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Leisure-time physical activity and leukocyte telomere length among older women

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ABSTRACT

Background: Shortened leukocyte telomere length (LTL), a purported marker of cellular aging, is associated with morbidity and mortality. However, the association of physical activity, a modifiable lifestyle behavior, with LTL has not been adequately studied among older adults.
Methods: In this cross-sectional study, we examined associations of various intensity levels of leisure-time physical activity with LTL among 1476 older white and African American women from the Women's Health Initiative Objective Physical Activity and Cardiovascular Health study. Self-reported physical activity was assessed by questionnaire, and LTL was measured by Southern blot. The association between physical activity and LTL was evaluated using multiple linear regression models adjusted for demographic characteristics, lifestyle behaviors, and health-related variables.
Results: Women were on average aged 79.2 (standard deviation 6.7) years old. In the final model adjusted for age, race/ethnicity, education, marital status, smoking, alcohol, body mass index, a history of chronic diseases, and hormone therapy use, LTL was on average 110 (95% confidence interval, 20–190) base pairs longer among women in the highest (≥17.00 MET-hours/week) compared with the lowest (<1.25 MET-hours/week) level of total leisure-time physical activity (P for trend = 0.02). Higher levels of moderate-to-vigorous physical activity (P for trend = 0.04) and faster walking speed (P for trend = 0.03) were also associated with longer LTL in the fully-adjusted models.
Conclusion: Older women participating in greater amounts of total leisure-time physical activity and moderate-to-vigorous physical activity had longer LTL.

1. Introduction

Telomeres are repeating DNA sequences at the ends of linear chromosomes that maintain genomic stability (O'Sullivan and Karlseder, 2010). Telomeres shorten with increasing age and are considered potential markers of biological aging (Aviv, 2004; Muezzinler et al., 2013). Several studies have observed associations between shortened leukocyte telomere length (LTL) and major chronic diseases including cardiovascular disease, type 2 diabetes, and cancer (Muezzinler et al., 2013; Haycock et al., 2014; Zhao et al., 2013; Wentzensen et al., 2011).

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HT, hormone therapy; LTL, leukocyte telomere length; MET, metabolic equivalent task; MVPA, moderate-to-vigorous physical activity.

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Some studies have found that modifiable lifestyle behaviors, such as obesity and smoking, may be associated with LTL (Valdes et al., 2005; Latifovic et al., 2016). Physical activity has also been studied in relation to LTL, but findings have been conflicting (Latifovic et al., 2016; Mundstock et al., 2015; Du et al., 2012; Cherkas et al., 2008; Woo et al., 2008; Kim et al., 2012; Ludlow et al., 2008; Soares-Miranda et al., 2015; Loprinzi et al., 2015; Loprinzi and Sng, 2016). In the Nurses' Health Study, higher levels of total physical activity and moderate-to-vigorous intensity physical activity (MVPA) were associated with longer LTL among women aged 43–70 years old (Du et al., 2012). However, a cross-sectional study among Chinese adults aged 65 years or older and a recent prospective investigation among 582 adults aged on average 73 years old from the Cardiovascular Health Study observed no association of physical activity with LTL after adjustment for age, sex, body mass index (BMI), and smoking (Woo et al., 2008; Soares-Miranda et al., 2015). Few studies have evaluated the association between physical activity and LTL among older adults. Further, the relationship between light intensity activities and LTL among older adults is unclear. From a public health perspective, understanding the relationship between light intensity activities and LTL is increasingly important for older adults, who are the least physically active age group, have a high prevalence of chronic diseases, and have shortened LTL (Aviv, 2004; Centers for Disease Control and Prevention, 2008). Finally, limited studies have measured LTL using the Southern blot method, which has low measurement error compared with other approaches (Aviv et al., 2011).

In this cross-sectional study, we evaluated the association of leisure-time physical activity with LTL in a sample of older white and African American women from the Women's Health Initiative Objective Physical Activity and Cardiovascular Health study.

