 1.216)	0.050	1.084 (0.983 to 1.195)	0.107	1.038 (0.941 to 1.144)	0.459
Q4	1 312/ 22 267	7.493 (7.093 to 7.910)	1.513 (1.381 to 1.659)	<0.001	1.371 (1.250 to 1.504)	<0.001	1.247 (1.135 to 1.370)	<0.001
Cardiovascular mortality								
Q1	203/ 22 242	1.146 (0.994 to 1.315)	1 (Reference)		1 (Reference)		1 (Reference)	
Q2	247/ 22 264	1.396 (1.228 to 1.582)	1.052 (0.874 to 1.267)	0.591	1.050 (0.871 to 1.265)	0.611	1.032 (0.857 to 1.243)	0.740
Q3	288/ 22 237	1.635 (1.451 to 1.835)	1.169 (0.976 to 1.399)	0.090	1.139 (0.951 to 1.364)	0.157	1.075 (0.898 to 1.288)	0.429
Q4	485/ 22 267	2.770 (2.529 to 3.028)	1.812 (1.533 to 2.140)	<0.001	1.582 (1.338 to 1.871)	<0.001	1.389 (1.174 to 1.644)	<0.001
CVD incidence								
Q1	1 895/ 18 969	13.121 (12.537 to 13.726)	1 (Reference)		1 (Reference)		1 (Reference)	
Q2	2 173/ 18 973	15.217 (14.584 to 15.871)	1.095 (1.030 to 1.164)	0.004	1.095 (1.030 to 1.164)	0.004	1.087 (1.023 to 1.156)	0.007
Q3	2 250/ 18 967	15.787 (15.141 to 16.453)	1.098 (1.033 to 1.167)	0.003	1.094 (1.029 to 1.164)	0.004	1.073 (1.009 to 1.142)	0.024
Q4	2 565/ 18 980	18.173 (17.477 to 18.890)	1.249 (1.176 to 1.327)	<0.001	1.207 (1.136 to 1.282)	<0.001	1.159 (1.089 to 1.233)	<0.001
Number of sedentary breaks†								
All-cause mortality								
Q1	1 230/ 21 103	7.424 (7.015 to 7.851)	1 (Reference)		1 (Reference)		1 (Reference)	
Q2	931/ 23 248	5.051 (4.731 to 5.386)	0.705 (0.647 to 0.767)	<0.001	0.766 (0.703 to 0.835)	<0.001	0.798 (0.732 to 0.870)	<0.001
Q3	755/ 21 428	4.432 (4.122 to 4.760)	0.642 (0.587 to 0.704)	<0.001	0.717 (0.654 to 0.786)	<0.001	0.752 (0.686 to 0.825)	<0.001
Q4	814/ 23 231	4.403 (4.105 to 4.716)	0.659 (0.603 to 0.720)	<0.001	0.731 (0.668 to 0.799)	<0.001	0.763 (0.697 to 0.835)	<0.001

Table 2 (continued)

Exposure/ Outcome	Events/ total number	Event rate (per 1 000 person- years, 95% <i>CI</i>)	Model 1		Model 2		Model 3	
			<i>HR</i> (95% <i>CI</i>)	<i>P</i>	<i>HR</i> (95% <i>CI</i>)	<i>P</i>	<i>HR</i> (95% <i>CI</i>)	<i>P</i>
Cardiovascular mortality								
Q1	438/ 21 103	2.644 (2.402 to 2.903)	1(Reference)		1 (Reference)		1 (Reference)	
Q2	308/ 23 248	1.671 (1.489 to 1.868)	0.682 (0.589 to 0.789)	<0.001	0.770 (0.664 to 0.893)	0.001	0.816 (0.704 to 0.946)	0.007
Q3	236/ 21 428	1.385 (1.214 to 1.574)	0.600 (0.512 to 0.704)	<0.001	0.704 (0.600 to 0.827)	<0.001	0.756 (0.644 to 0.888)	0.001
Q4	241/ 23 231	1.303 (1.144 to 1.479)	0.586 (0.500 to 0.687)	<0.001	0.681 (0.580 to 0.798)	<0.001	0.727 (0.620 to 0.852)	<0.001
CVD incidence								
Q1	2 403/ 18 709	17.199 (16.519 to 17.901)	1 (Reference)		1 (Reference)		1 (Reference)	
Q2	2 151/ 18 533	15.443 (14.797 to 16.109)	0.932 (0.880 to 0.988)	0.018	0.968 (0.913 to 1.026)	0.273	0.984 (0.928 to 1.043)	0.585
Q3	2 048/ 18 505	14.645 (14.018 to 15.294)	0.892 (0.840 to 0.948)	<0.001	0.938 (0.883 to 0.996)	0.038	0.955 (0.899 to 1.015)	0.138
Q4	2 281/ 20 142	15.003 (14.393 to 15.631)	0.936 (0.883 to 0.993)	0.027	0.979 (0.923 to 1.038)	0.479	0.994 (0.937 to 1.054)	0.839

