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# Movement-Based Behaviors and Leukocyte Telomere Length among U. S. Adults

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# **Abstract**

**Introduction**—Short leukocyte telomere length (LTL) has become a hallmark characteristic of aging. Some, but not all evidence suggests that physical activity may play an important role in attenuating age-related diseases and may provide a protective effect for telomeres. The purpose of this study was to examine the association between physical activity and LTL in a national sample of U.S. adults from the National Health and Nutrition Examination Survey (NHANES).

**Methods**—NHANES data from the 1999–2002 (n = 6,503; 20–84 yrs) were used. 4 self-report questions related to movement based behaviors (MBB) were assessed. The 4 MBB included whether individuals participated in moderate-intensity physical activity (MPA), vigorous-intensity physical activity (VPA), walking/cycling for transportation, and muscle strengthening activities (MSA). A MBB index variable was created by summing the number of MBB each individual engaged in (range: 0–4).

**Results**—A clear dose-response relationship was observed between MBB and LTL; across the LTL tertiles, respectively, the mean number of MBB was 1.18, 1.44, and 1.54 ( $P_{trend}$ <0.001). After adjustments (including age), and compared to those engaging in 0 MBB, those engaging in 1, 2, 3, and 4 MBB, respectively, had a 3% (p=0.84), 24% (p=0.02), 29% (p=0.04), and 52% (p=0.004) reduced odds of being in the lowest (vs. highest) tertile of LTL; MBB was not associated with being in the middle (vs. highest) tertile of LTL.

**Conclusions**—Greater engagement in MBB was associated with reduced odds of being in the lowest LTL tertile.

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#### CONFLICTS OF INTEREST

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# **Keywords**

Aging; epidemiology; physical activity; NHANES

# INTRODUCTION

Shortened leukocyte telomere length (LTL) characterizes human aging (5,26,27). Potentially reflecting systemic oxidative stress and inflammation (10,51), short LTL is linked with various cardiometabolic diseases (2,4,13,18,19,21,46,47). Physical activity (PA) may help attenuate age-related diseases, as previous research (8,14,20,23–25,34,37,39,44,49) demonstrates that physically active adults have a longer mean LTL. However, some studies show no relationship (22,32,33,40,45,48,52) with others reporting an inverted U relationship (9,31,43) (review papers see Ludlow (29,30)).

Given these mixed findings, coupled with the fact that the majority of these studies were convenience-based samples or employed targeted populations (e.g., post-menopausal women) (29,30), here, we examine the association between PA and LTL in a national sample of U.S. adults. To improve our understanding of associations between PA and LTL, specific attention was focused on data from 4 movement-based behaviors (MBB). These include moderate-intensity PA (MPA), vigorous-intensity PA (VPA), walking and cycling for transportation, and muscle strengthening activities (MSA).

# **METHODS**

# **Design and Participants**

Data were extracted from the 1999–2002 NHANES (only cycles with LTL data at the time of this writing). Procedures were approved by the NCHS review board. Consent was obtained from all participants. Analyses are based on data from 6,503 adults (20–84 yrs) who provided complete data for the study variables. In the 1999–2002 NHANES cycles, 9,882 participants were between 20 and 84 years of age; after excluding those with missing MBB data, 9,369 remained; 7,283 remained after excluding those with missing covariate data; lastly, after excluding those with missing telomere data, 6,503 remained (resultant sample; Figure 1). When comparing the final analytic sample (N=6,503) to the 780 participants with missing telomere data (7,283–6,503=780), there were no differences in age, number of MBB, body mass index (BMI), C-reactive protein (CRP), or smoking (all p's > 0.05); however, those that were excluded were more likely to be female (60% vs. 51.1%; p<0.001), less likely to be non-Hispanic white (38.1% vs. 50.4%, p<0.001), and had a lower poverty-to-income ratio (PIR) (2.56 vs. 2.71, p=0.01). These are unweighted estimates.

# **Leukocyte Telomere Length**

Detailed methodology of the NHANES procedures for assessing LTL has been previously reported (35). Briefly, DNA was extracted from whole blood and the LTL assay was performed using quantitative polymerase chain reaction to measure LTL relative to standard reference DNA (T/S ratio) (35). Each sample was assayed at least twice, and among samples with a T/S ratio within 7% variability, the average value was used; for samples with a

variability greater than 7%, a third assay was run and in this case, the average of the two closest T/S values was used. Notably, in NHANES, telomere length in leukocytes was assessed. We acknowledge that LTL is not specific to skeletal muscle tissue; however, it may not be feasible to take muscle biopsies in large epidemiological studies. Previous work suggests that LTL is modestly (r=0.39) associated with muscle telomere length (1), which is in accordance with other studies (12), providing some justification for continued use of LTL measures, particularly in epidemiological studies.

