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Authors

Nguyen, Steve

Bellettiere, John

Anuskiewicz, Blake

et al.

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ORIGINAL RESEARCH

Prospective Associations of Accelerometer-Measured Machine-Learned Sedentary Behavior With Death Among Older Women: The OPACH Study

Steve Nguyen , PhD; John Bellettiere , PhD; Blake Anuskiewicz , MS; Chongzhi Di , PhD; Jordan Carlson , PhD; Loki Natarajan , PhD; Michael J. LaMonte , PhD; Andrea Z. LaCroix , PhD

BACKGROUND: Sedentary behavior is a recognized mortality risk factor. The novel and validated convolutional neural network hip accelerometer posture algorithm highly accurately classifies sitting and postural changes compared with accelerometer count cut points. We examined the prospective associations of convolutional neural network hip accelerometer posture–classified total sitting time and mean sitting bout duration with all-cause and cardiovascular disease (CVD) death.

METHODS AND RESULTS: Women (n=5856; mean±SD age, 79±7 years; 33% Black women, 17% Hispanic or Latina women, 50% White women) in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health (OPACH) Study wore the ActiGraph GT3X+ for ~7 days from May 2012 to April 2014 and were followed through February 19, 2022 for all-cause and CVD death. The convolutional neural network hip accelerometer posture algorithm classified total sitting time and mean sitting bout duration from GT3X+ output. Over follow-up (median, 8.4 years; range, 0.1–9.9), there were 1733 deaths (632 from CVD). Adjusted Cox regression hazard ratios (HRs) comparing women in the highest total sitting time quartile (>696 min/d) to those in the lowest (<556.0 min/d) were 1.57 (95% CI; 1.35–1.83; P-trend<0.001) for all-cause death and 1.78 (95% CI; 1.36–2.31; P-trend<0.001) for CVD death. HRs comparing women in the longest mean sitting bout duration quartile (>15 minutes) to the shortest (<9.3 minutes) were 1.43 (95% CI; 1.23–1.66; P-trend<0.001) for all-cause death and 1.52 (95% CI; 1.18–1.96; P-trend<0.001) for CVD death. Apparent nonlinear associations for total sitting time suggested higher all-cause death (P nonlinear=0.009) and CVD death (P nonlinear=0.008) risk after ~660 to 700 min/d.

CONCLUSIONS: Higher total sitting time and longer mean sitting bout duration are associated with higher all-cause and CVD mortality risk among older women. These data support interventions aimed at reducing both total sitting time and interrupting prolonged sitting.

Key Words: aging ■ epidemiology ■ public health ■ women's health

Cardiovascular disease (CVD) is the leading cause of death worldwide and in the United States. Among US adults aged ≥85 years, the annual rate of new, recurrent, or fatal coronary heart disease is higher among women (125 per 1000) than men (90 per 1000).[1] Sedentary behavior (SB), defined as waking behavior involving sitting or reclining with low energy expenditure (<1.5 metabolic equivalents), is recognized for its adverse associations with CVD and death independent of physical activity.[2–4] Laboratory studies have shown that the role of SB in cardiometabolic health is in part due to reduced muscle contractions, blood

Nonstandard Abbreviations and Acronyms

CHAP	convolutional neural network hip accelerometer posture
MSBD	mean sitting bout duration
MVPA	moderate-to-vigorous intensity physical activity
OPACH	Objective Physical Activity and Cardiovascular Health
SB	sedentary behavior
WHI	Women's Health Initiative
WHISH	Women's Health Initiative Strong and Healthy

flow, and glucose metabolism during prolonged sitting.[5–7] Thus, more epidemiologic evidence from specific investigation of sitting is needed.

The recently developed and validated convolutional neural network hip accelerometer posture (CHAP) algorithm is an innovative machine learning approach that accurately classifies sitting and postural transitions from accelerometer output.[8,9] Most previous studies classified SB by applying accelerometer cut point methods to low-resolution count data (eg, ≤100 vertical axis counts/min). This conventional approach does not capture sitting as accurately and, importantly, can misclassify low-intensity physical activity and less risky behaviors (eg, standing) as SB.[8,10] The present study is the first to examine whether higher amounts of CHAP-classified total sitting time and longer mean sitting bout durations were prospectively associated with higher all-cause and CVD mortality risk among a racially and ethnically diverse cohort of older women in the OPACH (Objective Physical Activity and Cardiovascular Health) Study. We additionally examined dose–response characteristics of these associations and evaluated effect modification by age, race and ethnicity, body mass index (BMI), physical functioning, CVD risk profile, and accelerometer-measured moderate-to-vigorous intensity physical activity (MVPA). For completeness, we also present associations of conventional cut point–classified SB with death.

METHODS

Study Population

The data supporting the present study findings are available on reasonable request from the Women's Health Initiative (WHI) Program in accordance with publications and presentations policies (https://sp.whi.org/researchers/data/WHIStudies/StudySites/AS286/Pages/home.aspx).

The OPACH Study is ancillary to the WHI Program and collected accelerometer data from 6489 ambulatory community-living women aged 63 to 99 from May 2012 to April 2014 with follow-up through February 19, 2022, for death.[11,12] OPACH protocol details have been published.[12] In this report, data were excluded from 270 (4.2%) women who returned accelerometers with data that the CHAP algorithm could not be successfully applied on and 363 women who returned devices that did not meet the adherent wear criteria (≥4 days with ≥10 hours of wear), yielding an analytic sample of 5856.[11,12] The WHI Coordinating Center (Fred Hutchinson Cancer Research Center, Seattle, WA) approved the study protocols; all women provided informed written consent. This study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[13]

Mortality Outcomes

The WHI mortality surveillance ascertained vital status through annual mailed outcome questionnaires, National Death Index searches, obituaries, and proxy queries.[14] All deaths and cardiovascular events were physician-adjudicated using hospital records, autopsy reports, next-of-kin reports, and National Death Index searches.[11] CVD deaths included fatal coronary heart disease, stroke, heart failure, or death from CVD defined via confirmatory evidence from medical records as ascertained by physician adjudication.[11,14] Kappa statistics for interrater agreement on cause-specific death in the WHI ranged from 0.75 to 0.89.[15]

Accelerometer Measures of Sitting, Sedentary Behavior, and Physical Activity

Women wore the ActiGraph GT3X+ (ActiGraph LLC, Pensacola, FL), which collected data at 30 Hz, over the right hip 24 h/d up to 7 consecutive days except during water submersion (eg, swimming, bathing).[11] The accelerometers were turned on before being mailed to participants, who were instructed to proceed with their usual daily living activities.[11] There was no research related interference with participants' daily living activities.[11] The Choi algorithm identified periods of accelerometer nonwear.[16] We removed sleep time using in-bed and out-of-bed times recorded in sleep diaries kept contemporaneous to accelerometer wear. Missing sleep time was imputed using individual average sleep time, if available, otherwise using the OPACH cohort average (10:45 PM for in-bed time, 7:22 AM for out-of-bed time).