Model 1: Adjusted for age and gender. Model 2: Adjusted for Model 1+ethnicity, education, employment, TDI, smoking status, alcohol intake volume, diet, self-reported health, and family history of CVD. Model 3: Adjusted for Model 2+daily MVPA time. *The quartile cutoff points of total ST were Q1: <7.8 h/d, Q2: 7.8–<9.1 h/d, Q3: 9.1–<10.4 h/d, Q4: ≥10.4 h/d. †The quartile cutoff points of number of SB breaks were Q1: <11 bouts/d, Q2: 11–<13 bouts/d, Q3: 13–<15 bouts/d, Q4: ≥15 bouts/d. *HRs* for all-cause mortality and CVD incidence were estimated using Cox proportional hazards models, whereas subdistribution *HRs* for cardiovascular mortality were estimated using Fine-Gray competing-risk models, with non-CVD death treated as a competing event. *HR*: Hazard ratio; *CI*: Confidence interval.

2.3 Associations of number of SB breaks with all-cause mortality, CVD morbidity and mortality, CVD-free LE, and total LE

When expressed as quartiles, a higher number of sedentary breaks was dose-dependently associated with lower risks of all-cause and cardiovascular mortality, compared with those in the lowest quartile (<11 bouts/d) (Table 2). The association between the number of SB breaks and CVD incidence was not significant after adjustment for confounders. The results persist after adjustment for total ST (Supplementary Table 5, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). Dose-response relationships of the number of SB breaks with all-cause and cardiovascular mortality were both L-shaped (both *P* nonlinear <0.001, Figure 1).

As shown in Figure 2, compared with the lowest

quartile, participants in higher quartiles had a longer total LE at age 50 years. Notably, women in the higher quartiles (second to highest) showed prolonged CVD-free LE; using the lowest quartile as the reference, the corresponding years of life gained were 1.712 (95% *CI* 1.089 to 2.335), 1.555 (95% *CI* 0.933 to 2.176), and 1.560 (95% *CI* 0.950 to 2.169), respectively.

2.4 Joint associations: Total ST and number of SB breaks

Adjusted for potential confounders and MVPA, participants with high ST and low interruptions had the greatest risks of all-cause mortality, cardiovascular mortality, and CVD incidence, the corresponding *HRs* (95% *CI*s) were 1.515 (1.380 to 1.663), 1.553 (1.325 to 1.820), and 1.100 (1.030 to 1.174), respectively,

compared with those with low ST and high interruptions (Figure 3A). Effect sizes of all-cause and cardiovascular mortality, and CVD incidence were smaller among participants with high ST and high interruptions; the corresponding *HRs* (95% *CI*s) were 1.146 (1.047 to 1.255), 1.136 (0.969 to 1.331), 1.038 (0.981 to 1.099), respectively. Behavioral characteristics of participants across the 4 joint groups are shown in Supplementary Table 6 (<https://doi.org/10.57760/sciencedb.xbyxb.00165>). For all-cause mortality, an antagonistic interaction between total ST and the number of SB breaks was only observed on the additive scale ($RERI = -0.144$; 95% *CI* -0.286 to -0.001), indicating that the joint association of high ST with a higher number of SB breaks was lower than expected on the additive scale. For cardiovascular mortality, antagonistic interactions between total ST and the number of SB breaks were observed on both additive and multiplicative scales ($RERI = -0.303$; 95% *CI* -0.577 to -0.028 ; P for multiplicative interaction $= 0.049$), suggesting that the association of high ST with cardiovascular mortality differed by the number of SB breaks (Figure 3A). Consistently, in the stratified analysis, achieving SB

breaks ≥ 12 bouts/d was associated with 25.4% lower risks of all-cause mortality ($HR = 0.746$, 95% *CI* 0.675 to 0.825) and 27.8% lower risk of cardiovascular mortality ($HR = 0.722$, 95% *CI* 0.610 to 0.853) among participants with high ST, compared with participants with high ST and low interruptions (Supplementary Figure 4, <https://doi.org/10.57760/sciencedb.xbyxb.00165>).

Similarly, participants with high ST and low interruptions had the shortest CVD-free and total LE at age 50 years, compared with the least sedentary group (Figure 3B). The reductions were primarily observed in CVD-free LE; the corresponding differences in CVD-free life expectancy were -2.770 (95% *CI* -3.392 to -2.148) years for men, and -3.113 (95% *CI* -3.794 to -2.432) years for women. In the stratified analysis, achieving SB breaks ≥ 12 bouts/d was associated with extended CVD-free LE, particularly among participants with high ST; the corresponding increased CVD-free LE were 1.650 (95% *CI* 0.972 to 2.327) years for men and 2.031 (95% *CI* 1.264 to 2.798) years for women (Supplementary Figure 5, <https://doi.org/10.57760/sciencedb.xbyxb.00165>).

