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### Authors

Bellettiere, John  
LaMonte, Michael J  
Healy, Genevieve N  
[et al.](#)

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# Sedentary Behavior and Diabetes Risk Among Women Over the Age of 65 Years: The OPACH Study

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John Bellettiere,<sup>1,2</sup> Michael J. LaMonte,<sup>3</sup>  
Genevieve N. Healy,<sup>4,5,6</sup> Sandy Liles,<sup>1,2</sup>  
Kelly R. Evenson,<sup>7</sup> Chongzhi Di,<sup>8</sup>  
Jacqueline Kerr,<sup>1</sup> I-Min Lee,<sup>9</sup>  
Eileen Rillamas-Sun,<sup>8</sup> David Buchner,<sup>10</sup>  
Melbourne F. Hovell,<sup>2,11</sup> and  
Andrea Z. LaCroix<sup>1</sup>

## OBJECTIVE

To evaluate whether sedentary time (ST) and/or sedentary behavior patterns are related to incident diabetes in the U.S.'s oldest age-groups.

## RESEARCH DESIGN AND METHODS

Women without physician-diagnosed diabetes ( $n = 4,839$ , mean  $\pm$  SD age =  $79 \pm 7$  years) wore accelerometers for  $\geq 4$  days and were followed up to 6 years for self-reported newly diagnosed diabetes requiring treatment with medications. Hazard ratios (HRs) for incident diabetes were estimated across quartiles of accelerometer-measured ST and mean bout duration with use of Cox proportional hazards models. We conducted isotemporal substitution analyses using Cox regression and tested associations with risk for diabetes after statistically replacing ST with light physical activity (PA) or moderate-to-vigorous PA (MVPA) and after replacing light PA with MVPA.

## RESULTS

During 20,949 person-years, 342 diabetes cases were identified. Women in ST quartile (Q)2, Q3, and Q4 (vs. Q1) had incident diabetes HR 1.20 (95% CI 0.87–1.65), 1.33 (0.97–1.82), and 1.21 (0.86–1.70);  $P_{\text{trend}} = 0.04$ . Respective HRs following additional adjustment for BMI and MVPA were 1.04 (95% CI 0.74–1.47), 1.04 (0.72–1.50), and 0.85 (0.56–1.29);  $P_{\text{trend}} = 0.90$ . Fully adjusted isotemporal substitution results indicated that each 30 min of ST replaced with MVPA (but not light PA) was associated with 15% lower risk for diabetes (HR 0.85 [95% CI 0.75–0.96];  $P = 0.01$ ); the HR for replacing 30 min of light PA with MVPA was 0.85 (95% CI 0.73–0.98);  $P = 0.03$ . Mean bout duration was not associated with incident diabetes.

## CONCLUSIONS

Statistically replacing ST or light PA with MVPA was associated with lower diabetes risk in older women. While reducing ST is important for several health outcomes, results indicate that to reduce diabetes risk among older adults, the primary public health focus should be on increasing MVPA.

Type 2 diabetes is epidemic in the U.S., affecting 13.0% of those over the age of 17 years and 28.6% of those over age 64 years (1). Among adults with diabetes, older adults are at the highest risk for complications such as vascular disease, renal impairment, and severe or fatal hypoglycemia (2–4). Furthermore, diabetes accelerates the decline of physical functioning (5), impacting key aspects of healthy aging such as independence and overall quality of life.

<sup>1</sup>Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA

<sup>2</sup>Center for Behavioral Epidemiology and Community Health, Graduate School of Public Health, San Diego State University, San Diego, CA

<sup>3</sup>Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, State University of New York at Buffalo, Buffalo, NY

<sup>4</sup>School of Public Health, University of Queensland, Queensland, Australia

<sup>5</sup>Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia

<sup>6</sup>School of Physiotherapy, Curtin University, Perth, Western Australia, Australia

<sup>7</sup>Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

<sup>8</sup>Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

<sup>9</sup>Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

<sup>10</sup>Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Champaign, IL

<sup>11</sup>Division of Health Promotion and Behavioral Science, Graduate School of Public Health, San Diego State University, San Diego, CA

Corresponding author: John Bellettiere, [jbellettiere@ucsd.edu](mailto:jbellettiere@ucsd.edu)

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Each year, 0.9% of older adults are diagnosed with diabetes for the first time (1). As many as 9 out of 10 new cases can be attributed to modifiable lifestyle factors such as physical inactivity, poor diet, smoking, alcohol use, and BMI (obesity) (6). Several review articles conclude that sedentary behavior (i.e., waking behavior requiring low energy expenditure and occurring in a sitting, reclining, or lying posture) (7) is another important contributor to the development of diabetes (e.g., 8). However, nearly all the studies reviewed relied on self-reported measures of sedentary behavior, which are inaccurate (9), and few focused on older adults, for whom sedentary time (ST) is higher than at younger ages and in whom these behaviors are especially challenging to measure with questionnaires.

