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Sedentary behavior and cardiovascular disease in older women: The Objective Physical Activity and Cardiovascular Health (OPACH) Study

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Abstract

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 Objective Physical Activity and Cardiovascular Health (OPACH) Study (n=5638, aged 63–97, mean age=79±7) with no history of myocardial infarction (MI) or

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DISCLOSURES

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stroke wore accelerometers for 4-to-7 days and were followed 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 estimated hazard ratios (HR) and 95% confidence intervals (CI) for CVD using models adjusted for covariates and subsequently adjusted for potential mediators (body mass index (BMI), diabetes, 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. Adjusting for covariates, women in the highest (≥ ~11 hr/day) vs. the lowest (≤ ~9 hr/day) quartile of sedentary time had higher risk for CVD (HR=1.62; 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<.05, each). Longer vs. shorter mean bout duration was associated with higher risks for CVD (HR=1.54; 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 vs. quartile 1 HR=1.36; 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 high sedentary time and long bout durations had significantly higher risk for CVD (HR=1.34; CI=1.08–1.65) than women with both low sedentary time and short bout duration. All analyses were repeated for incident coronary heart disease (MI or CVD death) and associations were similar with notably stronger hazard ratios.

Conclusions: Both high sedentary time and long mean bout durations were associated in a dose-response manner with increased CVD risk in older women, suggesting that efforts to reduce CVD burden may benefit from addressing either or both component(s) of sedentary behavior.

Keywords

Patterns of sedentary behavior; epidemiology; lifestyle; physical activity; sedentary time; aging

INTRODUCTION

Through the 20th century, cardiovascular disease (CVD) killed more Americans than any other disease, currently causing one in three deaths annually.[1] CVD incidence increases with age and is highest among adults ≥85 years.[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 using objective measures of sedentary time to evaluate relations with cardio-metabolic 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 cardio-metabolic risk factors.[10,11] Epidemiologic evidence suggests that prolonged accumulation patterns are associated with higher cardio-metabolic 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. Since 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 upon reasonable request [alacroix@ucsd.edu] in accordance with the Women's Health Initiative (WHI) Publications and Presentations Policy.

Study participants

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

OPACH participants were distributed ActiGraph GT3X+ accelerometers to wear over their right hip 24 hours/day 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 [17] for a detailed Strobe diagram). Of the 6489 women who wore accelerometers, 6133 met the recommended data processing criteria for estimating average daily sedentary time among older adults (i.e., ≥ 10 waking wear hours on ≥ 4 days per week).[19] Women with an MI or stroke before OPACH baseline (n=495) were excluded leaving data from 5638 women available for the present study. The protocol for this study was approved by the Fred Hutchinson Cancer Research Center IRB and all women provided informed consent either in writing or by telephone.

Cardiovascular disease 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 from any CVD among women without that event. We also investigated incident CHD events (nonfatal MI or coronary death) as a separate endpoint. CVD ascertainment methods are described in detail elsewhere.[17] Briefly, each women 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 here [[20]]. Inter-rater agreement on CVD outcome ascertainment was strong with kappa statistics ranging from .67 to .94.[21] Women were followed 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 non-wear 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/day with vector magnitude acceleration counts ≤18 per 15-second epoch, an accelerometer cutpoint specifically calibrated to our sample in the lab-based OPACH Calibration Study[24] conducted among 200 women aged 60–91. Mean bout duration and all other sedentary accumulation metrics were based on the most commonly used[19] measure of sedentary time (having <100 counts/minute [cpm] measured on the vertical axis) which is the only method used to date for measuring sedentary accumulation patterns with ActiGraph data [eg, [25]]. The OPACH 18 counts/15-second cutpoint was not used to measure accumulation patterns because it was overly sensitive to breaks in sedentary time. With it, the average breaks/day among OPACH women was over 300. Using the 100 cpm cutpoint, there were 86 breaks/day, which is 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. Since there lacks consensus on a 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 minutes/day]; breaks in sedentary time [the frequency of

transitions from sedentary to non-sedentary 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 (using the RAND-36), alcohol consumption, and current smoking were measured by questionnaire nearest to the OPACH baseline. The number of chronic health conditions (cancer, cognitive impairment; constructive obstructive pulmonary disease; depression; and osteoarthritis) reported at or before OPACH baseline was used to represent multimorbidity.[27] Prevalent diabetes and hypertension at OPACH baseline were measured using 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 (m) and weight (kg) were measured using a tape measure and calibrated bathroom scale, respectively, and body mass index (BMI) was computed as weight divided by height squared. Blood pressure, after 5 minutes of sitting quietly, was measured by auscultation using an aneroid sphygmomanometer; two measures each of systolic and diastolic blood pressure were averaged. Fasting blood samples were obtained and serum levels of glucose, high-density lipoprotein (HDL), 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]

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

Statistical analysis

Socio-demographic and health-related characteristics were described using means and standard deviations or percentages across quartiles of total sedentary time. Differences across quartiles were tested using F-tests and the Jonckheere-Terpstra trend test for continuous variables and Pearson’s chi-square tests for categorical variables.