Total sitting time (minutes/day) and mean sitting bout duration (MSBD; minutes/bout), were classified using the CHAP algorithm, which is intended for application on hip-worn GT3X+ data.[8] The 30 Hz GT3X+ data were downsampled to 10 Hz using boxcar aggregation to reduce file sizes.[8] The CHAP algorithm was developed among 709 older adults in the Adult Changes in Thought Study (mean [SD] age=77 [6.5] years; 59% women) who concurrently wore a GT3X+ over the right hip and a thigh-worn activPAL micro3 (criterion measure).[8] CHAP had high agreement with the activPAL micro3 at classifying minute-level sitting versus nonsitting (sensitivity, 97.1%, specificity, 88.6%, balanced accuracy, 92.9%).[8] The CHAP algorithm and its documentation are available for research use at https://github.com/ADALabUCSD/DeepPostures/.

We applied OPACH Calibration Study triaxial vector magnitude count cut points to classify MVPA (>518 counts/15 s; minutes/day) and total sedentary time (≤18 counts/15 s; minutes/day).[17] Cut point MSBD was classified using the common <100 counts/min vertical axis cut point, calculated as the arithmetic mean of all sedentary bout durations.[18,19] Accelerometer awake-wear time was accounted for using the residuals method.[20]

Covariates

Questionnaires assessed age, race and ethnicity (Black, White, Hispanic or Latina), education (high school equivalent or less, some college, college graduate), alcohol consumption (nondrinker, <1 drink/wk, ≥1 drink/wk, unknown), current smoking status (no, yes), and self-rated general health (excellent/very good, good, poor/very poor) at OPACH Study baseline. The RAND-36 questionnaire assessed health limitations on physical functioning during daily activities; scores ranged from 0 to 100; higher scores indicated higher physical functioning.[21] Participants self-reported physician diagnosis of hypertension and medication use. Multimorbidity was categorized as 0, 1, 2, or ≥3 of 12 prevalent conditions: history of CVD, cancer, diabetes, hip fracture, osteoarthritis, depression, chronic obstructive pulmonary disease, cognitive impairment, self-reported moderate/severe vision or hearing loss, ≥2 falls in past 12 months, and urinary incontinence.[22] Study staff measured systolic and diastolic blood pressure by auscultation using an aneroid sphygmomanometer with participants seated after 5 minutes of quiet rest; 2 measurements were averaged. Height and weight were assessed by tape measure and bathroom scale to calculate BMI (kg/m^2). Fasting (12-hour) blood samples were collected close in time (≤6 months) to the accelerometer wear interval. Serum glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein were measured using standardized Clinical Laboratory Improvement Act–approved methods at the University of Minnesota Fairview Advanced Research and Diagnostics Laboratory.[23] We calculated the Reynolds Risk Score, a summary CVD risk score, using age, systolic blood pressure, high-sensitivity C-reactive protein, total and high-density lipoprotein cholesterol, diabetes, smoking, and family history of myocardial infarction.[24]

Statistical Analysis

We used R 4.2.2 (https://www.r-project.org/) for analyses. We calculated means and SDs or counts and proportions for study characteristics and compared these across CHAP total sitting time quartiles using *F*-tests for continuous variables and chi-square tests for categorical variables. We calculated Pearson correlations to understand relationships between accelerometer variables.

Multivariable Cox proportional hazards regression models estimated hazard ratios (HRs) and 95% CIs for associations of quartiles of CHAP SB variables with

mortality end points. For completeness, we repeated the analysis using cut point–classified SB variables. We calculated follow-up time as number of days from OPACH Study baseline to date of death, loss to follow-up, last obtained annual WHI medical update, or end of follow-up, whichever occurred first. Schoenfeld residuals tested the proportional hazards assumption; no violations were observed. Model 1, the minimally adjusted model, contained age and race and ethnicity, as published studies of OPACH data showed that both age and SBs vary by race and ethnicity.[4,25] Model 2 additionally contained potential confounders: education, alcohol use, smoking status, self-reported health, multimorbidity, and hypertension. Model 3 contained model 2 covariates plus additional confounders: BMI and RAND-36 physical functioning. In models examining MSBD, model 3A contained model 3 covariates plus total sitting time in continuous functional form. Model 4 additionally contained MVPA, which is considered a confounder or competing behavior in compositional or isotemporal frameworks.[26,27] Model 5 contained model 4 covariates plus CVD biomarkers considered mediators or confounders: systolic blood pressure, serum glucose, total cholesterol/high-density lipoprotein ratio, natural-log trigylcerides and log high-sensitivity C-reactive protein. To characterize the dose–response relationship between sitting exposures and mortality risk, we used the *rms* package to test the linearity of associations using restricted cubic splines with knots placed at the 10th, 50th, and 90th percentiles and computed a Wald test for the nonlinear spline components.[28]

To evaluate the joint dose–response associations of total sitting time and MSBD, we specified models containing both variables. We calculated the adjusted all-cause and CVD mortality rates separately using the method described in an analysis carried out in the National Health and Nutrition Examination Survey as $(1 - PAR) \times m$ where PAR is the adjusted population attributable risk and m is the mortality rate per 1000 person-years.[29] The adjusted population attributable risks were calculated using the confounder-adjusted (model 3) Cox regression models as $(R - Rc)/R$ where the observed mortality rate was calculated as $R = I \sum r_i$ with I as the baseline hazard rate and r_i as the estimated relative risk for participant i and their observed total sitting time and mean sitting bout duration. The counterfactual mortality rate Rc was calculated as $R = I \sum r_{ci}$ with r_{ci} as the estimated relative risk for participant i with total sitting time and mean sitting bout duration set to fixed levels. In the adjusted population attributable risk calculation, the baseline hazard cancels out.

To evaluate the consistency of associations within cohort subgroups, we carried out stratified analysis across strata of age, BMI, RAND-36 physical function,

MVPA, Reynolds Risk Score, and race and ethnicity. We statistically evaluated effect modification with cross-product terms between SB variables and stratification variables (continuous format). To account for missing covariate data, we carried out multiple imputation by chained equations using the R *mice* package, specifying all outcomes, exposures, and covariates, with 100 imputations and 5 iterations.

In sensitivity analyses, we repeated the quartile Cox regression models excluding data from women who died within the first 2 years of follow-up to evaluate the potential of reverse causality influencing our primary results. The threshold for statistical significance was $P<0.05$ for all tests.

RESULTS

Study Population Characteristics

At baseline, women were aged 78.7 years on average; 49.8%, 33.2%, and 17.0% were White, Black, and Hispanic or Latina, respectively. Women averaged 621.5 min/d of CHAP total sitting time and 12.8 min/bout for MSBD (Table 1). Compared with women with total sitting time in the lowest quartile, women in higher total sitting time quartiles were older; were similar in education; were more likely to be White and current smokers; had higher BMI and multimorbidity; less often reported excellent/very good health; and had lower physical function scores, less favorable CVD biomarker levels, and lower MVPA levels (Table 1). Pearson correlations for CHAP total sitting time with MSBD and MVPA with cut point–classified total sedentary time were 0.56, −0.49, and 0.75, respectively (Figure S1).

Associations of SB Measures With all-Cause and CVD Death

There were 1733 deaths (632 from CVD) over a median follow-up of 8.4 years. Unadjusted all-cause and CVD mortality rates were higher across higher quartiles of CHAP total sitting time and MSBD (Table 2). Based on these rates, women in the highest versus lowest quartile of each SB exposure had more than double the absolute mortality risks.