Recent improvements in technology and cost-efficiency have permitted use of accelerometers in population studies of sedentary behavior and health outcomes. Several studies have examined associations between accelerometer-measured sedentary behavior and risk factors related to diabetes (10). Just three studies (11–13) examined the cross-sectional association of ST with diabetes as a clinical end point, and all found higher odds of diabetes with higher ST. The only prospective study to date examining ST and diabetes incidence did not find a significant association among 1,718 adults mean  $\pm$  SD age = 45  $\pm$  3 years with 5 years of follow-up (11). The paucity of high-quality evidence relating sedentary behavior to incident diabetes, especially among older adults, has led to consensus that evidence from prospective studies that measure sedentary behavior using accelerometers is a high research priority (14).

To address this research priority, we examined associations of accelerometer-measured ST and ST patterns with incident diabetes in 4,834 older women. Our hypotheses were that women with higher cumulative ST and/or a pattern of frequent prolonged sedentary bouts at baseline would have higher risk for diabetes. A secondary aim of the study was to examine whether statistically replacing ST with light-intensity physical activity (PA) or moderate-to-vigorous PA (MVPA) was associated with diabetes risk. Findings will address key evidence gaps regarding the role of sedentary behavior, and sedentary behavior patterns, in the development of late-life diabetes.

## RESEARCH DESIGN AND METHODS

### Study Participants

As part of the Women's Health Initiative (WHI) 2010–2020 Extension Study and the ancillary Long Life Study conducted from 2012 to 2013, 7,058 ambulatory community-living women aged 63 years and older were enrolled in the Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) Study. Detailed methods have previously been published (15). Briefly, at OPACH Study baseline (March 2012–April 2014), women were asked to wear ActiGraph GT3X+ accelerometers at their hip secured to an elastic belt around their waist 24 h/day for 7 days (except when showering or swimming) and to concurrently record in-bed and out-of-bed times using sleep logs. Women were subsequently followed annually for morbidity and mortality as part of annual WHI follow-up. Of the 6,489 (91.9%) women enrolled in the OPACH Study who returned accelerometers, 6,133 were included in the current study because they met the commonly used wear criteria of having at least 4 days, each with  $\geq 10$  h of awake wear time (16). After exclusion of 12 women with missing diabetes follow-up data and 1,282 women with physician-diagnosed diabetes at OPACH Study baseline, the analytic sample for this study included 4,839 women who were at risk for developing diabetes during follow-up.

### Identification of Diabetes

At WHI baseline, between 1993 and 1998, participants were asked, "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" Then, at regular intervals (at least annually) during follow-up, standardized medical history updates were mailed to participants that included questions about new physician-diagnosed diabetes requiring insulin or oral hypoglycemic medication. Incident diabetes cases were defined as any participant reporting physician-diagnosed diabetes treated with insulin or oral medication after OPACH Study baseline through 31 March 2018. With the same case definition, a separate study of 715 WHI participants showed that reported incident diabetes was concordant with expert medical record review in 82% of reported confirmed cases; reports of being without diabetes were concordant in 95% of women confirmed as not having diabetes (17).

### ST, ST Patterns, and PA

Accelerometer data measured at 30 Hz were converted to 1-min epochs with use of the low-frequency extension filter and to 15-s epochs with the normal filter in ActiLife, version 6. With the Choi algorithm we identified data collected while devices were unworn; periods while participants were in bed were identified with use of recorded times from sleep diaries. When at least one in-bed or out-of-bed time was missing, each woman's average time was used if available; otherwise, the overall mean in-bed (10:45 P.M.) and out-of-bed (7:22 A.M.) times were used.

The accelerometer cut points for classifying sedentary behavior, light PA, and MVPA—determined in a laboratory-based calibration study of 200 WHI participants aged 60–91 years—were 0–18, 19–518, and  $>518$  vector magnitude counts/15 s, respectively (18). How ST is accrued in long and short uninterrupted periods (sedentary bouts) describes one's ST patterns. Using the acceleration cut points described above to measure ST patterns was problematic because vector magnitude acceleration values within 15-s epochs were overly sensitive to breaks in ST (i.e., in our sample, on average there were  $>300$  breaks in ST per day). Thus, to classify breaks, we measured ST using a common ActiGraph data-processing protocol for older adults (100 counts/min applied to the vertical axis using the low-frequency extension filter) (16) and then identified bouts of consecutive sedentary minutes that were below this threshold, with no minimum bout duration required. With use of this data processing protocol that we have successfully implemented in previous studies (e.g., 13), the 86 average breaks/day observed in the OPACH Study were similar to those previously reported in another separate sample of older women (19). We then computed our measure of ST patterns as the arithmetic mean sedentary bout duration, using all adherent days from each participant. High mean bout durations indicated prolonged ST patterns; low mean bout durations indicated frequently interrupted patterns.

