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The Association of Sarcopenia, Telomere Length and Mortality: Data from the NHANES 1999–2002

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Abstract

Background—Sarcopenia is defined as the loss of muscle mass or function with aging and is associated with adverse outcomes. Telomere shortening is associated with mortality, yet its relationship with sarcopenia is unknown.

Methods—Adults ≥60 years from the 1999–2002 NHANES with body composition measures were identified. Sarcopenia was defined using the two Foundation for the National Institute of Health definitions: appendicular lean mass (ALM) (men<19.75; women<15.02kg); or ALM divided by body mass index (BMI) (ALM:BMI, men<0.789; women<0.512). Telomere length was assessed using quantitative PCR. Regression models predicted telomere length with sarcopenia (referent=no sarcopenia).

Results—We identified 2,672 subjects. Mean age was 70.9 years (55.5% female). Prevalence of ALM and ALM:BMI sarcopenia was 29.2 and 22.1%. Deaths were higher in persons with sarcopenia as compared to those without sarcopenia (ALM: 46.4 vs. 33.4%; p<0.001; ALM:BMI: 46.7 vs.33.2%; p<0.001). No adjusted differences were observed in telomere length in those with/without sarcopenia (ALM: 0.90 vs. 0.92; p=0.74, ALM:BMI 0.89 vs. 0.92; p=0.24). In men with ALM:BMI defined sarcopenia, adjusted telomere length was significantly lower compared to men

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without sarcopenia (0.85 vs 0.91, p=0.013). With sarcopenia, we did not observe a significant association between telomere length and mortality (ALM: HR 1.11 [0.64, 1.82], p=0.68; ALM:BMI: HR 0.97 [0.53,1.77], p=0.91), but noted significance in those without sarcopenia with mortality (ALM: HR 0.59 [0.40, 0.86], p=0.007; ALM:BMI: HR 0.62 [0.42, 0.91]; p=0.01).

Conclusions—We observed a potentially inverse relationship between telomere length and mortality in those without sarcopenia but did not observe a significant relationship between telomere length and mortality in the presence of sarcopenia.

Keywords

sarcopenia; telomere; mortality; epidemiology; aging

Introduction

Sarcopenia has been defined as the loss of muscle mass and/or strength with aging[1]. The aging process can be affected by many epigenetic factors including smoking, air pollution, and diet[2–4]. Partly due to the impaired muscle enzymatic system that degrades reactive oxygen species, there is an increased exposure to these toxic entities that develops with aging that may hasten the development of sarcopenia[5]. This results in reduced redox regulation and leads to further increases in reactive oxygen species[6] both of which can lead to senescence[5].

Increased oxidative stress in the absence of preserved protective mechanisms can damage DNA, including telomere segments[7]. Telomeres are lengths of non-transcriptional DNA which serve to protect DNA from degradation[8], and their shortening is strongly associated with the aging process[9]. Smoking and exposure to air pollution are both known to cause oxidative stress and resultant shortening of telomeres, which in turn can have a significant negative impact on health[3, 10]. Individuals with shorter telomeres have a higher risk of developing cardiovascular disease[11], reduced angiogenic potential[12], and are at an increased risk of mortality[13].

Both sarcopenia and decreased telomere length are affected by oxidative stress and are each related to mortality[5, 8]. Yet, the relationship between these two entities is unknown. The purpose of this study was to evaluate the relationship between telomere length, sarcopenia, and mortality. The recently proposed sarcopenia definitions by the Foundation for the National Institutes of Health (FNIH)[14] were applied in this study to assist with the classification of individuals at risk for functional decline. We hypothesized that: 1) the presence of muscle mass defined sarcopenia among adults aged 60 and older is associated with decreased telomere length; and 2) that all-cause mortality will be directly associated with decreased telomere length and sarcopenia.

METHODS

Survey & Study Cohort

The National Health and Nutrition Examination Survey 1999–2002 (NHANES) is a cross-sectional survey that is representative of non-institutionalized, community-dwelling adults.