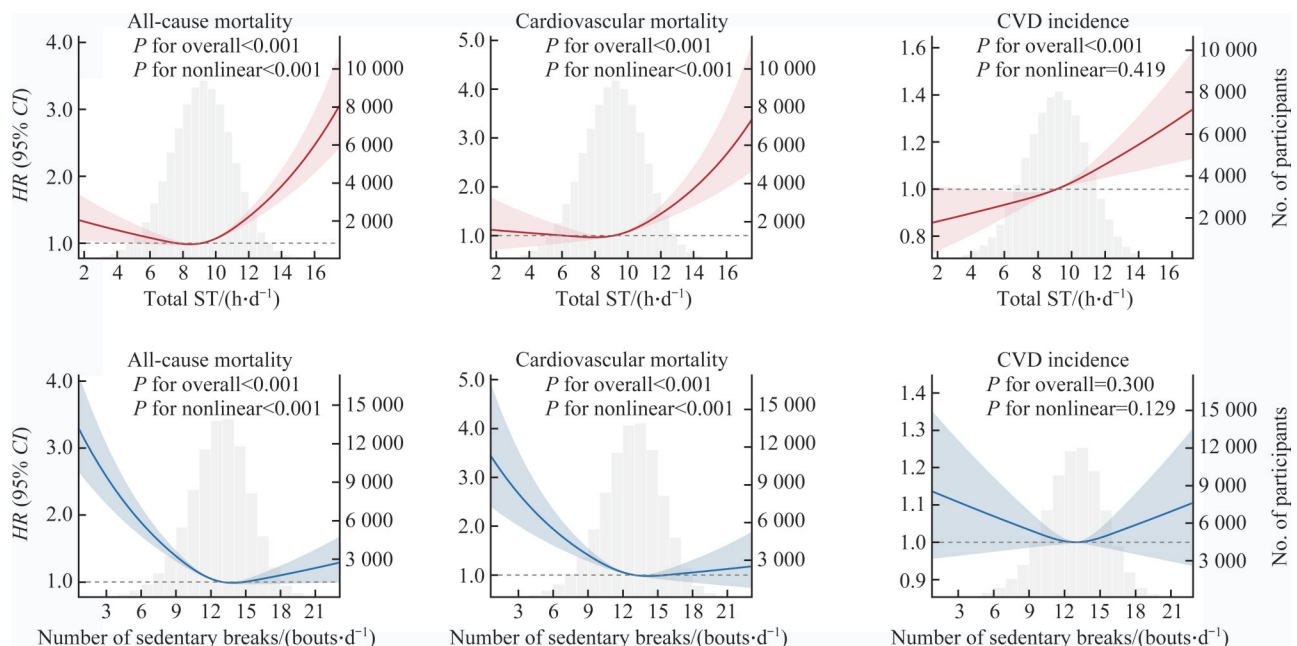


Figure 1 Dose-response relationships of total ST and number of sedentary breaks with all-cause mortality, cardiovascular mortality, and CVD incidence using restricted cubic splines

All adjusted for age, gender, ethnicity, educational attainment, employment status, TDI, smoking status, alcohol consumption, diet, self-reported health, family history of CVD, and daily MVPA time. ST: Sedentary time; *HR*: Hazard ratio; *CI*: Confidence interval; CVD: Cardiovascular disease; TDI: Townsend deprivation index; MVPA: Moderate-to-vigorous physical activity.