### Covariates

Age, race/ethnicity, education level, and family history of diabetes were measured by questionnaire at WHI baseline. Family history of diabetes was assessed with the

question, “Did your mother or father, or full-blooded sisters, full-blooded brothers, daughters, or sons ever have sugar diabetes or high blood sugar that first appeared as an adult?” Self-reported health status, physical functioning (from the RAND 36-Item Short-Form Survey [SF-36]) (20), alcohol consumption, and current smoking status (smoker, nonsmoker [missing values were classified as nonsmokers]) were measured by questionnaire at OPACH Study baseline. Near OPACH Study baseline, trained research assistants conducted in-person visits as part of the Long Life Study; measured height and weight, which was used to compute BMI; and drew blood for biomarker assays including fasting glucose. Multimorbidity was measured as the number of chronic health conditions (cardiovascular disease, cancer, cognitive impairment, depression, osteoarthritis, history of frequent falls, chronic obstructive pulmonary disease, hypertension, cerebrovascular disease) at or before OPACH Study baseline.

### Statistical Analysis

To account for differences in accelerometer wear time while subjects were awake, we adjusted ST for awake wear time using the residuals method. Then, ST, mean bout duration, and covariates were summarized by quartile of ST.

Cox proportional hazards models estimated hazard ratios (HRs) of incident diabetes in relation to ST and mean bout duration, in separate models. Time to event was computed as the number of days from OPACH Study baseline to the date of the returned questionnaire on which diabetes diagnosis was reported, death, or the last medical update received. HRs were estimated for quartiles of each sedentary behavior–related exposure variable. Four models were fit for each sedentary behavior–related exposure variable as follows: model 1, adjustment for age and race/ethnicity; model 2, model 1 adjustments plus potential confounders (education, family history of diabetes, self-rated health, physical functioning, alcohol consumption, and smoking status); model 3a further controlled for BMI, which can be considered to be on the causal pathway between sedentary behavior and diabetes and was separately tested as an effect modifier; and model 3b included model 2 covariates and MVPA, which has previously been conceptualized as a confounder, a mediator, and a

competing behavior (21–23). We also report results for model 3c, which includes model 2 covariates plus BMI and MVPA. Tests for linear trend used Cox regression models that included the continuous form of each sedentary behavior–related exposure variable. Adherence to Cox proportional hazards assumptions was confirmed by tests based on Schoenfeld residuals and review of plots of the scaled residuals over time. To account for the interdependency of ST and MVPA (24), we fit isotemporal substitution models using model 3a to estimate how statistically replacing ST with equivalent time spent in light-intensity PA or MVPA was associated with incident diabetes. For a complete isotemporal analysis, we also fit a model for statistically replacing light PA with MVPA.

Tests of effect modification were conducted by inclusion in model 2 of a multiplicative interaction term between the exposure and each potential effect modifier that was a priori selected based on our previous work (13): women <80 and ≥80 years old, <30 and ≥30 kg/m<sup>2</sup>, <75 and ≥75 on the SF-36 (median split), <43 and ≥43 min per day of MVPA (median split), and with or without family history of diabetes and according to race/ethnicity (White, Black, or Hispanic). For visualization of differential associations by subgroups, models were repeated, stratified by each potential modifier. Tests were also performed with use of model 3c.

### Sensitivity Analyses

Subclinical diabetes and its complications could cause increased ST, leading to associations with new-onset diabetes that could reflect reverse causation. Two approaches were used to address this: first, we removed from our analytic sample women reporting newly diagnosed diabetes within the first 6 months after OPACH Study baseline and repeated model 2 and isotemporal substitution models. Second, from a subsample of 3,832 women who received phlebotomy as part of the Long Life Study, we removed 147 women with fasting glucose ≥126 mg/dL and repeated model 2 and isotemporal substitution models. We also repeated isotemporal substitution models after additional adjustment for fasting glucose and insulin to test whether associations were present independent of these expected mediators. Finally, we repeated all analyses using a consistent sample from model 3c ( $n =$

4,438) to test whether using complete cases analyses influenced changes in estimates.

All statistical tests were two tailed, with  $\alpha = 0.05$ , and conducted using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Mean  $\pm$  SD age for participants was 78.9  $\pm$  6.7 years, and 53.1% were White, 30.4% Black, and 16.6% Hispanic. During a mean follow-up time of 4.3  $\pm$  1.2 years, 342 women reported being newly diagnosed with diabetes requiring oral medication or insulin. Health-related characteristics of the cohort are described in Table 1. Generally, women in the fourth quartile (quartile [Q]4) of ST were oldest and in the poorest health as measured by self-rated health and physical functioning. Women in the highest ST quartile also had the lowest levels of MVPA (26.9  $\pm$  17.4 min per day) and light PA (205.1  $\pm$  34.8 min per day) and the most prolonged ST patterns as measured by mean bout duration (10.3  $\pm$  3.2 min).