This study performed a secondary analysis of data from this specific survey. The Centers for Disease Control and Prevention has conducted this survey since 1971, and its content can be found at https://www.cdc.gov/nchs/nhanes/index.htm (accessed July 2016). The use of de-identified data exempted this study from review by the local institutional review board.

There were a total of 25,316 participants screened, of which 21,004 were interviewed and 19,759 were examined in a standardized mobile examination center. Individuals without telomere data or body composition data were excluded from the final analytic sample (n=8,044). As the prevalence of sarcopenia is higher in adults aged 60 and over[15], we restricted our analysis to this age group. Our final analytical cohort consisted of 2,672 subjects.

Body Composition Measures

Duel energy x-ray absorptiometry (DEXA), using a QDR-4500 Hologic Scanner (Bedford, MA), assessed body composition (muscle mass and body fat). This assessment excluded individuals with a height of >192.5 cm or a weight of >136.4 kg. All metal, excluding false teeth and hearing aids, was removed prior to assessment. Appendicular lean mass (ALM) was defined as the combined fat-free mass for all four extremities (arms and legs). We used the FNIH criteria for ALM-defined sarcopenia (<19.75kg in males, <15.02kg in females) and ALM adjusted for body mass index (BMI) (<0.789 kg for males, <0.512 kg for females). For this study, we defined obesity in males as a body fat percentage >25%, and for female >35%, as defined in our previous studies[16].

Telomere Data

Blood samples were obtained from participants, and the assay was performed at the University of California, San Francisco using quantitative polymerase chain reaction to compare the telomere length of the subjects relative to a standard reference DNA (T/S ratio)[17, 18]. Each sample was duplicated and assayed 3 times on 3 different days. Each assay plate contained 96 control wells with 8 control DNA samples. Assay runs with 8 or more invalid control wells, or those runs with more than 4 control DNA values falling outside 2.5 standard deviations from the mean for all assay runs were excluded from further analysis (<1% and <6% of runs, respectively). Potential outliers were also identified and excluded (<2% of samples). Control DNA values were used to normalize between-run variability. The mean and standard deviation of the T/S ratio were calculated. Interassay coefficient of variation was 6.5%. Quality control assurance and monitoring was regularly performed.

Baseline Characteristics

A self-report questionnaire assessed race, medical comorbidities, smoking status, and physical activity. All races were included (non-Hispanic White, non-Hispanic Black, Hispanic, and other). Smoking status was classified as never smoker, former smoker, and current smoker of cigarettes. Physical activity level was classified according to the degree of strenuousness (sitting, walking, light loads, and heavy loads). Anthropometric measurements were estimated to the nearest tenth of a centimeter on the right side of the body, except where amputations, casts, and other factors impeded such measurements. Weight was determined with an electronic digital scale (kilograms), and height (meters) was determined

by a stadiometer after deep inhalation. Body Mass Index (BMI) was calculated as weight (kilograms) divided by height squared (meters squared). Waist Circumference (WC) was measured standing at the height of the iliac crest by wrapping a tape around the trunk, making sure that it crossed the mid-axillary line at right angles.

Mortality Analysis

Data was obtained through the NHANES 1999–2002 survey which used a probabilistic match to a National Death Index, as well as information from the Social Security Administration to determine mortality status. Mortality data was complete up to December 31st, 2011. Cause of death was classified as cardiovascular (including stroke) or other, following the International Statistical Classification of Disease, Injuries and Causes of Death guidelines with the 9th revision used for those dying in 1999, and the 10th revision for all others. Procedures are in place to harmonize the differences in definitions and causes of death. Time of follow-up was calculated in months from interview date, to date of death or most recent vital record. Vital status was accounted for in >99% of our sample.