2. Material and methods

2.1. Study population

Details of the Women's Health Initiative design and study population were previously described (Anderson et al., 2003; The Women's Health Initiative Study Group, 1998). Briefly, a racially and ethnically diverse cohort of 161,808 postmenopausal women aged 50–79 years was recruited from 40 United States clinical centers between 1993 and 1998. Participants were enrolled into an Observational Study (n = 93,676) or one or more of three Clinical Trials (n = 68,133), including one of two hormone therapy (HT) trials. In 2005, 77% of eligible women enrolled for an additional five years of follow-up in the first Extension Study; in 2010, 87% enrolled in the second Extension Study for follow-up through 2015.

More than 7,800 women from the second Extension Study enrolled in the Long Life Study, which involved a one time in-person visit conducted between 2012 and 2013. A random sample of 1942 women from the Long Life Study was selected for participation in a case-cohort study on the relationship between LTL and coronary heart disease (CHD). Furthermore, 7048 women from the Long Life Study participated in the Objective Physical Activity and Cardiovascular Health study, an ancillary study on physical activity among older women, as previously described (LaCroix et al., 2017; Shadyab et al., 2017). The final analytic sample of the present study consisted of 1476 women with both LTL measurements and complete information on physical activity (Supplementary Fig. 1). All participants provided written informed consent, and institutional review board approval was received by all participating institutions.

2.2. Physical activity assessment

Leisure-time physical activity was assessed during 2012–2013 using the Women's Health Initiative Physical Activity Questionnaire, which classifies the frequency and duration of various intensities of physical activity. Participants were asked how frequently each week they engage in light (e.g., slow dancing, bowling, and golf), moderate (e.g., biking outdoors, calisthenics, and easy swimming), and vigorous (i.e., that increased heart rate and produced sweating such as aerobics, aerobic dancing, and jogging) activities and for how long at each session. Frequency categories included rarely or never and 1, 2, 3, 4, or ≥5 days/week. Duration categories included <20 min, 20–39 min, 40–59 min, or ≥1 h. In a separate question, participants were asked how often they walk outside the home for >10 min without stopping (rarely or never, 1–3 times/month, 1 time/week, 2–3 times/week, 4–6 times/week, or ≥7 times/week), how many minutes they usually walk (<20 min, 20–39 min, 40–59 min, or ≥1 h), and their usual walking speed (casual [<2 miles per hour (mph)], average or normal [2–3 mph], fairly fast [3–4 mph], or very fast [>4 mph]). The questionnaire has acceptable reliability, with high intraclass correlation coefficients for MVPA (r = 0.77) and total physical activity (r = 0.76) (Meyer et al., 2009).

Midpoint values for ranges of frequency and duration were determined, and duration was multiplied by frequency to create an "hours/week" variable. Metabolic equivalent task (MET) values were assigned for walking and light, moderate, and vigorous intensity activities (Ainsworth et al., 2000). MET values were multiplied by hours/week to create variables summarizing the amount of walking, light, and moderate-to-vigorous intensity activities in MET-hours/week. MVPA included moderate and vigorous activities as well as average or normal and fast walking. Total leisure-time physical activity in MET-hours/week was determined by summing across all activities.

2.3. Covariates

Covariates were collected at either the 1993–1998 baseline visit, at the 2012–2013 visit, or during ongoing study follow-up. Age, race/ethnicity, education, marital status, smoking, and alcohol consumption were assessed at the baseline visit. Height, weight, and systolic and diastolic blood pressures were measured by trained clinic staff at the 2012–2013 visit. BMI was calculated as weight in kilograms divided by height in meters squared, and categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥ 30 kg/m^2) (National Institutes of Health, 1998). Physical functioning status was measured at the 2012–2013 visit using the Established Populations for Epidemiologic Studies of the Elderly Short Physical Performance Battery, which provides a total score from the sum of balance, chair stand, and gait speed scores (Guralnik et al., 2000; Vasunilashorn et al., 2009). A higher score (range, 0–12) indicates better physical performance.