Crude incidence rates for diabetes per 1,000 person-years in ST Q1, Q2, Q3, and Q4 were 13.3, 16.6, 18.1, and 17.6, respectively (Table 2). Following adjustment for model 2 covariates, women with the highest ST (Q4) had 21% higher relative risk for diabetes (HR 1.21 [95% CI = 0.86–1.70];  $P_{\text{trend}} = 0.04$ ) than women in Q1. Following adjustment for BMI (Q4 vs. Q1 HR 1.14 [95% CI 0.79–1.64];  $P_{\text{trend}} = 0.12$ ) and, separately, for MVPA (Q4 vs. Q1 HR 0.92 [95% CI 0.62–1.36];  $P_{\text{trend}} = 0.76$ ), HRs were further attenuated and there was no longer a significant linear trend.

The interaction of ST with BMI in model 2 had a  $P$  value of 0.08 with stratified analyses indicating that associations (for 1 interquartile range [IQR] higher ST [2 h/day]) were stronger among those with BMI <30 kg/m<sup>2</sup> (HR 1.29 [95% CI 1.03–1.60]; 203 diabetes cases) than women with higher BMI (HR 0.94 [95% CI 0.70–1.26]; 120 diabetes cases) (Supplementary Table 1). The interaction of ST and family history of diabetes did not reach common ( $P < 0.05$ ) or conservative ( $P < 0.10$ ) thresholds for effect modification, though stratified analyses indicated that one IQR higher of ST was associated with an HR of 1.12 (95% CI 0.91–1.38) for women without a family history of diabetes and 1.29 (95% CI 0.99–1.68) among women with a family history;  $P_{\text{interaction}} = 0.11$ .

**Table 1—Baseline sociodemographic and health-related characteristics by quartile of ST (n = 4,839): the OPACH Study (2012–2018)**

Characteristics	Q1 (low)	Q2	Q3	Q4 (high)	P
Age, years, mean ± SD	76.6 ± 6.3	78.5 ± 6.7	79.3 ± 6.7	81.4 ± 6.4	<b>&lt;0.001</b>
Age category, n (%)					<b>&lt;0.001</b>
63–69 years	180 (14.9)	140 (11.6)	104 (8.6)	63 (5.2)	
70–79 years	589 (48.7)	482 (39.8)	460 (38.0)	333 (27.5)	
80–89 years	423 (35.0)	545 (45.0)	581 (48.1)	719 (59.4)	
90+ years	18 (1.5)	43 (3.6)	64 (5.3)	95 (7.9)	
Race/ethnicity, n (%)					<b>&lt;0.001</b>
White	493 (40.7)	606 (50.1)	660 (54.6)	809 (66.9)	
Black	414 (34.2)	395 (32.6)	372 (30.8)	288 (23.8)	
Hispanic/Latina	303 (25.0)	209 (17.3)	177 (14.6)	113 (9.3)	
Highest education level, n (%)					0.05
High school or less	252 (20.9)	231 (19.2)	246 (20.6)	222 (18.5)	
Some college	429 (35.5)	433 (35.9)	465 (38.9)	490 (40.8)	
College graduate	527 (43.6)	541 (44.9)	483 (40.5)	489 (40.7)	
Health behavior/status					
Current smoker, n (%)	22 (1.8)	28 (2.3)	32 (2.6)	51 (4.2)	<b>0.002</b>
Alcohol intake, n (%)					<b>&lt;0.001</b>
Nondrinker	356 (29.4)	390 (32.2)	403 (33.3)	399 (33.0)	
<1 drink per week	422 (34.9)	382 (31.6)	308 (25.5)	279 (23.1)	
≥1 drinks per week	346 (28.6)	357 (29.5)	394 (32.6)	429 (35.5)	
Unknown alcohol intake	86 (7.1)	81 (6.7)	104 (8.6)	103 (8.5)	
BMI, kg/m <sup>2</sup> , mean ± SD	26.0 (4.7)	26.8 (5.0)	28.1 (5.4)	29.5 (5.9)	<b>&lt;0.001</b>
Self-rated health, n (%)					<b>&lt;0.001</b>
Excellent or very good	776 (64.4)	658 (54.5)	646 (53.6)	553 (45.9)	
Good	371 (30.8)	467 (38.7)	467 (38.8)	515 (42.7)	
Fair or poor	58 (4.8)	82 (6.8)	92 (7.6)	138 (11.4)	
Physical function (SF-36), mean ± SD	81.0 ± 19.7	73.8 ± 23.1	69.2 ± 24.5	58.6 ± 27.2	<b>&lt;0.001</b>
Parental history of diabetes, n (%)	397 (32.9)	392 (32.6)	415 (34.4)	395 (32.8)	0.76
History of hypertension, n (%)	736 (60.8)	792 (65.5)	869 (71.9)	913 (75.5)	<b>&lt;0.001</b>
No. of chronic conditions†, n (%)					<b>&lt;0.001</b>
None	187 (15.5)	152 (12.6)	115 (9.5)	94 (7.8)	
1–2	459 (37.9)	452 (37.4)	377 (31.2)	371 (30.7)	
≥3	414 (34.2)	395 (32.6)	479 (39.6)	432 (35.7)	
ST, min/day, mean ± SD‡	432.9 ± 48.4	524.0 ± 17.9	584.5 ± 17.2	662.8 ± 38.0	<b>&lt;0.001</b>
Sedentary bout duration, min, mean ± SD	5.1 ± 0.9	6.3 ± 1.0	7.6 ± 1.3	10.3 ± 3.2	<b>&lt;0.001</b>
MVPA, min/day, mean ± SD‡	84.9 ± 37.6	56.8 ± 27.1	42.0 ± 21.9	26.9 ± 17.4	<b>&lt;0.001</b>
Light PA, min/day, mean ± SD‡	377.0 ± 47.8	314.1 ± 29.9	268.3 ± 25.3	205.1 ± 34.8	<b>&lt;0.001</b>