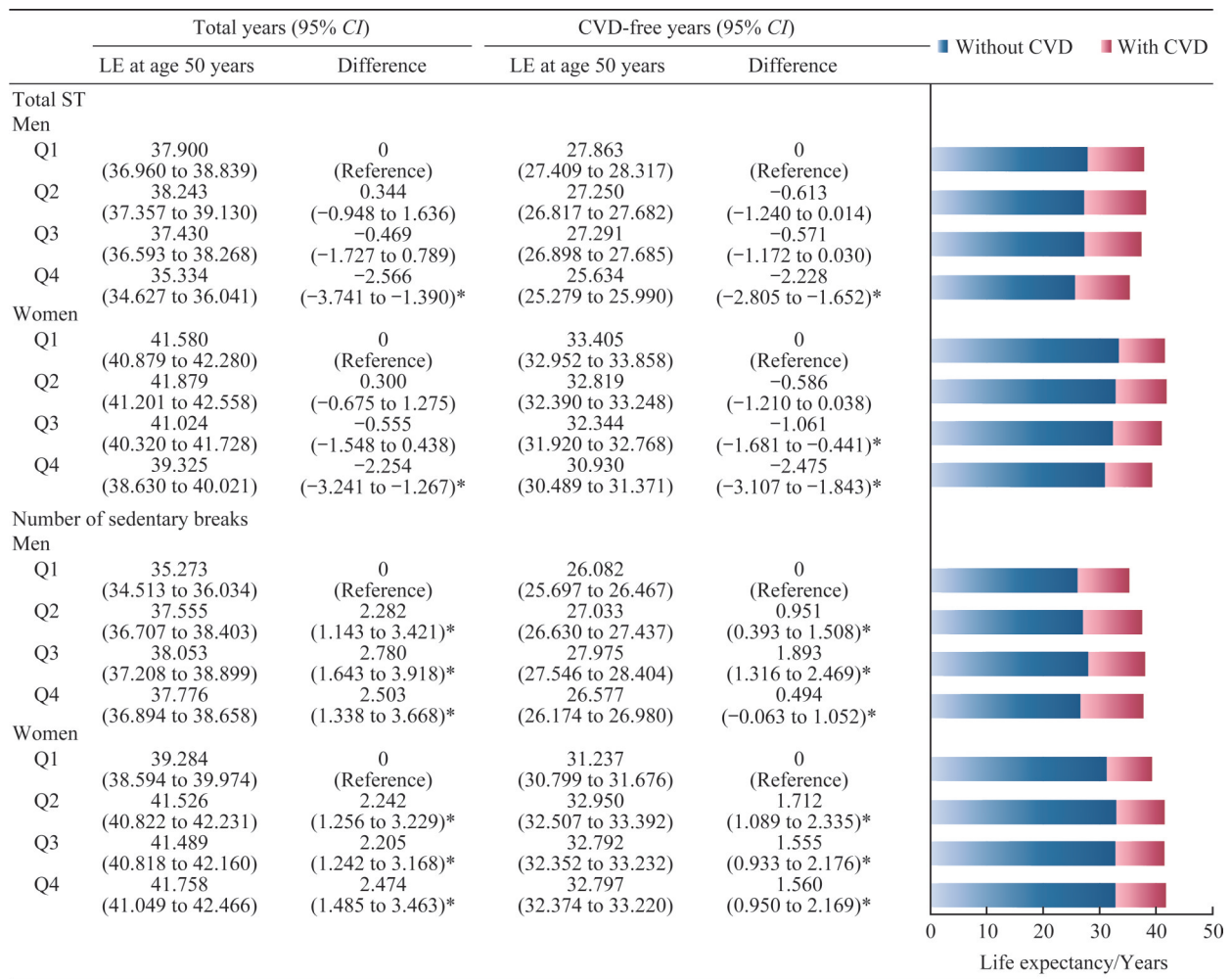


Figure 2 Total life expectancy and years lived with and without CVD at age 50 years by quartiles of total ST and number of sedentary breaks in men and women

The quartile cutoff points of total ST were Q1: <7.8 h/d, Q2: 7.8–<9.1 h/d, Q3: 9.1–<10.4 h/d, Q4: ≥10.4 h/d. The quartile cutoff points of number of sedentary breaks were Q1: <11 bouts/d, Q2: 11–<13 bouts/d, Q3: 13–<15 bouts/d, Q4: ≥15 bouts/d. Total LE and years lived with and without CVD were estimated by multi-state survival analysis. *Differences are statistically significant at $P < 0.05$. LE: Life expectancy.

2.5 Effects of reallocating ST to PA among all sedentary participants

Among all participants with high ST, reallocating SB to MVPA was associated with lower risks of all-cause mortality, cardiovascular mortality, and CVD incidence (Figure 4A). For example, among participants with high ST and low interruptions, replacing 30-min ST with the same duration of MVPA was associated with a 17.2% risk reduction in all-cause mortality ($HR=0.828$, 95% CI 0.792 to 0.867), an 18.4% risk reduction in cardiovascular mortality ($HR=0.816$, 95% CI 0.760 to

0.875), and a 9.9% risk reduction in CVD incidence ($HR=0.901$, 95% CI 0.867 to 0.936). Among participants with high ST and high interruptions, the corresponding effects were a 14.0% risk reduction in all-cause mortality ($HR=0.860$, 95% CI 0.818 to 0.904), an 18.6% risk reduction in cardiovascular mortality ($HR=0.814$, 95% CI 0.750 to 0.883), and a 7.5% risk reduction in CVD incidence ($HR=0.925$, 95% CI 0.892 to 0.958). However, replacing SB with LPA was only beneficial for participants with high ST and low interruptions (Figure 4B).