Statistical Analysis

All data was merged into a single dataset for analysis. Weighting using NHANES analytical procedures to account for the complex, stratified sampling was performed for all analyses. Continuous variables are represented as means ± standard errors, and categorical variables as counts (weighted percentages). T-tests compared means and chi-squares for categorical values, or their non-parametric equivalents assessed differences among baseline characteristics. Data are presented as the overall cohort age ≥60 years, by age group (60–69.9, 70–79.9, and ≥80 years), and by the presence/absence of sarcopenia based on the ALM and ALM:BMI definitions. Differences among age groups were tested by ANOVA. The primary goal was: a) to present the adjusted mean telomere length in those with/without muscle mass defined sarcopenia; b) assess the association of telomere length (independent variable) with mortality in those with and without sarcopenia. Three separate linear regression models were created: model 1 was unadjusted; model 2 adjusted for age, sex, race, education and smoking status; model 3 additionally adjusted for diabetes, congestive heart failure, non-skin cancer, coronary artery disease, and physical activity. Sex-specific modeling was also performed to ascertain mean adjusted telomere length. Separate Cox proportional hazard models were created to ascertain the risk of death with and without sarcopenia associated with telomere length. We further added a sarcopenia × telomere interaction in each model. Hazard ratios [95% confidence intervals] are presented. All analyses were performed with STATA version 13 (College Station, TX). A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics are presented in Table 1. Of the 2,672 participants, the mean age was 70.9±0.28 (49.1% females). The prevalence of ALM and ALM:BMI defined sarcopenia was 14.6 and 27.0%, in males, and 40.7% and 18.1%, in females, respectively. Patterns of clinical comorbidities, such as diabetes mellitus, congestive heart failure, and coronary artery disease vary based on the definition of sarcopenia. Table 2 displays the unadjusted

mean telomere length and death rates by sarcopenia definition. Telomere length decreased with age. The unadjusted telomere length in the over 60 age group was different in those with sarcopenia compared to those without sarcopenia (ALM: 0.90±0.02 vs. 0.92±0.02; p=0.09; ALM:BMI: 0.88±0.02 vs. 0.92±0.02; p=0.004). Examining the pre-specified age categories, the ≥80 year age group significantly demonstrated a difference between telomere length by sarcopenia status (ALM: 0.82±0.02 vs.0.86±0.02; p=0.02; ALM:BMI: 0.81±0.02 vs. 0.86±0.02; p=0.02). Overall mortality rates were higher with sarcopenia compared to without (ALM: 46.4 vs. 33.4%, p<0.001; ALM:BMI: 46.7 vs. 33.2%, p<0.001), as was cardiovascular mortality (ALM: 12.6 vs 7.7%; p=0.012; ALM:BMI: 14.0 vs 7.1%; p=0.008).

After adjusting for covariates (Table 3) no significant overall association was observed between telomere length and the presence of sarcopenia (ALM: 0.90 vs. 0.92, p=0.74; ALM:BMI 0.89 vs. 0.92, p=0.24). However, we observed sex-specific differences in the adjusted association of telomere length and sarcopenia. Adjusted telomere length was shorter in men (0.89±0.02 vs. 0.93±0.02; p<0.001). In men, a significant difference in telomere length was observed when the ALM:BMI definition of sarcopenia was applied and mean lengths were adjusted for age, race, education (Model 2: 0.85±0.02 vs 0.90±0.02; p=0.004). This difference remained between men with or without sarcopenia when means were adjusted for diabetes, congestive heart failure, non-skin cancer, coronary artery disease, arthritis, physical activity, and smoking status (Model 3: 0.85±0.02 vs 0.91±0.02; p=0.013). Further adjustment for CRP did not alter these differences (data not shown).

Table 4 highlights the univariate and multivariable models for the association of sarcopenia and telomere length with mortality. In the absence of sarcopenia, telomere length was significantly associated with overall mortality (ALM: HR 0.59 [0.40, 0.86]; ALM:BMI: HR 0.62 [0.42,0.91]. The presence of sarcopenia did not contribute to any significant differences in risk of death (ALM: HR 1.11 [0.64, 1.82]; ALM:BMI: HR 0.97 [0.53,1.77]). Importantly, an interaction was observed between sarcopenia and telomere length using both definitions of sarcopenia (p=0.03 and p=0.04, respectively) for overall mortality. We did not observe an association between telomere length and cardiovascular mortality.

DISCUSSION

The study results confirm the known inverse relationship between age and telomere length but despite our previously reported association between sarcopenia and mortality[16], we did not observe a significant relationship between telomere length and mortality. We also observed differences in telomere length by overall sarcopenia status in men only. Finally, increased telomere length, in the presence of sarcopenia, was not associated with reduced risk of mortality.