In multivariable-adjusted analyses, higher quartiles of CHAP total sitting time and MSBD were significantly associated with higher all-cause and CVD mortality risk (models 1 and 2, all P-trend<0.001). After additional adjustment for BMI and RAND-36 physical functioning in model 3, the HRs comparing women with total sitting time in the highest quartile (≥696 min/d) to those in the lowest (<556.0 min/d) were 1.57 (95% CI, 1.35–1.83; P-trend<0.001) for all-cause death and 1.78 (95% CI, 1.36–2.31; P-trend<0.001) for CVD death (Table 2). The model 3 HRs comparing women with MSBD in the highest quartile (≥15.2 min) to those in the lowest

Table 1. Baseline (2012–2014) Sociodemographic and Health-Related Characteristics by Quartiles of CHAP-Classified Sitting Time in the OPACH Cohort (n=5856)

Characteristics	Total	Quartile 1 (low): <556.0	Quartile 2: 556.0–625.6	Quartile 3: 625.6–695.6	Quartile 4 (high): ≥695.6	P
Age, y, mean (SD)	78.7 (6.7)	76.9 (6.3)	77.9 (6.6)	79.1 (6.7)	80.8 (6.5)	<0.001
Race and ethnicity, n (%)						<0.001
White	2916 (49.8)	603 (41.2)	679 (46.4)	772 (52.7)	862 (58.9)	
Black	1944 (33.2)	432 (29.5)	504 (34.4)	516 (35.2)	492 (33.6)	
Hispanic or Latina	996 (17)	429 (29.3)	281 (19.2)	176 (12)	110 (7.5)	
Highest education level, n (%)						0.47
High school/GED or less	1169 (20.1)	307 (21.0)	292 (20.0)	286 (19.8)	284 (19.5)	
Some college	2243 (38.5)	565 (38.7)	546 (37.4)	542 (37.5)	590 (40.5)	
College graduate	2409 (41.4)	587 (40.2)	620 (42.5)	619 (42.8)	583 (40.0)	
Health behavior/status						
Current smoking, n (%)	153 (2.6)	23 (1.6)	34 (2.3)	39 (2.7)	57 (3.9)	0.001
Alcohol use in past 3mo, n (%)						<0.002
Nondrinker	1998 (34.1)	429 (29.3)	477 (32.6)	495 (33.8)	597 (40.8)	
<1 drink/wk	1852 (31.6)	470 (32.1)	461 (31.5)	481 (32.9)	440 (30.1)	
≥1 drink/wk	1526 (26.1)	454 (31)	430 (29.4)	376 (25.7)	266 (18.2)	
Unknown	480 (8.2)	111 (7.6)	96 (6.6)	112 (7.7)	161 (11)	
BMI, kg/m², mean (SD)	28.1 (5.7)	26.1 (4.7)	27.5 (5.0)	28.7 (5.6)	30.1 (6.6)	<0.001
Self-rated health, n (%)						<0.001
Excellent or very good	2974 (51.0)	867 (59.5)	804 (55)	755 (51.7)	548 (37.6)	
Good	2301 (39.4)	511 (35.1)	547 (37.4)	572 (39.2)	671 (46.0)	
Poor or very poor	562 (9.6)	79 (5.4)	110 (7.5)	134 (9.2)	239 (16.4)	
Physical functioning, mean (SD)	68.9 (25.9)	79.5 (20.3)	74.5 (23.0)	67.2 (25.4)	54.4 (27.4)	<0.001
Number of chronic conditions[†], n (%)						<0.001
0	1417 (24.3)	426 (29.2)	370 (25.4)	333 (22.8)	288 (19.8)	
1	2441 (41.9)	625 (42.9)	628 (43.1)	624 (42.8)	564 (38.7)	
2	1391 (23.9)	305 (20.9)	335 (23)	353 (24.2)	398 (27.3)	
≥3	582 (10.0)	101 (6.9)	124 (8.5)	149 (10.2)	208 (14.3)	
CVD risk factors						
History of CVD, n (%)	461 (7.9)	72 (4.9)	100 (6.8)	121 (8.3)	168 (11.5)	<0.001
Hypertension, n (%)	4199 (71.7)	926 (63.3)	1034 (70.6)	1091 (74.5)	1148 (78.4)	<0.001
Diabetes, n (%)	1184 (20.2)	205 (14.0)	263 (18.0)	307 (21.0)	409 (27.9)	<0.001
Systolic blood pressure, mmHg, mean (SD)	125.7 (14.2)	124.2 (13.7)	124.9 (13.9)	126.3 (14.0)	127.9 (15.2)	<0.001
Diastolic blood pressure, mmHg, mean (SD)	72.3 (8.7)	71.7 (8.3)	72.1 (8.4)	72.9 (8.8)	72.82 (9.3)	0.001
Total cholesterol, mg/dL, mean (SD)	197.4 (39.3)	202.6, (37.7)	199.4, (39.22)	195.6, (39.4)	191.6, (40.4)	
HDL cholesterol, mg/dL, mean (SD)	60.5 (15.0)	63.9, (15.4)	61.0, (15.2)	59.2, (14.4)	57.3, (14.0)	
Total cholesterol/HDL cholesterol ratio, mg/dL, mean (SD)	3.41 (0.93)	3.31, (0.87)	3.42, (0.95)	3.43, (0.89)	3.49, (1)	
Log triglycerides, mg/dL, mean (SD)	4.58 (0.45)	4.5 (0.45)	4.58 (0.45)	4.62 (0.44)	4.66 (0.45)	<0.001

(Continued)

Table 1. Continued

Characteristics	Total	Sitting time (min/d) quartiles*				P
		Quartile 1 (low): <556.0	Quartile 2: 556.0–625.6	Quartile 3: 625.6–695.6	Quartile 4 (high): ≥695.6	
Log hs-CRP, mg/L, mean (SD)	0.63 (1.05)	0.4 (0.98)	0.59 (1.0)	0.71 (1.07)	0.83 (1.12)	<0.001
Glucose, mg/dL, mean (SD)	98.2 (27.6)	95.0 (26.0)	96.5 (24.8)	98.6 (25.6)	103.4 (33.1)	<0.001
Accelerometry, mean (SD)						
Total sedentary time* (CP), min/d	555.6 (90.4)	466.4 (68.2)	535.2 (59.1)	582.0 (59.9)	638.7 (70.9)	<0.001
Mean sedentary bout duration* (CP), min	7.38 (2.7)	5.6 (1.3)	6.75 (1.6)	7.74 (2.1)	9.44 (3.5)	<0.001
CHAP total sitting time*, min/d	621.5 (103)	486.5 (57.8)	592.4 (20.2)	658.6 (20.0)	748.7 (40.8)	<0.001
CHAP mean sitting bout duration,* min	12.8 (5.3)	9.81 (3.0)	11.3 (3.5)	12.9 (4.0)	17.3 (6.7)	<0.001
MVPA*, min/d	50.8 (33.7)	72.1 (39.5)	56.6 (30.2)	44.5 (26.2)	30.1 (20.7)	<0.001

BMI indicates body mass index; CHAP, convolutional neural network hip accelerometer posture; CP, cutpoint; CVD, cardiovascular disease; GED, General Educational Development; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; MVPA, moderate-to-vigorous intensity physical activity; and OPACH, Objective Physical Activity and Cardiovascular Health.

*Adjusted for awake wear time using the residuals method.

