

Associations of Accelerometer-Measured Physical Activity and Sedentary Time With All-Cause Mortality by Genetic Predisposition for Longevity

Alexander Ivan B. Posis,^{1,2} John Bellettiere,¹ Rany M. Salem,¹ Michael J. LaMonte,³
JoAnn E. Manson,^{4,5} Ramon Casanova,⁶ Andrea Z. LaCroix,¹ and Aladdin H. Shadyab¹

¹Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, La Jolla, CA, USA; ²School of Public Health, San Diego State University, San Diego, CA, USA; ³Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, State University of New York at Buffalo, Buffalo, NY, USA; ⁴Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; ⁵Harvard Medical School, Boston, MA, USA; ⁶Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA

The goal of this study was to examine associations between accelerometer-measured physical activity (PA) and sedentary time (ST) with mortality by a genetic risk score (GRS) for longevity. Among 5,446 women, (mean [SD]: age, 78.2 [6.6] years), 1,022 deaths were observed during 33,350 person-years of follow-up. Using multivariable Cox proportional hazards models, higher light PA and moderate to vigorous PA were associated with lower mortality across all GRS for longevity categories (low/medium/high; all $p_{\text{trend}} < .001$). Higher ST was associated with higher mortality (p_{trend} across all GRS categories $< .001$). Interaction tests for PA and ST with the GRS were not statistically significant. Findings support the importance of higher PA and lower ST for reducing mortality risk in older women, regardless of genetic predisposition for longevity.

Keywords: healthy aging, sedentary behavior, women's health

Engaging in physical activity (PA) and reducing sedentary time (ST) are important to achieve healthy aging (U.S. Department of Health and Human Services, 2018). Several studies have reported inverse associations between PA and mortality (Almeida et al., 2014; Lee et al., 2018; Mok et al., 2019; Oguma et al., 2002). Moderate to vigorous PA (MVPA), even below the recommended amount of 150 min per week for older adults (U.S. Department of Health and Human Services, 2018), was associated with 22% lower mortality risk in a meta-analysis (Hupin et al., 2015). Another meta-analysis showed that individuals at the highest levels of accelerometer-measured ST had higher mortality risk (Ekelund et al., 2019).

Longevity is likely due to environmental (e.g., lifestyle behaviors) and genetic factors (Hjelmborg et al., 2006). Genome-wide association studies (GWAS) have identified multiple single-nucleotide polymorphisms (SNPs) associated with longevity (Deelen et al., 2019; Pilling et al., 2017; Shadyab & LaCroix, 2015). Despite consistent evidence of associations of PA and ST with mortality, it is unknown whether associations of PA and ST with mortality vary by genetic predisposition for longevity. If these associations do not vary by genetic predisposition for longevity, then this would provide further support for the importance of a physically active lifestyle, regardless of genetic tendency for greater longevity.

Previous studies examining the Objective Physical Activity and Cardiovascular Health (OPACH) cohort of older women found strong associations of accelerometer-measured light PA, MVPA, and ST with all-cause mortality during a mean follow-up of 3.1 years (LaMonte et al., 2018). However, no attempt was made to understand the genetic contribution to these associations.

Therefore, the goal of this study was to leverage a longer mean follow-up of 6.1 years in the OPACH cohort to replicate these associations and extend them by determining the extent to which findings vary by a weighted genetic risk score (GRS) for longevity. We also tested for effect modification by GRS for longevity in these associations.

Methods

Study Participants

OPACH is an ancillary study to the Women's Health Initiative (WHI) designed to investigate accelerometer-measured PA and ST in relation to cardiovascular and fall events among 7,058 U.S. postmenopausal women aged ≥ 63 years. Complete details on study design have been extensively reported elsewhere for the WHI (Anderson et al., 2003) and OPACH study (LaCroix et al., 2017). Briefly, OPACH participants were recruited from a subset of the WHI Clinical Trial or the Observational Study from 40 clinical sites throughout the United States from 1993 to 1998. WHI participants were followed annually until 2005, with extension studies that enrolled consenting participants for continued follow-up through 2010, 2015, and 2020. OPACH women were enrolled from March 2012 to April 2014 and followed through February 28, 2020, at the time of this analysis. All baseline covariate information was obtained using self-report questionnaires and an in-home clinical examination. Covariates from OPACH baseline assessments were used in the present analysis.

OPACH participants were provided an ActiGraph GT3X+ triaxial accelerometer (ActiGraph), which they were instructed to wear over their right hip for 24 hr/day (except when bathing or swimming) for 7 consecutive days. Participants reported in-bed and out-of-bed times using sleep logs on days of accelerometer wear. Of the 7,058 enrolled OPACH sample, 10 died before

receiving OPACH materials, 327 did not return the accelerometer, 232 returned the accelerometer with unusable data, and 363 had nonadherent wear (i.e., they did not wear accelerometers for at least 10 hr for 4 days, which is the recommended period for accurately measuring usual behavior; Migueles et al., 2017). Of the 6,126 with adherent accelerometer wear, 680 did not have genotyping data, yielding an analytic sample of 5,446 women for the present study (Figure 1). The WHI program, including the collection of genetic data, and the OPACH study were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board in Seattle, WA in accordance with the U.S. Department of Health and Human Services regulations at 45 CFR 46 (approval number 3467-EXT). All participants provided

informed consent either in writing, or via a telephone-based consent process.

Outcome: All-Cause Mortality

The primary outcome of interest was all-cause mortality from 2012 to 2014 baseline through February 28, 2020. In the WHI, mortality surveillance is conducted using annual mailed outcomes questionnaires supplemented by National Death Index searches, proxy queries, obituaries, and hospital records (Curb et al., 2003).

Exposures: PA and ST

The primary exposures of interest were time spent in light PA, MVPA, and total ST, defined as the average of each behavior over all adherent days. Accelerometer data were converted to 15-s epochs using ActiLife (version 6), processed using the Choi algorithm to flag nonwear time with a 90-min window, 30-min streamframe, and 2-min tolerance (Choi et al., 2011). The 15-s epochs allowed for lower misclassification of movement that may have been missed in longer epochs and is consistent with prior OPACH work (LaMonte et al., 2018). In-bed time was identified using sleep diaries. Awake-time epochs were classified into ST and PA intensities using cut points determined in a previous calibration study (Evenson, Wen, Herring, et al., 2015). Total PA was defined as movement resulting in energy expenditure ≥ 1.6 metabolic equivalents. PA intensity and ST minutes were categorized using calibrated cut points applied to 15-s epochs of vector magnitude accelerometer counts, as follows: light PA (1.6–2.9 metabolic equivalents) defined as 19–518 counts/15 s, MVPA (≥ 3.0 metabolic equivalents) as ≥ 519 counts/15 s, and total ST as ≤ 18 counts/15 s.

Effect Modifier: GRS for Longevity

The weighted GRS for longevity included three SNPs significantly associated with longevity in a large meta-analysis of 18 GWAS that included 11,262 cases surviving to the 90th percentile (defined by study population census data) and 25,483 controls of European ancestry: *rs429358*, *rs7412*, and *rs7676745* (Deelen et al., 2019). *rs429358* and *rs7412* are SNPs for the *APOE* gene (Mahley & Rall, 2000).

In the overall WHI sample, 27,131 women had relevant genotyping data from previous core and ancillary studies (see <https://www.whi.org/gwas>; accessed April 4, 2021; Supplementary Methods S1 [available online]). For the present study, directly genotyped SNPs were coded as 0, 1, or 2, indicating the number of longevity alleles present, and imputed SNPs used mean dosages between 0 and 2. The GRS was calculated by weighting the sum of longevity-influencing alleles for each SNP by their estimated effect sizes reported in the meta-analysis of GWAS described above (see Supplementary Methods S2 [available online]). We validated this GRS for longevity in the WHI cohort (described below).