Telomere length was no different by overall sarcopenia status both univariately and multivariately in older adults. These results support those by Woo[19] and Mather[20] and differ slightly than the weak association observed in the Berlin Aging Study II[21] or by the results from Marzetti[22] who used the European Working Group on the Study of Sarcopenia[23]. We were surprised as sarcopenia has been shown to lead to shorter lifespans[23]. Aging also leads to both the development of sarcopenia and to telomere shortening. These findings provide an

important understanding as to the underlying biology. While aging[24, 25], telomere length[26] and sarcopenia[27] are all associated with pro-inflammatory cytokines, the lack of a causal relationship, perhaps due to the cross-sectional nature of the data, suggests that the impact of inflammation and/or differences in length may have occurred later in life. Using both the ALM and ALM:BMI definitions, we observed significantly higher telomere lengths in individuals without sarcopenia in the age ≥80 years, as compared to those with sarcopenia. These results may indicate a survivor effect of the very old that has been observed in other studies[28]. NHANES oversamples this age group as it is under-represented, and as such, future analyses should focus on this particular age demographic.

Importantly, we observed sex-specific differences in the relationship between telomere length and sarcopenia using the ALM:BMI definition of sarcopenia. Males with sarcopenia had lower telomere lengths than those without in all models. Estrogen has been shown to protect telomeres from oxidative stress[29] as evidenced by the longer telomere segments in females than in males. Previous studies have demonstrated conflicting results between sexes among the association of functional impairments, inflammation and mortality with muscle mass[16, 30]. In fact, this may partly be due to the adjustment of BMI which preferentially has different diagnostic accuracy for adiposity in males than in females[31]. This could also be due to differences in body composition between sexes and the distribution of adipose tissue[32]. Future research is needed to better understand the sex-specific changes that impact muscle biology.

The absence of sarcopenia suggests an improvement in overall mortality with higher telomere length. Epidemiologically, this is consistent with the inverse relationship between telomere length and death. Our study complements the literature evaluating telomere length and mortality, and expands the analysis to include sarcopenia. We deliberately used the standardized FNIH definitions to assess the telomere/sarcopenia relationship and found a weak interaction in our mortality models suggesting that sarcopenia modified the relationship between telomere length and mortality. One possible hypothesis is due to the impact of increased inflammation on telomere length. Muscles release myokines with each contraction, which serve a protective role[33] against chronic diseases associated with low-grade inflammation[34]. We speculated that the decreased muscle mass among those with sarcopenia would contribute to fewer anti-inflammatory mediators being released following contractions, and thus expose muscles to a more pro-inflammatory environment. This would cause myocyte apoptosis and atrophy[8].

There was no statistically significant relationship observed between cardiovascular mortality and telomere length in those with and without sarcopenia. A number of potential reasons could explain these results. First, we were reliant on cause of death from death certificates. Second, the number of deaths in each category was rather low. Third, our results confirm those by Rode et al who demonstrated a lack of a relationship between telomere length and cardiovascular mortality[35]. Recently, some authors have proposed a robust hypothesis that telomere length is inversely associated with atherosclerosis and its outcomes. This paradigm was based on an accelerated rate of telomere length attrition due to heightened oxidative stress and inflammation. In a more pro-inflammatory environment, telomeres experience more rapid shortening[8]. The number of inflammatory mediators assessed in NHANES are

minimal and do not include important cytokines (IL-1, IL-6, TNF-a). Even after adjusting for C-reactive protein, our results were no different (data not shown). We could not ascertain the progression of telomere length shortening for each participant throughout their lifetime, nor could we ascertain the extent of inflammation or change in telomere length each participant experienced. Testing and evaluating these theories in this population requires not only larger sample sizes but markers of inflammation beyond C-reactive protein.