†Multimorbidity consisted of 12 conditions: coronary disease (coronary artery bypass graft, coronary heart disease, congestive heart failure, clinical myocardial infarction, or percutaneous transluminal coronary angioplasty), stroke (carotid artery disease, stroke, transient ischemic attack), cancer (excluding nonmelanoma skin cancer), diabetes (self-reported physician diagnosis or use of diabetes medications), hip fracture, osteoarthritis, chronic obstructive pulmonary disease, cognitive impairment, sensory impairment (vision or hearing loss), ≥2 falls in the past 12 months, and urinary incontinence.[22]

(<9.3) were 1.43 (95% CI, 1.23–1.66; P-trend<0.001) for all-cause death and 1.52 (95% CI, 1.18–1.96; P-trend<0.001) for CVD death (Table 2). The HRs after further adjustment for total sitting time in model 3A were 1.18 (95% CI, 1.01–1.40; P-trend<0.001) for all-cause death and 1.20 (95% CI, 0.91–1.58; P-trend=0.043) for CVD death (Table 2). Associations remained significant after additional adjustment for MVPA and CVD biomarkers (all P-trend<0.01; Table 2).

We repeated the primary analysis using cutpoint-classified SB exposures. The model 3 HR comparing women in the highest quartile of cut point–classified total sedentary time (≥619.3 min/d) to those in the lowest (<497.1 min/d) was 1.74 (95% CI, 1.48–2.04; P-trend<0.001) for all-cause death and 1.39 (95% CI, 1.19–1.61; P-trend<0.001) for CVD death (Table S1). The model 3 HR comparing women in the highest quartile of cut point–classified MSBD (≥8.48 minutes) to those in the lowest (<5.60 minutes) was 1.60 (95% CI, 1.23–2.09; P-trend<0.001) for all-cause death and 1.42 (95% CI, 1.10–1.83; P-trend<0.001) for CVD death (Tables S1 and S2).

Restricted cubic spline analyses showed evidence of nonlinear dose–responses for CHAP total sitting time with all-cause death (P-nonlinearity=0.009) and CVD death (P-nonlinearity=0.008), but not for MSBD (P-nonlinearity=0.237 and 0.087 for all-cause and CVD death, respectively; Figure 1). Therefore, we proceeded with modeling CHAP total sitting time using restricted cubic splines and MSBD in continuous linear functional form. Higher total sitting time associated with higher all-cause mortality risk after ~660 min/d and higher

CVD mortality risk after ~700 min/d (Figure 1). The HRs for the interquartile range in total sitting time (140 min/d) were 1.31 (95% CI, 1.21–1.41) for all-cause death and 1.36 (95% CI, 1.2–1.54) for CVD death (Table 3). The HRs for the interquartile range in MSBD (5.9 minutes) were 1.17 (95% CI, 1.12–1.23) for all-cause death and 1.19 (95% CI, 1.10–1.28) for CVD death (Table 3).

Results from complete case analysis were consistent in direction and significance to main analyses; however, the HR attenuated when comparing women in the highest quartile of MSBD with those in the lowest after adjustment for CVD biomarkers in model 5 was 1.02 (95% CI, 0.84–1.23; P-trend=0.532) for all-cause death and 1.10 (95% CI, 0.79–1.53; P-trend=0.686) for CVD death (Table S3). In sensitivity analyses that excluded data from 189 women who died during the first 2 years of follow-up were generally consistent in direction and magnitude with those from the main analysis results. However, the MSBD-CVD mortality association was no longer statistically significant after adjustment for MVPA and CVD biomarkers (Table S4).

Joint Association of SB Measures With All-Cause and CVD Death

Multiplicative interactions between CHAP total sitting time modeled using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles and MSBD modeled in continuous functional form were not statistically significant for all-cause death (β=P-interaction=0.670) or CVD

Table 2. Associations of Quartiles of Total Sitting Time and Mean Sitting Bout Duration With All-Cause and CVD Death in the OPACH Cohort (n=5856) 2012 to 2022

	Total sitting time (min/d) quartiles*				
	Quartile 1 (low): <556.0	Quartile 2: 556.0–625.6	Quartile 3: 625.6–695.6	Quartile 4 (high): ≥695.6	P trend†
All-cause death					
Deaths [rate‡]	286 [23.9]	355 [30.6]	450 [40.3]	642 [63.7]	
Model 1§	1 (ref)	1.17 (1.00–1.37)	1.35 (1.16–1.56)	1.97 (1.71–2.28)	<0.001
Model 2§	1 (ref)	1.07 (0.91–1.25)	1.17 (1.01–1.36)	1.59 (1.37–1.84)	<0.001
Model 3§	1 (ref)	1.09 (0.93–1.27)	1.17 (1.01–1.37)	1.57 (1.35–1.83)	<0.001
Model 4§	1 (ref)	1.03 (0.88–1.21)	1.07 (0.92–1.25)	1.36 (1.16–1.60)	<0.001
Model 5§	1 (ref)	1.03 (0.88–1.21)	1.06 (0.91–1.24)	1.35 (1.15–1.58)	<0.001
CVD death					
Deaths [rate‡]	85 [7.1]	122 [10.5]	159 [14.2]	266 [26.4]	
Model 1§	1 (ref)	1.30 (0.99–1.72)	1.47 (1.12–1.91)	2.44 (1.90–3.13)	<0.001
Model 2§	1 (ref)	1.15 (0.87–1.52)	1.21 (0.93–1.59)	1.82 (1.41–2.35)	<0.001
Model 3§	1 (ref)	1.16 (0.88–1.54)	1.20 (0.91–1.58)	1.78 (1.36–2.31)	<0.001
Model 4§	1 (ref)	1.12 (0.85–1.49)	1.13 (0.86–1.48)	1.60 (1.22–2.10)	<0.001
Model 5§	1 (ref)	1.13 (0.85–1.49)	1.13 (0.85–1.48)	1.59 (1.21–2.09)	<0.001
	MSBD (min) quartiles*				
	Quartile 1 (low): <9.3	Quartile 2: 9.3–11.9	Quartile 3: 11.9–15.2	Quartile 4 (high): ≥15.2	P-trend†
All-cause death					
Deaths [rate‡]	289 [25.2]	380 [33.0]	447 [39.6]	617 [58.8]	
Model 1§	1 (ref)	1.14 (0.98–1.33)	1.28 (1.11–1.49)	1.65 (1.43–1.90)	<0.001
Model 2§	1 (ref)	1.09 (0.93–1.27)	1.20 (1.03–1.39)	1.45 (1.26–1.68)	<0.001
Model 3§	1 (ref)	1.08 (0.93–1.27)	1.20 (1.04–1.40)	1.43 (1.23–1.66)	<0.001
Model 3A§	1 (ref)	1.02 (0.87–1.19)	1.09 (0.93–1.27)	1.18 (1.01–1.40)	0.001
Model 4§	1 (ref)	1.02 (0.87–1.19)	1.08 (0.93–1.26)	1.21 (1.03–1.41)	<0.001
Model 5§	1 (ref)	1.02 (0.87–1.19)	1.07 (0.92–1.25)	1.18 (1.01–1.38)	<0.001
CVD death					
Deaths [rate‡]	95 [8.3]	126 [10.9]	170 [15.1]	241 [22.9]	
Model 1§	1 (ref)	1.15 (0.88–1.51)	1.48 (1.15–1.91)	1.88 (1.48–2.39)	<0.001
Model 2§	1 (ref)	1.08 (0.83–1.41)	1.34 (1.04–1.73)	1.58 (1.24–2.01)	<0.001
Model 3§	1 (ref)	1.07 (0.82–1.41)	1.33 (1.03–1.72)	1.52 (1.18–1.96)	<0.001
Model 3A§	1 (ref)	0.99 (0.75–1.30)	1.17 (0.90–1.52)	1.20 (0.91–1.58)	0.043
Model 4§	1 (ref)	1.03 (0.78–1.34)	1.23 (0.94–1.59)	1.34 (1.03–1.75)	0.001
Model 5§	1 (ref)	1.01 (0.77–1.33)	1.21 (0.93–1.57)	1.30 (1.00–1.70)	0.002