Covariates

Covariates were selected based on previous literature (LaMonte et al., 2018) and included age (years), race/ethnicity (White, Black, and Hispanic), education (\leq high school, some college, and \geq college graduate), body mass index (BMI; kg/m^2), self-reported health

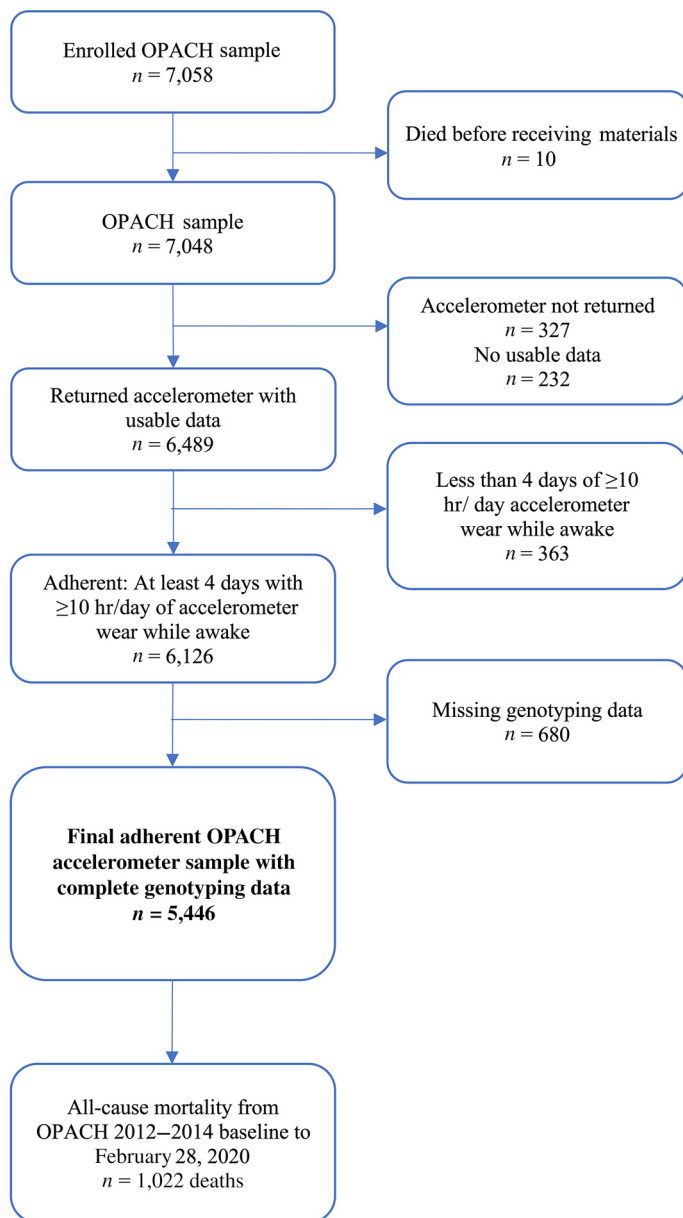


Figure 1 — Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram for derivation of analytic sample with accelerometer and genotyping data in the OPACH study, 2012–2014 baseline through February 28, 2020. OPACH = Objective Physical Activity and Cardiovascular Health.

status (excellent or very good, good, and fair or poor), physical functioning as defined by the RAND-36 questionnaire (Hays & Morales, 2001), alcohol consumption (nondrinker, <1, 1–4, and ≥5 drinks per week), smoking status (current and not current), and comorbidities (0, 1, and ≥2). Comorbidities were analyzed as the sum of nine chronic conditions present at or before accelerometer wear: cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cognitive impairment, depression, diabetes, frequent falls, and osteoarthritis (Rillamas-Sun et al., 2016).

Statistical Analysis

The GRS was split into tertiles (low, medium, or high genetic predisposition for longevity). Participant characteristics were described across tertiles of GRS and total PA. Comparisons across tertiles of GRS and total PA were performed using analysis of variance or Kruskal–Wallis tests for normally distributed and nonnormally distributed continuous variables, respectively, and Pearson's χ^2 for categorical variables.

The GRS was validated in the overall WHI sample and in the OPACH cohort. To validate the GRS in the present study, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for relations between the GRS for longevity and survival to age 90 versus death before this age using logistic regression models in OPACH ($n = 1,641$) and the overall WHI sample ($n = 11,660$). Women who were born on or before February 28, 1930, who had the ability to survive to age 90 as of the last date of follow-up, were eligible to be included in this analysis. Both models adjusted for age, race/ethnicity, and the first five principal components (PCs) to control for population stratification (i.e., differences in allele frequency due to ancestry) and account for genetic ancestry (Price et al., 2006).

Associations of PA and ST with mortality were estimated using Cox proportional hazards regression models. Time to mortality was defined as number of days from first day of accelerometer wear at OPACH baseline to date of death, loss to follow-up, or February 28, 2020, whichever came first. Two sequentially adjusted models were computed. Model 1 adjusted for accelerometer wear time, age, race/ethnicity, education, BMI, smoking status, self-reported health status, alcohol consumption, and comorbidities. Model 2 additionally adjusted for physical functioning. To examine whether these associations varied by a GRS for longevity, we stratified models by GRS tertiles. Two sequentially adjusted models were computed. Model 1 adjusted for accelerometer wear time, age, race/ethnicity, and the first five PCs to control for population stratification; Model 2 additionally adjusted for education, BMI, smoking status, self-reported health status, alcohol consumption, comorbidities, and physical functioning. To test for effect modification by GRS, Wald test statistics compared Model 2 with and without a multiplicative interaction term between continuous PA/ST and GRS using p values for interaction ($p_{\text{interaction}}$). Linear trends for PA and ST were evaluated by treating PA and ST as continuous variables in the models using p values for trend (p_{trend}). To account for missing covariate data, we employed multiple imputation analysis by chained equations using the *mice* package (van Buuren & Groothuis-Oudshoorn, 2011). There were nine imputed data sets, corresponding to the highest proportion of covariate missingness (i.e., 9% missing smoking status). For visualization, we plotted dose–response associations of PA/ST with mortality by GRS tertiles using complete case, cubic spline analysis with the *rms* package (Harrell, 2020). We used Akaike's information criterion to help

determine whether three or four knots provided the optimal fit, and used three knots at the 10th, 50th, and 90th percentiles (Harrell, 2015). The proportional hazards assumption was tested using Schoenfeld residuals; no violations of this assumption were observed (Therneau et al., 2021).

Several sensitivity analyses were performed. To evaluate potential survival bias due to selection of older women, we plotted survival curves by GRS tertiles for the first 10 years of WHI enrollment and among those who survived >10 years, which was approximately the time of OPACH enrollment. We also plotted survival curves based on Cox proportional hazards regression models adjusted for age, race/ethnicity, and the first five principal components in OPACH. To evaluate reverse causation, primary analyses were repeated after excluding participants who died within 2 years of OPACH baseline. Because GRS SNPs were derived from individuals of European descent, primary analyses were repeated after restricting to women of White race/ethnicity. Finally, we tested interactions between PA/ST and the *APOE* $\epsilon 2/\epsilon 4$ genotype given their contribution to the GRS (Deelen et al., 2019).

All statistical analyses were conducted in R (version 4.0.3; R Core Team, 2020). Statistical tests were two-tailed, and p values were considered significant at $p < .05$.

Results

Descriptive Characteristics

Of the 5,446 women in the analytic sample, there were 1,022 deaths during 33,350 person-years of follow-up (mean follow-up = 6.1 years; range = 0.1–7.9 years). Based on GRS tertile distributions in the WHI ($N = 27,131$), 36.0% of OPACH women were classified as high genetic predisposition for longevity (i.e., high GRS), 33.1% as medium GRS for longevity, and 30.9% as low GRS for longevity (Table 1). The number of deaths (rate per 1,000 person-years) in the low, medium, and high GRS groups were 295 (28.6), 381 (34.6), and 346 (28.8), respectively. Women in the low GRS group were younger, had higher physical functioning scores, lower ST time, higher total PA time, and higher light PA time relative to other GRS groups. Women in the low GRS group were more likely to be of Black race/ethnicity (42.4%) than the medium and high GRS groups. Women of White race/ethnicity constituted most of the medium (55.8%) and high (42.7%) GRS groups compared with the low GRS group.

Women in the highest tertile of accelerometer-measured total PA were younger, rated their health more favorably, and reported fewer comorbidities compared with women in the lower total PA tertiles (Table 2). They were also least likely to be current smokers but reported more alcohol consumption than women in the lower tertiles of PA. They had greater physical functioning scores and lower BMI. GRS for longevity did not vary across total PA tertiles.

