Circulation

ORIGINAL RESEARCH ARTICLE

Sedentary Behavior and Cardiovascular Disease in Older Women

The OPACH Study

BACKGROUND: Evidence that higher sedentary time is associated with higher risk for cardiovascular disease (CVD) is based mainly on self-reported measures. Few studies have examined whether patterns of sedentary time are associated with higher risk for CVD.

METHODS: Women from the OPACH Study (Objective Physical Activity and Cardiovascular Health; n=5638, aged 63–97 years, mean age 79±7 years) with no history of myocardial infarction or stroke wore accelerometers for 4 to 7 days and were followed up for up to 4.9 years for CVD events. Average daily sedentary time and mean sedentary bout duration were the exposures of interest. Cox regression models were used to estimate hazard ratios (HRs) and 95% CIs for CVD using models adjusted for covariates and subsequently adjusted for potential mediators (body mass index, diabetes mellitus, hypertension, and CVD risk biomarkers [fasting glucose, high-density lipoprotein, triglycerides, and systolic blood pressure]). Restricted cubic spline regression characterized dose-response relationships.

RESULTS: There were 545 CVD events during 19 350 person-years. With adjustment for covariates, women in the highest (≈11 h/d or more) versus the lowest (≈9 h/d or less) quartile of sedentary time had higher risk for CVD (HR, 1.62; 95% CI, 1.21–2.17; *P* trend <0.001). Further adjustment for potential mediators attenuated but did not eliminate significance of these associations (*P* trend <0.05, each). Longer versus shorter mean sedentary bout duration was associated with higher risks for CVD (HR, 1.54; 95% CI, 1.27–2.02; *P* trend=0.003) after adjustment for covariates. Additional adjustment for CVD risk biomarkers attenuated associations, resulting in a quartile 4 versus quartile 1 HR of 1.36 (95% CI, 1.01–1.83; *P* trend=0.10). Dose-response associations of sedentary time and bout duration with CVD were linear (*P* nonlinear >0.05, each). Women jointly classified as having both high sedentary time and long bout durations had significantly higher risk for CVD (HR, 1.34; 95% CI, 1.08–1.65) than women with low sedentary time and short bout duration. All analyses were repeated for incident coronary heart disease (myocardial infarction or CVD death), and associations were similar, with notably stronger HRs.

CONCLUSIONS: Both high sedentary time and long mean bout durations were associated in a dose-response manner with increased CVD risk in older women, which suggests that efforts to reduce CVD burden might benefit from addressing either or both components of sedentary behavior.

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Clinical Perspective

What Is New?

- Sedentary behaviors, which include all sitting or reclining with low energy expenditure (<1.5 metabolic equivalents), are poorly recalled by patients.
- Accelerometers more accurately measure sedentary time and also enable the quantification of sedentary bout durations that measure how sedentary time is accumulated.
- This was the first prospective study of sedentary time, sedentary bout duration, and cardiovascular disease (CVD).
- Our results showed a linear dose-response association of both total sedentary time and sedentary bout duration with CVD that was independent of health status, physical function, and CVD risk factors including moderate to vigorous physical activity.

What Are the Clinical Implications?

- In this subcohort of 5638 racially/ethnically diverse Women's Health Initiative participants aged 63 to 97 years, lower sedentary time of 1 hour/d was associated with a 12% lower risk of CVD and a 26% lower risk of heart disease.
- Sedentary time reductions (eg, 1 hour/d) do not need to occur all at once; they can be accumulated throughout the day with short (light intensity) interruptions to sitting.
- Regular and frequent interruptions can lower sedentary bout durations, which we found to be associated with lower CVD risk.
- Encouraging reduced sedentary time and shorter sedentary bouts in older women could have large public health benefits.

Through the 20th century, cardiovascular disease (CVD) killed more Americans than any other disease, currently causing 1 in 3 deaths annually.[1] CVD incidence increases with age and is highest among adults ≥85 years old.[2]

Significant evidence has amassed that physical inactivity,[3] often defined as failure to meet physical activity guidelines, is a major risk factor for CVD.[4] Despite known health benefits of moderate to vigorous physical activity (MVPA), few adults and fewer older adults meet recommended guidelines.[1] Recent evidence shows that high levels of sedentary behaviors, often independent of MVPA, are associated with modest increases in CVD risk.[5] Nearly all existing evidence was obtained using self-reported sedentary time, which is biased[6] and could potentially underestimate the magnitude of associations.[7] This prompted the American Heart Association[8] and others[9] to call for the use of objective measures of sedentary time to evaluate relations with cardiometabolic health.

The use of accelerometers to quantify sedentary behavior also enables measurement of patterns that describe how sedentary time is accumulated. These sedentary accumulation patterns can range from highly interrupted, which represent a tendency to be sedentary only in short bouts throughout the day, to highly prolonged, which indicate a tendency to accumulate sedentary time in long, continuous sedentary bouts. Experimental evidence indicates that long sedentary bouts are associated with impaired glucose control and with several other cardiometabolic risk factors.[10,11] Epidemiological evidence suggests that prolonged accumulation patterns are associated with higher cardiometabolic risk factors[12,13] and increased risk for mortality.[14,15] No prospective studies have examined whether prolonged sedentary accumulation patterns are associated with higher risk for CVD in older women. Because sedentary time is high among older adults[16] and little is known about sedentary accumulation patterns and CVD in this age group, studies are needed to evaluate objectively measured sedentary behavior and CVD risk in later life.

This prospective study investigated accelerometer-measured sedentary time and sedentary accumulation patterns in relation to CVD events in an ethnically diverse cohort of older women with no prior history of myocardial infarction (MI) or stroke.

METHODS

The data that support the findings of this study are available from Dr Andrea LaCroix on reasonable request (email alacroix@ucsd.edu) in accordance with the WHI (Women's Health Initiative) publications and presentations policy.

Study Participants

Between 2012 and 2014, 7058 ambulatory, community-dwelling women aged ≥63 years were enrolled in the OPACH Study (Objectively Measured Physical Activity and Cardiovascular Health). All participants were part of the WHI, which recruited and enrolled the original cohort at 40 clinical sites throughout the United States during 1993 to 1998. Details on the OPACH Study and WHI have been published previously.[17,18]

OPACH participants were distributed ActiGraph GT3X+ accelerometers (ActiGraph, Pensacola, FL) to wear over their right hip 24 h/d for 7 consecutive days, removing devices only when showering or swimming. Participants self-reported in-bed and out-of-bed times using sleep logs on days when the accelerometer was worn.

Of the 7058 consented women, 10 died before receiving study materials, accelerometers were not received from 327, and 232 devices were returned without usable data (see LaCroix et al[17] for a detailed STROBE [Strengthening the Reporting of Observational Studies in Epidemiology] diagram). Of the 6489 women who wore accelerometers, 6133 met the recommended data processing criteria for estimating average daily sedentary time among older adults (ie, ≥10 waking wear hours on ≥4 days per week).[19] Women with an

MI or stroke before OPACH baseline (n=495) were excluded, which left data from 5638 women available for the present study. The protocol for this study was approved by the Fred Hutchinson Cancer Research Center institutional review board, and all women provided informed consent either in writing or by telephone.