Self-rated health and a history of HT use, hypertension, and chronic diseases were assessed during ongoing Women's Health Initiative follow-up. The most recent value for self-rated health that was collected within two years of the 2012–2013 visit was used (Ware, 2000). History of HT use was defined according to self-reported use or participation in the HT trials. History of hypertension was defined as self-reported physician diagnosis of hypertension, use of antihypertensive medications, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg (assessed at baseline, follow-up, and the 2012–2013 visit). History of chronic diseases was defined as occurrence of CHD, stroke, diabetes, or cancer (excluding non-melanoma skin cancer), all of which have been previously associated both with physical activity and LTL (Haycock et al., 2014; Zhao et al., 2013; Wentzensen et al., 2011; Lee et al., 2001; Hu et al., 2000; Jeon et al., 2007; Friedenreich and Orenstein, 2002). Participants reported disease status during the 1993–1998 baseline visit, and diseases were identified through the date of the 2012–2013 visit via periodic clinic visits and mailed questionnaires conducted biannually for Clinical Trial participants through 2005, annually for Observational Study participants, and then annually by mail for all Extension Study participants. Physicians adjudicated chronic diseases except for diabetes by review of medical records.

Diabetes was defined as self-reported physician diagnosis of diabetes treated with either oral medication or insulin.

2.4. Measurement of LTL

Blood samples were collected at the time of the 2012–2013 visit. DNA samples were extracted by the 5-prime method (5 PRIME, Inc.; Gaithersburg, MD) and sent in batches to the Center of Human Development and Aging Laboratory at Rutgers University to determine LTL. Samples for each batch were randomly selected. The laboratory performing the LTL measurements was blinded to all participant characteristics. For quality control purposes, DNA integrity was assessed prior to LTL measurement visually after ethidium bromide-stained 1% agarose gel electrophoresis (200 V for 2 h) and required that DNA appear as a single compact crown-shaped band migrating in parallel with other samples on the gel. Telomere length in kilobases was determined by the mean length of the terminal restriction fragments using the Southern blot method (Kimura et al., 2010). Each sample was run in duplicate on different gels, and mean LTL was used for analysis. The average inter-assay coefficient of variation for blinded pair sets was 2.0%.

Table 1
Characteristics of older women in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health study by total leisure-time physical activity.