NHANES collects and analyzes telomere length in a highly standardized manner which allows for more consistent comparisons across the study populations. Telomere assays were performed at the University of California, a distant site to laboratory collection and processing. The integrity of the analysis and the long-term degradation of the samples are dependent on multiple factors, including storage, DNA extraction, processing, transportation and de-thawing. This may ultimately impact the results observed. Importantly, the ability to relate clinical measures to biological biomarkers is a unique strength of NHANES. Yet, the cross-sectional nature of the study does not allow for the determination of causality. This iteration of NHANES does not contain data on muscle strength which has better predictive validity in ascertaining long-term outcomes than muscle mass. Muscle strength has been shown to be a better mortality predictor in older adults[36]. Additionally, while the analysis accounted for the complex, stratified, sampling, the results cannot be extrapolated to a non-institutionalized population who may be at higher risk for developing sarcopenia than community-dwelling persons. While the mean age of the sample is within the range observed in the FNIH validation cohorts, it nonetheless suggests that this cohort may not approximate populations at highest risk. Lastly, we acknowledge that this survey lends itself to self-report bias.

Implications

This research has a number of important potential clinical implications for future studies. Our results provide preliminary evidence that while reduced telomere length may predict mortality in older adults, telomere length in individuals with sarcopenia, due to complexities of adiposity associated with sarcopenia, may have less predictive validity and may not be as useful of a biomarker as originally believed. Telomeres could potentially be used in healthier populations to predict longer term outcomes, earlier in the disablement process. Future research should evaluate the relationship between telomere length in individuals with sarcopenia defined using a measure of muscle strength (ie: grip strength) to confirm/refute this relationship. Telomere lengths are dependent on lifelong physical activity. Even though we adjusted for self-reported physical activity, without having a firm understanding of a life-course approach to such suggests that it may act as a confounding factor, as a sedentary lifestyle increases the risk of death. Future studies should evaluate such longitudinal approaches but also further evaluate inflammatory conditions of older adults, such as osteoarthritis, rheumatoid arthritis, chronic low grade infections, and dementia, and evaluate these diseases in relation to telomere length and sarcopenia.

CONCLUSIONS

In the presence of sarcopenia, decreased telomere length had no potentially significant effect on predicted mortality in adults age 60 and older.

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ABBREVIATIONS

ALM	appendicular lean mass
BMI	body mass index
CDC	Centers for Disease Control and Prevention
DEXA	dual-energy x-ray absorptiometry
FNIH	Foundation for the National Institutes of Health
NHANES	National Health and Nutrition Examination Surveys
WC	waist circumference

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Table 1

Baseline Characteristics of Included Subjects: NHANES 1999–2002 Cohort

	Overall	ALM			ALM:BMI		
		Present	Absent	P-value	Present	Absent	p-value
Age, years ± s.e.	70.9±0.28	73.4±0.42	69.6±0.33	<0.001	72.0±0.32	70.2±0.30	<0.001
Female Sex	1, 312 (49.1)	530 (40.7)	743 (59.3)	<0.001	278 (18.1)	955 (81.9)	<0.001
Weight, kg	77.5±0.40	60.4±0.48	84.5±0.44	<0.001	78.5±0.89	77.3±0.46	0.22
Race				<0.001			<0.001
Hispanic American	664 (7.8)	241 (10.9)	405 (6.4)		269 (13.4)	360 (6.0)	
Non-Hispanic White	1,557 (82.7)	461 (82.9)	1,045 (82.9)		346 (81.0)	1,103 (83.3)	
Non-Hispanic Black	397 (6.9)	34 (2.2)	345 (8.6)		24 (2.0)	347 (8.1)	
Other	54 (2.7)	22 (4.1)	30 (2.1)		14 (3.7)	38 (2.5)	
Co-Morbid Conditions							
Hypertension	1,192 (88.5)	323 (88.0)	824 (88.6)	0.83	300 (85.9)	802 (88.8)	0.28
Diabetes Mellitus	537 (16.9)	113 (11.6)	537 (18.9)	0.002	153 (21.8)	343 (15.2)	0.01
Congestive Heart Failure	175 (6.2)	62 (7.6)	102 (5.3)	0.11	62 (9.4)	94 (5.0)	0.009
Non-skin cancer	471 (20.6)	136 (20.3)	317 (20.6)	0.90	128 (26.0)	268 (14.9)	<0.001
Stroke	186 (6.7)	60 (8.0)	113 (5.8)	0.08	57 (8.6)	102 (5.5)	0.09
COPD	252 (11.6)	102 (17.4)	145 (9.4)	0.002	71 (13.8)	167 (11.1)	0.26
Osteoporosis	60 (2.0)	18 (2.3)	35 (1.7)	0.47	15 (2.3)	32 (1.6)	0.34
Kidney Disease	61 (4.0)	18 (3.1)	42 (4.4)	0.38	22 (5.1)	37 (3.7)	0.46
Coronary Artery Disease	444 (18.0)	119 (18.0)	303 (17.6)	0.82	128 (26.0)	268 (14.9)	<0.001
Arthritis	1,241 (49.2)	347 (49.8)	854 (49.0)	0.82	317 (50.7)	843 (48.5)	0.60
Current Smoker				0.002			0.86
Current	326 (12.2)	114 (16.2)	201 (10.7)		79 (11.6)	225 (12.3)	
Never	1,253 (47.0)	385 (50.9)	825 (45.4)		293 (46.8)	879 (47.3)	
Former	1,087 (40.8)	256 (32.9)	797 (44.0)		280 (41.7)	740 (40.3)	
Physical Activity Level				0.11			0.02

