Title Page:

Effect of adiposity on leukocyte telomere length in US adults by race/ethnicity: The National Health and Nutrition Examination Survey

Short title:

Adiposity and leukocyte telomere by race/ethnicity in the US

Author list:

[1]Sharon K. Davis, PhD (Corresponding author)

[1]Ruihua Xu, PhD

[1]Rumana J. Khan, PhD

[2]Amadou Gaye, PhD

[3]Yie Liu, PhD

1National Institutes of Health, National Human Genome Research Institute, Social Epidemiology Research Unit, Bethesda, MD, United States of America, **2** National Institutes of Health, National Human Genome Research Institute, Cardiovascular Disease Section, Bethesda, MD, United States of America, **3**National Institutes of Health, National Institute of Aging, Section for Telomere Maintenance, Baltimore, MD, United States of America

Abstract

Objective

Obesity is associated with telomere attrition – a marker of cellular and biological aging. The US has the highest proportion of obesity and is comprised of a racially/ethnic diverse population. Little is known about the relationship between obesity and telomere attrition according to race/ethnicity in the US. Our objective is to examine the differential association.

Design and setting

The effect of body mass index (BMI), % total body fat (TBF) and waist circumference (WC) on leukocyte telomere length (LTL) were examined as adiposity measures according to race/ethnicity and sex specific race/ethnicity using separate adjusted linear regressions on a sample of 4,919 respondents aged 20-84 years from cross-sectional 1999-2002 data using the US National Health and Nutrition Examination Survey. Mediation analyses assessed health behaviors associated with relationship between adiposity measures and LTL.

Main outcome measure

LTL

Results

African Americans (AA) experienced a 28% and 11% decrease in LTL associated with increasing BMI and WC, (p=.02 and .03) respectively. Mexican Americans (MA) experienced a 33% decrease in LTL associated with increasing %TBF (p=.04). Whites experienced a 19%, 23%, and .08% decrease in LTL associated with increasing BMI, %TBF, and WC, (p=.05, .003, .02) respectively. White men experienced a 26% decrease in LTL due to increasing BMI (p=.05). AA women experienced a 41%, 44%, and 16% decrease in LTL due to increasing BMI, %TBF, and WC, respectively (p=.007, .02, .04). White women experienced a 29% decrease in LTL associated with increasing %TBF (p=.006). Selected health behaviors were associated with the relationship between adiposity measures and LTL.

Conclusion

Overall, AA and Whites have worse cellular and biological aging related to collective adiposity measures. According to sex, AA women experienced more deleterious cellular and biological

aging. Findings suggest tailored interventions to improve adverse behaviors that contribute to obesity may improve telomere attrition in US adults.

Introduction

Secular rates of risk factors associated with cardiovascular disease (CVD) have been declining among US adults across all racial/ethnic groups.[1] Obesity rates, on the other hand, have increased. [2] Worldwide obesity has nearly tripled since 1975.[3] The US has the highest proportion of obesity.[2] More than one-third of US adults are obese.[4] Prevalence rates differ by race/ethnicity and by sex according to race/ethnicity.[4] Obesity is a major risk factor for many age-related CVD chronic conditions such as hypertension, type 2 diabetes and dyslipidemia which increases the risk for heart failure, heart attack and stroke.[5] It is the leading cause of preventable deaths globally and occurs, in part, due to adverse modifiable lifestyle behaviors such as sedentary physical activity and unhealthy diet.[3]

Telomeres are the DNA-protein complex at the ends of chromosomes.[6] It consists of highly conserved tandem hexameric nucleotide repeats (TTAGGG). Telomere are needed for the replication of DNA and provides protection to chromosomes from nuclease degradation and cellular senescence which promotions the integrity and stability of chromosomes. During the cellular process, telomeres progressively shorten with each cell division. When telomeres shorten to a critical length, replicative senescence is triggered resulting in cell-cycle arrest.[7] In human peripheral leukocytes, telomere shortening has been demonstrated to be a maker for cellular and biologic aging as well as a biomarker for age-related diseases such as CVD.[8] Evidence shows that the pathways through which obesity promotes morbidities include increasing systemic inflammation and oxidative stress; inflammation and oxidative stress have also been linked to telomere attrition.[9-11] Studies have investigated the relationship between adiposity and

telomere length. Such studies have produced equivocal results [12-20]. Studies have also examined the association between adverse lifestyle health behaviors and telomere length with similar mixed results. [19, 21-26] One factor that may account for these conflicting findings may be inadequate statistical power due to small sample size, study design, and sample characteristics. Little is known about racial/ethnic differences between adiposity and telomere length. In addition, we are unaware of any studies that have investigated adverse health behaviors as a pathway associated with adiposity and telomere length. The objective of our research was to examine a large US representative, socioeconomically and racially/ethnic diverse population. This represents the first study to examine adiposity and telomere length according to race/ethnicity, sex according to race/ethnicity and mediating pathways due to adverse lifestyle in the US. We hypothesize that the association between telomere length and adiposity will be moderated by race/ethnicity and sex. We further hypothesize that adverse health behaviors will have a mediating effect between adiposity and telomere length. Findings will provide important information about the rate of biological aging due to telomere length and adiposity across major race/ethnic groups in the US and according to corresponding sex; as well as the implications associated with adverse health behaviors.