CVD Events

The primary outcome for this study was CVD events, defined as the first occurrence of an MI, revascularization, hospitalized angina, heart failure, stroke, or death attributable to any CVD among women without that event. We also investigated incident coronary heart disease (CHD) events (nonfatal MI or coronary death) as a separate end point. CVD ascertainment methods are described in detail elsewhere.[17] Briefly, each woman returned an annual medical history update, which included reports of new CVD events. For the first reported occurrence of each CVD event (except hospitalized angina, which was not adjudicated), trained study physicians obtained and reviewed relevant medical records to confirm whether the outcome met the strict defining criteria, which are listed in Curb et al.[20] Inter-rater agreement on CVD outcome ascertainment was strong, with κ-statistics ranging from 0.67 to 0.94.[21] Women were followed up for CVD events through February 28, 2017.

Accelerometer Data Processing

ActiGraph GT3X+ accelerometers measured acceleration at 30 Hz. The resulting data were converted to 15-second epochs using the normal filter and to 1-minute epochs using the low-frequency extension filter supplied with ActiLife version 6.[22] Periods of accelerometer nonwear were removed from data by the commonly used Choi algorithm applied to the vector magnitude acceleration counts with a 90-minute window, 30-minute stream frame, and 2-minute tolerance.[23] Self-reported in-bed and out-of-bed times were used to remove periods during which participants were in bed. Missing bed times were imputed using person-specific averages, when available, or the OPACH population average otherwise (in-bed=10:45 PM; out-of-bed=7:22 AM).

Sedentary Behavior

Total sedentary time was defined as the average minutes per day with vector magnitude acceleration counts ≤18 per 15-second epoch, an accelerometer cut point specifically calibrated to our sample in the laboratory-based OPACH Calibration Study[24] conducted among 200 women aged 60 to 91 years. Mean bout duration and all other sedentary accumulation metrics were based on the most commonly used[19] measure of sedentary time (having <100 counts/min [cpm] measured on the vertical axis), which is the only method used to date to measure sedentary accumulation patterns with ActiGraph data (eg, Shiroma et al[25]). The OPACH cut point of 18 counts per 15 seconds was not used to measure accumulation patterns, because it was overly sensitive to breaks in sedentary time. With it, the average number of breaks per day among OPACH women was >300. Using the 100 cpm cut point, there were 86 breaks per day, which was identical to reports from a separate cohort of 7247 older women.[25] Therefore, consecutive minutes with <100 cpm were classified as sedentary bouts (no minimum duration required and no tolerance allowed), and for each participant, the mean sedentary bout duration using data from all adherent days was computed for the primary measure of sedentary accumulation patterns. Higher bout durations indicate more prolonged accumulation patterns, whereas lower bout durations indicate interrupted patterns. Because a consensus is lacking on the best measure of sedentary accumulation patterns, we report results for other commonly used accumulation pattern metrics in the supplemental material: prolonged sedentary time (time spent in sedentary bouts ≥30 min/d); breaks in sedentary time (the frequency of transitions from sedentary to nonsedentary bouts); usual bout duration (the midpoint of the cumulative bout duration distribution computed over all adherent days using nonlinear regression[26]); and alpha (which characterizes the shape of the power-law distribution of bout durations computed over all adherent days using maximum likelihood estimation[26]).

Covariates

At WHI baseline, information on age, race/ethnicity, education, and family history of MI was obtained by questionnaire. Self-reported health, physical functioning (assessed with the RAND-36 survey instrument), alcohol consumption, and current smoking were measured by questionnaire nearest to the OPACH baseline. The number of chronic health conditions (cancer, cognitive impairment, chronic obstructive pulmonary disease, depression, and osteoarthritis) reported at or before OPACH baseline was used to represent multimorbidity.[27] Prevalent diabetes mellitus and hypertension at OPACH baseline were measured by self-reports of physician diagnoses and treatment with medication reported at WHI enrollment or through OPACH baseline. A subset of participants (n=4458) received in-home visits at or near the OPACH baseline as part of the WHI Long Life Study.[17] At those visits, height and weight were measured with a tape measure and calibrated bathroom scale, respectively, and body mass index (BMI) was computed as weight divided by height squared. Blood pressure was measured by auscultation with an aneroid sphygmomanometer after the subject had been sitting quiety for 5 minutes; 2 measures each of systolic and diastolic blood pressure were averaged. Fasting blood samples were obtained, and serum levels of glucose, high-density lipoprotein, and triglycerides were later quantified at the University of Minnesota with respective coefficients of variation equal to 1.8%, 2.9%, and 2.1%.[28]

MVPA (activity intensity of ≥3 metabolic equivalents) was measured by accelerometer and defined based on the OPACH Calibration Study[24] as the mean minutes per day with ≥519 vector magnitude accelerometer counts per 15 seconds.

Statistical Analysis

Sociodemographic and health-related characteristics were described using means and SDs or percentages across quartiles of total sedentary time. Differences across quartiles were tested with F tests and the Jonckheere-Terpstra trend test for continuous variables and Pearson χ^2 tests for categorical variables.

Hazard ratios (HRs) and 95% CIs for CVD events were estimated with Cox proportional hazards regression. Time to event

was calculated as the number of days from OPACH baseline to either the first event, death unrelated to the outcome, or the last available medical update. For each outcome, 5 Cox models were examined. Model 1 was adjusted for age and ethnicity, and model 2, hereafter referred to as the confounder-adjusted model, was additionally adjusted for potential confounders (education, self-reported health status, family history of MI, multimorbidity, physical functioning, alcohol consumption, and current smoking status). Models 3a, 3b, and 3c were secondary analyses to test associations of sedentary behavior and CVD after additional adjustment for risk factors thought to be in the causal pathway and to test whether direct effects were present after adjustment for MVPA, which in previous studies has been viewed as a confounder, a mediator, an effect modifier, or a competing behavior (when using a compositional[29] or isotemporal[30] framework).[31] Model 3a added hypertension, diabetes mellitus, and BMI to model 2; model 3b added serum glucose, triglycerides, high-density lipoprotein cholesterol, and systolic blood pressure to model 2 in the subset of women for whom these biomarkers were available; and model 3c added MVPA to model 2. Tests of linear trend were computed with Cox models that treated total sedentary time and mean bout duration as continuous variables. Proportional hazards assumptions were assessed with tests based on Schoenfeld residuals, and no variables violated the assumption. To account for differences in time spent wearing accelerometers while awake, total sedentary time was adjusted for awake wear time using the residuals method[32]; mean bout duration was unrelated to awake wear time and was not adjusted.

The dose-response relation of CVD and CHD risks with the continuous variables total sedentary time and mean bout duration were examined by means of 2 steps. First, we tested the dose-response trajectory for nonlinearity by repeating model 2 after including restricted cubic spline functions of total sedentary time and mean bout duration using the Regression Modeling Strategies (rms) package in R (R Foundation for Statistical Computing; Vienna, Austria). To test whether the shapes of the dose-response trajectories were sensitive to the number of knots used, we ran models with 3 and 4 knots placed at the 10th, 50th, and 90th and the 5th, 35th, 65th, and 95th percentiles, respectively. Plots of the dose-response trajectories were reviewed for each outcome for each model fit, and χ^2 tests for nonlinearity were performed. After determining the most appropriate functional form of the dose-response trajectories, we plotted them for each outcome, specifying the 10th percentile of the sedentary time/mean bout duration distribution as the referent category.[33] Dose-response trajectories were plotted for model 2 with and without the addition of MVPA to visualize the influence of adjustment. The trajectories were not meaningfully different when modeled with 3 or 4 knots, so χ^2 tests were performed for restricted cubic spline models with 3 knots to maximize statistical power.