	Overall	ALM			ALM:BMI		
		Present	Absent	P-value	Present	Absent	p-value
Sits	780 (27.8)	213 (26.1)	506 (26.8)		204 (31.1)	466 (23.9)	
Walks	1,521 (56.4)	457 (59.3)	1,042 (56.5)		366 (52.6)	1,106 (59.6)	
Light Loads	300 (13.8)	74 (13.7)	223 (14.2)		65 (14.0)	227 (14.4)	
Heavy Work	63 (2.1)	11 (0.95)	49 (2.6)		16 (2.2)	43 (2.1)	
Anthropometric Measures							
% Body Fat	36.9±0.15	37.4±0.29	36.7±0.19	0.05	39.6±0.38	36.2±0.19	<0.001
ALM	19.8±0.12	14.4±0.10	22.0±0.11	<0.001	18.5±0.28	20.2±0.12	<0.001
% Skeletal Mass	60.7±0.001	60.1±0.003	60.9±0.002	0.03	58.1±0.004	61.5±0.002	<0.001
BMI, kg/m^2	28.2±0.14	24.1±0.19	29.8±0.16	<0.001	30.3±0.24	27.6±0.17	<0.001
WC, cm	99.6±0.29	88.4±0.52	104.2±0.37	<0.001	104.5±0.74	98.2±0.33	<0.001

Data are mean ± standard errors or counts (%). Data are weighted according to the National Health and Nutrition Examination Survey protocol

Abbreviations: ALM: appendicular lean mass; BMI – body mass index; COPD – chronic obstructive pulmonary disease; WC – waist circumference;

Cutpoints for ALM were <19.75kg and <15.02kg in males and females, and for ALM:BMI were <0.789 kg and <0.512 kg

Table 2

Unadjusted Mean Telomere Length and Death Rates by Sarcopenia Definition

	ALM Definition			ALM:BMI Definition		
Age Group	**Present**	**Absent**	**P-value** *	**Present**	**Absent**	**p-value**
Age > 60 years	0.90±0.02	0.92±0.02	0.09	0.88±0.02	0.92±0.02	0.004
60–69.9 years	0.96±0.02	0.96±0.02	0.86	0.96±0.03	0.96±0.02	0.89
70–79.9 years	0.90±0.03	0.87±0.02	0.36	0.85±0.03	0.88±0.02	0.11
80+ years	0.82±0.02	0.86±0.02	0.02	0.81±0.02	0.86±0.02	0.02
p-value#	<0.001	<0.001	----	<0.001	<0.001	----
	ALM Definition			**ALM:BMI Definition**		
Deaths	**Present**	**Absent**	**P-value**	**Present**	**Absent**	**p-value**
Overall	380 (46.4)	640 (33.4)	<0.001	288 (46.7)	668 (33.2)	<0.001
Cardiovascular	116 (12.6)	156 (7.7)	0.012	95 (14.0)	155 (7.1)	0.008