BMI indicates body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; MSBD, mean sitting bout duration; MVPA, moderate to vigorous intensity physical activity; and OPACH, Objective Physical Activity and Cardiovascular Health. Model 1 adjusted for age and race and ethnicity; model 2 adjusted for model 1 covariates plus educational attainment, alcohol use, smoking status, self-reported health, multimorbidity, and hypertension; model 3 adjusted for model 2 covariates plus BMI and RAND-36 physical functioning; model 3A adjusted for model 3 covariates plus total sitting time; model 4 adjusted for model 3 covariates plus MVPA; model 5 adjusted for model 4 covariates plus average systolic blood pressure, serum glucose, total cholesterol/HDL cholesterol ratio, log-triglycerides, and log hs-CRP. Model results were estimated with missing covariate data imputed using multiple imputation by chained equations from the R *mice* package.

*Adjusted for awake wear time using the residuals method.

†P values from Cox multivariate regression models including total sedentary time or mean sitting bout duration in continuous form.

‡Crude incidence rate per 1000 person-years.

§Data are hazard ratio (95% CI).

death (*P*-interaction=0.256). When modeled as jointly classified exposures (total sitting time modeled using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles and MSBD in continuous functional form) using the 10th percentile of total sitting time and MSBD as the reference group, there was a much stronger gradient of higher all-cause and CVD mortality rates and
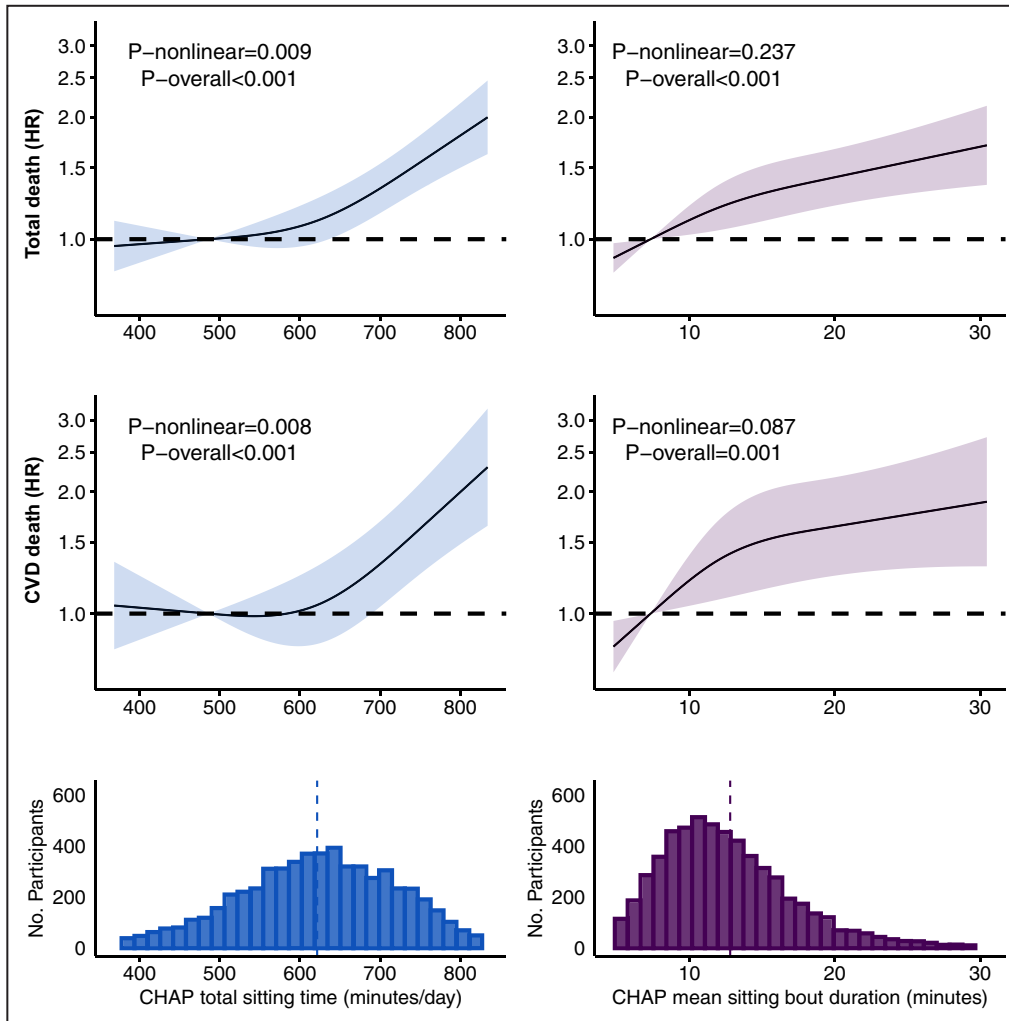
Figure 1. Dose–response associations of total sitting time and mean sitting bout duration (MSBD) with all-cause and CVD death in the OPACH 2012 to 2022.
Models adjusted for age, race and ethnicity, education, smoking status, alcohol use, multimorbidity, RAND-36 physical function, self-rated health, body mass index, and hypertension. Results were trimmed at the 1st and 99th percentiles. The reference was set to the 10th percentile. Bottom panels show histograms for the distributions of total sitting time and MSBD. The vertical dashed lines in the histograms correspond to the arithmetic mean of CHAP total sitting time or CHAP mean sitting bout duration. CHAP indicates convolutional neural network hip accelerometer posture; CVD, cardiovascular disease; HR, hazard ratio; and OPACH, Objective Physical Activity and Cardiovascular Health.

risks with higher total sitting time when holding MSBD constant than with longer MSBDs when holding total sitting time constant (Figures 2 and 3, Table S5). Women with the highest total sitting time and longest MSBD had the highest all-cause and CVD mortality rate and risk. The rates and HRs comparing women in the 90th percentile of both total sitting time (751.6 min/d) and MSBD (19.0 minutes) to those in the 10th percentile of total sitting time (486 min/d) and MSBD (7.3 minutes) were 47.8 per 1000 person-years and 1.60 (95% CI, 1.36–1.89) for all-cause death and 17.8 per 1000 person-years and 1.67 (95% CI, 1.27–2.19) for CVD death (Figures 2 and 3 and Table S5).