Hazard ratios (HR) and 95% confidence intervals (CI) for CVD events were estimated using 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, five 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, and/or a competing behavior (when using a compositional[29] or isotemporal framework[30]).[31] Model 3a added to Model 2 hypertension, diabetes, and BMI; Model 3b added to Model 2 serum glucose, triglycerides, HDL-cholesterol, and systolic blood pressure in the subset of women for whom these biomarkers were available; and Model 3c added to Model 2 MVPA. Tests of linear trend were computed using Cox models treating total sedentary time and mean bout duration as continuous variables. Proportional hazards assumptions were assessed using 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 using 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 dose-response trajectories were sensitive to the number of knots used, we ran models with 3 and 4 knots placed at 10^{th}, 50^{th}, 90^{th} and the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles, respectively. Plots of the dose-response trajectories were reviewed for each outcome for each model fit and chi-squared 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 10^{th} 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 chi-squared 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 <44 and ≥44 minutes/day of MVPA (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's 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 employed the analytic method used by Diaz et al.[14] by splitting our sample into high and low sedentary time and median bout duration (using a median split) and creating the following four 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 two-tailed with $p \leq .05$ 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 were repeated. We initially imputed in-bed and out-of-bed times using OPACH population average bed times for 482 women that did not return sleep logs. To see 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: (i) additional adjustment for the Healthy Eating Index-2010 measured near OPACH baseline, a valid and reliable measure of diet quality[35]; (ii) additional adjustment for antihypertension and antilipidemia medication use; and (iii) after measuring total sedentary time using the 100 cpm cutpoint. Joint analyses were also repeated measuring total sedentary time using the 100 cpm cutpoint.

RESULTS

Over 19,350 person-years of follow-up, 545 CVD and 137 CHD events were observed. Socio-demographic and health-related characteristics were associated with total sedentary time (Table 1). Women in quartile 4 were older, more likely to be White, had the highest BMI, and often had more unfavorable cardio-metabolic biomarker levels as compared to 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, 42.9, respectively. Controlling for potential confounders, women with the highest sedentary time had 69% higher risk for CVD (HR=1.69; 9% CI=1.27–2.26; p-trend=0.001) than women in quartile 1. Hazard ratios 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, 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. Hazard ratios were slightly attenuated after adjustment for potential mediators, with adjustment for CVD-risk biomarkers yielding quartile 4 vs. quartile 1 hazard ratios 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; Supplemental Table 1). As with mean bout duration, the most prolonged accumulation patterns were associated with higher CVD risk than the most interrupted patterns, independent of confounders (Supplemental Tables 2 and 3). However, breaks in sedentary time was not significantly associated with CVD (p-trend=0.06).

The dose-response trajectories were all linear (P-linear <0.008, P-nonlinear>0.08 | all). 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 or sedentary time was 1.12 (1.05–1.19) and for 1 minute of mean bout duration was 1.04 (1.01–1.07). The steeper trajectories observed for total sedentary time were partially explained by the different units of measure used (1 hour vs. 1 minute) and partially explained by higher standardized HRs for total sedentary time than mean bout duration (Supplemental Figures 1 and 2). Associations were attenuated after adjustment for MVPA and remained statistically significant (sedentary time p-trend=0.045; mean bout duration p-trend=0.04).

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 when compared to women with only high sedentary time or with only high bout duration, suggesting 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 when compared to women with low sedentary time and low bout duration (Figure 1), 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 Supplemental Figure 1. 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 hazard ratios were observed for CHD,

often by a factor of 2 (Supplemental Table 4; Supplemental Figures 2 and 3). All associations remained significant after further adjustment for potential mediators. Following 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 and for mean bout duration were 1.57 (0.80–3.08), 1.37 (0.70–2.67), 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, though for most secondary analyses, the linear trend tests were no longer statistically significant (see Supplemental Table 5). Model 3b hazard ratios tended to be larger when using multiple imputation 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 and for mean bout duration were 1.14 (0.86–1.52), 1.33 (1.02–1.75), 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 hazard ratios (95% CI) for quartiles 2, 3, and 4 were similar before 1.20 (0.91–1.60), 1.32 (1.00–1.74), 1.54 (1.17–2.02) and after adjustment 1.23 (0.90–1.68), 1.22 (0.90–1.66), 1.42 (1.05–1.92).