We further explored associations of sedentary time and mean bout duration with CVD and CHD risks among cohort subgroups for women <80 and ≥80 years of age; with BMI <30 kg/m^2 and ≥30 kg/m^2; with MVPA <44 and ≥44 min/d (median split); with physical functioning scores of <75 and ≥75 (median split); and for white, black, and Hispanic women. Effect modification was tested by adding multiplicative interaction terms (effect modifier×exposure variable) to model 2, with statistical significance set to $P<0.05$. The continuous functional form of effect modifiers was used where appropriate, and continuous variables were first mean centered to prevent error associated with multicollinearity.

Pearson correlation coefficients were computed for all accelerometer-derived exposures. To explore the association of jointly classified sedentary time and bout duration with CVD risks, we used the analytic method used by Diaz et al,[14] by categorizing our sample into high and low sedentary time and high and low mean bout duration (using median splits) to create the following 4 mutually exclusive groups: low sedentary time, low bout duration (reference group); low sedentary time, high bout duration; high sedentary time, low bout duration; and high sedentary time, high bout duration. The HR for each jointly classified exposure group associated with CVD events was then estimated using the confounder-adjusted model (model 2). A post hoc examination of effect modification was conducted by including the cross-product of mean-centered total sedentary time and mean bout duration in the confounder-adjusted model. All analyses were conducted using R, and statistical tests were 2-tailed, with $P\leq0.05$ considered significant.

Sensitivity Analyses

Women with a history of angina, revascularization, and heart failure were included in our primary analysis to avoid excluding large numbers of women who remain at risk of other CVD events and for whom studying risk factors for the first occurrence of a different CVD event has important clinical and public health implications. Greater inclusion was also chosen to make our results generalizable to a larger proportion of the older adult population. To test whether these prevalent conditions were driving the observed associations between sedentary behavior and CVD, we repeated all quartile analyses after excluding women with a history of hospitalized angina, revascularization, or heart failure at OPACH baseline. To account for missing data among women who did not have a blood draw,[17] we conducted a multiple imputation analysis to impute the missing data using the MICE package in R, with 100 iterations, and including all relevant outcomes (including time to event), exposures, and covariates in the process. To explore the possibility of reverse-causation bias, all CVD cases that occurred within 6 months after OPACH baseline were removed and model 2 analyses repeated. We initially imputed in-bed and out-of-bed times using OPACH population average bed times for 482 women who did not return sleep logs. To determine whether the results were sensitive to the imputation method, we repeated model 2 using an automated algorithm[34] that was first calibrated for use in our sample. Model 2 was also repeated after (1) additional adjustment for the Healthy Eating Index-2010, a valid and reliable measure of diet quality,[35] measured near OPACH baseline; (2) additional adjustment for antihypertension and antilipidemia medication use; and (3) measuring total sedentary time using the 100 cpm cut point. Joint analyses were also repeated measuring total sedentary time using the 100 cpm cut point.

RESULTS

During 19 350 person-years of follow-up, 545 CVD and 137 CHD events were observed. Sociodemographic and health-related characteristics were associated with to-

tal sedentary time (Table 1). Women in quartile 4 were older, were more likely to be white, had the highest BMI, and often had more unfavorable cardiometabolic biomarker levels compared with those in quartile 1.

Crude CVD rates were progressively higher over increasing quartiles of sedentary time (Table 2). Rates per 1000 person-years in quartiles 1, 2, 3, and 4 were 15.0, 26.0, 30.2, and 42.9, respectively. Controlling for potential confounders, women with the highest sedentary time had 69% higher risk for CVD (HR, 1.69; 95% CI, 1.27–2.26; *P* trend=0.001) than women in quartile 1. HRs were attenuated after adjustment for potential mediators and, separately, MVPA, but all remained statistically significant.

Crude rates for CVD were also progressively higher over increasing quartiles of mean bout duration, with rates of 17.1, 22.4, 30.3, and 44.3 per 1000 person-years (Table 2). Controlling for potential confounders, women with the most prolonged accumulation patterns (quartile 4) had 54% higher risk for CVD (HR, 1.54; 95% CI, 1.17–2.02; *P* trend=0.003) than women in quartile 1, who had the most interrupted accumulation patterns. HRs were slightly attenuated after adjustment for potential mediators, with adjustment for CVD risk biomarkers yielding a quartile 4 versus quartile 1 HR of 1.36 (95% CI, 1.01–1.83; *P* trend=0.10) for CVD. All trend tests yielded similar results when exposure variables were included in ordinal (as quartiles) functional form (data not shown).

Correlations were high between mean bout duration and the other sedentary accumulation pattern metrics (prolonged sedentary time *r*=0.92, breaks in sedentary time *r*=–0.62, usual bout duration *r*=0.95, and alpha *r*=–0.83; Table I in the online-only Data Supplement). As with mean bout duration, the most prolonged accumulation patterns were associated with higher CVD risk than the most interrupted patterns, independent of confounders (Tables II and III in the online-only Data Supplement). However, breaks in sedentary time were not significantly associated with CVD (*P* trend=0.06).

The dose-response trajectories were all linear (*P* linear <0.008, *P* nonlinear >0.08). Trajectories for 1 hour of sedentary time and 1 minute of mean bout duration were therefore plotted using the linear form of model 2 and are shown in Figure 1. The CVD risk HR (95% CI) associated with 1 hour of sedentary time was 1.12 (1.05–1.19), and for 1 minute of mean bout duration, it was 1.04 (1.01–1.07). The steeper trajectories observed for total sedentary time were explained in part by the different units of measure used (1 hour versus 1 minute) and in part by higher standardized HRs for total sedentary time than mean bout duration (Figures I and II in the online-only Data Supplement). Associations were attenuated after adjustment for MVPA and remained statistically significant (sedentary time *P* trend=0.045; mean bout duration *P* trend=0.037).

Multiplicative associations of sedentary time and mean bout duration with CVD risk were not statistically significant (*P*=0.67). Results from the joint analysis are shown in Figure 2. CVD risk was higher for women with both high sedentary time and high bout duration than for women with only high sedentary time or with only high bout duration, which suggests an additive interaction. After adjustment for potential confounders, significantly higher CVD risk (HR, 1.34; CI, 1.08–1.65) was observed for women with both high sedentary time and high bout duration than for women with low sedentary time and low bout duration (Figure 2), but the association no longer suggested an additive interaction.

Associations of sedentary time and mean bout duration with CVD risk according to cohort subgroups are shown in Figure I in the online-only Data Supplement. There was no statistical evidence of effect modification by age, BMI, physical functioning, MVPA, or race/ethnicity with either sedentary time or bout duration in relation to CVD risk.

Confounder-adjusted associations of sedentary time, mean bout duration, and incident CHD were similar to those observed for CVD, but stronger HRs were observed for CHD, often by a factor of 2 (Table IV and Figures II and III in the online-only Data Supplement). All associations remained significant after further adjustment for potential mediators. After adjustment for MVPA, quartile 2, 3, and 4 HRs (95% CIs) for sedentary time were 1.58 (0.77–3.24), 1.38 (0.66–2.90), and 1.68 (0.78–3.60) (*P* trend=0.10); for mean bout duration, they were 1.57 (0.80–3.08), 1.37 (0.70–2.67), and 1.83 (0.95–3.55) (*P* trend=0.048).