Characteristic	Total leisure-time physical activity (MET-hours/week)				p-Value
	<1.25 (n = 346)	1.25–<7.50 (n = 391)	7.50–<17.00 (n = 368)	≥17.00 (n = 371)	
Age, years, mean (SD)	80.7 (6.7)	79.8 (6.4)	78.7 (6.7)	77.7 (6.8)	<0.001
Age, years	(n = 346)	(n = 391)	(n = 368)	(n = 371)	<0.001
64–69	26 (7.5)	21 (5.4)	33 (9.0)	49 (13.2)	
70–74	44 (12.7)	68 (17.4)	80 (21.7)	84 (22.6)	
75–79	56 (16.2)	90 (23.0)	72 (19.6)	78 (21.0)	
80–84	111 (32.1)	118 (30.2)	100 (27.2)	92 (24.8)	
≥85	109 (31.5)	94 (24.0)	83 (22.6)	68 (18.3)	
Race/ethnicity[a]	(n = 346)	(n = 391)	(n = 368)	(n = 371)	0.03
White	217 (62.7)	236 (60.4)	218 (59.2)	194 (52.3)	
African American	129 (37.3)	155 (39.6)	150 (40.8)	177 (47.7)	
Education[a]	(n = 344)	(n = 388)	(n = 367)	(n = 371)	<0.001
Less than high school	13 (3.8)	19 (4.9)	9 (2.5)	7 (1.9)	
High school	60 (17.4)	79 (20.4)	50 (13.6)	44 (11.9)	
Some college	144 (41.9)	151 (38.9)	127 (34.6)	127 (34.2)	
College graduate	127 (36.9)	139 (35.8)	181 (49.3)	193 (52.0)	
Baseline marital status[a]	(n = 344)	(n = 388)	(n = 368)	(n = 371)	0.17
Married/living as married	187 (54.4)	207 (53.4)	220 (59.8)	213 (57.4)	
Widowed	71 (20.6)	85 (21.9)	55 (15.0)	56 (15.1)	
Divorced/separated	70 (20.4)	79 (20.4)	82 (22.3)	88 (23.7)	
Never married	16 (4.7)	17 (4.4)	11 (3.0)	14 (3.8)	
Baseline smoking history[a]	(n = 344)	(n = 385)	(n = 365)	(n = 367)	0.10
Never smoked	178 (51.7)	221 (57.4)	191 (52.3)	191 (52.0)	
Past smoker	141 (41.0)	133 (34.6)	158 (43.3)	155 (42.2)	
Current smoker	25 (7.3)	31 (8.1)	16 (4.4)	21 (5.7)	
Baseline alcohol consumption[a]	(n = 345)	(n = 388)	(n = 367)	(n = 370)	0.03
Non-drinker	39 (11.3)	51 (13.1)	42 (11.4)	39 (10.5)	
Past drinker	87 (25.2)	78 (20.1)	67 (18.3)	56 (15.1)	
Current drinker	219 (63.5)	259 (66.8)	258 (70.3)	275 (74.3)	
Body mass index, kg/m^2	(n = 341)	(n = 386)	(n = 364)	(n = 368)	<0.001
Underweight/normal weight	89 (26.1)	110 (28.5)	122 (33.5)	141 (38.3)	
Overweight	100 (29.3)	136 (35.2)	133 (36.5)	144 (39.1)	
Obese	152 (44.6)	140 (36.3)	109 (30.0)	83 (22.6)	
Self-rated health	(n = 327)	(n = 369)	(n = 351)	(n = 364)	<0.001
Excellent	13 (4.0)	19 (5.2)	39 (11.1)	61 (16.8)	
Very good	95 (29.1)	126 (34.2)	166 (47.3)	178 (48.9)	
Good	153 (46.8)	176 (47.7)	128 (36.5)	111 (30.5)	
Fair/poor	66 (20.2)	48 (13.0)	18 (5.1)	14 (3.9)	
Systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg	(n = 336)	(n = 386)	(n = 363)	(n = 362)	0.07
	71 (21.1)	73 (18.9)	62 (17.1)	50 (13.8)	
History of hypertension	(n = 346)	(n = 391)	(n = 368)	(n = 371)	<0.001
	299 (86.4)	326 (83.4)	297 (80.7)	269 (72.5)	
History of hormone therapy use	(n = 342)	(n = 386)	(n = 363)	(n = 365)	0.13
	247 (72.2)	258 (66.8)	268 (73.8)	249 (68.2)	
History of chronic diseases	(n = 346)	(n = 391)	(n = 368)	(n = 371)	
Coronary heart disease	29 (8.4)	28 (7.2)	17 (4.6)	13 (3.5)	0.02
Stroke	16 (4.6)	15 (3.8)	13 (3.5)	10 (2.7)	0.58
Diabetes	99 (28.6)	90 (23.0)	65 (17.7)	62 (16.7)	<0.001
Cancer	73 (21.1)	78 (20.0)	61 (16.6)	60 (16.2)	0.23
Any disease	168 (48.6)	165 (42.2)	140 (38.0)	127 (34.2)	<0.001
Experienced a fall in the past 12 months	(n = 335)	(n = 382)	(n = 362)	(n = 365)	0.01
	121 (36.1)	129 (33.8)	93 (25.7)	104 (28.5)	
Physical performance score, mean (SD)	6.9 (2.7)	7.4 (2.5)	8.5 (2.2)	8.9 (2.3)	<0.001
Leukocyte telomere length, kilobases, mean (SD)	6.49 (0.60)	6.60 (0.60)	6.64 (0.60)	6.72 (0.59)	<0.001
Age and race-adjusted leukocyte telomere length, kilobases, mean (SE)	6.56 (0.03)	6.64 (0.03)	6.65 (0.03)	6.69 (0.03)	0.02

Abbreviations: MET, metabolic equivalents; SD, standard deviation; SE, standard error.
All characteristics represent current status as n (%), unless stated otherwise. Total sample sizes for variables in each column do not sum to total due to missing data.
[a] Determined at the 1993–1998 baseline visit.