DISCUSSION

In this ethnically diverse cohort study of older community-dwelling women, nearly half of whom were over the age of 80, 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, indicating that prolonged sedentary accumulation patterns are associated with higher CVD risk in older women. Similar conclusions about 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 examining associations with incident CHD (i.e., fatal MI, non-fatal MI and stroke), the hazard ratios were as much as two times higher compared to those for CVD. The totality of evidence suggests that both sedentary time *and* the way in which it is accumulated may 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 vs. lowest total sedentary time was only 1.14 (1.09–1.19).[37] The magnitude of health associations attributed

to sedentary behavior tend to be higher when exposure is measured by accelerometer.[7] For example, two studies of CVD-mortality showed that HRs for the highest vs. 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 over 40,[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 due to the differing age groups under study or because our study had a larger sample size (n=5,638) and was focused on both fatal and non-fatal CVD. In both studies, however, the observed interrelationship of CVD with sedentary time and MVPA suggests that the two 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 typically spend sedentary, could reduce CVD risk by reducing their sedentary time. For example, a one-hour reduction in sedentary time could reduce CVD risk by 12% for women who are typically sedentary for 8 hours/day as well as for women who are typically sedentary for 12 hours/day. This result, when viewed over the relevant range of exposure (OPACH 1st-99th percentile of sedentary time=5.5–12.4 hours/day), was similar to findings from a recent meta-analysis that showed increased risk for CVD associated with reported daily sitting times beginning above 6.8 hours/day though not reaching statistical significance until siting times were above 10 hours/day.[37]

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 long) has acute 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 epidemiologic investigation of sedentary time and sedentary accumulation patterns, examining independent associations is analytically challenging because the two exposures are strongly related and the etiologic 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 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 (i.e.,

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, 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 non-fatal CVD events that used objective measures of sedentary time. Other noteworthy strengths include the 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, 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 sixteen 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 five 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 in the population-at-risk women with a history of heart failure, revascularization, and angina. 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 including 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 due to reduced sample size and CVD events, as 475 women and 18% of CVD cases were excluded. Alternatively, the attenuated associations could be due to stronger associations among the excluded women resulting 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, that 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. While accelerometers objectively measured sedentary behavior, the devices were worn over the right hip with data processed using common techniques, precluding 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 and/or its risk factors should be the subject of future studies. Sedentary behavior was measured during a seven-day period, which has been shown to be a reliable measure of 2-to-3 year behavior patterns, but may 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 resulting in wide confidence intervals; 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 gender differences.

In conclusion, both sedentary time and prolonged sedentary accumulation patterns were associated in a dose-response manner to 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 regularly interrupting 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL PERSPECTIVE

What's new?

- Sedentary behaviors, which include all sitting or reclining with low energy expenditure (< 1.5 METS), 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.

Clinical implications

- In this subcohort of 5638 racial-ethnically diverse Women's Health Initiative participants aged 63–97, lower sedentary time of 1 hour/day was associated with a 12% lower risk of CVD and a 26% lower risk of heart disease.
- Sedentary time reductions (e.g. one hour/day) do not need to occur all at once, they can be accumulated throughout the day with short (light intensity) interruptions to sitting.
- Regular 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.