ST quartile cut points: Q1, 196–491 min; Q2, 492–554 min; Q3, 555–615 min; Q4, 616–830 min. P value:  $\chi^2$  for categorical variables and trend test for continuous. Boldface type indicates  $P < 0.05$ . †Chronic conditions: cardiovascular disease, cancer, cognitive impairment, depression, osteoarthritis, history of falls, chronic obstructive pulmonary disease, hypertension, cerebrovascular disease. ‡We adjusted for awake wear time using the residuals method.

When stratified analyses were further adjusted for MVPA + BMI, HRs for 1 IQR increment in ST were 1.04 (95% CI 0.80–1.36) among women with BMI <30 kg/m<sup>2</sup> and 0.91 (95% CI 0.62–1.28) among women with higher BMI ( $P_{\text{interaction}} = 0.09$ ) (Supplementary Table 2). And for family history, HRs were 0.90 (95% CI 0.68–1.19) for women without a family history of diabetes and 1.15 (95% CI 0.81–1.64) among women with a family history;  $P_{\text{interaction}} = 0.15$ .

Crude incidence rates for diabetes per 1,000 person-years in Q1, Q2, Q3, and Q4 of mean bout duration were 15.1, 15.7, 18.6, and 16.0, respectively (Table 2). Following adjustment for model 2 covariates, mean bout duration was not associated

with risk for diabetes (Q4 vs. Q1 HR 1.01 [95% CI 0.72–1.42];  $P_{\text{trend}} = 0.08$ ).

There was no statistical evidence of effect modification of mean bout duration in association with incident diabetes by age, BMI, physical functioning, MVPA, race/ethnicity, or family history of diabetes (Supplementary Tables 1 and 2).

#### Isotemporal Analyses

We performed isotemporal substitution analyses using model 3a covariates and estimated the association with incident diabetes when statistically replacing 30 min per day of ST with 30 min of light PA or MVPA. The results, shown in Fig. 1, indicate that each 30-min substitution reducing ST by adding light-PA time was associated with an HR of 0.99

(95% CI 0.94–1.04), whereas each 30-min substitution of ST with MVPA was associated with a 15% lower risk for diabetes (HR 0.85 [95% CI 0.75–0.96]). Isotemporal modeling indicated that statistically replacing 30 min of light PA with equal time in MVPA was also associated with 15% lower risk for incident diabetes (HR 0.85 [95% CI 0.73–0.98];  $P = 0.03$ ).

#### Sensitivity Analyses

After removal from our analytic sample of 34 women (out of 342 total case subjects [9.9%]) who reported newly diagnosed diabetes within the first 6 months of follow-up, ST HRs for Q1, Q2, Q3, and Q4 were 1.00 (reference), 1.11 (95% CI 0.80–1.54), 1.21 (95% CI 0.87–1.68), and 1.14 (95% CI 0.80–1.62),

**Table 2—ST, mean sedentary bout duration, and incident diabetes in older women: the OPACH Study (2012–2018)**

	Q1 (low)	Q2	Q3	Q4 (high)	$P_{\text{trend}}^{\dagger}$
<b>ST<sup>‡</sup></b>					
Diabetes cases [rate <sup>§</sup> ]	73 [13.3]	88 [16.6]	94 [18.1]	87 [17.6]	
Model 1	1 (ref)	1.27 (0.93–1.74)	1.41 (1.04–1.93)	1.43 (1.04–1.97)	<b>0.003</b>
Model 2	1 (ref)	1.20 (0.87–1.65)	1.33 (0.97–1.82)	1.21 (0.86–1.70)	<b>0.04</b>
Model 3a	1 (ref)	1.21 (0.87–1.68)	1.30 (0.93–1.80)	1.14 (0.79–1.64)	0.12
Model 3b	1 (ref)	1.04 (0.74–1.45)	1.07 (0.75–1.52)	0.92 (0.62–1.36)	0.76
Model 3c	1 (ref)	1.04 (0.74–1.47)	1.04 (0.72–1.50)	0.85 (0.56–1.29)	0.90
<b>Mean bout duration</b>					
Diabetes cases [rate <sup>§</sup> ]	84 [15.1]	83 [15.7]	96 [18.6]	79 [16.0]	
Model 1	1 (ref)	1.08 (0.79–1.46)	1.29 (0.96–1.74)	1.15 (0.84–1.60)	<b>0.008</b>
Model 2	1 (ref)	1.09 (0.80–1.48)	1.20 (0.88–1.63)	1.01 (0.72–1.42)	0.08
Model 3a	1 (ref)	1.08 (0.79–1.48)	1.15 (0.84–1.58)	0.97 (0.68–1.38)	0.06
Model 3b	1 (ref)	0.98 (0.72–1.34)	1.04 (0.75–1.43)	0.83 (0.58–1.19)	0.45
Model 3c	1 (ref)	0.98 (0.71–1.36)	1.00 (0.72–1.40)	0.80 (0.55–1.17)	0.34