Validation of GRS

The GRS for longevity was associated with survival to age 90 in the overall WHI ($p_{\text{trend}} < .001$) and OPACH ($p_{\text{trend}} = .04$; Supplementary Table S1 [available online]). WHI women in the medium GRS group had 29% (OR = 1.29, 95% CI [1.18, 1.41]) higher odds of survival to age 90 (vs. death before this age) relative to the low GRS group. WHI women in the high GRS group had 37% (OR = 1.37, 95% CI [1.25, 1.50]) higher odds of survival to age 90 compared to the low GRS group. In OPACH,

Table 1 Baseline Sociodemographic and Health-Related Characteristics by GRS for Longevity Among OPACH Participants, 2012–2014 (N = 5,446)

Characteristics	Teriles of GRS for longevity ^a			p ^b
	Low (n = 1,681)	Medium (n = 1,804)	High (n = 1,961)	
Age (years)	77.6 (6.7)	79.1 (6.5)	78.0 (6.5)	<.001
Follow-up time (years), median (IQR)	6.5 (1.3)	6.7 (1.3)	6.6 (1.3)	.63
Accelerometer wear time (hr/day)	14.86 (1.3)	14.92 (1.3)	14.89 (1.3)	.37
Race/ethnicity, n (%)				<.001
White	686 (40.8%)	1,006 (55.8%)	838 (42.7%)	
Black	713 (42.4%)	448 (24.8%)	765 (39.0%)	
Hispanic	282 (16.8%)	350 (19.4%)	358 (18.3%)	
Highest education level, n (%)				.37
≤ High school/GED	324 (19.4%)	377 (21.0%)	409 (21.0%)	
Some college	638 (38.2%)	706 (39.4%)	728 (37.5%)	
≥ College graduate	710 (42.5%)	710 (39.6%)	807 (41.5%)	
BMI (kg/m ²), median (IQR)	27.2 (7.4)	27.2 (7.0)	27.5 (7.1)	.07
Self-reported health status				.56
Excellent or very good	859 (51.3%)	939 (52.2%)	969 (49.5%)	
Good	659 (39.4%)	688 (38.3%)	793 (40.5%)	
Fair or poor	156 (9.3%)	171 (9.5%)	194 (9.9%)	
Comorbidities, ^c n (%)				.58
0	388 (23.1%)	401 (22.2%)	439 (22.4%)	
1	673 (40.0%)	700 (38.8%)	748 (38.1%)	
≥2	620 (36.9%)	703 (39.0%)	774 (39.5%)	
Physical functioning (RAND-36), median (IQR)	80.0 (35.0)	75.0 (40.0)	75.0 (40.0)	.007
Alcohol consumption (per week)				.07
Nondrinker	604 (40.1%)	588 (35.3%)	677 (37.8%)	
<1 drink	498 (33.1%)	578 (34.7%)	627 (35.0%)	
1–4 drinks	254 (16.9%)	293 (17.6%)	305 (17.0%)	
≥5 drinks	149 (9.9%)	205 (12.3%)	182 (10.2%)	
Smoking status, n (%)				.92
Not current	1,457 (97.0%)	1,619 (97.2%)	1,735 (97.2%)	
Current	45 (3.0%)	46 (2.8%)	50 (2.8%)	
Total ST (min/day)	546.2 (100.2)	558.6 (97.9)	556.1 (100.5)	<.001
PA (min/day)				
Total	345.1 (98.2)	336.5 (97.4)	337.4 (96.5)	.02
Light	292.6 (77.3)	286.1 (78.3)	286.5 (76.6)	.02
Moderate to vigorous, median (IQR)	45.8 (45.5)	43.0 (43.5)	44.2 (44.9)	.46

Note. Total ST is average minutes per day with accelerometer counts of ≤18 counts/15 s. Total PA is defined as average minutes per day with accelerometer counts of ≥18 counts/15 s, low light PA is 19–225 counts/15 s, high light PA is 226–518 counts/15 s, and moderate to vigorous PA is ≥519 counts/15 s. n missing: education = 37 (0.7%), BMI = 346 (6.4%), self-reported health status = 18 (0.3%), physical functioning = 60 (1.1%), alcohol consumption = 486 (8.9%), and smoking status = 494 (9.1%). BMI = body mass index; GED = General Educational Development; IQR = interquartile range; OPACH = Objective Physical Activity and Cardiovascular Health; PA = physical activity; ST = sedentary time; WHI = Women's Health Initiative; GRS = genetic risk score.

^aHigher GRS is indicative of higher genetic predisposition for longevity. Tertile cut points based on larger WHI population with genetic data, resulting in slightly uneven tertiles in OPACH study. ^bThe p value derived from F tests or Kruskal–Wallis tests for continuous variables or χ^2 categorical variables. ^cComorbidities is defined as the sum of the following chronic conditions present at or before accelerometer wear: cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cognitive impairment, depression, diabetes, frequent falls, and osteoarthritis.

the odds of survival to age 90 were 68% (OR = 1.68, 95% CI [1.14, 2.48]) higher for the high compared to low GRS group.

Association Between Light PA, MVPA, and ST With Mortality

Accelerometer-measured amounts of light PA and MVPA per day were inversely associated with mortality ($p_{\text{trend}} < .001$, all;

Table 3). After adjusting for accelerometer wear time, age, race/ethnicity, education, BMI, smoking status, self-reported health status, alcohol consumption, and comorbidities, women in higher quartiles of light PA had lower risk of mortality compared with the lowest quartile of light PA (Quartiles 2, 3, and 4 hazard ratios [HRs] [95% CI] vs. Quartile 1: 0.72 [0.61, 0.84]; 0.70 [0.59, 0.84]; 0.55 [0.45, 0.67]). These associations were attenuated but remained statistically significant after further

Table 2 Baseline Sociodemographic and Health-Related Characteristics by Tertiles of Total PA Among OPACH Participants, 2012–2014 (N = 5,446)

Characteristics	Tertiles of total PA ^a			p ^b
	T1 (n = 1,816)	T2 (n = 1,815)	T3 (n = 1,815)	
GRS for longevity, median (IQR)	1.8 (0.2)	1.8 (0.2)	1.8 (0.3)	.17
Age (years)	80.2 (6.5)	78.0 (6.4)	76.4 (6.3)	<.001
Accelerometer wear time (hr/day)	14.4 (1.3)	14.9 (1.2)	15.4 (1.1)	<.001
Race/ethnicity, n (%)				<.001
White	1,000 (55.1%)	815 (44.9%)	715 (39.4%)	
Black	604 (33.3%)	675 (37.2%)	647 (35.7%)	
Hispanic	212 (11.7%)	325 (17.9%)	453 (25.0%)	
Highest education level, n (%)				.005
≤High school/GED	384 (21.3%)	352 (19.6%)	374 (20.7%)	
Some college	735 (40.8%)	688 (38.2%)	649 (35.9%)	
≥College graduate	681 (37.8%)	760 (42.2%)	786 (43.5%)	
BMI (kg/m ²), median (IQR)	29.2 (8.1)	27.4 (6.8)	25.7 (6.0)	<.001
Self-reported health status				<.001
Excellent or very good	704 (38.9%)	956 (52.9%)	1,107 (61.2%)	
Good	836 (46.2%)	706 (39.0%)	598 (33.0%)	
Fair or poor	269 (14.9%)	147 (8.1%)	105 (5.8%)	
Comorbidities, ^c n (%)				<.001
0	294 (16.2%)	411 (22.6%)	523 (28.8%)	
1	643 (35.4%)	729 (40.2%)	749 (41.3%)	
≥2	879 (48.4%)	675 (37.2%)	543 (29.9%)	
Physical functioning (RAND-36), median (IQR)	60.0 (45.0)	80.0 (35.0)	85.0 (25.0)	<.001
Alcohol consumption (per week)				<.001
Nondrinker	704 (43.4%)	606 (36.5%)	559 (33.4%)	
<1 drink	565 (34.8%)	597 (35.9%)	541 (32.3%)	
1–4 drinks	209 (12.9%)	294 (17.7%)	349 (20.8%)	
≥5 drinks	146 (9.0%)	164 (9.9%)	226 (13.5%)	
Smoking status, n (%)				.02
Not current	1,564 (96.3%)	1,609 (97.2%)	1,638 (98.0%)	
Current	60 (3.7%)	47 (2.8%)	34 (2.0%)	

Note. Total PA is defined as average minutes per day with accelerometer counts of ≥18 counts/15 s, low light PA is 19–225 counts/15 s, high light PA is 226–518 counts/15 s, and moderate to vigorous PA is ≥519 counts/15 s. n missing: education = 37 (0.7%), BMI = 346 (6.4%), self-reported health status = 18 (0.3%), physical functioning = 60 (1.1%), alcohol consumption = 486 (8.9%), and smoking status = 494 (9.1%). BMI = body mass index; GED = General Educational Development; IQR = interquartile range; OPACH = Objective Physical Activity and Cardiovascular Health; PA = physical activity; T = tertiles; GRS = genetic risk score.