2.5. Statistical analysis

Total leisure-time physical activity in MET-hours/week was categorized into quartiles. Light physical activity could not be ordered into quartiles or tertiles due to the large proportion of women with 0 MET-hours/week of light activity; therefore, this variable had a separate category for 0 MET-hours/week, and the remainder of the data were divided according to the median. MVPA was categorized into three categories according to current recommendations of ≥7.5 MET-hours/week of MVPA (Nelson et al., 2007): 0, 0.1–<7.5, or ≥7.5 MET-hours/week. Walking speed was evaluated using the following categories: rarely or never; casual (<2 mph); average or normal (2–3 mph); and fairly fast or very fast (>3 mph).

Chi-square tests were used to compare categorical variables across quartiles of total physical activity. Normally and non-normally distributed continuous variables were compared across quartiles of total physical activity using analysis of variance and Kruskal-Wallis tests, respectively. Correlations between LTL and age were measured using the Pearson correlation coefficient. Least squares means of LTL adjusting for age and race/ethnicity were determined for quartiles of total physical activity using linear regression models.

Since LTL was approximately normally distributed, multiple linear regression models were used to evaluate associations of physical activity variables with LTL. Separate analyses were conducted for total physical activity, MVPA, light physical activity, and walking speed. The first model was adjusted for age and race/ethnicity, and subsequent models were adjusted for other potential confounders including education, marital status, smoking, alcohol, BMI, history of chronic diseases, and history of HT use. Multicollinearity was evaluated using tolerance values; however, no multicollinearity was observed. Linear trend tests were performed by including physical activity variables as continuous variables in the models. Interactions between physical activity variables and race/ethnicity, physical performance score, and BMI were tested by including product terms of these factors in the models. All p-values were two-sided and considered nominally statistically significant at values < 0.05. Analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

In the overall sample, there were 865 (58.6%) white and 611 (41.4%) African American women. Women were on average 79.2 (standard deviation [SD] 6.7; range, 64–95) years old. Women spent a median of 7.5 (interquartile range [IQR], 1.3–17.0) MET-hours/week in total leisure-time physical activity, 0 (IQR, 0–0.5) MET-hours/week in light physical activity, and 4.9 (IQR, 0–14.6) MET-hours/week in MVPA. Approximately 20% of women reported not engaging in any physical activity. Current recommendations of ≥7.5 MET-hours/week of MVPA were achieved in 43% of women. Average LTL was 6.6 (SD 0.6; range, 4.9–8.9) kilobases. LTL was inversely associated with age ($r = -0.38$; $p < 0.001$) and longer in African-American than white women (age-adjusted mean [standard error] = 6.76 [0.02] kilobases and 6.52 [0.02] kilobases, respectively; $p < 0.001$; Supplementary Figs. 2 and 3).

Women with greater amounts of total leisure-time physical activity were more likely to be younger, college graduates, have excellent self-rated health, and have higher physical performance scores (Table 1). They were less likely to be obese, have a history of hypertension, have a history of CHD or diabetes, or have experienced a fall in the previous 12 months.

Across all multivariable models, there were significant linear trends toward longer LTL for higher levels of total leisure-time physical activity (Table 2). In the final model adjusting for age, race/ethnicity, education, marital status, smoking, alcohol, BMI, a history of chronic diseases, and HT use, the association of total leisure-time physical activity with LTL was significant only when comparing the highest with the lowest level of total physical activity. On average, LTL was 110 (95% confidence interval [CI], 20–190) base pairs longer in those with ≥17.00 compared with <1.25 MET-hours/week of total physical activity. Furthermore, for every 1 MET-hour/week increase in total physical activity, LTL was on average 3 (95% CI, 0.4–5) base pairs longer (P for trend = 0.02).

There was no association between light physical activity and LTL in the final model (Table 3). LTL was not significantly longer among women meeting current recommendations of ≥7.5 MET-hours/week of MVPA than among those reporting no MVPA in the final model (Table 4). However, there was a significant linear association of MVPA with LTL (P for trend = 0.04). For each 1 MET-hour/week increase in MVPA, LTL was on average 3 (95% CI, 0.2–5) base pairs longer.

There was a significant linear trend toward longer LTL for increasing walking speed in the final model (Table 5; P for trend = 0.03). LTL was on average 40 (95% CI, 4–70) base pairs longer for each incremental increase in walking speed.