#### **Movement-Based Behaviors**

In the 1999–2002 NHANES, 4 self-report items related to MBB were assessed, including PA participation during transportation and leisure time; notably, objective measures of PA (e.g., accelerometry) were not released until the 2003–2004 NHANES cycle. The 4 MBB included the degree of participation in *MPA*, *VPA*, *walking/cycling* for transportation, and *MSA* (yes/no responses).

For MPA: "Over the past 30 days, did you do moderate activities for at least 10 minutes that cause only light sweating or a slight to moderate increase in breathing or heart rate?"

For VPA: "Over the past 30 days, did you do vigorous activities for at least 10 minutes that caused heavy sweating, or large increases in breathing or heart rate?"

For walking/cycling for transportation: "Over the past 30 days, did you walk or bicycle as part of getting to and from work, or school, or to do errands?"

For MSA: "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles such as lifting weights, push-ups or sit-ups?"

# **Movement-Based Behavior Index**

A MBB index variable was created by summing the number of MBB each individual engaged in (range: 0–4).

#### Covariates

Covariates included *age* (continuous), *age-squared* (due to nonlinearity between age and LTL), *gender*, *race-ethnicity*, *PIR*, *smoking status* (smokes every day, some days, no longer smokes, and never smoked), measured BMI (kg/m²), and CRP (mg/dL).

### **Analysis**

Statistical analyses were performed using procedures from survey data using Stata (v.12). Polytomous regression was used to examine the odds of being in the two lower tertiles (6,53) (vs. upper tertile) of LTL based on the degree of engagement in MBB; those with a MBB index score of "0" served as the referent group.

## **RESULTS**

Table 1 displays the characteristics of the sample. The weighted mean number of MBB across the LTL tertiles, respectively, was 1.18, 1.44, and 1.54 (Table 1; Figure 2). The

weighted proportion of participants with 2+ MBB across the LTL tertiles, respectively, were 34.7%, 43.6% and 49.2% (Figure 2). Table 2 displays the polytomous regression results. After adjustments (including age), and compared to those engaging in 0 MBB, those engaging in 1, 2, 3, and 4 MBB, respectively, had a 3% (p=0.84), 24% (p=0.02), 29% (p=0.04), and 52% (p=0.004) reduced odds of being in the lowest (vs. highest) tertile of LTL; MBB was not associated with being in the middle (vs. highest) tertile of LTL. When changing the referent group to the middle tertile (not shown in table), and compared those engaging in 0 MBB, those engaging in 1, 2, 3, and 4 MBB, respectively, had a 5% (p=0.60), 12% (p=0.40), 28% (p=0.02), and 56% (p=0.009) reduced odds of being in the lowest (vs. *middle*) tertile of LTL. Taken together, these findings suggest a dose response relationship between MBB and LTL; greater engagement in MBB was associated with a lower odds of being in lowest vs. highest LTL tertile and lowest vs. middle tertile.

Given that some studies suggest a non-linear relationship between telomere length and morbidity (11,15), in addition to considering tertiles of LTL, further analyses examined the relationship between MBB and 5 quintiles of LTL; across these 5 quintiles, respectively, the mean LTL was 0.73, 0.88, 1.01, 1.14 and 1.44 – notably, the 90<sup>th</sup> and 95<sup>th</sup> percentiles for LTL in this sample were 1.37 and 1.50, respectively. The mean number of MBB across the 5 quintiles of LTL, respectively, were 1.15, 1.27, 1.46, 1.52 and 1.55. This observed monotonic relationship suggests that, in this sample, LTL had a linear, rather than an inverted U-shaped, association with mean MBB number.

Additional analyses (not shown in tabular format) were computed to see if age moderated the association between MBB and LTL. Three additional multivariable polytomous regression models were computed for those 20–39 yrs, 40–64 yrs, and 65–84 yrs. Results were not significant for the 20–39 and 65–84 yr-old age groups (data not shown); among those who were 40–64 yrs, and compared to those engaging in 0 MBB, those engaging in 1, 2, 3, and 4 behaviors, respectively, had a 15% (p=0.44), 32% (p=0.08), 42% (p=0.01), and 61% (p=0.03) reduced odds of being in the lowest (vs. highest) tertile of LTL.