Data are HR (95% CI) unless otherwise indicated. ST quartile cut points: Q1, 196–491 min; Q2, 492–554 min; Q3, 555–615 min; Q4, 616–830 min. Mean sedentary bout duration quartile cut points: Q1, 2.6–5.5 min; Q2, 5.6–6.7 min; Q3, 6.8–8.3 min; Q4, 8.4–52.4 min. Model 1, adjustment for age and ethnicity ( $n = 4,839$ ); model 2, model 1 adjustments + potential confounders ( $n = 4,734$ ); model 3a, model 2 adjustments + BMI ( $n = 4,438$ ); model 3b, model 2 adjustments + MVPA ( $n = 4,734$ ); model 3c, model 2 adjustments + BMI and MVPA ( $n = 4,438$ ). Potential confounders include education, self-reported health, family history of diabetes, number of chronic conditions, physical functioning (SF-36), alcohol consumption, and current smoking status. Boldface type indicates  $P < 0.05$ . ref, reference. <sup>†</sup> $P$  values from Cox multivariable linear regression models including ST in models in continuous form. <sup>‡</sup>We adjusted for awake wear time using the residuals method. <sup>§</sup>Crude incidence rate per 1,000 person-years.

respectively;  $P_{\text{trend}} = 0.09$ . Each 30-min substitution reducing ST by adding light-PA time was associated with incident diabetes HR of 1.01 (95% CI 0.95–1.07), while adding MVPA was associated with incident diabetes HR of 0.84 (95% CI 0.74–0.96). After removal of 147 women with fasting glucose  $\geq 126$  mg/dL from a subsample ( $n = 3,832$ ) who had phlebotomy, ST HRs for Q1, Q2, Q3, and Q4 were 1.00 (reference), 1.18 (95% CI 0.81–1.71), 1.21 (95% CI 0.83–1.76), and 1.08 (95% CI 0.72–1.63);  $P_{\text{trend}} = 0.28$ . Each 30-min substitution reducing ST by adding light PA time was associated with incident diabetes HR of 1.03 (95% CI 0.97–1.10), while adding MVPA was associated with incident diabetes HR of 0.82 (95% CI 0.71–0.95). In the full subsample ( $n = 3,832$ ), isothermal substitution results were nearly identical to those above after additional adjustment for fasting glucose and insulin. There were no changes when the consistent sample was used.

## CONCLUSIONS

In this cohort of older ambulatory women, nearly half of whom were over age 80 years, higher accelerometer-measured ST was

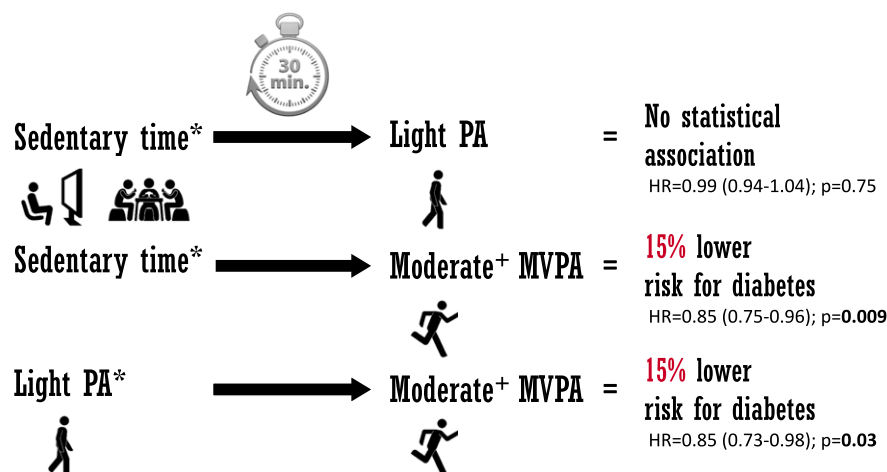
associated with greater risk for diabetes, though the association was not independent of BMI or MVPA. Use of isothermal substitution analysis to hypothetically replace 30 min/day of ST with equivalent time spent in MVPA resulted in a 15% lower risk for diabetes. Replacing 30 min of light PA with MVPA was also associated with a 15% lower risk for diabetes, whereas replacement of ST with light PA was not associated with lower risk for diabetes. Study results failed to confirm our hypothesis, based on acute and cross-sectional diabetes studies and longitudinal studies that used self-reported ST, that longer STs would be associated with higher risk for diabetes in late life, and suggest that moderate reductions in ST may be insufficient to delay or prevent diabetes unless MVPA is increased. We also did not observe significant associations between ST patterns and incident diabetes.