All values are mean ± standard error. Data are weighted according to the National Health and Nutrition Examination Survey protocol

ALM: Appendicular lean mass
ALM defined sarcopenia is defined as an appendicular lean mass <19.75 in men, or <15.02 in females;
ALM:BMI defined sarcopenia is defined as ALM:BMI ratio <0.789 and <0.512.

p-value represents the difference between age categories (60–69.9, 70–79.9, 80+)

* p-value represents difference in telomere length in subjects with/without sarcopenia

Table 3

Multivariable Analysis of Adjusted Mean Telomere Length with Sarcopenia Definition

	ALM Sarcopenia		P-value	ALM:BMI Sarcopenia		P-value
Overall	**Present**	**Absent**		**Present**	**Absent**	
Model 1	0.90±0.02	0.92±0.02	0.09	0.88±0.02	0.92±0.02	0.004
Model 2	0.89±0.02	0.92±0.02	0.74	0.88±0.02	0.92±0.02	0.13
Model 3	0.90±.02	0.92±0.02	0.74	0.89±0.02	0.92±0.02	0.24
Males						
Model 1	0.85±0.02	0.90±0.02	0.01	0.85±0.02	0.91±0.02	<0.001
Model 2	0.86±0.02	0.90±0.02	0.45	0.85±0.02	0.90±0.02	0.004
Model 3	0.86±0.02	0.90±0.02	0.56	0.85±0.02	0.91±0.02	0.013
Females						
Model 1	0.91±0.02	0.94±0.02	0.08	0.93±0.03	0.93±0.02	0.99
Model 2	0.90±0.02	0.93±0.02	0.94	0.92±0.03	0.93±0.02	0.54
Model 3	0.91±0.02	0.93±0.02	0.94	0.93±0.03	0.93±0.02	0.47

All values are adjusted mean ± standard error

Data are weighted according to the National Health and Nutrition Examination Survey protocol

ALM: Appendicular lean mass
ALM defined sarcopenia is defined as an appendicular lean mass <19.75 in men, or <15.02 in females;
ALM:BMI defined sarcopenia is defined as ALM:BMI ratio <0.789 and <0.512.

Model 1: no adjustment
Model 2: adjusted for age, gender, race, education, smoking status
Model 3: adjusted for model 2 plus diabetes mellitus, congestive heart failure, non-skin cancer, coronary artery disease, arthritis, physical activity

p-value represents the difference in telomere length between individuals with and without sarcopenia

Table 4

Telomere Length and Risk of Death by Sarcopenia Status

	ALM Sarcopenia		Sarcopenia## Telomere interaction	ALM:BMI sarcopenia		Sarcopenia## Telomere interaction
Overall Death	**Present**	**Absent**		**Present**	**Absent**	
Model 1	0.39 [0.23, 0.66]	0.30[0.20,0.44]	0.47	0.50[0.28,0.90]	0.25[0.17,0.37]	0.06
Model 2	1.01[0.61,1.67]	0.57[0.39,0.83]	0.05	0.98[0.53,1.79]	0.56[0.38,0.81]	0.02
Model 3	1.11[0.64,1.82]	0.59[0.40,0.86]	0.03	0.97[0.53,1.77]	0.62[0.42,0.91]	0.04
Cardiovascular death						
Model 1	0.26[0.10,0.69]	0.25[0.11,0.55]	0.97	0.48[0.17,1.34]	0.17[0.08,0.39]	0.13
Model 2	0.83[0.32,2.14]	0.54[0.25,1.16]	0.50	1.05[0.37,2.98]	0.41[0.19,0.91]	0.08
Model 3	0.86[0.33,2.23]	0.57[0.26,1.26]	0.48	0.95[0.32,2.75]	0.49[0.22,1.08]	0.15

All values represented are hazard ratios [95% confidence interval]. Reference category is no sarcopenia, based on ALM or ALM:BMI defined sarcopenia

Model 1: no adjustment
Model 2: adjusted for age, gender, race, education, and smoking
Model 3: adjusted for model 2 plus diabetes mellitus, congestive heart failure, non-skin cancer, coronary artery disease, arthritis, physical activity