Further, all 4 MBB were entered separately into a multivariable polytomous regression model to examine their potential *independent* associations. After adjustments, those engaging in VPA and walking/cycling for transportation, respectively, had a 25% (p=0.01) and 30% (p=0.004) lower odds of being in the lowest (vs. highest) LTL tertile; MPA (OR=1.13, p=0.15) and MSA (OR=0.92, p=0.50) were not independently associated with being the in the lowest (vs. highest) LTL tertile.

In addition to examining independent associations of the different MBB on LTL, it is of interest to examine whether MBB exclusivity (e.g., only engaging in MPA and not any of the 3 other MBB) is associated with LTL. Among the 6,503 participants, 386 engaged in *only* VPA (i.e., reporting engaging in VPA but not in MPA, MSA or walking for transportation), 1,057 engaged in *only* MPA, 176 engaged in only MSA and 417 engaged in only walking/cycling for transportation. Results for only VPA, MSA and walking/cycling for transportation were not statistically significant (data not shown). Interestingly, however, those who only engaged in MPA had a 36% (OR=1.36, p=0.01) and 25% (OR=1.25, p=0.06) increased odds, respectively, in being in the lowest and middle tertiles (vs. highest

tertile) after adjustments. This is an unexpected finding, but this association, coupled with our observed finding of a dose-response association between MBB engagement and LTL, suggests that engaging in some MBB in isolation may not be favorable, but there may be a combined effect of attenuating the shortening of LTL when multiple MBB are engaged in regularly.

Lastly, given that some studies have demonstrated an inverted U relationship between PA and LTL (29,30), we attempted to examine whether such a relationship was observed for frequency of MSA; duration/frequency of MPA and VPA were not asked in the 1999–2002 NHANES cycles and the majority (76%) of participants did not walk/cycle for transportation so evaluating a dose-response relationship between walking/cycling for transportation and LTL was not possible. No dose-response relationship was observable for MSA; compared to those in the lowest MSA tertile (mean # of MSA in past 30 days: 5.6), and after adjustments in a linear regression, no association was observed between those in the middle (mean MSA 12.9;  $\beta$ =-0.02, p=0.13) and upper (mean MSA: 27.4;  $\beta$ =-0.002, p=0.88) MSA tertiles with LTL.

# DISCUSSION

Using a national sample of U.S. adults, we observed a dose-response relationship between MBB engagement (i.e., # of MBB they engaged in) and lower LTL. The potential mechanisms to explain a PA-LTL relationship are not fully established. Among rodent models, several exercise-specific signaling mechanisms (e.g., TERT, IGF-1, eNOS, and AKT) have been associated with altered telomere biology (29,30), and thus, may play an important role in preserving telomere phenotype (30,49,50). Future work is needed to improve our understanding of the mechanisms underlying this potential relationship.

Importantly, the relationship between MBB and LTL was observed only among those 40–64 yrs, which suggests that, if confirmed by prospective and experimental work, this may be an important age-group in which targeted PA interventions should be developed, implemented and evaluated. The unexpected finding that those who only engaged in MPA had increased odds of being in the lowest and middle tertiles (vs. highest tertile) needs further investigation. It is possible that engaging in only MPA may result in an inadequate exercise stimulus to achieve exercise-induced LTL adaptations. The observed findings should be interpreted in the context of the study's limitation, which include, for example, the cross-sectional design and an inability to fully tease out potential intensity/duration effects. Also, given that the excluded sample due to missing LTL data differed by gender, race-ethnicity and PIR when compared to the analytic sample, generalizability to these subpopulations may be limited.

Owing to the limitations of the MBB items, we were not able to determine the duration and frequency of most of the MBB items, but rather whether they engaged in the behavior or not. Previous research, however, suggests that there is likely a range in the amount of PA which provides health benefits without negatively affecting LTL (22,38,40,43). Data in very active adults suggest that if this range is exceeded, then PA may result in a detrimental effect on LTL (22,43). For example, high levels of PA may increase demand on the body

to repair and regenerate, resulting in a shortening of LTL. This may explain why some studies don't always find a dose-response relationship between the amount of PA and LTL (22,32,33,40,45,48,52). Our findings suggest that engaging in more MBB is associated with reduced odds of being in the lowest LTL tertile, suggesting that engaging in multiple MBB may have a combined effect in minimizing LTL shortening.