Sensitivity Analyses

We excluded 475 women (8.4% of the analytic sample) who had heart failure, revascularization, or hospitalized angina at OPACH baseline; 92 of these women had subsequent CVD events of other types (excluding 18% of cases in the primary analysis). The overall pattern of results for total sedentary time and mean bout duration were similar to those observed using the full analytic sample, although for most secondary analyses, the linear trend tests were no longer statistically significant (Table V in the online-only Data Supplement). Model 3b HRs tended to be larger when multiple imputation was used, with notably stronger linear trends; for total sedentary time, quartile 2, 3, and 4 HRs (95% CIs) were 1.39 (1.04–1.85), 1.41 (1.06–1.88), and 1.57 (1.17–2.09) (*P* trend=0.004), whereas for mean bout duration, they were 1.14 (0.86–1.52), 1.33 (1.02–1.75), and 1.47 (1.12–1.93) (*P* trend=0.009). For all other sensitivity analyses, the magnitude and statistical significance of HRs were not meaningfully changed. We note that after adjustment for the Healthy Eating Index, the linear trend of mean sedentary bout duration in relation to CVD was 0.06, but the HRs [95% CI] for quartiles 2, 3, and 4 were similar before (1.20 [0.91–1.60], 1.32 [1.00–1.74],

Table 1. Baseline Sociodemographic and Health-Related Characteristics, by Quartile of Total Sedentary Time (n=5638): OPACH (2012–2014)

Characteristics	Total Sedentary Time Quartiles*†				*P* Value‡
	1 (Low)	2	3	4 (High)	
Age, y	76.3±6.2	78.1±6.6	78.9±6.6	80.9±6.5	<0.001
Race/ethnicity, n (%)					<0.001
White	546 (38.7)	641 (45.5)	714 (50.7)	872 (61.8)	
Black	509 (36.1)	489 (34.7)	485 (34.4)	397 (28.2)	
Hispanic	355 (25.2)	279 (19.8)	210 (14.9)	141 (10.0)	
Highest education level, n (%)					0.01
High school/GED or less	294 (20.9)	295 (21.1)	291 (20.9)	251 (17.9)	
Smoke now (yes), n (%)	21 (1.5)	32 (2.3)	37 (2.6)	47 (3.3)	0.02
BMI, kg/m^2	26.3±4.9	27.5±5.4	28.5±5.6	30.1±6.1	<0.001
Self-rated health, n (%)					<0.001
Excellent or very good	883 (62.9)	719 (51.2)	719 (51.2)	605 (43.1)	
Good	445 (31.7)	574 (40.9)	553 (39.4)	619 (44.1)	
Poor or very poor	76 (5.4)	112 (8.0)	132 (9.4)	181 (12.9)	
Physical functioning	80.5±20.1	73.6±22.9	67.8±25.6	57.8±27.3	<0.001
Number of chronic conditions, n (%)†					<0.001
0	539 (38.2)	486 (34.5)	450 (31.9)	441 (31.3)	
1	658 (46.7)	678 (48.1)	678 (48.1)	651 (46.2)	
2 or more	213 (15.1)	245 (17.4)	281 (19.9)	318 (22.6)	
History of heart failure at baseline, n (%)	5 (0.4)	17 (1.2)	35 (2.5)	54 (3.8)	<0.001
History of revascularization at baseline, n (%)	24 (1.7)	40 (2.8)	42 (3.0)	46 (3.3)	0.06
History of hospitalized angina at baseline, n (%)	36 (2.6)	56 (4.0)	68 (4.8)	96 (6.8)	<0.001
Systolic blood pressure, mm Hg	123.7±13.2	125.0±13.8	125.9±13.7	128.0±15.3	<0.001
Glucose, mg/dL	93.7±20.0	98.0±27.2	98.4±27.0	101.4±30.7	<0.001
HDL cholesterol, mg/dL	64.5±15.2	62.0±15.3	59.6±13.9	56.5±13.9	<0.001
Log triglycerides, mg/dL	4.5±0.4	4.5±0.4	4.6±0.4	4.7±0.5	<0.001
Total sedentary time,§ min/d	436.6±48.8	526.5±16.7	585.0±17.1	665.1±38.4	<0.001
Mean sedentary bout duration, min/d	5.1±0.9	6.4±1.0	7.5±1.4	10.3±3.2	<0.001
Prolonged sedentary time,§ min/d	113.8±53.3	175.9±61.0	231.2±72.4	338.5±106.5	<0.001
Breaks in sedentary time,‖ n/d	92.3±16.3	90.0±14.8	85.7±15.0	76.9±15.9	<0.001
Usual sedentary bout duration, min	11.0±3.6	15.0±4.3	18.9±5.9	27.7±11.6	<0.001
Alpha	2.0±0.1	1.9±0.1	1.8±0.1	1.7±0.1	<0.001
MVPA, min/d	83.5±36.5	55.5±26.6	41.2±21.2	26.1±16.8	<0.001

Data are mean±SD unless otherwise indicated. BMI indicates body mass index; GED, general educational development; HDL, high-density lipoprotein; MVPA, moderate to vigorous physical activity; and OPACH, Objective Physical Activity and Cardiovascular Health.

*Quartile (Q) ranges: Q1=197–495 min, Q2=496–555 min, Q3=556–616 min, Q4=617–845 min.

†Cancer, cognitive impairment, chronic obstructive pulmonary disease, depression, and osteoarthritis.

‡Results for continuous variables using the F test and the Jonckheere-Terpstra trend test were similar.

§Adjusted for awake wear time using the residuals method.

‖Adjusted for total sedentary time using the residuals method.

and 1.54 [1.17–2.02]) and after (1.23 [0.90–1.68], 1.22 [0.90–1.66], and 1.42 [1.05–1.92]) adjustment.

DISCUSSION

In this ethnically diverse cohort study of older community-dwelling women, nearly half of whom were over the age of 80 years, we found a linear dose-response relationship of sedentary time with CVD events. Each additional hour of sedentary time, on average, was associated with a 12% increase in multivariable-adjusted risk for CVD. Dose-dependent increased risk of 4% was also observed for each 1-minute increase in sedentary bout duration, which indicates that prolonged sedentary accumulation patterns are associated with higher CVD risk in older women. Similar conclusions a-

Table 2. Associations of CVD Events With Total Sedentary Time and Mean Sedentary Bout Duration: OPACH (2012–2017)