Effect Modification by Participant Characteristics for the Associations of Sitting Variables With All-Cause and CVD Death

In stratified analyses, results were consistent across most cohort subgroups with few interaction tests achieving statistical significance. The MSBD-CVD mortality association was somewhat weaker among women aged ≥80 years (HR, 1.16 [95% CI, 1.06–1.26]) than for women aged <80 years (HR, 1.30 [95% CI, 1.12–1.51]; P-interaction=0.013; Table 3). There was borderline evidence of effect modification by race and ethnicity for the MSBD-CVD mortality association

Table 3. Associations of Interquartile Range in CHAP-Classified Total Sitting Time and CHAP-Classified Mean Sitting Bout Duration With All-Cause and CVD Death by Selected Baseline Characteristics in the OPACH Cohort (n=5856) 2012 to 2022

	Total sitting time (min/d)*†						
		All-cause death			CVD death		
	n	n events	HR (95% CI)	P interaction	n events	HR (95% CI)	P interaction
Total sample	5856	1733	1.31 (1.21–1.41)		632	1.36 (1.20–1.54)	
Age				0.083			0.166
<80y	2957	415	1.36 (1.16–1.59)		119	1.42 (1.08–1.87)	
≥80y	2899	1318	1.26 (1.16–1.38)		513	1.33 (1.15–1.54)	
BMI				0.478			0.486
<30kg/m²	4023	1247	1.33 (1.22–1.45)		440	1.51 (1.30–1.74)	
≥30kg/m²	1833	486	1.19 (0.98–1.44)		192	1.01 (0.74–1.38)	
RAND-36 physical functioning				0.673			0.330
<75	2681	1115	1.31 (1.17–1.46)		428	1.34 (1.11–1.62)	
≥75	3175	618	1.31 (1.14–1.51)		204	1.29 (1.02–1.64)	
Reynolds Risk Score				0.232			0.652
<10	3027	560	1.31 (1.10–1.55)		174	1.33 (1.00–1.78)	
≥10	2829	1173	1.22 (1.09–1.35)		458	1.30 (1.09–1.56)	
MVPA				0.803			0.227
<43min/d	2928	1188	1.18 (1.05–1.31)		453	1.20 (1.00–1.44)	
≥43min/d	2928	545	1.30 (1.08–1.56)		179	1.20 (0.88–1.64)	
Race and ethnicity‡				0.203			0.702
White	2916	1189	1.27 (1.16–1.40)		461	1.40 (1.19–1.65)	
Black	1944	387	1.38 (1.16–1.64)		129	1.34 (1.03–1.74)	
Hispanic or Latina	996	157	1.26 (0.92–1.71)		42	1.16 (0.68–2.00)	
	MSBD (min)*†						
	n	All-cause death			CVD death		
		n events	HR (95% CI)	P-interaction	n events	HR (95% CI)	P-interaction
Total sample	5856	1733	1.17 (1.12–1.23)		632	1.19 (1.10–1.28)	
Age				0.038			0.013
<80y	2957	415	1.17 (1.06–1.29)		119	1.30 (1.12–1.51)	
≥80y	2899	1318	1.18 (1.12–1.24)		513	1.16 (1.06–1.26)	
BMI				0.580			0.723
<30kg/m²	4023	1247	1.20 (1.13–1.28)		440	1.24 (1.12–1.37)	
≥30kg/m²	1833	486	1.12 (1.02–1.23)		192	1.11 (0.96–1.28)	
RAND-36 physical functioning				0.470			0.792
<75	2681	1115	1.16 (1.09–1.23)		428	1.19 (1.09–1.29)	
≥75	3175	618	1.20 (1.10–1.32)		204	1.18 (1.01–1.38)	
Reynolds Risk Score				0.183			0.372
<10	3027	560	1.12 (0.99–1.28)		174	1.06 (0.85–1.34)	
≥10	2829	1173	1.14 (1.07–1.22)		458	1.15 (1.04–1.28)	
MVPA				0.092			0.275
<43min/day	2928	1188	1.16 (1.10–1.22)		453	1.18 (1.09–1.29)	
≥43min/day	2928	545	1.03 (0.89–1.19)		179	1.04 (0.81–1.33)	
Race and ethnicity‡				0.341			0.047
White	2916	1189	1.19 (1.12–1.25)		461	1.14 (1.04–1.25)	
Black	1944	387	1.15 (1.04–1.26)		129	1.32 (1.14–1.52)	
Hispanic or Latina	996	157	1.29 (1.02–1.63)		42	1.66 (1.08–2.54)	

BMI indicates body mass index; CHAP, convolutional neural network hip accelerometer posture; CVD, cardiovascular disease; HR, hazard ratio; MSBD, mean sitting bout duration; and MVPA, moderate-to-vigorous physical activity; and OPACH, Objective Physical Activity and Cardiovascular Health. Models adjusted for age, race and ethnicity, education, smoking status, alcohol use, multimorbidity, physical functioning, self-rated health, BMI, and hypertension. RAND-36 physical functioning and MVPA were split at the median. Model results were estimated with missing covariate data imputed using multiple imputation by chained equations from the R *mice* package.

*The interquartile ranges for total sitting time and MSBD are 139.6 and 5.9min, respectively.

†Total sitting time was modeled using restricted cubic splines with knots placed at the 10th, 50th, and 90th percentiles. MSBD was modeled in continuous functional form.

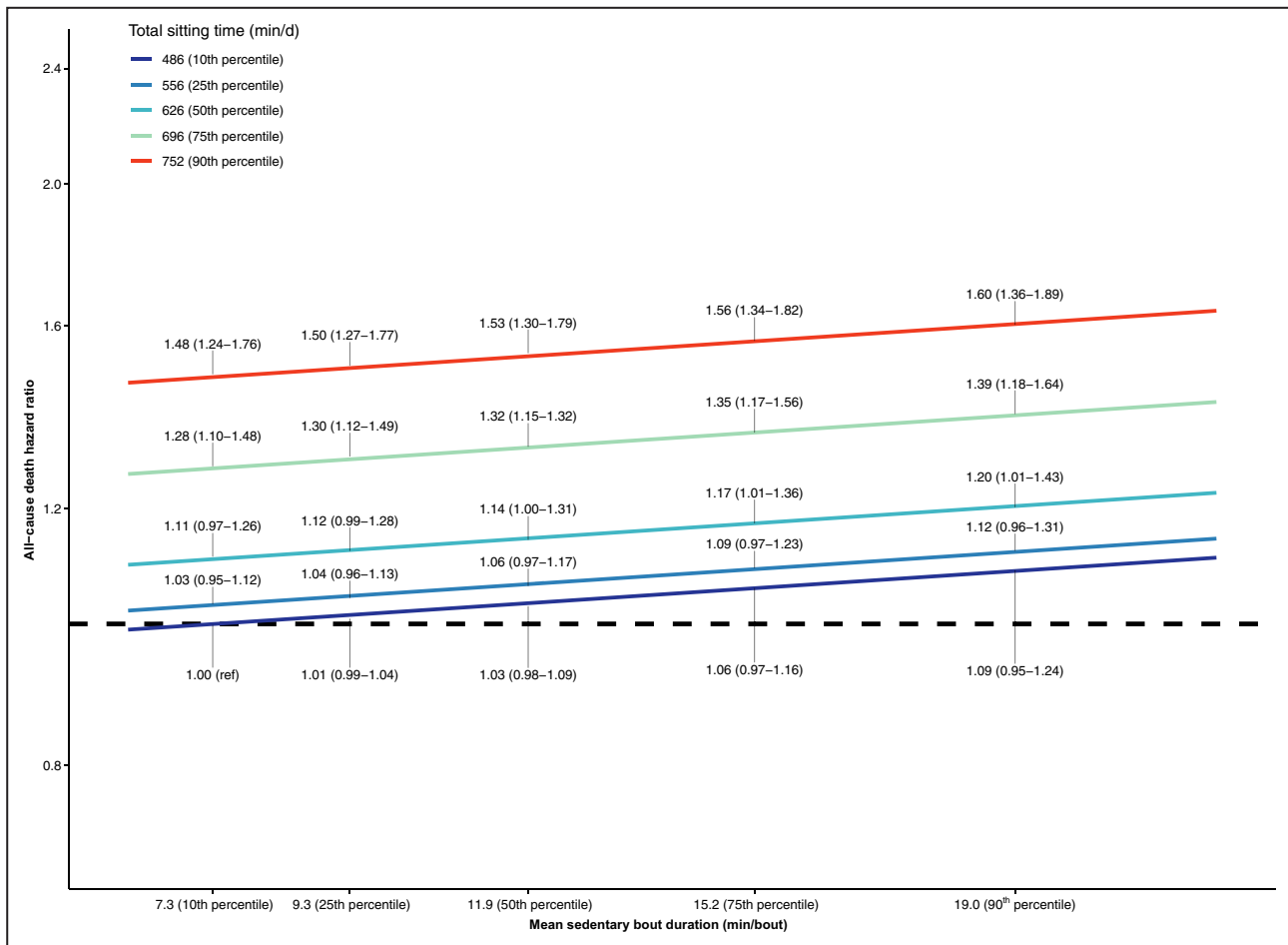‡Models for each level of race and ethnicity were not mutually adjusted for race and ethnicity.