^aTotal physical activity (min/day) tertiles are defined as follows: T1 ≤ 295.58, T2 = 295.59–379.42, and T3 ≥ 379.43. ^bThe p value derived from F tests or Kruskal–Wallis tests for continuous variables or χ^2 categorical variables. ^cComorbidities is defined as the sum of the following chronic conditions present at or before accelerometer wear: cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cognitive impairment, depression, diabetes, frequent falls, and osteoarthritis.

adjustment for physical functioning. For MVPA, women in higher quartiles of MVPA had lower risk of mortality compared with the lowest quartile of MVPA in fully adjusted models (Quartiles 2, 3, and 4 HRs [95% CI] vs. Quartile 1: 0.76 [0.65, 0.90]; 0.60 [0.49, 0.73]; 0.46 [0.36, 0.58]).

Higher ST per day was associated with higher mortality risk ($p_{\text{trend}} < .001$; Table 4). After adjusting for accelerometer wear time, age, race/ethnicity, education, BMI, smoking status, self-reported health status, alcohol consumption, and comorbidities, women in higher quartiles of ST had higher risk of mortality compared with the lowest quartile of ST (Quartiles 2, 3, and 4 HRs [95% CI] vs. Quartile 1: 1.22 [0.99, 1.50]; 1.69 [1.38, 2.07]; 2.05 [1.65, 2.56]). Associations remained statistically significant after further adjustment for physical functioning.

Association Between Light PA and MVPA With Mortality by GRS Categories

Inverse associations between PA and mortality followed a similar pattern after stratification by GRS tertiles (Table 5; shown in Figure 2). Among women in the high GRS group, the highest quartile of light PA was associated with 56% (HR = 0.44, 95% CI [0.31, 0.63]) lower risk of mortality compared with the lowest quartile, after adjustment for accelerometer wear time, age, race/ethnicity, and the first five PCs. This association was slightly attenuated but remained statistically significant after further adjustment for education, BMI, smoking status, self-reported health status, alcohol consumption, comorbidities, and physical functioning (HR = 0.55, 95% CI [0.38, 0.80]). In the high GRS group, the

Table 3 Hazard Ratios and 95% CIs Relating PA With Mortality: OPACH Women Enrolled in 2012–2014 and Followed Through February 28, 2020 (N = 5,446)

	Quartiles of PA				p value for trend ^a
	Q1	Q2	Q3	Q4	
	(n = 1,362)	(n = 1,362)	(n = 1,361)	(n = 1,361)	
Light PA					
Mortality events, n (rate)	399 (51.0)	258 (30.9)	207 (24.4)	158 (18.2)	
Model 1	1.00 [reference]	0.72 [0.61, 0.84]	0.70 [0.59, 0.84]	0.55 [0.45, 0.67]	<.001
Model 2	1.00 [reference]	0.76 [0.64, 0.89]	0.75 [0.63, 0.90]	0.59 [0.48, 0.72]	<.001
MVPA					
Mortality events, n (rate)	482 (63.9)	267 (32.0)	169 (19.5)	104 (11.8)	
Model 1	1.00 [reference]	0.72 [0.62, 0.84]	0.55 [0.45, 0.66]	0.41 [0.32, 0.52]	<.001
Model 2	1.00 [reference]	0.76 [0.65, 0.90]	0.60 [0.49, 0.73]	0.46 [0.36, 0.58]	<.001

Note. Measures of effect from multivariable Cox proportional hazards regression models. Light PA (min/day) Q are defined as follows: Q1 ≤ 233.96; Q2 = 233.97–287.13; Q3 = 287.14–337.94; Q4 ≥ 337.95. Moderate to vigorous PA (min/day) Q are defined as follows: Q1 ≤ 25.17; Q2 = 25.18–44.33; Q3 = 44.34–69.75; Q4 ≥ 69.76. Data for mortality events are n (crude rate per 1,000 person-years). Model 1 includes PA as the exposure of interest and adjusts for accelerometer wear time, age, race/ethnicity, education, BMI, smoking status, self-reported health status, alcohol consumption, and comorbidities. Model 2 includes Model 1 and additionally adjusts for physical functioning. Comorbidities are defined as the sum of the following chronic conditions present at or before accelerometer wear: cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cognitive impairment, depression, diabetes, frequent falls, and osteoarthritis. BMI = body mass index; OPACH = Objective Physical Activity and Cardiovascular Health; PA = physical activity; Q = quartile; CI = confidence interval; MVPA = moderate to vigorous PA.

^ap values from Cox multivariable regression models using continuous light PA or moderate to vigorous PA.

Table 4 Hazard Ratios and 95% CIs Relating ST With Mortality: OPACH Women Enrolled in 2012–2014 and Followed Through February 28, 2020 (N = 5,446)

	Quartiles of ST				p value for trend ^a
	Q1	Q2	Q3	Q4	
	(n = 1,362)	(n = 1,362)	(n = 1,361)	(n = 1,361)	
Mortality events, n (rate)	168 (19.4)	216 (25.4)	294 (35.9)	344 (42.9)	
Model 1	1.00 [reference]	1.22 [0.99, 1.50]	1.69 [1.38, 2.07]	2.05 [1.65, 2.56]	<.001
Model 2	1.00 [reference]	1.17 [0.95, 1.43]	1.59 [1.30, 1.96]	1.83 [1.47, 2.29]	<.001

Note. Measures of effect from multivariable Cox proportional hazards regression models. ST (min/day) Q are defined as follows: Q1 ≤ 489.04; Q2 = 489.05–555.85; Q3 = 555.86–620.50; Q4 ≥ 620.51. Data for mortality events are n (crude rate per 1,000 person-years). Model 1 includes ST as the exposure of interest and adjusts for accelerometer wear time, age, race/ethnicity, education, BMI, smoking status, self-reported health status, alcohol consumption, and comorbidities. Model 2 includes Model 1 and additionally adjusts for physical functioning. Comorbidities are defined as the sum of the following chronic conditions present at or before accelerometer wear: cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cognitive impairment, depression, diabetes, frequent falls, and osteoarthritis. BMI = body mass index; OPACH = Objective Physical Activity and Cardiovascular Health; ST = sedentary time; Q = quartile; CI = confidence interval.

^ap values from Cox multivariable regression models using continuous ST.

highest quartile of MVPA was associated with 57% (HR = 0.43; 95% CI [0.28, 0.65]) lower risk of mortality relative to the lowest quartile in fully adjusted models. In the low GRS group, the highest versus the lowest quartile of MVPA was associated with 51% (HR = 0.49; 95% CI [0.30, 0.77]) lower mortality risk in fully adjusted models. Interactions between continuous light PA ($p_{\text{interaction}} = .66$) and MVPA ($p_{\text{interaction}} = .24$) with the GRS were not statistically significant.

Association Between ST and Mortality by GRS Categories

Associations were similar across GRS categories (Table 5, shown in Figure 2). Among women in the high GRS group, the highest total ST quartile had 2.91 (95% CI [2.01, 4.21]) times higher risk of mortality compared with the lowest quartile after adjustment for accelerometer wear time, age, race/ethnicity, and the first five PCs.

This association was attenuated but remained statistically significant in fully adjusted models (HR = 1.99, 95% CI [1.34, 2.95]). The interaction between continuous ST and the GRS was not statistically significant ($p_{\text{interaction}} = .64$).

Sensitivity Analyses

Women in the high GRS group had the highest survival probabilities in WHI and OPACH (Supplementary Figures S1 and S2 [available online]). After excluding deaths within the first 2 years of follow-up, HRs for associations of light PA, MVPA, and ST with mortality across all GRS categories were slightly attenuated (Supplementary Table S2 [available online]). Analyses repeated after restriction to White women yielded similar results (Supplementary Table S3 [available online]). Interactions of PA/ST with APOE ε2 or ε4 were not statistically significant (Supplementary Table S4 [available online]).