Future epidemiological studies examining the extent to which MBB duration and frequency influence LTL are needed. Further, future work examining tissue and cell-specific telomere adaptations from exercise is warranted (30). Given the protective effects of telomerase activity (42), future epidemiological studies examining the effects of MBB on telomerase activity is warranted. Due to the combined effects of multiple health-enhancing behaviors on health (28,41), as well as LTL (16,17,36), future epidemiological work examining the additive and additive interaction effects of multiple health behaviors on LTL is warranted. Lastly, given that it is not entirely certain whether LTL is a cause or consequence of morbidity (e.g., cardiovascular disease), future longitudinal mediational models examining whether LTL mediates the relationship between MBB and morbidity/mortality is warranted. However, prospective studies are starting to emerge showing that shorter LTL is predictive of premature mortality from an increased risk of various chronic diseases (e.g., cardiovascular disease) (7), but several issues (e.g., methodology used to assess LTL and potential regression to the mean) need to be carefully considered when examining and interpreting the prospective interrelationships between PA, LTL, and morbidity/mortality (3).

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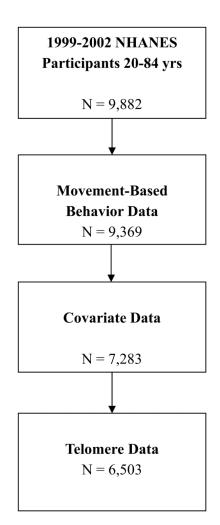
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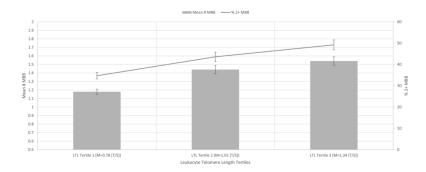
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**Figure 1.** Participant flow chart



**Figure 2.** Weighted mean number of movement-based behaviors (MBB) and the weighted proportion of adults having 2+ MBB across leukocyte telomere length (LTL) tertiles (Mean (M) LTL across the LTL tertiles was 0.78, 1.01, and 1.34 T/S).

 $\label{eq:Table 1} \textbf{Table 1}$  Weighted characteristics of the analyzed sample, NHANES 1999–2002 (N=6503).

	LTL Tertile 1 (n=2168)	LTL Tertile 2 (n=2168)	LTL Tertile 3 (n=2167)	P-Value †
Leukocyte telomere length (T/S ratio)	0.78 (0.77-0.79)	1.01 (1.00–1.02)	1.34 (1.31–1.36)	< 0.001
Moderate Physical Activity in past 30 days, %				
Yes	48.3 (44.8–51.8)	53.7 (49.3–58.1)	48.7 (43.7–53.5)	0.03
Vigorous Physical Activity in past 30 days, %				
Yes	28.7 (26.1–31.1)	39.2 (34.8–43.5)	45.0 (40.8–49.1)	< 0.001
Walked/Cycled in past 30 days, %				
Yes	19.9 (17.6–22.2)	23.7 (20.1–27.3)	27.7 (23.8–31.5)	< 0.001
Strengthening activities in past 30 days, %				
Yes	21.6 (18.2–25.0)	27.6 (24.3–30.9)	33.3 (29.9–36.6)	< 0.001
Mean # of Movement Behaviors	1.18 (1.11–1.25)	1.44 (1.32–1.56)	1.54 (1.42–1.66)	< 0.001
Sum # Movement Behaviors, %				
0	30.7 (27.0–34.3)	24.8 (21.3–28.3)	22.4 (19.7–25.2)	< 0.001
1	34.6 (32.0–37.1)	31.6 (29.3–33.8)	28.4 (25.3–31.6)	
2	21.8 (19.0–24.6)	22.7 (20.4–25.1)	26.1 (23.7–28.4)	
3	10.9 (9.0–12.9)	16.0 (13.5–18.5)	17.8 (14.5–21.0)	
4	1.8 (1.0–2.6)	4.7 (3.0–6.2)	5.1 (3.2–7.0)	
Age, yrs	52.7 (51.4–54.0)	44.6 (43.2–45.9)	38.2 (36.8–39.5)	< 0.001
Gender, %				
Male	51.7 (48.9–54.4)	47.4 (44.5–50.4)	49.0 (47.1–51.0)	0.10
Race-Ethnicity, %				
Mexican American	6.7 (3.9–9.5)	7.7 (5.7–9.8)	6.9 (4.9–8.9)	0.03
Other Hispanic	5.8 (1.2–10.5)	5.6 (2.6–8.6)	7.8 (4.4–11.2)	
Non-Hispanic white	76.4 (71.3–81.6)	75.3 (71.2–79.4)	68.6 (63.8–73.4)	
Non-Hispanic black	7.0 (4.9–9.1)	7.4 (5.2–9.7)	12.1 (9.1–15.1)	
Other	3.7 (2.0–5.5)	3.6 (2.5–4.8)	4.4 (2.5–6.3)	
Smoking Status, %				
Every day	19.7 (17.1–22.3)	20.4 (17.3–23.5)	21.8 (19.1–24.6)	< 0.001
Some days	2.6 (1.8–3.3)	3.4 (2.4–4.5)	5.5 (4.0–6.9)	
No longer smoke	30.9 (28.0–33.8)	25.3 (22.3–28.4)	19.7 (17.0–22.3)	
Never smoked	46.6 (43.1–50.1)	50.6 (47.5–53.8)	52.9 (48.4–57.3)	
Body Mass Index, kg/m <sup>2</sup>	28.6 (28.2–29.0)	28.0 (27.7–28.3)	27.4 (26.9–27.8)	< 0.001
Poverty-to-Income ratio	3.06 (2.8–3.2)	3.14 (2.9–3.3)	2.97 (2.7–3.2)	0.38
C-reactive protein, mg/dL	0.49 (0.44–0.54)	0.39 (0.36–0.42)	0.35 (0.31–0.39)	< 0.001