Epidemiologic studies, mostly in younger and middle-aged adults, have shown strong and consistent associations between self-reported TV time and incident diabetes, even after adjustment for MVPA (8). However, TV time might reflect an interaction of several health behaviors (sitting + snacking, for example) or lifestyle

patterns that have independent effects on incident diabetes (25). When sitting time (a measure that includes other sedentary behaviors in addition to TV time specifically) has been assessed by self-report, associations with incident diabetes have been mixed, with some studies reporting associations only among those with high BMI and/or low MVPA and one showing null results with adjustment for BMI (26–29). For example, among 88,829 participants of the WHI observational study (mean  $\pm$  SD age =  $62 \pm 7$  years) followed for an average of 14.4 years, obese women who self-reported sitting  $\geq 16$  h per day had 1.25 times higher odds of new-onset diabetes than obese women reporting sitting  $\leq 7$  h per day (29); however, no significant associations were observed for normal weight or overweight women. Our contrasting results from the current study that associations of ST are higher in women with  $<30$  kg/m<sup>2</sup> BMI suggest possibly differential mechanisms for ST and incident diabetes associations that depend on age of diabetes onset—for example, among women with diabetes onset at a younger age, fat accretion associated with ST (30) might be a mechanism, while among women with older-onset diabetes, accelerated sarcopenia associated with ST (31) might play a role. Future studies over longer periods of time that include repeated measures for physical behavior, adiposity, and diabetes are now needed.

In our previous study within this OPACH Study cohort, we found strong associations of accelerometer-measured ST and ST patterns with prevalent diabetes at OPACH Study baseline (13). These findings remained strong after adjustment for BMI and MVPA and were present in every subgroup of women analyzed: high versus low MVPA, high versus low physical functioning, BMI  $>$  vs.  $<30$  kg/m<sup>2</sup>; age  $>$  vs.  $<80$  years, family history of diabetes yes versus no, and race/ethnicity White, Black, Hispanic (13). In the current study on diabetes incidence, after removing from the OPACH Study cohort 1,282 women (20.9% of the sample) who were diagnosed with diabetes earlier in their life, we focused exclusively on incident diabetes cases in our older adult sample. Newly diagnosed diabetes among older adults, compared with younger adults, is more likely to be asymptomatic (32) and milder, and therefore abnormal glucose levels may be less likely to be labeled as diabetes in late life. Also, the pathophysiology of newly





**Figure 1**—Statistically replacing (reducing) ST with (increasing) light PA or MVPA and statistically replacing (reducing) light PA with (increasing) MVPA. Results from isotemporal substitution Cox proportional hazards models adjusted for age, race/ethnicity, education, smoking status, alcohol use, family history of diabetes, multimorbidity, physical functioning, self-rated health, and BMI. HRs are shown with 95% CIs. \*Statistically replacing 30 min with light PA or MVPA.

acquired diabetes in older adults is different than in younger adults; adults over 75 years of age have age-related changes in mitochondrial dysfunction and sarcopenia that can accelerate decreased insulin secretion and increased insulin resistance, leading to clinical diabetes at older ages (33). The accelerated deficiencies in glucose metabolism may require a larger neurohormonal and metabolic counterregulatory stimulus to mitigate progression to frank diabetes. This could explain why we did not observe a clear inverse association with diabetes incidence when hypothetically replacing sitting time with equivalent time spent in light-intensity PA, whereas we did find a beneficial association for replacement with MVPA. A recent compositional analysis of accelerometer-measured MVPA, light PA, and ST with biomarkers of prediabetes and type 2 diabetes in an adult sample, mean  $\pm$  SD age = 64.4  $\pm$  7.7 years, lends support to this speculation. Investigators found that statistically substituting light PA for ST had generally small associations, while substituting MVPA for ST was related to larger, beneficial associations with most biomarkers (34). Indeed, controlled trials among older men and women have shown that higher-intensity activities like combining resistance training and aerobic exercise can maximize weight loss, skeletal muscle mass gain, and strength gain and can improve insulin resistance (5). The current study shows that MVPA, when replacing ST, is associated with lower diabetes risk.

These results are supported by experimental studies showing that engaging in lifestyle modification that is heavily focused on improving diet and increasing MVPA can prevent or delay the onset of diabetes (35), even 10 years following intervention, with more pronounced effects in older adults than younger adults (36).