	Q1 (Low)	Q2	Q3	Q4 (High)	*P* Trend*
Total sedentary time†‡					
New events, n (rate)	76 (15.0)	127 (26.0)	145 (30.2)	197 (42.9)	
Model 1	1 (ref)	1.55 (1.16–2.06)	1.70 (1.28–2.24)	2.15 (1.63–2.82)	<0.001
Model 2	1 (ref)	1.47 (1.10–1.97)	1.42 (1.06–1.89)	1.69 (1.27–2.26)	0.001
Model 3a	1 (ref)	1.37 (1.02–1.85)	1.36 (1.01–1.83)	1.57 (1.16–2.12)	0.007
Model 3b	1 (ref)	1.43 (1.05–1.95)	1.28 (0.93–1.76)	1.49 (1.09–2.05)	0.05
Model 3c	1 (ref)	1.40 (1.03–1.89)	1.31 (0.95–1.80)	1.53 (1.09–2.14)	0.05
Mean sedentary bout duration†					
New events, n (rate)	87 (17.1)	109 (22.4)	147 (30.3)	202 (44.3)	
Model 1	1 (ref)	1.19 (0.90–1.58)	1.46 (1.12–1.91)	1.83 (1.41–2.38)	<0.001
Model 2	1 (ref)	1.20 (0.91–1.60)	1.32 (1.00–1.74)	1.54 (1.17–2.02)	0.003
Model 3a	1 (ref)	1.16 (0.87–1.55)	1.24 (0.94–1.63)	1.42 (1.07–1.87)	0.02
Model 3b	1 (ref)	1.13 (0.83–1.53)	1.13 (0.84–1.53)	1.36 (1.01–1.83)	0.10
Model 3c	1 (ref)	1.15 (0.86–1.54)	1.23 (0.93–1.63)	1.40 (1.04–1.87)	0.04

Data for new events are n (crude rate per 1000 person-years); other data are hazard ratio (95% CI). Model 1=age and ethnicity adjusted (n=5638); Model 2=Model 1 + potential confounders (n=5471); Model 3a=Model 2 + body mass index + diabetes mellitus + hypertension (n=5132); Model 3b=Model 2 + glucose + HDL cholesterol + log(triglycerides) + systolic blood pressure (n=4339); Model 3c=Model 2 + moderate to vigorous physical activity (n=5471). Potential confounders: education; self-reported health; family history of myocardial infarction; multimorbidity; physical functioning (RAND-36); alcohol consumption; and current smoking status. CVD indicates cardiovascular disease; HDL, high-density lipoprotein; OPACH, Objective Physical Activity and Cardiovascular Health; Q, quartile; and ref, referent.

**P* values from Cox multivariable linear regression models including total sedentary time in models in continuous form.

†Quartile (Q) cut points. Total sedentary time (min): Q1=197–495, Q2=496–555, Q3=556–616, Q4=617–845; mean sedentary bout duration (min): Q1=2.6–5.6, Q2=5.7–6.8, Q3=6.9–8.4, Q4=8.5–52.4.

‡Adjusted for awake wear time using the residuals method.

bout CVD risk were drawn when accumulation patterns were measured using different metrics. When total volume and sedentary accumulation patterns were jointly classified, women with the highest sedentary time and the highest bout durations had the greatest CVD risk. When we examined associations with incident CHD (ie, fatal MI, nonfatal MI, and stroke), the HRs were as much as 2 times higher than those for CVD. The totality of evidence suggests that both sedentary time and the way in which it is accumulated could be relevant for cardiovascular health in older women.

Results of the present study were in line with early meta-analyses that reported increased CVD risk was associated with higher levels of self-reported sedentary time.[5,36] The most recent review included 10 prospective studies, all of which measured total sedentary time using self-reports, and showed that the CVD HR for adults with the highest versus lowest total sedentary time was only 1.14 (95% CI, 1.09–1.19).[37] The magnitude of health associations attributed to sedentary behavior tends to be higher when exposure is measured by accelerometer.[7] For example, 2 studies of CVD mortality showed that HRs for the highest versus lowest total sedentary time were 2.67 (95% CI, 1.28–5.54) among 3809 US adults (average age, 53 years) and 1.71 (95% CI, 0.99–2.97) among 2918 US men (average age, 79 years)[38,39]; both associations are similar in magnitude to the HRs observed in the present study. In the cohort of adults aged >40 years,[38] adjustment for MVPA attenuated HRs for CVD, just as happened in our study. However, as shown in Figure 1, the elevated CVD risk observed in our study remained significant in mutually adjusted models, which was not the case in the previous study.[38] Results could differ because of the differing age groups under study or because our study had a larger sample size (n=5638) and was focused on both fatal and nonfatal CVD. In both studies, however, the observed interrelationship of CVD with sedentary time and MVPA suggests that the 2 exposures are associated with increased CVD risk through related yet somewhat independent pathways.

Associations of sedentary time with CVD and CHD risk increased in a linear dose-dependent manner across the full range of measured total sedentary time. If confirmed to be causal, this finding indicates that women, regardless of how often they are typically sedentary, could reduce CVD risk by reducing their sedentary time. For example, a 1-hour reduction in sedentary time could reduce CVD risk by 12% for women who are typically sedentary for 8 h/d, as well as for women who are typically sedentary for 12 h/d. This result, when viewed over the relevant range of exposure (OPACH 1st–99th percentile of sedentary time, 5.5–12.4 h/d), was similar to findings from a recent meta-analysis that showed increased risk for CVD associated with reported daily sitting times beginning at >6.8 h/d, although this did not reach statistical significance until siting times were >10 h/d.[37]

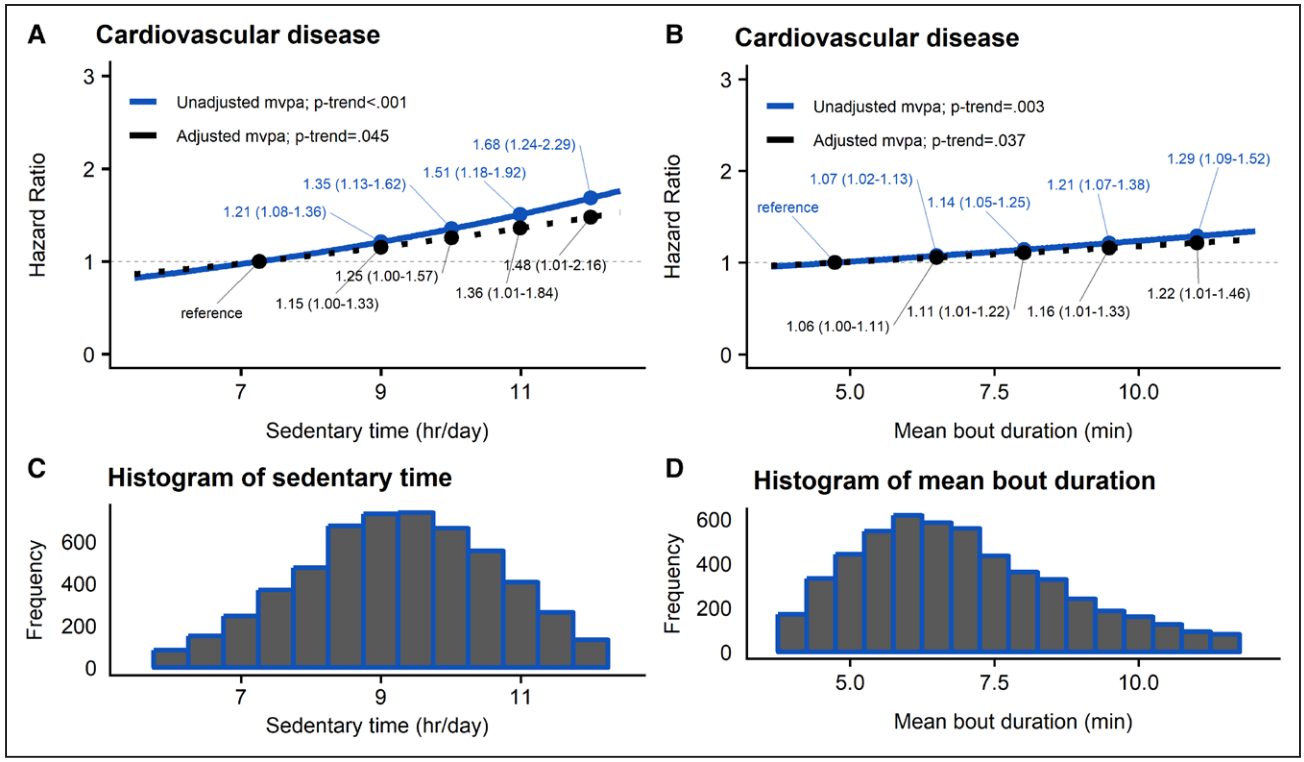

Figure 1. Continuous dose-response relation of sedentary time and mean sedentary bout duration with cardiovascular disease events, estimated using linear Cox regression models.