Associations between physical activity variables and LTL did not vary by race/ethnicity, physical performance score, or BMI in stratified analyses, and interaction terms were not significant. In sensitivity analyses, the final models were fit using individual diseases (coronary heart disease, stroke, diabetes, and cancer) rather than overall history of chronic diseases; however, findings were similar. Findings were also similar after adjusting for hypertension in the final models. Finally, as participants selected for LTL measurement were part of a case-cohort study on CHD, models were additionally adjusted for case-control status; however, this adjustment did not alter the findings (data not shown).

4. Discussion

Among older white and African American women, greater amounts of total leisure-time physical activity and MVPA, as well as higher walking speed, were associated with longer LTL, independent of demographic characteristics, lifestyle behaviors, BMI, chronic diseases, and HT use.

Table 2
Association of total leisure-time physical activity with leukocyte telomere length (in kilobases) among older women (N = 1409).

	Total leisure-time physical activity (MET-hours/week)				
	<1.25	1.25–<7.50	7.50–<17.00	≥17.00	*P* for trend
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	
Model 1[a]	Reference	0.10 (0.006,0.18)	0.14 (0.05,0.23)	0.22 (0.13,0.31)	<0.001
Model 2[b]	Reference	0.08 (−0.005,0.16)	0.09 (0.10,0.18)	0.12 (0.04,0.20)	<0.01
Model 3[c]	Reference	0.08 (−0.001,0.16)	0.09 (0.002,0.17)	0.11 (0.03,0.20)	<0.01
Model 4[d]	Reference	0.08 (−0.002,0.16)	0.09 (0.001,0.17)	0.12 (0.03,0.20)	<0.01
Model 5[e]	Reference	0.08 (−0.005,0.16)	0.08 (−0.005,0.16)	0.11 (0.02,0.19)	0.02

β = beta estimate; CI = confidence interval; MET = metabolic equivalent.
[a] Model 1: unadjusted.
[b] Model 2: adjusted for model 1 + age and race/ethnicity.
[c] Model 3: adjusted for model 2 + education and baseline marital status, smoking behavior and alcohol consumption.
[d] Model 4: adjusted for model 3 + body mass index.
[e] Model 5: adjusted for model 4 + history of chronic diseases and hormone therapy use.

Table 3
Association of light intensity physical activity with leukocyte telomere length (in kilobases) among older women (N = 1409).

	Light intensity physical activity (MET-hours/week)			
	0	0.10–≤3	>3	*P* for trend
	β (95% CI)	β (95% CI)	β (95% CI)	
Model 1[a]	Reference	−0.07 (−0.17,0.02)	0.07 (−0.02,0.17)	0.05
Model 2[b]	Reference	−0.10 (−0.18,−0.01)	0.06 (−0.03,0.15)	0.05
Model 3[c]	Reference	−0.10 (−0.18,−0.01)	0.05 (−0.04,0.14)	0.09
Model 4[d]	Reference	−0.10 (−0.19,−0.01)	0.05 (−0.04,0.14)	0.10
Model 5[e]	Reference	−0.10 (−0.18,−0.01)	0.05 (−0.04,0.14)	0.12

β = beta estimate; CI = confidence interval; MET = metabolic equivalent.
[a] Model 1: unadjusted.
[b] Model 2: adjusted for model 1 + age and race/ethnicity.
[c] Model 3: adjusted for model 2 + education and baseline marital status, smoking behavior and alcohol consumption.
[d] Model 4: adjusted for model 3 + body mass index.
[e] Model 5: adjusted for model 4 + history of chronic diseases and hormone therapy use.

The average difference in LTL between the most physically active and least physically active women was 110 base pairs in the fully-adjusted model. Since women lose on average 21 base pairs/year (Cherkas et al., 2008), this suggests that the most physically active women were 5 years younger biologically according to LTL as a measure of cellular age.