In the only other prospective study of accelerometer-measured ST and incident diabetes that we found, over a 5-year period, 81 cases of incident diabetes were reported among 1,718 U.S. adults mean  $\pm$  SD age = 45  $\pm$  3 years, and the odds of incident diabetes did not significantly vary by ST, with or without adjustment for MVPA (11). While our results suggested that ST was related to incident diabetes in older adults, as in our previous study, results were not statistically independent of MVPA. A common explanation for this lack of statistical independence is confounding, which in our case requires that 1) women with low ST also had high MVPA (the correlation between MVPA and ST in the OPACH Study was  $-0.67$ ), 2) MVPA is causally related to incident diabetes, and 3) once MVPA is accounted for, associations between ST and diabetes are attenuated—overall, the confounding explanation implies that the initial ST and diabetes association was at least somewhat spurious. Another explanation for the lack of association when MVPA was accounted for is that the behaviors themselves are interdependent, such that reducing one will cause

increases in another, which is the case with ST and PA. The results of our isotemporal substitution analyses showing associations with incident diabetes after statistically reducing ST and replacing it with an equal amount of MVPA time suggest that this latter explanation is plausible. Furthermore, the null results observed for statistically replacing ST with light PA suggest that higher-intensity activity might be needed to prevent diabetes among older adults. This hypothesis was further supported by our findings that statistically replacing light PA with equal time in MVPA was associated with lower diabetes risk. Future studies that experimentally test these theories are needed, as are studies that investigate how patterns of sitting might play a role in metabolic dysregulation and late-life-onset diabetes in older adults.

#### Limitations

This study was limited by having shorter follow-up time than previous studies of reported sedentary behavior and incident diabetes. Despite the short follow-up, we had sufficient power to detect associations using multivariable Cox models, likely due to our use of objectively measured sedentary behavior and our relatively large sample size. The self-reported diabetes question used to identify diabetes did not distinguish between type 1 and type 2 diabetes; however, type 2 diabetes accounts for >95% of total diagnosed diabetes in U.S.

older adults (37) and the measure has demonstrated high accuracy when compared with physician adjudication based on medical record reviews (17). Still, use of reported medically treated diabetes may miss those with subclinical or undiagnosed disease, which among older adults occurs in 2.9% of the U.S. population (1). Assuming those with undiagnosed diabetes are more sedentary and engage in less MVPA, this could introduce a bias toward the null, suggesting that our findings may underestimate the association between physical behavior and incident diabetes in older women. The detection of ST patterns in the current study was limited by measurement with hip-worn accelerometers, which are less accurate for identifying postural transitions than devices specifically designed for this purpose (e.g., activPAL) (38). Such measurement error may lead to misclassification that reduces effect sizes and could account for the null findings. Future studies would benefit from use of posture-based devices to evaluate ST patterns in relation to incident diabetes. Additionally, accelerometer data were collected over a period of  $\leq 7$  days, which is adequately reproducible over a 2–3 year period (39) but may not reflect longer-term patterns of sedentary behavior. The current study was also conducted among older women only, and generalizability would be enhanced by testing of these associations in cohorts of older and younger women and men. Finally, the isothermal substitution analysis relied on longitudinal data collected during an observational study in which there was no experimental intervention for replacement of behaviors. The results should therefore be interpreted as associations, and future studies are needed in older people to test whether interventions to replace ST with PA prevent incidence of type 2 diabetes in later life.

### Strengths

Notable strengths of our study are the relatively large and diverse (53.1% White, 30.4% Black, and 16.6% Hispanic) cohort of older community-dwelling women with objective measures of sedentary behavior based on a 24-h wear protocol. Objective measures are important for characterizing sedentary behavior because sitting is the default position for many older adults, making it an automatic behavior that is difficult to quantify

by self-report (9). The need for higher-quality evidence concerning diabetes in this older age-group was a major theme of a recent consensus statement by the American Diabetes Association (40). And the wide variation in race/ethnicity and educational attainment (42% had a bachelor's degree or higher) limited threats to external validity to older U.S. women. Finally, the prospective design of the study and sensitivity analyses are also distinct strengths in that they help establish temporal order of the association between sedentary behavior and diabetes.

In conclusion, our findings indicate that reducing ST or light PA while increasing MVPA might mitigate diabetes risk in older women. Findings also suggest that substituting time in light PA for ST may be insufficient to delay or prevent diabetes in late life; replacement of ST by the stronger physiologic stimulus provided by MVPA may be necessary. Because older adults have a lower resting metabolic rate and higher energy cost of movement, the types of PA and efforts needed to achieve MVPA are different for them than for younger adults. For example, a usual-paced 400-m walk was shown to be sufficient to achieve MVPA for most women average age 80 years (18). MVPA has also been shown to be attainable for ambulatory older adults even in the presence of clinical mobility limitations (41). Our results, which pertain to older ambulatory community-living women who reach late life without getting diabetes, add to mounting evidence warranting the conduct of interventions in age-, sex-, and ethnicity-diverse populations to test replacement of ST with MVPA for the prevention of late-life-onset diabetes. Until data from such trials are available, the totality of the evidence related to cardiometabolic health supports recommendations, such as the national 2018 Physical Activity Guidelines for Americans and those from the American Diabetes Association (42), to reduce ST in whatever ways are feasible, safe, and easy to incorporate into daily life and to increase PA levels as part of a healthy lifestyle strategy aimed at improvement of personal and public health.

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