Table 5 Hazard Ratios and 95% CIs Relating PA and ST With Mortality Stratified by GRS for Longevity: OPACH Women Enrolled in 2012–2014 and Followed Through February 28, 2020 (N = 5,446)

	Teriles of GRS for longevity ^a			<i>p</i> _{interaction} ^b
	Low (n = 1,681)	Medium (n = 1,804)	High (n = 1,961)	
Mortality events, <i>n</i> (rate per 1,000 person-years)	295 (28.6)	381 (34.6)	346 (28.8)	
PA ^c				
Light				.66
Model 1				
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	
Q2	0.80 [0.59, 1.08]	0.60 [0.47, 0.78]	0.71 [0.54, 0.94]	
Q3	0.76 [0.55, 1.06]	0.49 [0.36, 0.66]	0.74 [0.55, 0.99]	
Q4	0.57 [0.40, 0.83]	0.53 [0.39, 0.72]	0.44 [0.31, 0.63]	
Model 2				
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	
Q2	0.84 [0.61, 1.14]	0.65 [0.50, 0.86]	0.74 [0.56, 0.98]	
Q3	0.82 [0.58, 1.15]	0.56 [0.41, 0.77]	0.91 [0.67, 1.24]	
Q4	0.59 [0.40, 0.87]	0.58 [0.41, 0.81]	0.55 [0.38, 0.80]	
Moderate to vigorous				.24
Model 1				
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	
Q2	0.83 [0.62, 1.10]	0.64 [0.50, 0.82]	0.49 [0.38, 0.65]	
Q3	0.59 [0.42, 0.83]	0.43 [0.31, 0.58]	0.40 [0.29, 0.55]	
Q4	0.39 [0.25, 0.60]	0.34 [0.24, 0.49]	0.28 [0.19, 0.41]	
Model 2				
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	
Q2	0.93 [0.69, 1.25]	0.78 [0.60, 1.01]	0.61 [0.46, 0.81]	
Q3	0.71 [0.50, 1.02]	0.55 [0.40, 0.77]	0.56 [0.40, 0.77]	
Q4	0.49 [0.30, 0.77]	0.47 [0.32, 0.69]	0.43 [0.28, 0.65]	
Total ST ^d				.64
Model 1				
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	
Q2	0.90 [0.62, 1.31]	1.21 [0.86, 1.69]	1.73 [1.21, 2.49]	
Q3	1.58 [1.12, 2.23]	1.81 [1.29, 2.53]	2.27 [1.59, 3.23]	
Q4	1.83 [1.27, 2.65]	2.28 [1.62, 3.21]	2.91 [2.01, 4.21]	
Model 2				
Q1	1.00 [reference]	1.00 [reference]	1.00 [reference]	
Q2	0.86 [0.59, 1.26]	1.17 [0.83, 1.66]	1.46 [1.01, 2.11]	
Q3	1.54 [1.07, 2.22]	1.58 [1.11, 2.23]	1.74 [1.21, 2.50]	
Q4	1.72 [1.14, 2.60]	1.81 [1.25, 2.63]	1.99 [1.34, 2.95]	

Note. Measures of effect from multivariable Cox proportional hazards regression models. *p* for trend for light PA, moderate to vigorous PA, or ST for all 18 models < .01. Model 1 adjusts for accelerometer wear time, age, race/ethnicity, and the first five principal components to control for population stratification. Model 2 includes Model 1 and additionally adjusts for education, BMI, smoking status, self-reported health status, alcohol consumption, comorbidities, and physical functioning. Comorbidities are defined as the sum of the following chronic conditions present at or before accelerometer wear: cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cognitive impairment, depression, diabetes, frequent falls, and osteoarthritis. BMI = body mass index; GRS = genetic risk score; PA = physical activity; OPACH = Objective Physical Activity and Cardiovascular Health; ST = sedentary time; Q = quartile; CI = confidence interval.

^aHigher GRS is indicative of higher genetic predisposition for longevity. ^b*p*_{interaction} corresponds to the Wald test statistic comparing the Model 2 with and without the interaction continuous PA/ST by GRS terms. ^cLight PA (min/day) Q are defined as follows: Q1 ≤ 233.96; Q2 = 233.97–287.13; Q3 = 287.14–337.94; Q4 ≥ 337.95. Moderate to vigorous PA (min/day) Q are defined as follows: Q1 ≤ 25.17; Q2 = 25.18–44.33; Q3 = 44.34–69.75; Q4 ≥ 69.76. ^dST (min/day) Q are defined as follows: Q1 ≤ 489.04; Q2 = 489.05–555.85; Q3 = 555.86–620.50; Q4 ≥ 620.51.

Discussion

In this prospective study of 5,446 older women, higher accelerometer-measured light PA and MVPA were associated with lower risk of mortality, and higher ST was associated with higher risk of mortality, during an average follow-up of 6.1 years. Furthermore,

we found that these associations persisted irrespective of one's genetic predisposition for longevity. These findings extend previous OPACH studies with shorter follow-up (LaMonte et al., 2018) and provide strong support for the importance of engaging in PA to lower risk of mortality among older women.