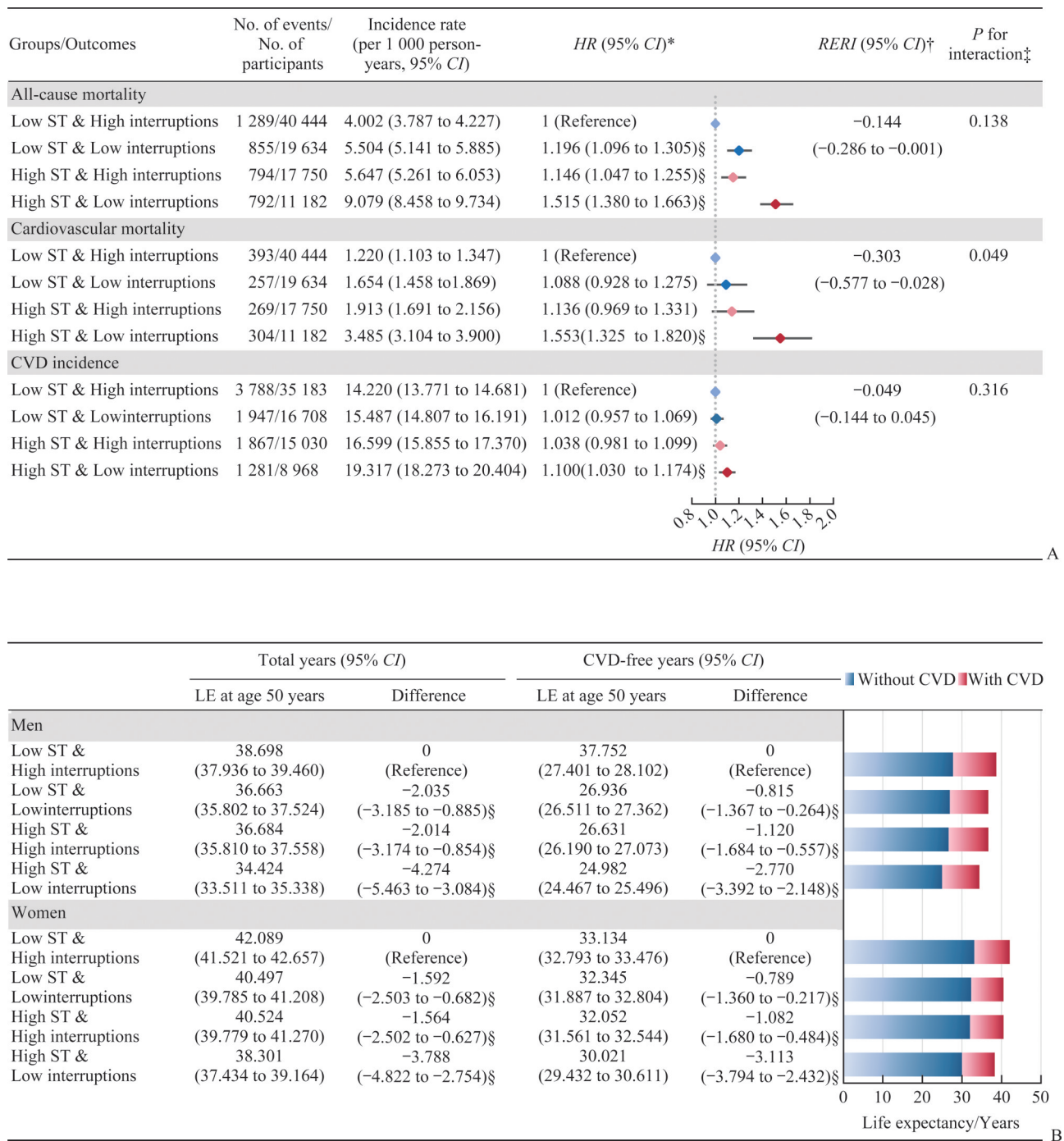


Figure 3 Joint associations of total ST and number of sedentary breaks with all-cause mortality, cardiovascular mortality, CVD incidence, and CVD-free and total life expectancy

A: Joint effects of total ST and number of sedentary breaks on risk of all-cause mortality, cardiovascular mortality, and CVD incidence. B: Estimated total life expectancy and years lived with and without CVD at age 50 years in men and women by 4 overall SB patterns. Low groups were defined as <10 h/d for total ST and <12 bouts/d for number of sedentary breaks; high groups were defined as ≥10 h/d for total ST and ≥12 bouts/d for number of sedentary breaks. *All adjusted for age, gender, ethnicity, educational attainment, employment status, TDI, smoking status, alcohol consumption, diet, self-reported health, family history of CVD, and daily MVPA time. †The estimates of *RERI* were calculated based on the reference group with low ST and low interruptions. ‡Likelihood ratio tests were conducted to assess the significance of multiplicative interaction by comparing models with and without the cross-product term. §Differences are statistically significant at $P < 0.05$. *RERI*: Relative excess risk due to interaction.