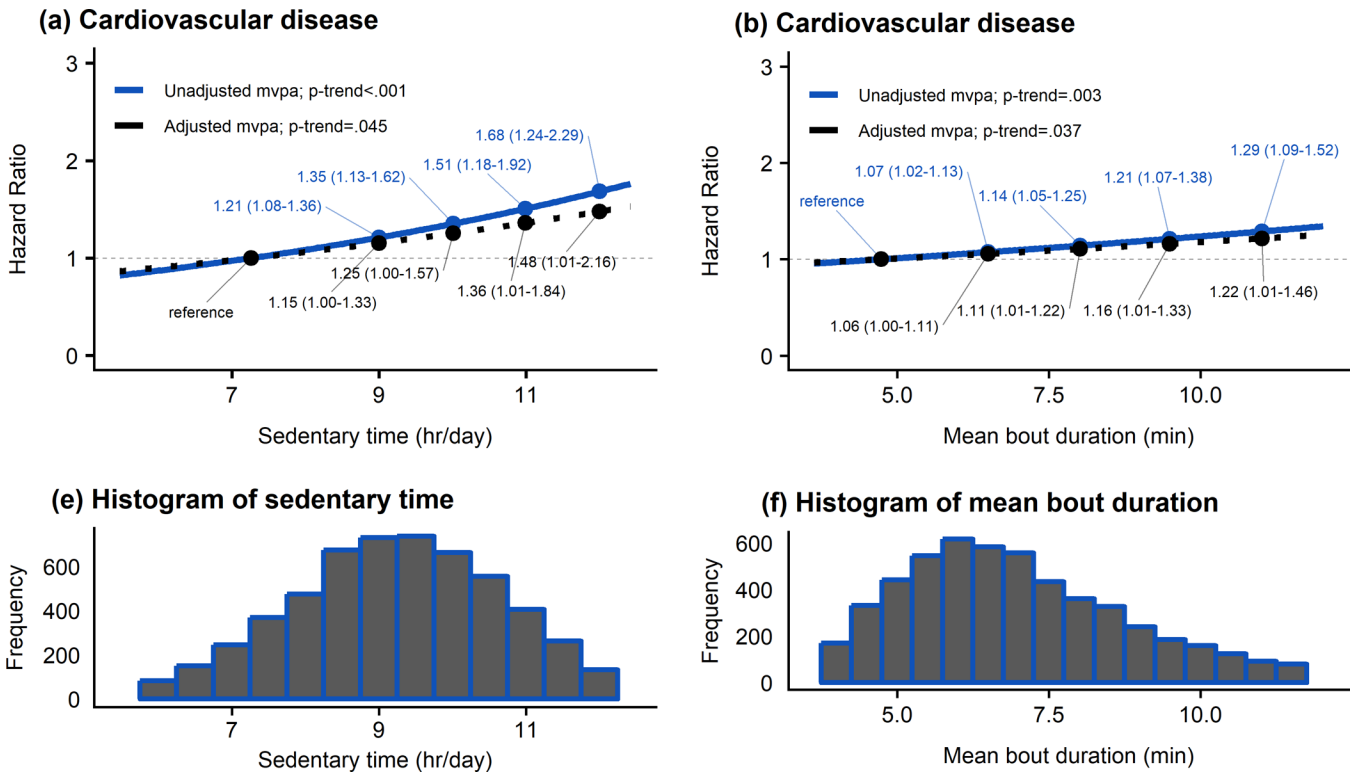

Figure 1:

Continuous dose-response relation of sedentary time and mean sedentary bout duration with cardiovascular disease events, estimated using linear Cox regression models adjusted for age, race/ethnicity, education, smoking status, alcohol consumption, self-reported health, multimorbidity, physical functioning, and family history of myocardial infarction (blue lines). Results following additional adjustment for moderate-to-vigorous physical activity (MVPA) are shown using black dotted lines. The reference category was set to the 10th percentile of each exposure (sedentary time = 7.3 hours per day; mean bout duration = 4.7 minutes). Results for sedentary time were trimmed at the 1st and 99th percentiles and results for mean bout duration were trimmed at the 1st and 95th percentiles.