Figure 2.   Joint associations of sitting time and mean sitting bout duration (MSBD) with all-cause death in the OPACH cohort 2012 to 2022.

CVD indicates cardiovascular disease; MSBD, mean sitting bout duration; and OPACH, Objective Physical Activity and Cardiovascular Health. Model adjusted for age, race and ethnicity, education, smoking status, alcohol use, multimorbidity, RAND-36 physical function, self-rated health, body mass index, and hypertension. Results were trimmed at the 1st and 99th percentiles. Sitting time was modeled using restricted cubic splines with knots placed at the 10th, 50th, and 90th percentiles and mean sitting bout duration was modeled in continuous linear functional form. The reference was set to the 10th percentile of both total sitting time and MSBD.

(*P*-interaction=0.047), suggesting a somewhat stronger association among Hispanic and Latina women (HR, 1.66 [95% CI, 1.08–2.54]) than for Black women (HR, 1.32 [95% CI, 1.14–1.52]) and White women (HR, 1.14 [95% CI, 1.04–1.25]; Table 3). Results from complete case analysis were consistent in direction and magnitude (Table S6).

DISCUSSION

In this racially and ethnically diverse prospective study among older ambulatory women, both higher amounts of CHAP-classified total sitting time and longer MSBD were significantly associated with higher all-cause and CVD mortality risk after adjusting for device awake–wear time, sociodemographic and CVD risk factors, and accelerometer-measured MVPA. Compared with women with less than ~9.3h/d of total sitting time, those

with ~11.6h/d or more had a 57% higher risk of all-cause death and a 78% higher risk of CVD death. Compared with women with MSBDs <9.3minutes, those with MSBDs of ~15minutes or more had 43% higher risk of all-cause death and 52% higher risk of CVD death. There were significant nonlinear dose–response associations for CHAP total sitting time, suggesting a threshold of ~660 to 700min/d demarcating higher mortality risks thereafter. Associations were generally directionally consistent across key subgroups, enhancing confidence in the primary findings for the overall cohort.

These findings have important public health implications. Older women accumulate substantial SB amounts when awake (eg, screen use, transportation, leisure pursuits, and at home).[30–32] When examined as jointly classified exposures, women with the highest total sitting time and longest MSBD had the highest all-cause and CVD mortality risks, but the additional
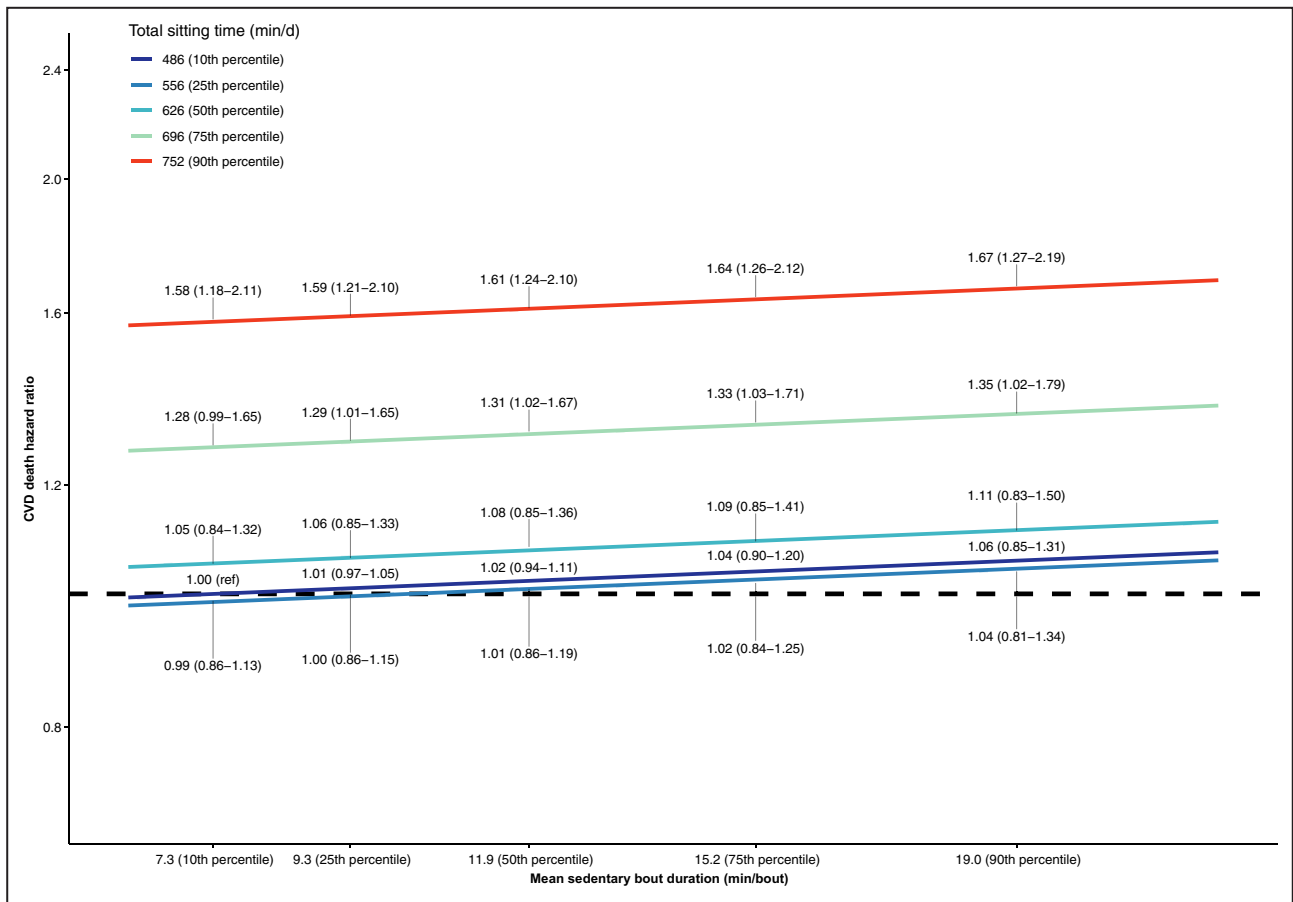
Figure 3. Joint associations of sitting time and mean sitting bout duration (MSBD) with CVD death in the OPACH cohort 2012–2022.