Results after adjustment for age, race/ethnicity, education, smoking status, alcohol consumption, self-reported health, multimorbidity, physical functioning, and family history of myocardial infarction (blue lines) and after additional adjustment for moderate-to-vigorous physical activity (mvpa; black dotted lines) are shown. The reference category was set to the 10th percentile of each exposure (sedentary time=7.3 h/d; mean bout duration=4.7 minutes). Results for sedentary time (**A, C**) were trimmed at the 1st and 99th percentiles, and results for mean bout duration (**B, D**) were trimmed at the 1st and 95th percentiles.

Sitting reduces voluntary energy expenditure, limits activation of the largest skeletal muscles in the human body, and reduces venous and arterial blood flow, all of which contribute to impaired glucose metabolism.[40] In as little as 1 week, high volumes of sitting were associated with higher insulin resistance among otherwise active adults, and in those same adults, prolonged sitting patterns had an even larger effect.[41] Additionally, prolonged sitting (ranging from 3–8 hours) has short-term effects on cardiovascular health in part by promoting endothelial dysfunction and the production of reactive oxygen species.[42] The combined evidence has led some to postulate that sedentary accumulation patterns confer more CVD risk than does overall sitting volume.[42] In this early stage of the epidemiological investigation of sedentary time and sedentary accumulation patterns, examining independent associations is analytically challenging because the 2 exposures are strongly related and the causative nature of their relationship is not yet known. Instead, recent studies have focused on how sedentary time and sedentary accumulation patterns are jointly related to health.[12–14] We followed suit by stratifying women into high and low levels of sedentary time and high and low levels of mean bout duration and showed that women with high sedentary time and high bout duration had the greatest CVD risk and that their risk was significantly higher than women with low sedentary time and low bout duration. These findings extend results from a cross-sectional analysis of glycemic biomarkers in US Hispanic adults[13] and results from a prospective analysis of all-cause mortality among black and white older adults.[14] Two previous cross-sectional analyses of CVD risk biomarkers[12,13] reported multiplicative (ie, synergistic) interactions between sedentary time and sedentary accumulation patterns, which we did not observe in relation to CVD. More studies examining joint associations (including multiplicative interactions) between sedentary time, sedentary accumulation patterns, and cardiometabolic health are needed. In the meantime, strong correlations between sedentary time and mean bout duration,[13–15] robust associations of each exposure with CVD, prevalent diabetes mellitus, and all-cause mortality,[14,15,43] and the joint association observed in this study and in others[12–14] suggest that a combined approach might be appropriate. For example, sedentary behavior reduction and improved patterns of sedentary time could be targeted by increasing the frequency and duration of (light) activity breaks specifically during long bouts of sedentary time.

This was the first prospective study of fatal and nonfatal CVD events that used objective measures of sedentary time. Other noteworthy strengths include the

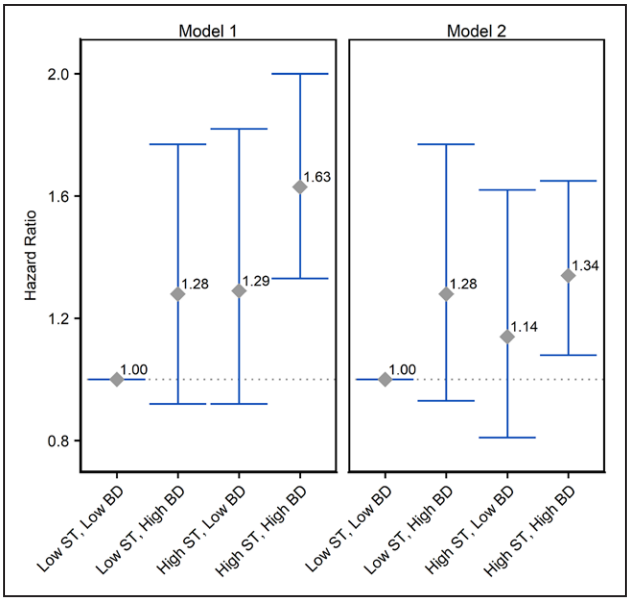

Figure 2. Joint association of sedentary time (ST) and mean bout duration (BD) with cardiovascular disease events.
Model 1 is adjusted for age and race/ethnicity, and model 2 is additionally adjusted for smoking status, alcohol consumption, self-reported health, multimorbidity, physical functioning, and family history of myocardial infarction. ST and BD were split at their respective median values (9.3 h/d and 6.8 minutes). Gray diamonds represent hazard ratios, with the top and bottom error bars designating the 95% CI. The total number of women (number of cases) for each group was as follows: Low ST, Low BD=2322 (154); low ST, high BD=498 (42); high ST, low BD=497 (49); high ST, high BD=2321 (300).

racial/ethnic diversity of our sample, who had a wide range of physical and functional health characteristics. Nearly 50% of the women studied were over the age of 80 years, which is one of the fastest-growing segments of American society who are also at the highest risk for CVD events and for sedentary behavior.[1,16] Our large sample size and well-characterized cohort enabled us to consider 16 variables as potential confounders or mediators, including physical function, which has not typically been examined in past studies. We also evaluated sedentary accumulation patterns using 5 metrics, with nearly all of them yielding similar inferences.

Our study focused on understanding the association of sedentary behavior with clinical cardiovascular events in older women. Because prevalence of CVD is common in later life, we included women with a history of heart failure, revascularization, and angina in the population-at-risk. This inclusive approach provided the opportunity to evaluate associations among most women in their 70s, 80s, and 90s and to generalize to this population more broadly. To address the concern that the inclusion of women with heart failure, revascularization, or angina at baseline might produce a spurious association, we conducted sensitivity analyses that excluded women with these conditions. Results were somewhat attenuated, although associations remained in the confounder-adjusted model. The observed attenuations could be attributable to reduced sample size and CVD events, because 475 women and 18% of CVD cases were excluded. Alternatively, the attenuated associations could be attributable to stronger associations among the excluded women that resulted from reverse causation or a feedback loop, whereby sedentary time was associated with increased risk for prior CVD diagnoses, which led to higher levels of sedentary time, which was associated with increased risk for new manifestations of CVD. Studies including repeated measures of exposure and continued follow-up for CVD are needed to better understand the relationship of sedentary behavior and CVD in later life.