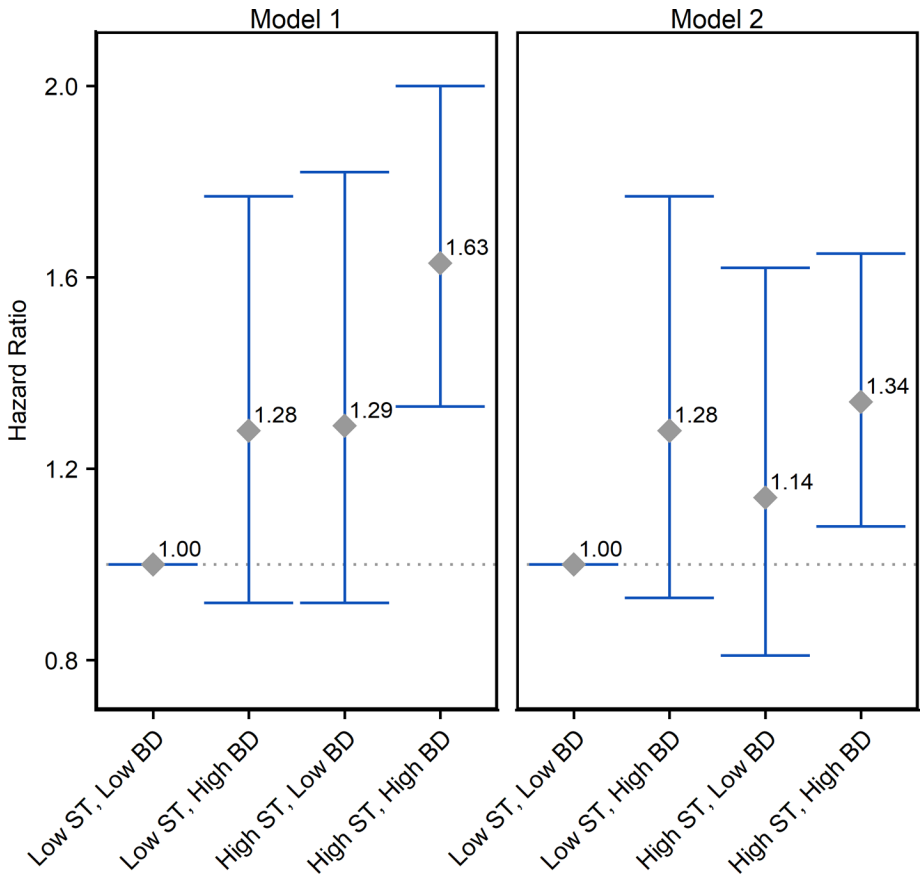

Figure 2:

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

Table 1.

Baseline Socio-demographic and health-related characteristics, by quartile of total sedentary time (n=5638): OPACH (2012–2014).

Characteristics	Total Sedentary Time Quartiles [*,†]				p [‡]
	1 (low)	2	3	4 (high)	
Age, mean (sd)	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, mean (sd)	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, mean (sd)	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**
Zero	539 (38.2)	486 (34.5)	450 (31.9)	441 (31.3)	
One	658 (46.7)	678 (48.1)	678 (48.1)	651 (46.2)	
Two 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, mean (sd)	123.7 (13.2)	125.0 (13.8)	125.9 (13.7)	128.0 (15.3)	**<0.001**
Glucose, mg/dL, mean (sd)	93.7 (20.0)	98.0 (27.2)	98.4 (27.0)	101.4 (30.7)	**<0.001**
HDL cholesterol, mg/dL, mean (sd)	64.5 (15.2)	62.0 (15.3)	59.6 (13.9)	56.5 (13.9)	**<0.001**
Log triglycerides, mg/dL, mean (sd)	4.5 (0.4)	4.5 (0.4)	4.6 (0.4)	4.7 (0.5)	**<0.001**
Total sedentary time [§]; min/day, mean (sd)	436.6 (48.8)	526.5 (16.7)	585.0 (17.1)	665.1 (38.4)	**<0.001**
Mean sedentary bout duration, min/day, mean (sd)	5.1 (0.9)	6.4 (1.0)	7.5 (1.4)	10.3 (3.2)	**<0.001**
Prolonged sedentary time [§]; min/day, mean (sd)	113.8 (53.3)	175.9 (61.0)	231.2 (72.4)	338.5 (106.5)	**<0.001**
Breaks in sedentary time [//]; n/day, mean (sd)	92.3 (16.3)	90.0 (14.8)	85.7 (15.0)	76.9 (15.9)	**<0.001**
Usual sedentary bout duration; min, mean (sd)	11.0 (3.6)	15.0 (4.3)	18.9 (5.9)	27.7 (11.6)	**<0.001**
Alpha, mean (sd)	2.0 (0.1)	1.9 (0.1)	1.8 (0.1)	1.7 (0.1)	**<0.001**
MVPA; min/day, mean (sd)	83.5 (36.5)	55.5 (26.6)	41.2 (21.2)	26.1 (16.8)	**<0.001**

Abbreviations: OPACH = Objective Physical Activity and Cardiovascular Health; SD = standard deviation; GED = general educational development; HDL = high density lipoprotein; MVPA = moderate to vigorous physical activity

[*] 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.

Table 2.

Associations of cardiovascular disease (CVD) events with total sedentary time and mean sedentary bout duration: OPACH (2012–2017).

	Total Sedentary Time Quartiles[*,†]				p-trend[‡]
	1 (low)	**2**	**3**	**4 (high)**	
New events [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 Quartiles[*]				
	1 (low)	**2**	**3**	**4 (high)**	
New events [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**

Abbreviations: OPACH = Objective Physical Activity and Cardiovascular Health; HDL = high density lipoprotein.

[*] Quartile cutpoints: 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.

[‡] P-values from Cox multivariable linear regression models including total sedentary time in models in continuous form.

[§] Crude rate per 1000 person-years.

[//] Data are hazard ratio (95% confidence interval).

Model 1 = age and ethnicity adjusted [n=5638]; Model 2 = Model 1 + potential confounders [n=5471]; Model 3a = Model 2 + body mass index + diabetes + 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.