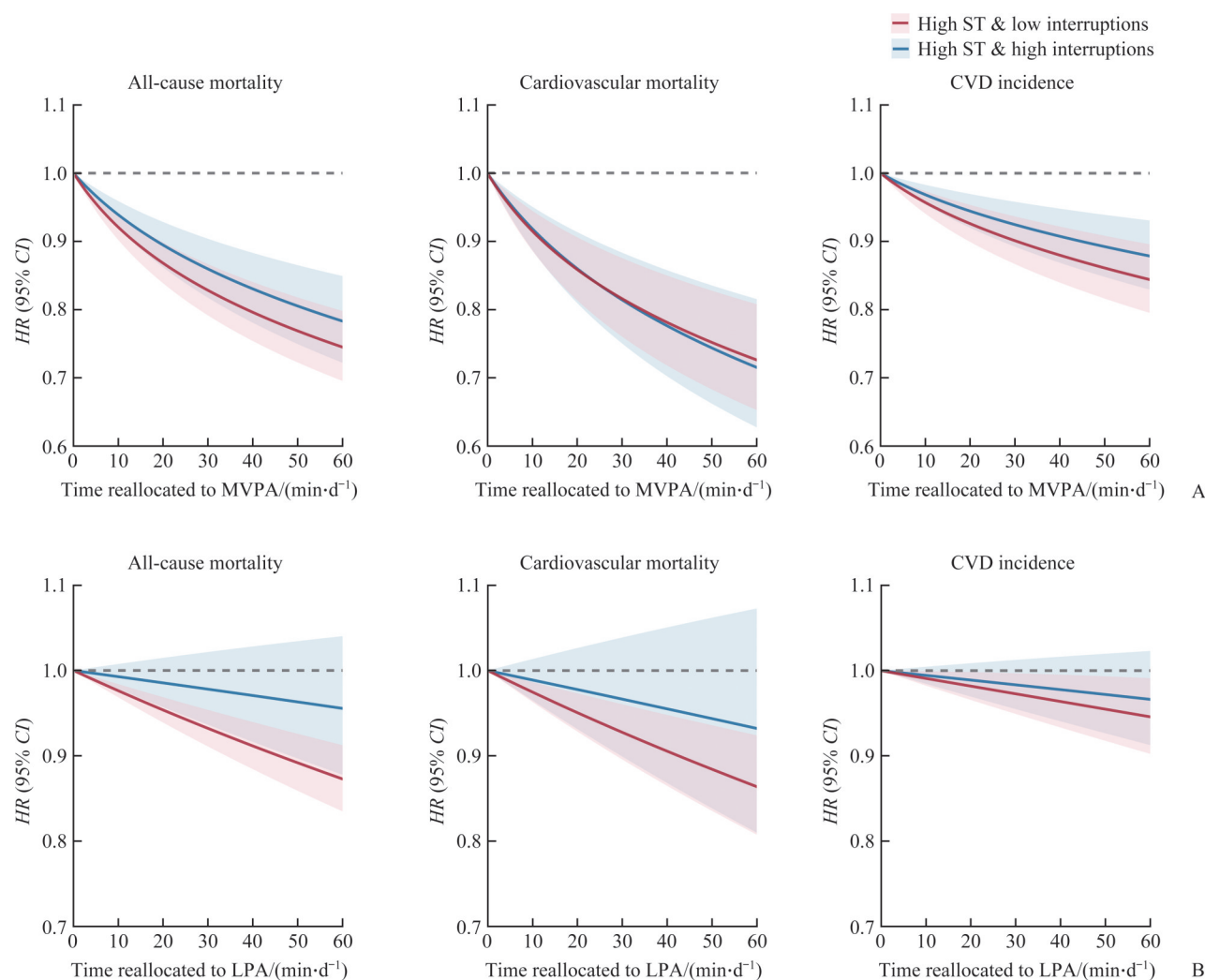


Figure 4 Estimated hazard ratios of all-cause mortality, cardiovascular mortality, and CVD incidence associated with reallocation of ST to physical activity among sedentary individuals across different levels of interruption

A: Estimated HRs of reallocating ST to MVPA. B: Estimated HRs of reallocating ST to LPA. High ST, total ST ≥ 10 h/d; High interruptions, number of sedentary breaks ≥ 12 bouts/d; low interruptions, number of sedentary breaks < 12 bouts/d. HRs for time reallocation to mortality and CVD were estimated using isothermal substitution models. Mean behavior composition was 3.0 h/d LPA, 0.3 h/d MVPA, 12.0 h/d SB, and 8.7 h/d sleep for participants with high ST and low interruptions. Mean behavior composition was 4.3 h/d LPA, 0.4 h/d MVPA, 11.4 h/d SB, and 7.9 h/d sleep for participants with high ST and high interruptions. All adjusted for age, gender, ethnicity, educational attainment, employment status, TDI, smoking status, alcohol consumption, diet, self-reported health, and family history of CVD. LPA: Light physical activity.

2.6 Secondary and sensitivity analyses

In the secondary analyses, as with total ST, the specific SB accumulation patterns (both mean sedentary bout length and maximum sedentary bout length) were similarly associated with all-cause mortality, CVD morbidity and mortality, and reductions in CVD-free and total LE (Supplementary Table 7 and 8, Figure 6–9, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). However, the association between mean sedentary bout length and CVD incidence was not significant after further

adjustment for MVPA (Supplementary Table 7, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). Moreover, higher levels of mean sedentary break length showed protective effects (Supplementary Table 9, Figure 10–11, <https://doi.org/10.57760/sciencedb.xbyxb.00165>).

Effect modifications observed with the number of SB breaks were similar to those observed in the primary analyses when the data were analyzed using median-based classification (Supplementary Figure 12–13, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). Associations

observed in primary analyses remained significant when additionally adjusted for body mass index (BMI), prevalent diabetes, hypertension, and hyperlipidemia (Supplementary Table 10, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). In subgroup analyses, the associations of total ST and the number of breaks with all-cause mortality were consistent across several subgroups. MVPA levels exhibited modifying effects on the association of total ST (P for interaction=0.045) and the number of SB breaks (P for interaction<0.001) with all-cause mortality, respectively (Supplementary Figure 14–15, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). Results of the subgroup analyses of CVD-free and total LE were mostly similar to the primary analyses (Supplementary Figure 16–17, <https://doi.org/10.57760/sciencedb.xbyxb.00165>). However, the association between the number of SB breaks and LE was not significant in participants with a BMI $\geq$ 30 kg/m². Findings were also consistent with those of the primary analyses when 2-year landmark and complete-case analyses were conducted, and when individuals with extreme ST values were included (Supplementary Table 11–13, Figure 18–20, <https://doi.org/10.57760/sciencedb.xbyxb.00165>).