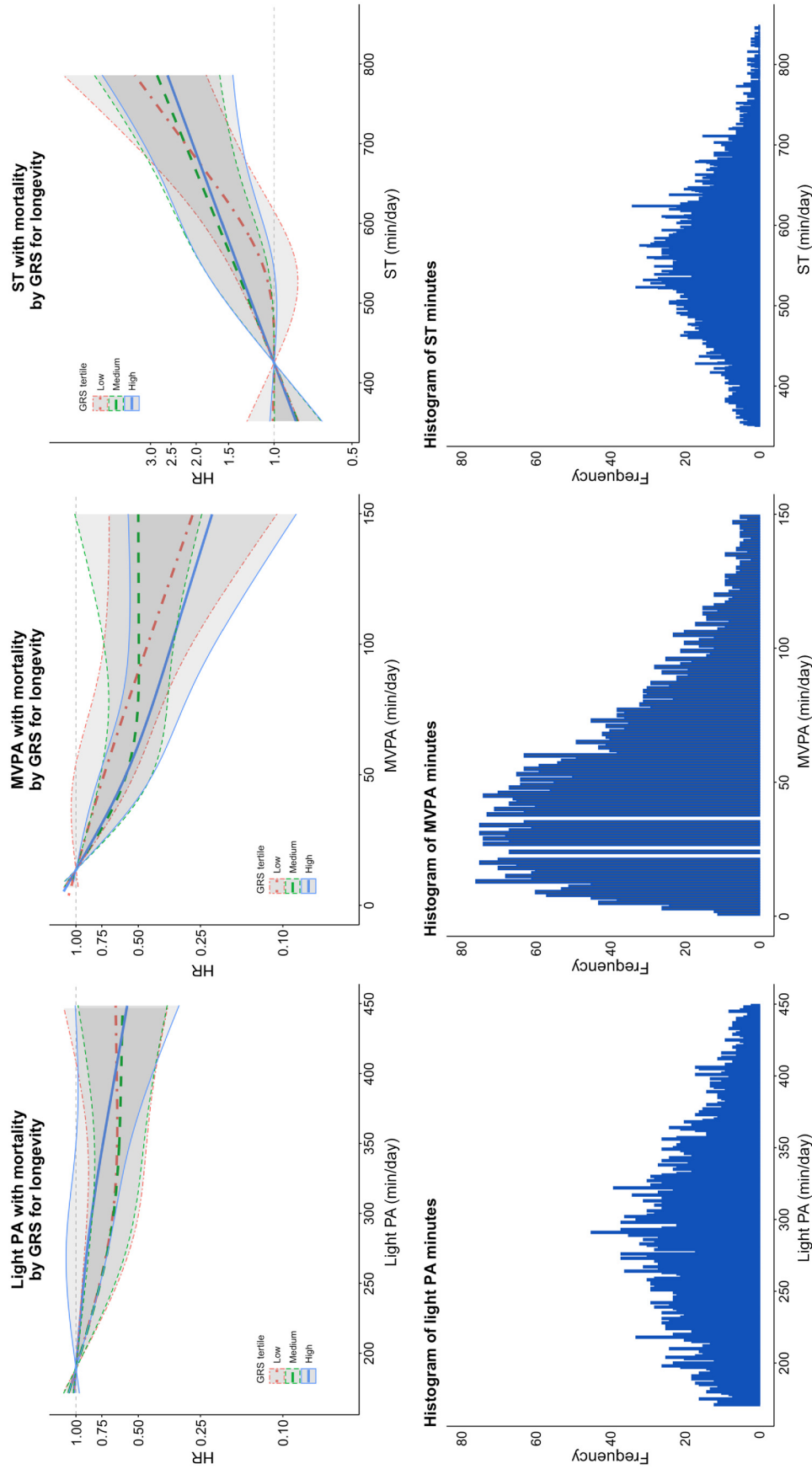


Figure 2 — Continuous dose-response association of PA and ST with mortality stratified by GRS for longevity tertiles for longevity among OPACH women enrolled in 2012–2014 and followed through February 28, 2020 ($N = 5,446$). Red and dot dashed, green and dashed, and blue and solid lines indicate low, medium, and high GRS tertiles, respectively. Dose-response curves are derived from multivariable Cox proportional hazards regression models for each GRS for longevity group (low/medium/high). The 10th percentile of each behavior is treated as the reference category for each GRS subgroup. Dose-response plots are trimmed at the first and 99th percentile. All models are adjusted for the first five principal components to control for population stratification, accelerometer wear time, age, race/ethnicity, education, BMI, smoking status, self-reported health status, alcohol consumption, comorbidities, and physical functioning. Comorbidities are defined as the sum of the following chronic conditions present at or before accelerometer wear: cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cognitive impairment, depression, diabetes, frequent falls, and osteoarthritis. n missing: education = 37 (0.7%); BMI = 346 (6.4%); self-reported health status = n (0.3%); physical functioning = 60 (1.1%); alcohol consumption = 486 (8.9%); and smoking status = 494 (9.1%). OPACH = Objective Physical Activity and Cardiovascular Health; PA = physical activity; ST = sedentary time; GRS = genetic risk score; BMI = body mass index; MVPA = moderate to vigorous PA; HR = hazard ratios.

The current findings suggest that there was little, if any, variation in the association of accelerometer-measured PA and ST with mortality according to a longevity GRS. Because survival into advanced age was an inherent characteristic of women who enrolled in OPACH and completed accelerometer assessments of free-living PA and ST, it is plausible that genetic survival advantage may be a key factor underlying mortality risks attributed to greater PA or ST (Dato et al., 2017; Rankinen & Bouchard, 2007). However, results of the present study indicate that a GRS, based on three selected SNPs, did not modify the strong multivariable adjusted associations with all-cause mortality for either PA or ST among women at older age.

Our results align with literature showing that greater light PA and MVPA are associated with lower risk of mortality among middle-aged and older adults (Ekelund et al., 2019), including older women (LaMonte et al., 2018). In a meta-analysis of 36,383 participants from eight studies (Ekelund et al., 2019), accelerometer-measured light PA and MPVA were associated with 62% and 48% lower risk of mortality at the highest (vs. the lowest) quartiles of activity, respectively. Additionally, our results align with evidence showing that the highest (vs. the lowest) quartiles of ST were associated with greater risk of mortality in middle-aged and older adults (Diaz et al., 2017; Ekelund et al., 2019). Given the aging of the U.S. adult population (Medina et al., 2020) and longer time spent in lower intensity activities (LaMonte et al., 2018; Matthews et al., 2008), these results support recommendations that older women should engage in PA, regardless of intensity, to reduce their mortality risk.

Because genetic factors likely contribute both to longevity (Deelen et al., 2019) and PA habits (Lin et al., 2017), it is possible that genes modify associations between PA and longevity (Rankinen & Bouchard, 2007). However, we did not find statistically significant interactions between PA or ST with the GRS for longevity, possibly due to inadequate power or unaccounted rare longevity-influencing variants (Broer et al., 2015). Several prior studies have examined gene by environment ($G \times E$) interactions in the relationships between PA and adverse health outcomes. For example, in $G \times E$ studies of PA and cognition, others found that relations between PA and cognitive decline (Stringa et al., 2020) and Alzheimer's disease (Luck et al., 2014) did not vary by *APOE* $\epsilon 4$ status. Another study found lifestyle factors (e.g., cigarette smoking, regular exercise) in relation to lifespan did not vary by a BMI GRS (Sakaue et al., 2020). In another study, genes for physical fitness did not modify associations between PA and coronary heart disease risk (Chomistek et al., 2013). These findings taken together with our results highlight the importance of engaging in PA and positive lifestyle behaviors to reduce risk of disease and premature mortality even among those who may have genetic traits that may be associated with certain health outcomes.

This study has some limitations. In this study, total ST is classified based on a calibrated cut point that captures all waking time spent below the threshold of light PA. Accelerometers may not be sensitive to posture, thus potentially misclassifying standing still as ST (Lyden et al., 2012). More sophisticated methods of processing accelerometer data are emerging that should improve accurate classification of ST in the future (Greenwood-Hickman et al., 2021). Such methods are likely to amplify the associations seen in the present study. In addition, our findings may have been biased by reverse causation due to changes in PA that possibly influenced factors underlying mortality. However, excluding women who died within the first 2 years of follow-up yielded similar results. The OPACH cohort included 33% Black women

and 17% Hispanic women; however, we were not powered to examine GRS by PA/ST interactions within strata of race/ethnicity. Moreover, our GRS was derived from European populations and may not apply to non-European populations. Future GWAS are needed to identify longevity-associated SNPs specific to diverse populations (Sirugo et al., 2019). Notably, previous OPACH reports have shown similar associations between PA and ST behaviors and mortality (LaMonte et al., 2018), incident cardiovascular disease (Bellettiere, Lamonte, et al., 2019; LaCroix et al., 2019), and diabetes (Bellettiere, Healy, et al., 2019) in White, Black, and Hispanic women. Because our study population included older women in WHI, generalizability of these results to men and other populations are unknown and should be investigated. Future studies should also evaluate sex differences, as other studies have reported sex differences in genetic associations with longevity (Zeng et al., 2018).

Our study has several strengths. Data were obtained from women in the OPACH study, a large, diverse, and well-characterized cohort of older women across the United States with long-term follow-up. The longitudinal data set allowed for sufficient sample size to assess associations across three GRS for longevity groups. Additionally, PA and ST were measured objectively using accelerometry and cut points specific to older women (Evenson, Wen, Herring, et al., 2015), allowing us to minimize recall bias and measurement error, which often occur with self-reported PA and ST (Sylvia et al., 2014), especially among older adults (Evenson, Wen, Metzger, et al., 2015).

In conclusion, among older women, higher accelerometer-measured light PA and MVPA were associated with lower risk of mortality, and higher accelerometer-measured ST was associated with higher risk of mortality during an average follow-up of 6.1 years. Findings were consistent across categories of a GRS for longevity. These results offer strong support that PA at older ages is associated with reduced risk of death. The complexity of longevity warrants further $G \times E$ interaction studies to improve our understanding of longevity, cause-specific mortality, and the intersecting roles of genes and lifestyle behaviors in achieving a long and healthy life.

Acknowledgments

The OPACH Study is funded by the National Heart, Lung, and Blood Institute; National Institutes of Health; and U.S. Department of Health and Human Services through RO1 HL105065 (PI: LaCroix). Funding also came from two grants supported by the National Institute on Aging: A program project (P01 AG052352 to LaCroix) and a T32 Predoctoral Training Fellowship (T32 AG058529 to Posis). The WHI program is funded by the National Heart, Lung, and Blood Institute; National Institutes of Health; and U.S. Department of Health and Human Services through 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, and 75N92021D00005. All funding agencies had no role in the design of the study and collection, analysis, or interpretation of the data and no role in writing the manuscript. The authors would like to acknowledge the WHI participants and staff for their participation. The authors would also like to acknowledge the WHI investigators in the short list below. The full list can be found at the following site: <https://s3-us-west-2.amazonaws.com/www-who-org/wp-content/uploads/WHI-Investigator-Long-List.pdf>. The WHI investigators: Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, 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, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner. WHI Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland.