Our findings agree with previous studies linking physical activity with longer telomere length (Du et al., 2012; Cherkas et al., 2008; Kim et al., 2012; Loprinzi et al., 2015; Loprinzi and Sng, 2016; Shadyab et al., 2017). In a cross-sectional study among Nurses' Health Study participants, total physical activity and MVPA were linearly associated with LTL (Du et al., 2012). Furthermore, there was an interaction between BMI and MVPA but not total physical activity. However, our findings did not vary by BMI. Although we observed that women meeting current recommendations of ≥7.5 MET-hours/week of MVPA did not have longer telomeres than those reporting no MVPA, we did observe a linear association between MVPA and LTL. A recent cross-sectional study among a sample of adults from the National Health and Nutrition Examination Survey also observed that meeting current physical activity guidelines was not associated with longer LTL (Loprinzi and Sng, 2016). We recently observed in the same study population that women with ≥2.5 h/week of accelerometer-measured MVPA had longer LTL than women with <2.5 h/week of MVPA; however, accelerometer-measured MVPA was not linearly associated with LTL (Shadyab et al., 2017). Accelerometer-measured MVPA does not correlate well with self-reported MVPA, which may be overestimated and biased due to misclassification (Tucker et al., 2011; Washburn, 2000; Dyrstad et al., 2014).

We observed that higher walking speed was associated with longer LTL among older women. Previous studies, including the Nurses' Health Study, have found no associations between walking and LTL (Du et al., 2012; Soares-Miranda et al., 2015; Loprinzi et al., 2015); however, walking speed was not specifically evaluated. Overall, the association of physical activity with LTL has been inconsistent, which may be attributed to differences in sample size, age ranges and characteristics of the study populations, and methods used to assess physical activity (Latifovic et al., 2016; Mundstock et al., 2015; Du et al., 2012; Cherkas et al., 2008; Woo et al., 2008; Kim et al., 2012; Ludlow et al., 2008; Soares-Miranda et al., 2015; Loprinzi et al., 2015; Loprinzi and Sng, 2016). For example, in a cross-sectional study among 2401 primarily female white twins aged 18–81 years old, a positive association between leisure-time physical activity and LTL was observed (Cherkas et al., 2008). However, participants were asked whether their activities during the past 12 months were of light, moderate, or vigorous intensity, without consideration for the duration or frequency of their activities. A recent study among adults aged 20–50 years old observed an association between vigorous, but not total physical activity and LTL (Latifovic et al., 2016). Unlike prior studies, our study consisted exclusively of older white and African American women, the majority of whom were ages 80 and above and did not largely engage in activities of moderate-to-vigorous intensity, making direct comparison of our results with other studies difficult.

The relationship between physical activity and LTL may be due to several mechanisms. Physical activity may stimulate anti-oxidant and anti-inflammatory responses to counteract acceleration of telomere attrition due to oxidative stress and inflammation (Aviv, 2004; Mundstock et al., 2015; Von Zglinicki, 2002; Gomez-Cabrera et al., 2008; Kasapis and Thompson, 2005). Exercise has been shown to stimulate activity of telomerase, an enzyme that elongates telomere length, and to upregulate messenger RNA expression of telomerase reverse transcriptase (Werner et al., 2009; Chilton et al., 2014). Physical inactivity and shortened LTL are associated with obesity (Valdes et al., 2005; Von Zglinicki, 2002), suggesting that obesity may partly mediate this association; however, our findings persisted after adjustment for BMI. Finally, women who have chronic diseases may have shortened LTL and are also less likely to be physically active (Muezzinler et al., 2013; Haycock et al., 2014; Zhao et al., 2013; Wentzensen et al., 2011); nevertheless, our findings persisted after adjustment for chronic diseases.

Our study was limited by a cross-sectional design and self-reported data for physical activity. Self-reported total energy expenditure determined using the Women's Health Initiative Physical Activity questionnaire has been shown to correlate weakly with objectively-measured total energy expenditure and may be prone to measurement error (Neuhouser et al., 2013). Our findings are not applicable to younger women, men, or telomere dynamics in other tissues; however, telomere length in leukocytes is the most frequently measured. Furthermore, previous studies that included men showed that a higher level of physical activity was associated with longer LTL (Latifovic et al., 2016; Cherkas et al., 2008; Ludlow et al., 2008). Women who enrolled for additional

Table 4
Association of moderate-to-vigorous intensity physical activity with leukocyte telomere length (in kilobases) among older women (N = 1409).