Other limitations are worth noting. Although accelerometers objectively measured sedentary behavior, the devices were worn over the right hip, with data processed using common techniques, which precluded the accurate detection of posture,[44] a key component of the sedentary behavior definition.[45] As a result, standing still could be misclassified as sedentary time. Furthermore, the wear location and processing protocol were not ideal for measuring transitions from sitting to standing,[44] leading to possible measurement error in estimates of sedentary accumulation patterns.[46] The extent to which the measurement error is related to CVD or its risk factors should be the subject of future studies. Sedentary behavior was measured during a 7-day period, which has been shown to be a reliable measure of 2- to 3-year behavior patterns but might not fully capture usual sedentary time in all women.[47] Future studies should consider longer measurement periods, if feasible. Our joint analyses were limited by few women falling into the groups with low sedentary time and high bout duration or high sedentary time and low bout duration, which resulted in wide CIs; results for these groups should be interpreted with caution. Finally, this study was conducted among a cohort of older women, and it is unknown whether these findings can be generalized to older men. Replication in prospective studies of older men is needed, as are studies investigating sex differences.

In conclusion, both sedentary time and prolonged sedentary accumulation patterns were associated in a dose-response manner with CVD risk in older women. Sedentary behavior guidelines in several industrialized countries and recommendations from the American Diabetes Association[48] call for an overall reduction in sedentary time and for regular interruption of long sedentary bouts. The results of this study, if replicated in other cohorts, support further consideration by US public health entities of guidelines to reduce sedentary time and sedentary bout durations as part of an effort to lessen the personal and public health burden of CVD in our growing population of older adults.

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Disclosures

None.

APPENDIX

The following is a short list of WHI Investigators; the full list can be found at the following site: www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf. Program Office: (National Heart, Lung, and Blood Institute, Bethesda, MD) Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller; Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg; Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus) Rebecca Jackson; (University of Arizona, Tucson/Phoenix) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville) Marian Limacher; (University of Iowa, Iowa City/Davenport) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics: 2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360. doi: 10.1161/CIR.0000000000000350
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–322. doi: 10.1161/CIR.0000000000000152
3. Thompson PD, Buchner D, Piña IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107:3109–3116. doi: 10.1161/01.CIR.0000075572.40158.77
4. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, Kumanyika S, Kraus WE, Fleg JL, Redeker NS, Meininger JC, Banks J, Stuart-Shor EM, Fletcher BJ, Miller TD, Hughes S, Braun LT, Kopin LA, Berra K, Hayman LL, Ewing LJ, Ades PA, Durstine JL, Houston-Miller N, Burke LE; American Heart Association Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:406–441. doi: 10.1161/CIR.0b013e3181e8edf1
5. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med*. 2015;162:123–132. doi: 10.7326/M14-1651
6. Chastin SFM, Dontje ML, Skelton DA, Čukić I, Shaw RJ, Gill JMR, Greig CA, Gale CR, Deary IJ, Der G, Dall PM; on behalf of the Seniors USP Team. Systematic comparative validation of self-report measures of sedentary time against an objective measure of postural sitting (activPAL). *Int J Behav Nutr Phys Act*. 2018;15:21. doi: 10.1186/s12966-018-0652-x
7. Celis-Morales CA, Perez-Bravo F, Ibañez L, Salas C, Bailey ME, Gill JM. Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers. *PLoS One*. 2012;7:e36345. doi: 10.1371/journal.pone.0036345
8. Young DR, Hivert M-F, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, Yong CM. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. *Circulation*. 2016;134:e262–e279. doi: 10.1161/CIR.0000000000000440
9. Gibbs BB, Hergenroeder AL, Katzmarzyk PT, Lee IM, Jakicic JM. Definition, measurement, and health risks associated with sedentary behavior. *Med Sci Sports Exerc*. 2015;47:1295–1300. doi: 10.1249/MSS.0000000000000517
10. Brocklebank LA, Falconer CL, Page AS, Perry R, Cooper AR. Accelerometer-measured sedentary time and cardiometabolic biomarkers: a systematic review. *Prev Med*. 2015;76:92–102. doi: 10.1016/j.ypmed.2015.04.013
11. Chastin SF, Egerton T, Leask C, Stamatakis E. Meta-analysis of the relationship between breaks in sedentary behavior and cardiometabolic health. *Obesity (Silver Spring)*. 2015;23:1800–1810. doi: 10.1002/oby.21180
12. Bellettiere J, Winkler EAH, Chastin SFM, Kerr J, Owen N, Dunstan DW, Healy GN. Associations of sitting accumulation patterns with cardio-metabolic risk biomarkers in Australian adults. *PLoS One*. 2017;12:e0180119. doi: 10.1371/journal.pone.0180119
13. Diaz KM, Goldsmith J, Greenlee H, Strizich G, Qi Q, Mossavar-Rahmani Y, Vidot DC, Buelna C, Brintz CE, Elfassy T, Gallo LC, Daviglus ML, Sotres-Alvarez D, Kaplan RC. Prolonged, uninterrupted sedentary behavior and glycemic biomarkers among US Hispanic/Latino adults: the HCHS/SOL (Hispanic Community Health Study/Study of Latinos). *Circulation*. 2017;136:1362–1373. doi: 10.1161/CIRCULATIONAHA.116.026858
14. Diaz KM, Howard VJ, Hutto B, Colabianchi N, Vena JE, Safford MM, Blair SN, Hooker SP. Patterns of sedentary behavior and mortality in U.S. middle-aged and older adults: a national cohort study. *Ann Intern Med*. 2017;167:465–475. doi: 10.7326/M17-0212
15. Di J, Leroux A, Urbanek J, Varadhan R, Spira A, Schrack J, Zipunnikov V. Patterns of sedentary and active time accumulation are associated with