 $<sup>^{\</sup>dagger}$ Design-based likelihood ratio test used to determine statistical significance for the categorical variables. Linear regression used to determine statistical significance for the continuous variables by comparing tertile 3 vs. tertile 1.

Table 2

Weighted multivariable polytomous regression examining the odds of being in the two lower tertiles (vs. upper tertile) of leukocyte telomere length based on the degree of engagement in movement-based behaviors, NHANES 1999-2002 (N=6503).

	Tertil	Tertile 1 vs. Tertile 3	.3	Tertile	Tertile 2 vs. Tertile 3	3
# Movement Behaviors	OR	95% CI	Р	OR	I2 %56	Ь
1 vs. 0	0.97	0.78-1.22	0.84	1.02	0.86-1.21	0.73
2 vs. 0	0.76	0.61–0.96	0.02	0.86	0.70-1.07	0.18
3 vs. 0	0.71	0.52-0.98	0.04	0.98	0.70-1.37	0.92
4 vs. 0	0.48	0.29–0.78	0.004	1.08	0.73-1.60	0.67
Covariates						
Age, 1 yr older	1.05	1.01-1.09	0.008	1.04	1.01-1.07	0.004
Age-squared	1.00	0.99-1.01	0.53	1.00	0.99-1.01	0.38
Gender						
Female vs Male	0.80	0.68-0.94	0.008	1.04	0.88-1.22	0.59
Race-Ethnicity						
Mexican American vs. white	1.40	0.84–2.33	0.18	1.29	0.94–1.77	0.10
Other Hispanic vs. white	98.0	0.34-2.20	0.76	0.74	0.45-1.23	0.24
Non-Hispanic black vs. white	0.56	0.38-0.84	0.007	0.59	0.43-0.80	0.002
Other vs. white	86.0	0.56-1.71	96.0	0.84	0.52-1.36	0.48
Smoking Status						
Every day vs. never smoked	1.16	0.95-1.40	0.11	1.03	0.84-1.27	0.70
Some days vs. never smoked	0.72	0.46–1.11	0.13	0.78	0.51-1.18	0.23
No longer smoke vs. never smoked	1.07	0.90-1.27	0.39	1.03	0.85-1.26	69.0
Body Mass Index, 1 kg/m <sup>2</sup> increase	1.02	1.01–1.04	0.009	1.01	1.00-1.02	0.04
Poverty-to-Income ratio, 1 unit increase	86.0	0.89-1.08	0.80	1.00	0.94-1.05	96.0
C-reactive protein, 1 mg/dL increase	1.16	1.00-1.35	0.04	1.02	0.88-1.19	69.0