3 Discussion

In this prospective cohort study of nearly 90 000 middle-aged and older adults with objectively measured SB, we found that a higher total ST was associated with an increased risk of all-cause mortality, CVD mortality and morbidity, and reduced CVD-free and total LE. Conversely, there was an L-shaped dose-response relationship between the number of SB breaks and both all-cause and cardiovascular mortality. Individuals with high ST and low interruptions had the highest risks of mortality and incident CVD, as well as the shortest CVD-free and total LE. A higher number of SB breaks partially attenuated the increased risk of all-cause mortality associated with high ST, and attenuated the increased risk of cardiovascular mortality; it was also associated with an extension of both CVD-free and total LE among sedentary participants. Further replacing ST with equivalent MVPA appeared beneficial among sedentary individuals, irrespective of interruption levels. Additionally, the effects of mean and maximum sedentary bout length on the outcomes were similar to

those of total ST; longer mean sedentary break length was protective. These findings provide evidence for the long-term benefits of breaking prolonged sitting.

This study firstly demonstrates that SB patterns modify the relationship between total ST and mortality and incident CVD. A key finding was that the association between high ST and mortality varied according to the frequency of SB breaks. Specifically, participants with a higher number of SB breaks had lower mortality risk, particularly cardiovascular mortality, among those with high ST. These findings suggest that increasing SB breaks may attenuate the adverse health implications of prolonged sitting, beyond the total amount of ST accumulated. Several mechanisms may partly explain our findings. First, more frequent SB breaks may improve glucose metabolism. Meta-analyses of clinical trials have consistently shown that frequent SB breaks confer greater reductions in blood glucose than less frequent SB breaks of similar energy expenditure (SMD : $-0.56^{[12]}$ and SMD : $-0.30^{[13]}$). More frequent transitions from SB to PA might promote increased skeletal muscle cell glucose uptake via contraction-mediated pathways^[37-38]. Second, blood pressure and vascular function, affected by prolonged sitting, may be improved by frequent SB breaks^[39-40]. Third, increased systemic inflammation caused by prolonged sitting might be attenuated by frequent SB breaks^[41]. This may help explain why the interaction was more pronounced for cardiovascular mortality. Other mechanisms might also be involved due to the multiple adverse effects of SB^[42], and future research is needed to elucidate the underlying mechanisms. However, we found that the number of SB breaks showed no significant association with incident CVD, either when examined independently or jointly with total ST. This may suggest that CVD incidence is more strongly affected by total ST or PA intensity^[2, 43-45]. In support of this interpretation, our analysis of the association between total ST and CVD incidence remained significant after additional adjustment for the number of SB breaks. The association between mean sedentary bout length (a commonly used SB pattern metric^[46]) and incident CVD was attenuated after adjustment for MVPA. Compared with previous research^[16-19] evaluating multiple SB pattern metrics in isolation, our findings highlight the potential benefits of interrupting

SB for preventing premature death, particularly for sedentary individuals.

It is worth noting that there is currently no gold standard for describing SB patterns^[18, 22]. Using a joint classification of total ST and the number of SB breaks, we identified 4 mutually exclusive SB patterns at the population level. Individual SB pattern metrics are usually insufficient for intuitively capturing the full picture of how SB is accumulated. Although a subsequent study used cluster analysis to classify 3 distinct SB profiles based on multiple SB features^[21], this approach failed to assess the interplay between total ST and its accumulation pattern. A national cohort study in U. S.^[14] and the Objective Physical Activity and Cardiovascular Health (OPACH) study^[15] examined the joint association of total ST and mean sedentary bout length with all-cause mortality and incident CVD events, respectively, but the significant intrinsic correlation between these 2 metrics led to few participants being classified as “high ST and short mean sedentary bout duration”, compromising the stability of the corresponding risk estimates. In this study, this 2-dimensional joint classification (i.e., taking into account both SB accumulation and breaks) provides a more intuitive and integrated perspective on SB patterns. Based on this classification, participants with high ST and low interruptions exhibited the worst ST distribution (e.g., the longest mean sedentary bout length and the lowest Alpha value). In line with previous findings^[14-15], we found that the most sedentary pattern was associated with a 51.5% increased risk of all-cause mortality, a 55.3% increased risk of cardiovascular mortality, and a 10.0% increased risk of CVD incidence, compared with the least sedentary pattern. More importantly, the key observation was that a higher number of SB breaks mitigated the mortality risk from high ST. Taken together, our analyses suggest that the number of SB breaks may be a more intuitive indicator of SB fragmentation, and the role of SB patterns may be better understood in the context of total ST.