CVD indicates cardiovascular disease; MSBD, mean sitting bout duration; and OPACH, Objective Physical Activity and Cardiovascular Health. Model adjusted for age, race and ethnicity, education, smoking status, alcohol use, multimorbidity, RAND-36 physical function, self-rated health, body mass index, and hypertension. Results were trimmed at the 1st and 99th percentiles. Sitting time was modeled using restricted cubic splines with knots placed at the 10th, 50th, and 90th percentiles and mean sitting bout duration was modeled in continuous linear functional form. The reference was set to the 10th percentile of both total sitting time and MSBD.

risk of both exposures was not synergistic regarding additive or multiplicative interaction. HRs for total sitting time (HRs for interquartile range, 1.31 for all-cause death and 1.36 for CVD death; Table 3) were stronger in magnitude than for MSBD (HRs for interquartile range, 1.17 for all-cause death and 1.19 for CVD death). Nonetheless, longer MSBDs were associated with mortality risk independent of total sitting time. Given that these SB exposures were moderately correlated (r=0.56) and travel together, our findings suggest a larger risk reduction potential with reducing total sitting time than with reducing MSBD and that introducing more breaks to sitting may reduce mortality risk by reducing total sitting time as well as sitting bout durations. Moreover, when total sitting time is longer than 11 to 12 h/d, it may be especially important to interrupt prolonged sitting to reduce mortality risks. Overall, the present study results support interventions to reduce both total sitting time and MSBD.

There were somewhat stronger HRs for CVD death with CHAP-classified SB than with cut point–classified SB (eg, model 3, quartile 4 versus quartile 1 HR for total sitting time, 1.78 versus 1.39 with total sedentary time) despite strong correlations between CHAP-classified and cut point–classified SB (r=0.67–0.75). These subtle differences could be attributable to the CHAP algorithm more accurately capturing sitting and postural transitions, whereas cut point methods capture movement intensity and are vulnerable to misclassifying as SB low-intensity physical activity and nonsitting behaviors like standing, which has been shown to inversely associate with death.[8,31] Additionally, confounding by MVPA was greater with cut point-classified SB than with CHAP-classified SB (eg, model 4, quartile 4 versus quartile 1 HR for total sitting time, 1.60 versus 1.14 with cut point–classified total sedentary time).

The present study results for CHAP-classified sitting align with published studies that used accelerometer

cut point–classified SB. In a published OPACH study (mean follow-up, 3.4 years), women with both high total sedentary time (≥558 min/d) and long MSBDs (≥6.8 min/bout) had the highest incident CVD risks (HR, 1.34 [95% CI, 1.08–1.65]), consistent with the present study, which incorporated an additional 5 years of follow-up.[4] The present study results also align with those among middle-aged and older adult Black and White participants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study where those with both high total sedentary time (≥750 min/d) and long MSBD (≥10 min/bout) had the highest all-cause mortality risk (HR, 2.00 [95% CI, 1.45–2.75]).[33] In the European Prospective Investigation into Cancer (EPIC)-Norfolk study, there were flat, nonsignificant associations between sedentary time and all-cause mortality risk up to 660 min/d, with a steep increase in HRs thereafter, consistent with the present study.[2] The present study results strengthen the published literature by showing congruent evidence of adverse SB–mortality associations despite differences in study population and SB measurement and classification methods.

Importantly, the application of CHAP-classified SB in the present study extends the literature on SB and death. First, the present study examined the joint associations of total sitting time and MSBD across their respective ranges by including both variables in models. Due to collinearity considerations, studies with cut point–classified SB instead classified participants with high or low total sedentary time and MSBD. Second, adjustment for accelerometer-measured MVPA in the present study did not eliminate the positive CHAP SB–mortality associations, in contrast with published studies. A meta-analysis of 9 studies (n=44 370 middle-aged and older adults) observed that higher tertiles of total sedentary time did not associate with higher all-cause mortality risk among those in the highest tertile of MVPA.[3] In the Whitehall II study, incident CVD risk was not higher with higher total sedentary time (HR, 1.02 [95% CI, 0.88–1.19]) and longer MSBD (HR, 1.09 [95% CI, 0.98–1.23]) after adjusting for MVPA.[34] Differences between the present study findings and those in the literature could be attributable to differences in study population, devices used, placement, wear interval duration, and method of classifying SB.

Several national and international guidelines including the US Physical Activity Guidelines, Australian Physical Activity Guidelines, and World Health Organization guidelines include recommendations to reduce and interrupt SB.[35–38] However, the World Health Organization guidelines did not specify a quantitative threshold for SB due to insufficient evidence as well as potential variation in SB measurement.[36] The CHAP algorithm as applied in the present study could address questions of variation in SB measurement

due to its high agreement with activPAL devices and CHAP's availability to researchers to apply on existing or future hip-worn device data.[8] Additionally, these guidelines indicated a need for additional research on the prospective associations of SB bouts with all-cause and CVD death and detailed examination of how factors inclusive of age, race and ethnicity, and adiposity relate to SB-CVD mortality associations.[35–37] The present study results support guidelines to reduce SB and contribute important information addressing these research gaps and could thereby inform future physical activity and SB guidelines for older adults.

Strengths and Limitations

Strengths of the present study include the large racially and ethnically diverse study population of older women and the application of the highly accurate CHAP algorithm to determine SB during up to 7 days under usual free-living conditions.[8] The WHI and OPACH collected extensive health information, enabling comprehensive adjustment for potential confounders including health status, physical functioning, and multimorbidity, and for stratified analysis across cohort subgroups to determine consistency of the primary results. Of the 6489 women who returned accelerometers with usable data, 363 returned devices that were not adherent (<4 days of ≥10 h/d of wear), indicating that women in OPACH were highly adherent to accelerometer wear at 94.4% (6126/6489). Limitations include the lack of ground truth sitting measures, for example, direct observation, or concurrent activPAL wear, which are not available in OPACH. However, the CHAP algorithm, developed using activPAL as the criterion sitting measure, has excellent accuracy.[8] Women wore accelerometers for up to 7 days, which has been shown to be reliable for capturing SB patterns over 2 to 3 years but may not reflect SB patterns over longer periods of time.[39] Finally, replication among men and among younger populations is warranted for reproducibility and generalizability.

CONCLUSIONS

Our study showed that among older women, higher total sitting time and longer MSBDs were associated with higher all-cause and CVD mortality risk. Large, randomized trials like the WHISH (Women's Health Initiative Strong and Healthy) trial are needed to evaluate the effectiveness of reducing SB accumulation in relation to health outcomes including CVD and death among older adults.[40] Health care providers and future physical activity guidelines could usefully address reducing both overall SB and interrupting prolonged sitting in addition to promoting physical activity for public health benefits in an aging society.

ARTICLE INFORMATION

Affiliations

Division of Epidemiology, Herbert Wertheim School of Public Health, University of California San Diego, La Jolla, CA (S.N., J.B., B.A., L.N., A.Z.L.); Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA (C.D.); Center for Children's Healthy Lifestyles and Nutrition, Children's Mercy Kansas City, Kansas City, MO (J.C.); and Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo – SUNY, Buffalo, NY (M.J.L.).

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Disclosures

Supplemental Material

Tables S1–S6
Figure S1

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