	Moderate-to-vigorous intensity physical activity (MET-hours/week)			
	0	0.10–<7.50	≥7.50	*P* for trend
	β (95% CI)	β (95% CI)	β (95% CI)	
Model 1[a]	Reference	0.03 (−0.06,0.11)	0.15 (0.08,0.22)	<0.001
Model 2[b]	Reference	0.005 (−0.07,0.08)	0.08 (0.01,0.14)	<0.01
Model 3[c]	Reference	0 (−0.08,0.08)	0.07 (−0.0005,0.13)	0.02
Model 4[d]	Reference	0.001 (−0.08,0.08)	0.07 (−0.003,0.13)	0.02
Model 5[e]	Reference	−0.0005 (−0.08,0.08)	0.06 (−0.009,0.13)	0.04

β = beta estimate; CI = confidence interval; MET = metabolic equivalent.
[a] Model 1: unadjusted.
[b] Model 2: adjusted for model 1 + age and race/ethnicity.
[c] Model 3: adjusted for model 2 + education and baseline marital status, smoking behavior and alcohol consumption.
[d] Model 4: adjusted for model 3 + body mass index.
[e] Model 5: adjusted for model 4 + history of chronic diseases and hormone therapy use.

Table 5
Association of walking speed with leukocyte telomere length (in kilobases) among older women (N = 1391).

	Walking speed				
	Rarely or never	Casual (<2 mph)	Average or normal (2–3 mph)	Fairly fast/very fast (>3 mph)	*P* for trend
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	
Model 1[a]	Reference	0.14 (0.06,0.23)	0.14 (0.05,0.22)	0.26 (0.12,0.39)	<0.001
Model 2[b]	Reference	0.09 (0.01,0.17)	0.11 (0.03,0.19)	0.14 (0.02,0.27)	<0.01
Model 3[c]	Reference	0.09 (0.01,0.17)	0.09 (0.01,0.17)	0.13 (0.01,0.26)	0.02
Model 4[d]	Reference	0.09 (0.01,0.17)	0.09 (0.01,0.18)	0.13 (0.01,0.26)	0.02
Model 5[e]	Reference	0.09 (0.01,0.17)	0.09 (0.01,0.17)	0.12 (−0.01,0.25)	0.03

β = beta estimate; CI = confidence interval; MET = metabolic equivalent.
[a] Model 1: unadjusted.
[b] Model 2: adjusted for model 1 + age and race/ethnicity.
[c] Model 3: adjusted for model 2 + education and baseline marital status, smoking behavior and alcohol consumption.
[d] Model 4: adjusted for model 3 + body mass index.
[e] Model 5: adjusted for model 4 + history of chronic diseases and hormone therapy use.

long-term follow-up in the Extension Studies were more likely to be healthier at baseline, which may have excluded those who experienced greater health-related LTL shortening from our study.

Strengths of our study include a diverse sample of white and African American women. We also adjusted for many potential confounders, including adjudicated chronic diseases. Finally, we used the Southern blot method to measure LTL, which is considered the gold standard (Aviv et al., 2011).

In conclusion, greater amounts of total leisure-time physical activity and MVPA and higher walking speed were associated with longer LTL among older women. Longitudinal studies evaluating the relationship between changes in physical activity and repeated LTL measurements over time among older adults are currently needed to confirm and extend these observations. Shortened LTL is associated with increased rate of aging, age-related diseases, and mortality. Longer LTL has been associated with better overall health and function in centenarians (Terry et al., 2008). Accordingly, understanding whether modifiable lifestyle behaviors, such as physical activity, are associated with LTL shortening in old age may have implications for healthy aging and may inform pathways linking LTL to age-related diseases, disability, and mortality.

Conflict of interest

The authors have no conflicts.

Role of the sponsor

The National Heart, Lung, and Blood Institute has representation on the WHI Steering Committee, which governed the design and conduct of the study, the interpretation of the data, and preparation and approval of manuscripts.

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Appendix A. Supplementary data

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