References

- Almeida, O.P., Khan, K.M., Hankey, G.J., Yeap, B.B., Golledge, J., & Flicker, L. (2014). 150 minutes of vigorous physical activity per week predicts survival and successful ageing: A population-based 11-year longitudinal study of 12 201 older Australian men. *British Journal of Sports Medicine*, 48(3), 220–225. <https://doi.org/10.1136/bjsports-2013-092814>
- Anderson, G.L., Manson, J., Wallace, R., Lund, B., Hall, D., Davis, S., Shumaker, S., Wang, C.Y., Stein, E., & Prentice, R.L. (2003). Implementation of the Women's Health Initiative study design. *Annals of Epidemiology*, 13(9), S5–S17. [https://doi.org/10.1016/S1047-2797\(03\)00043-7](https://doi.org/10.1016/S1047-2797(03)00043-7)
- Bellettiere, J., Healy, G.N., LaMonte, M.J., Kerr, J., Evenson, K.R., Rillamas-Sun, E., Di, C., Buchner, D.M., Hovell, M.F., & LaCroix, A.Z. (2019). Sedentary behavior and prevalent diabetes in 6,166 older women: The objective physical activity and cardiovascular health study. *The Journals of Gerontology: Series A, Biological Sciences and Medical Sciences*, 74(3), 387–395. <https://doi.org/10.1093/gerona/gy101>
- Bellettiere, J., Lamonte, M.J., Evenson, K.R., Rillamas-Sun, E., Kerr, J., Lee, I.M., Di, C., Rosenberg, D.E., Stefanick, M.L., Buchner, D.M., Hovell, M.F., & Lacroix, A.Z. (2019). Sedentary behavior and cardiovascular disease in older women: The OPACH study. *Circulation*, 139(8), 1036–1046. <https://doi.org/10.1161/CIRCULATION.AHA.118.035312>
- Broer, L., Buchman, A.S., Deelen, J., Evans, D.S., Faul, J.D., Lunetta, K.L., Sebastiani, P., Smith, J.A., Smith, A.V., Tanaka, T., Yu, L., Arnold, A.M., Aspelund, T., Benjamin, E.J., De Jager, P.L., Eiriksdottir, G., Evans, D.A., Garcia, M.E., Hofman, A., . . . Murabito, J.M. (2015). GWAS of longevity in CHARGE Consortium confirms APOE and FOXO3 candidacy. *The Journals of Gerontology: Series A*, 70(1), 110–118. <https://doi.org/10.1093/gerona/glu166>
- Choi, L., Liu, Z., Matthews, C.E., & Buchowski, M.S. (2011). Validation of accelerometer wear and nonwear time classification algorithm. *Medicine & Science in Sports & Exercise*, 43(2), 357–364. <https://doi.org/10.1249/MSS.0b013e3181ed61a3>
- Chomistek, A.K., Chasman, D.I., Cook, N.R., Rimm, E.B., & Lee, I.M. (2013). Physical activity, genes for physical fitness, and risk of coronary heart disease. *Medicine & Science in Sports & Exercise*, 45(4), 691–697. <https://doi.org/10.1249/MSS.0b013e3182784e9f>
- Curb, J.D., Mctiernan, A., Heckbert, S.R., Kooperberg, C., Stanford, J., Nevitt, M., Johnson, K.C., Proulx-Burns, L., Pastore, L., Criqui, M., & Dagherty, S. (2003). Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Annals of Epidemiology*, 13(9), S122–S128. [https://doi.org/10.1016/S1047-2797\(03\)00048-6](https://doi.org/10.1016/S1047-2797(03)00048-6)
- Dato, S., Rose, G., Crocco, P., Monti, D., Garagnani, P., Franceschi, C., & Passarino, G. (2017). The genetics of human longevity: An intricacy of genes, environment, culture and microbiome. *Mechanisms of Ageing and Development*, 165, 147–155. <https://doi.org/10.1016/j.mad.2017.03.011>
- Deelen, J., Evans, D.S., Arking, D.E., Tesi, N., Nygaard, M., Liu, X., Wojczynski, M.K., Biggs, M.L., van der Spek, A., Atzmon, G., Ware, E.B., Sarnowski, C., Smith, A.V., Seppälä, I., Cordell, H.J., Dose, J., Amin, N., Arnold, A.M., Ayers, K.L., . . . Murabito, J.M. (2019). A meta-analysis of genome-wide association studies identifies multiple longevity genes. *Nature Communications*, 10(1), 1–14. <https://doi.org/10.1038/s41467-019-11558-2>
- Diaz, K.M., Howard, V.J., Hutto, B., Colabianchi, N., Vena, J.E., Safford, M.M., Blair, S.N., & Hooker, S.P. (2017). Patterns of sedentary behavior and mortality in U.S. middle-aged and older adults. *Annals of Internal Medicine*, 167(7), 465. <https://doi.org/10.7326/M17-0212>
- Ekelund, U., Tarp, J., Steene-Johannessen, J., Hansen, B.H., Jefferis, B., Fagerland, M.W., Whincup, P., Diaz, K.M., Hooker, S.P., Chernofsky, A., Larson, M.G., Spartano, N., Vasani, R.S., Dohm, I.M., Hagströmer, M., Edwardson, C., Yates, T., Shirima, E., Andersen, S.A., & Lee, I.M. (2019). Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: Systematic review and harmonised meta-analysis. *The BMJ*, 366, Article 14570. <https://doi.org/10.1136/bmj.14570>
- Evenson, K.R., Wen, F., Herring, A.H., Di, C., LaMonte, M.J., Tinker, L.F., Lee, I.M., Rillamas-Sun, E., LaCroix, A.Z., & Buchner, D.M. (2015). Calibrating physical activity intensity for hip-worn accelerometry in women age 60 to 91 years: The Women's Health Initiative OPACH Calibration Study. *Preventive Medicine Reports*, 2, 750–756. <https://doi.org/10.1016/j.pmedr.2015.08.021>
- Evenson, K.R., Wen, F., Metzger, J.S., & Herring, A.H. (2015). Physical activity and sedentary behavior patterns using accelerometry from a national sample of United States adults. *International Journal of Behavioral Nutrition and Physical Activity*, 12(1), 20. <https://doi.org/10.1186/s12966-015-0183-7>
- Greenwood-Hickman, M.A., Nakandala, S., Jankowska, M.M., Rosenberg, D.E., Tuz-Zahra, F., Bellettiere, J., Carlson, J., Hibbing, P.R., Zou, J., Lacroix, A.Z., Kumar, A., & Natarajan, L. (2021). The CNN Hip Accelerometer Posture (CHAP) method for classifying sitting patterns from hip accelerometers: A validation study. *Medicine & Science in Sports & Exercise*, 53(11), 2445–2454. <https://doi.org/10.1249/MSS.0000000000002705>
- Harrell, F.E. (2015). *Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis* (2nd ed.). Springer. <https://doi.org/10.1007/978-3-319-19425-7>
- Harrell, F.E. (2020). rms: Regression modeling strategies. <https://hbiostat.org/R/rms/>
- Hays, R.D., & Morales, L.S. (2001). The RAND-36 measure of health-related quality of life. *Annals of Medicine*, 33(5), 350–357. <https://doi.org/10.3109/07853890109002089>
- Hjelmborg, J.B., Iachine, I., Skytthe, A., Vaupel, J.W., McGue, M., Koskenvuo, M., Kaprio, J., Pedersen, N.L., & Christensen, K. (2006). Genetic influence on human lifespan and longevity. *Human Genetics*, 119(3), 312–321. <https://doi.org/10.1007/s00439-006-0144-y>
- Hupin, D., Roche, F., Gremeaux, V., Chatard, J.C., Oriol, M., Gaspoz, J.M., Barthélémy, J.C., & Edouard, P. (2015). Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥60 years: A systematic review and meta-analysis. *British Journal of Sports Medicine*, 49(19), 1262–1267. <https://doi.org/10.1136/bjsports-2014-094306>
- LaCroix, A.Z., Bellettiere, J., Rillamas-Sun, E., Di, C., Evenson, K.R., Lewis, C.E., Buchner, D.M., Stefanick, M.L., Lee, I.M., Rosenberg,