Moreover, our study supports and extends prior research linking ST with cardiovascular and mortality risks^[2-5] by reporting the association between objectively measured SB and estimated CVD-free and total LE. The Atherosclerosis Risk in Communities (ARIC) Study^[25] using self-reported data found that LE free of coronary

heart disease, stroke, or heart failure at age 50 years for individuals who often watched television was approximately 1.0 to 1.1 years shorter in men and 0.8 to 0.9 years shorter in women, compared with those who seldom or never watched television. In a recent study^[47] using Life's Essential 10, an updated cardiovascular health score incorporating self-reported sedentary time, more favorable SB scores were associated with approximately 2 additional years of LE free of stroke and dementia at age 50 in both men and women. In the present study, using accelerometer data and the composite CVD incidence, we found that prolonged and uninterrupted SB was associated with a significantly decreased total LE at age 50 years, with the reduction primarily observed in healthy years free of CVD (2.2 to 2.8 years shorter in men, and 2.5 to 3.1 years shorter in women, compared with the least sedentary group). Notably, we also found that a higher number of SB breaks was associated with extended CVD-free LE among participants with high ST, compared with the most sedentary participants. As total LE cannot be extended indefinitely, these findings provide the public and policymakers with more comprehensive and intuitive information on the importance of reducing and breaking ST to improve healthy aging free of CVD.

Although several national guidelines recommend breaking prolonged sitting^[8-10, 48], the supporting evidence remains scarce^[49-50]. It should be noted that some individuals may be unable to adhere to frequency-specific or duration-specific SB breaks due to their occupation or personal circumstances^[9]. Our findings suggest that interrupting SB as frequently as possible should be encouraged, as it was observed that a higher number of SB breaks was associated with a partially offset risk of all-cause mortality, a fully offset risk of cardiovascular mortality, and an attenuated reduction of CVD-free LE, all of which were associated with high ST. In other words, when prolonged sitting cannot be avoided, increasing the frequency of SB breaks still offers benefits. Of note, excessive total ST is hazardous, regardless of how it is accumulated. In our analyses, replacing SB with MVPA further reduced the risk of mortality and incident CVD across all participants with high ST. This suggests that reducing total ST and promoting MVPA are still the priority for preventing premature death and future CVD risk. From a public

health translation perspective, our findings suggest that frequent SB breaks may serve as a feasible, low-burden adjunct strategy to mitigate the health risks associated with prolonged sitting, particularly for individuals who do not achieve recommended levels of physical activity. Brief activity bouts, such as moderate-to-vigorous intermittent lifestyle physical activity, or exercise snacks, may offer practical ways to implement this strategy into daily routines^[51-53].

This study has several strengths. Using accelerometer data from the UK Biobank, our study provides an intuitive and comprehensive assessment of SB patterns by joint classification of total ST and the number of SB breaks, demonstrating the interaction between total ST and its patterns. This study expands upon previous evidence of the hazards of SB by linking objectively measured SB to both CVD-free and total LE. The large sample size and long follow-up enhance the robustness of our findings. Additionally, using accelerometer data enables more precise measurement of SB than self-reported data. SB bouts and SB breaks were classified using a validated machine-learning algorithm, which has demonstrated a higher accuracy than the traditional cut-point-based method.

However, this study still has several limitations. First, wrist-worn accelerometers cannot precisely distinguish posture, which may have led to the misclassification of some standing or other low-movement time as SB and affected estimates of total ST, SB bouts, and SB breaks. Future investigations employing hip- or waist-worn devices are required to refine these behavioral classifications^[54]. Second, the machine-learning algorithm could not distinguish specific contexts of SB, such as television viewing or occupational sitting, which may have different health implications. Third, although accelerometer data were collected during a planned 7-day monitoring period, participants with 3 to 7 valid wear days were included in the analysis. Therefore, these measurements may not fully capture participants' long-term habitual SB and physical activity patterns. A longer monitoring period is needed in future research. Fourth, the response rate of the accelerometer substudy was relatively low, which may have introduced selection bias. However, the distribution of total ST was comparable with estimates from other developed countries^[1], supporting the

relevance of our findings to similar populations. Fifth, the accelerometer cohort consisted of middle-aged and elderly adults, mostly white, with better socioeconomic status and health conditions. Although population selection bias may limit the direct generalizability of our findings, this did not significantly affect the association between movement behaviors and health outcomes^[55]. Sixth, although this study attempted to control for confounding factors and reverse causality, it cannot fully establish causality. Seventh, a portion of baseline measurements was collected earlier than the accelerometer wearing time, which may lead to insufficient confounding adjustment. Eighth, the results of ISMs are only model estimates, which cannot confirm the health effects of actual behavioral replacement. The effects require confirmation in interventional studies.

In conclusion, both higher ST and its uninterrupted overall pattern are associated with a higher risk of incident CVD, all-cause and CVD-specific mortality, and shorter CVD-free and total LE. The increased mortality risk and the reduced CVD-free years associated with prolonged sitting may be mitigated by more frequent SB breaks. These findings provide compelling evidence to inform the importance of interrupting SB, particularly for sedentary individuals. Future randomized controlled trials are warranted to validate our findings and to help identify more specific strategies for breaking ST.

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