mortality in US adults: the NHANES study [published online August 31, 2017]. *bioRxiv*. 2017. doi: 10.1101/182337. https://www.biorxiv.org/content/early/2017/08/31/182337
16. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, Troiano RP. Amount of time spent in sedentary behaviors in the United States, 2003-2004. *Am J Epidemiol*. 2008;167:875–881. doi: 10.1093/aje/kwm390
17. Andrea Z. LaCroix, Rillamas-Sun E, Buchner D, Evenson KR, Di C, Lee I-M, Marshall S, LaMonte MJ, Hunt J, Tinker LF, Stefanick M, Lewis CE, Bellettiere J, Herring AH. The Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) Study. *BMC Public Health*. 2017;17:192. doi: 10.1186/s12889-017-4065-6
18. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61–109.
19. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nyström C, Mora-Gonzalez J, Löf M, Labayen I, Ruiz JR, Ortega FB. Accelerometer data collection and processing criteria to assess physical activity and other outcomes: a systematic review and practical considerations. *Sports Med*. 2017;47:1821–1845. doi: 10.1007/s40279-017-0716-0
20. Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, Daugherty S; WHI Morbidity and Mortality Committee. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(suppl):S122–S128.
21. Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, Gaziano JM, Frishman WH, Curb JD. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol*. 2004;160:1152–1158. doi: 10.1093/aje/
22. ActiGraph White Paper Low Frequency Extension Filter. ActiGraphcorp.com. 2015:1-32502. https://s3.amazonaws.com/actigraphcorp.com/wp-content/uploads/2017/11/26205810/Low-Frequency-Extension-Filter.pdf. Accessed February 2, 2019.
23. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. *Med Sci Sports Exerc*. 2011;43:357–364. doi: 10.1249/MSS.0b013e3181ed61a3
24. Evenson KR, Wen F, Herring AH, Di C, LaMonte MJ, Tinker LF, Lee IM, Rillamas-Sun E, LaCroix AZ, Buchner DM. Calibrating physical activity intensity for hip-worn accelerometry in women age 60 to 91 years: the Women's Health Initiative OPACH Calibration Study. *Prev Med Rep*. 2015;2:750–756. doi: 10.1016/j.pmedr.2015.08.021
25. Shiroma EJ, Freedson PS, Trost SG, Lee IM. Patterns of accelerometer-assessed sedentary behavior in older women. *JAMA*. 2013;310:2562–2563. doi: 10.1001/jama.2013.278896
26. Chastin SF, Granat MH. Methods for objective measure, quantification and analysis of sedentary behaviour and inactivity. *Gait Posture*. 2010;31:82–86. doi: 10.1016/j.gaitpost.2009.09.002
27. Rillamas-Sun E, LaCroix AZ, Bell CL, Ryckman K, Ockene JK, Wallace RB. The impact of multimorbidity and coronary disease comorbidity on physical function in women aged 80 years and older: the Women's Health Initiative. *J Gerontol A Biol Sci Med Sci*. 2016;71(suppl 1):S54–S61. doi: 10.1093/gerona/glv059
28. LaMonte MJ, Lewis CE, Buchner DM, Evenson KR, Sun ER-, Di C, Lee I-M, Bellettiere J, Stefanick ML, Eaton CB, Howard BV, Bird C, LaCroix AZ. Both light intensity and moderate-to-vigorous physical activity measured by accelerometry are favorably associated with cardiometabolic risk factors in older women: the Objective Physical Activity and Cardiovascular Health (OPACH) Study. *J Am Heart Assoc*. 2017;6:e007064. doi: 10.1161/JAHA.117.007064
29. Chastin SF, Palarea-Albaladejo J, Dontje ML, Skelton DA. Combined effects of time spent in physical activity, sedentary behaviors and sleep on obesity and cardio-metabolic health markers: a novel compositional data analysis approach. *PLoS One*. 2015;10:e0139984. doi: 10.1371/journal.pone.0139984
30. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol*. 2009;170:519–527. doi: 10.1093/aje/kwp163
31. Page A, Peeters G, Merom D. Adjustment for physical activity in studies of sedentary behaviour. *Emerg Themes Epidemiol*. 2015;12:10. doi: 10.1186/s12982-015-0032-9
32. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124:17–27.
33. Matthews CE, Keadle SK, Troiano RP, Kahle L, Koster A, Brychta R, Van Domelen D, Caserotti P, Chen KY, Harris TB, Berrigan D. Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults. *Am J Clin Nutr*. 2016;104:1424–1432. doi: 10.3945/ajcn.116.135129
34. McVeigh JA, Winkler EA, Healy GN, Slater J, Eastwood PR, Straker LM. Validity of an automated algorithm to identify waking and in-bed wear time in hip-worn accelerometer data collected with a 24 h wear protocol in young adults. *Physiol Meas*. 2016;37:1636–1652. doi: 10.1088/0967-3334/37/10/1636
35. Guenther PM, Kirkpatrick SI, Reedy J, Krebs-Smith SM, Buckman DW, Dodd KW, Casavale KO, Carroll RJ. The Healthy Eating Index-2010 is a valid and reliable measure of diet quality according to the 2010 Dietary Guidelines for Americans. *J Nutr*. 2014;144:399–407. doi: 10.3945/jn.113.183079
36. Ford ES, Caspersen CJ. Sedentary behaviour and cardiovascular disease: a review of prospective studies. *Int J Epidemiol*. 2012;41:1338–1353. doi: 10.1093/ije/dys078
37. Pandey A, Salahuddin U, Garg S, Ayers C, Kulinski J, Anand V, Mayo H, Kumbhani DJ, de Lemos J, Berry JD. Continuous dose-response association between sedentary time and risk for cardiovascular disease: a meta-analysis. *JAMA Cardiol*. 2016;1:575–583. doi: 10.1001/jamacardio.2016.1567
38. Evenson KR, Wen F, Herring AH. Associations of accelerometry-assessed and self-reported physical activity and sedentary behavior with all-cause and cardiovascular mortality among US adults. *Am J Epidemiol*. 2016;184:621–632. doi: 10.1093/aje/kww070
39. Ensrud KE, Blackwell TL, Cauley JA, Dam TT, Cawthon PM, Schousboe JT, Barrett-Connor E, Stone KL, Bauer DC, Shikany JM, Mackey DC; for the Osteoporotic Fractures in Men Study Group. Objective measures of activity level and mortality in older men. *J Am Geriatr Soc*. 2014;62:2079–2087. doi: 10.1111/jgs.13101
40. Hamilton MT. The role of skeletal muscle contractile duration throughout the whole day: reducing sedentary time and promoting universal physical activity in all people. *J Physiol*. 2018;596:1331–1340. doi: 10.1113/JP273284
41. Lyden K, Keadle SK, Staudenmayer J, Braun B, Freedson PS. Discrete features of sedentary behavior impact cardiometabolic risk factors. *Med Sci Sports Exerc*. 2015;47:1079–1086. doi: 10.1249/MSS.0000000000000499
42. Carter S, Hartman Y, Holder S, Thijssen DH, Hopkins ND. Sedentary behavior and cardiovascular disease risk: mediating mechanisms. *Exerc Sport Sci Rev*. 2017;45:80–86. doi: 10.1249/JES.0000000000000106
43. Bellettiere J, Healy GN, LaMonte MJ, Kerr J, Evenson KR, Rillamas-Sun E, Di C, Buchner DM, Hovell MF, LaCroix AZ. Associations of sedentary time and diabetes in 6166 older women: the Objective Physical Activity and Cardiovascular Health Study [published online May 3, 2018]. *J Gerontol A Biol Sci Med Sci*. 2018. doi: 10.1093/gerona/gly101. https://academic.oup.com/biomedgerontology/advance-article-abstract/doi/10.1093/gerona/gly101/4991878?redirectedFrom=fulltext
44. Lyden K, Kozey Keadle SL, Staudenmayer JW, Freedson PS. Validity of two wearable monitors to estimate breaks from sedentary time. *Med Sci Sports Exerc*. 2012;44:2243–2252. doi: 10.1249/MSS.0b013e318260c477
45. Sedentary Behavior Research Network. Letter to the Editor: Standardized use of the terms "sedentary" and "sedentary behaviours." *Appl Physiol Nutr Metab*. 2012;37:540–542. doi: 10.1139/h2012-24
46. Barreira TV, Zderic TW, Schuna JM Jr, Hamilton MT, Tudor-Locke C. Free-living activity counts-derived breaks in sedentary time: are they real transitions from sitting to standing? *Gait Posture*. 2015;42:70–72. doi: 10.1016/j.gaitpost.2015.04.008
47. Keadle SK, Shiroma EJ, Kamada M, Matthews CE, Harris TB, Lee IM. Reproducibility of accelerometer-assessed physical activity and sedentary time. *Am J Prev Med*. 2017;52:541–548. doi: 10.1016/j.amepre.2016.11.010
48. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2016;39:2065–2079. doi: 10.2337/dc16-1728