- D.E., & LaMonte, M.J. (2019). Association of light physical activity measured by accelerometry and incidence of coronary heart disease and cardiovascular disease in older women. *JAMA Network Open*, 2(3), Article e190419. <https://doi.org/10.1001/jamanetworkopen.2019.0419>
- LaCroix, A.Z., Rillamas-Sun, E., Buchner, D., Evenson, K.R., Di, C., Lee, I.M., Marshall, S., LaMonte, M.J., Hunt, J., Tinker, L.F., Stefanick, M., Lewis, C.E., Bellettiere, J., & Herring, A.H. (2017). The Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) Study. *BMC Public Health*, 17(1), 1–12. <https://doi.org/10.1186/s12889-017-4065-6>
- LaMonte, M.J., Buchner, D.M., Rillamas-Sun, E., Di, C., Evenson, K.R., Bellettiere, J., Lewis, C.E., Lee, I.-M., Tinker, L.F., Seguin, R., Zaslowsky, O., Eaton, C.B., Stefanick, M.L., & LaCroix, A.Z. (2018). Accelerometer-measured physical activity and mortality in women aged 63 to 99. *Journal of the American Geriatrics Society*, 66(5), 886–894. <https://doi.org/10.1111/jgs.15201>
- Lee, I.M., Shiroma, E.J., Evenson, K.R., Kamada, M., LaCroix, A.Z., & Buring, J.E. (2018). Accelerometer-measured physical activity and sedentary behavior in relation to all-cause mortality: The Women's Health Study. *Circulation*, 137(2), 203–205. <https://doi.org/10.1161/CIRCULATIONAHA.117.031300>
- Lin, X., Eaton, C.B., Manson, J.A.E., & Liu, S. (2017). The genetics of physical activity. *Current Cardiology Reports*, 19(12), 1–10. <https://doi.org/10.1007/s11886-017-0938-7>
- Luck, T., Riedel-Heller, S.G., Lupp, M., Wiese, B., Köhler, M., Jessen, F., Bickel, H., Weyerer, S., Pentzek, M., König, H.H., Prokein, J., Ernst, A., Wagner, M., Mösch, E., Werle, J., Fuchs, A., Brettschneider, C., Scherer, M., Maier, W., ... Van Den Bussche, H. (2014). Apolipoprotein E epsilon 4 genotype and a physically active lifestyle in late life: Analysis of gene-environment interaction for the risk of dementia and Alzheimer's disease dementia. *Psychological Medicine*, 44(6), 1319–1329. <https://doi.org/10.1017/S0033291713001918>
- Lyden, K., Kozey Keadle, S.L., Staudenmayer, J.W., & Freedson, P.S. (2012). Validity of two wearable monitors to estimate breaks from sedentary time. *Medicine & Science in Sports & Exercise*, 44(11), 2243–2252. <https://doi.org/10.1249/MSS.0b013e318260c477>
- Mahley, R.W., & Rall, S.C. (2000). Apolipoprotein E: Far more than a lipid transport protein. *Annual Review of Genomics and Human Genetics*, 1(1), 507–537. <https://doi.org/10.1146/annurev.genom.1.1.507>
- Matthews, C.E., Chen, K.Y., Freedson, P.S., Buchowski, M.S., Beech, B.M., Pate, R.R., & Troiano, R.P. (2008). Amount of time spent in sedentary behaviors in the United States, 2003–2004. *American Journal of Epidemiology*, 167(7), 875–881. <https://doi.org/10.1093/aje/kwm390>
- Medina, L.D., Sabo, S., & Vespa, J. (2020). *Living longer: Historical and projected life expectancy in the United States, 1960 to 2060*. <https://www.census.gov/content/dam/Census/library/publications/2020/demo/p25-1145.pdf>
- Migueles, J.H., Cadenas-Sanchez, C., Ekelund, U., Delisle Nyström, C., Mora-Gonzalez, J., Löf, M., Labayen, I., Ruiz, J.R., & Ortega, F.B. (2017). Accelerometer data collection and processing criteria to assess physical activity and other outcomes: A systematic review and practical considerations. *Sports Medicine*, 47(9), 1821–1845. <https://doi.org/10.1007/s40279-017-0716-0>
- Mok, A., Khaw, K.T., Luben, R., Wareham, N., & Brage, S. (2019). Physical activity trajectories and mortality: Population based cohort study. *The BMJ*, 365, Article 12323. <https://doi.org/10.1136/bmj.12323>
- Oguma, Y., Sesso, H.D., Paffenbarger, R.S., & Lee, I.M. (2002). Physical activity and all cause mortality in women: A review of the evidence. *British Journal of Sports Medicine*, 36(3), 162–172. <https://doi.org/10.1136/bjism.36.3.162>
- Pilling, L.C., Kuo, C.L., Sicinski, K., Tamosauskaite, J., Kuchel, G.A., Harries, L.W., Herd, P., Wallace, R., Ferrucci, L., & Melzer, D. (2017). Human longevity: 25 genetic loci associated in 389,166 UK Biobank participants. *Aging*, 9(12), 2504–2520. <https://doi.org/10.18632/aging.101334>
- Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics*, 38(8), 904–909. <https://doi.org/10.1038/ng1847>
- R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. <https://www.r-project.org/>
- Rankinen, T., & Bouchard, C. (2007). Invited commentary: Physical activity, mortality, and genetics. *American Journal of Epidemiology*, 166(3), 260–262. <https://doi.org/10.1093/aje/kwm130>
- Rillamas-Sun, E., LaCroix, A.Z., Bell, C.L., Ryckman, K., Ockene, J.K., & Wallace, R.B. (2016). The impact of multimorbidity and coronary disease comorbidity on physical function in women aged 80 years and older: The Women's Health Initiative. *The Journals of Gerontology: Series A, Biological Sciences and Medical Sciences*, 71(Suppl. 1), S54–S61. <https://doi.org/10.1093/gerona/glv059>
- Sakaue, S., Kanai, M., Karjalainen, J., Akiyama, M., Kurki, M., Matoba, N., Takahashi, A., Hirata, M., Kubo, M., Matsuda, K., Murakami, Y., Daly, M.J., Kamatani, Y., & Okada, Y. (2020). Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan. *Nature Medicine*, 26(4), 542–548. <https://doi.org/10.1038/s41591-020-0785-8>
- Shadyab, A.H., & LaCroix, A.Z. (2015). Genetic factors associated with longevity: A review of recent findings. *Ageing Research Reviews*, 19, 1–7. <https://doi.org/10.1016/j.arr.2014.10.005>
- Sirugo, G., Williams, S.M., & Tishkoff, S.A. (2019). The missing diversity in human genetic studies. *Cell*, 177(1), 26–31. <https://doi.org/10.1016/j.cell.2019.02.048>
- Stringa, N., van Schoor, N.M., Milaneschi, Y., Ikram, M.A., Del Panta, V., Koolhaas, C.M., Voortman, T., Bandinelli, S., Wolters, F.J., & Huismán, M. (2020). Physical activity as moderator of the association between APOE and cognitive decline in older adults: Results from three longitudinal cohort studies. *The Journals of Gerontology: Series A, Biological Sciences and Medical Sciences*, 75(10), 1880–1886. <https://doi.org/10.1093/gerona/glaa054>
- Sylvia, L.G., Bernstein, E.E., Hubbard, J.L., Keating, L., & Anderson, E.J. (2014). Practical guide to measuring physical activity. *Journal of the Academy of Nutrition and Dietetics*, 114(2), 199–208. <https://doi.org/10.1016/j.jand.2013.09.018>
- Therneau, T., Crowson, C., & Atkinson, E. (2021). Using time dependent covariates and time dependent coefficients in the Cox model. <https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf>
- U.S. Department of Health and Human Services. (2018). *Physical activity guidelines for Americans* (2nd ed.). https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf#page=68
- van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, 45(3), 1–67.
- Zeng, Y., Nie, C., Min, J., Chen, H., Liu, X., Ye, R., Chen, Z., Bai, C., Xie, E., Yin, Z., Lv, Y., Lu, J., Li, J., Ni, T., Bolund, L., Land, K.C., Yashin, A., O'Rand, A.M., Sun, L., ... Vaupel, J. (2018). Sex differences in genetic associations with longevity. *JAMA Network Open*, 1(4), Article e181670. <https://doi.org/10.1001/jamanetworkopen.2018.1670>