Materials and Methods

Study design and sampling procedures

Data was collected from the 1999-2000 and 2001-2002 cycles of the National Health and Nutrition Examination Survey (NHANES). This is a nationally representative cross-sectional survey and physical examination of civilian, noninstitutionalized US population conducted by the US Centers for Disease Control and Prevention (CDC) since 1960.[27] NHANES utilizes a 4- stage sampling design which includes 1) primary sampling units (PSUs) consisting of single

92 counties, 2) area segments within PSUs, 3) households within segment areas, and 4) persons
93 within households. On average 2-3 individuals per household were sampled. NHANES 1999-
94 2002 oversampled low-income individuals, African Americans and Mexican Americans to
95 obtain more accurate estimates in these populations. All respondents aged ≥20 during this period
96 were asked to provided DNA specimens to establish a national probability sample of genetic
97 material for future research. DNA from the most recent NHANES is only available in the form
98 of crude lysates of cell lines thereby precluding the assay of leukocyte telomere length (LTL).
99 However, DNA collected during 1999-2002 is purified from whole blood thus facilitating the
100 assay of LTL. Pooled data were available for public download
101 (http://www.cdc.gov/nchs/nhanes_questionnaires.htm).
102 Of the 10,291 respondents eligible to provided DNA, 7,825 provided DNA and consented
103 to future genetic research. We excluded 653 respondents whose self-reported race/ethnicity was
104 "other" or "other Hispanic," since our goal was to examine more discrete self-reported
105 race/ethnic groups (i.e. White, African American, Mexican American). We also excluded 225
106 respondents aged ≥85 because of survival bias among the extreme elderly.[28] An additional
107 2,037 were excluded due to missing data on one or more variables in the models - resulting in a
108 final sample size of 4,919. There were no significant sociodemographic differences between the
109 full sample and the final sample. Sampling weights were used to address oversampling and non-
110 response bias and to ensure that estimates are representative of the general US population.
111 Written informed consent was obtained from each participant. Human subject approval was
112 provided by the Institutional Review Board (IRB) at the CDC and the study protocol was
113 approved by the IRB of the National Institutes of Health.
114 **Data and data collection**

Aliquots of purified DNA were provided by the laboratory of the CDC. DNA was isolated from whole blood using the Puregene (D-50K) kit protocol and stored at -80^0. The LTL assay was performed in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, using the quantitative polymerase chain reaction (PCR) method to measure telomere length relative to standard reference DNA (T/S ratio).[29] The single-copy gene was used as a control to normalize input DNA was human beta-globin. Each sample was assayed twice. T/S ratios that fell into the 7% variability range were accepted; the average of the two was taken as the final value. A third assay was run for samples with greater than 7% variability and the average of the two closest T/S values was used. The inter-assay coefficient of variation was 4.4%.

Body mass index (BMI), estimated % total body fat, and waist circumference were analyzed separately as measures of adiposity. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2) using a calibrated electronic digital scale and a stadiometer. Estimated % total body fat was assessed using duel-energy X-ray absorptiometry of the whole body that lasted 3 minutes (Hologic scanner, QDR-4500, Bedford, MA, USA). Total % body fat was calculated as total body fat mass divided by total mass x 100. Waist circumference was measured in centimeters using a tape measure around the trunk, at the iliac crest, crossing at the mid-axillary line. The details of these assays have been described elsewhere.[30]

Adverse health behaviors were assessed as pathway mediators between adiposity exposures and LTL outcome; these include smoking, drinking, physical activity, and diet. Smoking was measured a cumulative exposure to tobacco smoke in pack-years, calculated as the average number of cigarettes smoked per day times the number of years smoked divided by 20 (number of cigarettes in one pack).[31] Dummy variables were 30-=>59 pack years, <30 pack

138 years, and never smoked was coded as the reference. Drinking was based on daily alcohol
139 consumption defined as heavy, moderate and abstainer.[27] Heavy drinkers were defined as
140 women reporting having drunk ≥2 alcoholic beverages in the past 12 months per day and men
141 reporting having drunk ≥3 alcoholic beverages in the past 12 months per day. Moderate drinkers
142 were defined as women reporting <2 drinks per day in the past 12 months and men reporting <3
143 drinks per day in the past 12 months. Men and women reporting no alcoholic beverages in the
144 past 12 months per day were the reference and defined as abstainers. Physical activity was based
145 on guidelines provided by the Department of Health and Human Services.[32] Respondents met
146 or exceeded recommended guidelines if they reported ≥150-≥300 minutes per week of physical
147 activity, such as brisk walking, gardening, and muscle-strengthening based on total number of
148 minutes reported for each activity. Those reporting <150 minutes of physical activity per week
149 were below the recommended guidelines. Diet was based on The Healthy Eating Index (HEI)
150 developed by the US Department of Agriculture in 2005.[33] The score is the sum of 10
151 components representing different aspects of a healthy diet. Each component of the index has a
152 maximum score of 10 and a minimum score of zero. The maximum overall score for the 10
153 components combined is 100. An overall index score ≥ 80 implies a "good" diet, an index score
154 between ≥51and 80 implies a diet that "needs improvement," and an index score <51 implies a
155 "poor" diet.

156 Race/ethnicity was based on self-reported non-Hispanic White, non-Hispanic Black and
157 Mexican American thereto referred to as White, African American and Mexican American.
158 Confounding demographic variables that may affect the relationship between adiposity and
159 telomere length included age in years at the time of the survey, age^2, sex, socioeconomic status
160 based on Poverty Income Ratio (PIR), adiposity related health outcomes, markers of

inflammation and oxidative stress, and characteristics of the blood from which DNA was extracted. PIR was calculated as the ratio of income to the poverty threshold for a household of a given size and composition. PIR values below 1.00 are below the official poverty threshold as defined by the US Census Bureau.[34] Adiposity related health status was based on respondents answer to the questions "have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure and "have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" Markers of inflammation and oxidative stress included C-reactive protein (CRP) and gamma glutamyltransferase (GGT) measured from serum. Characteristics of the blood samples from which DNA was extracted included white blood cells (μL), lymphocytes (%), monocytes (%), neutrophils (%), eosinophils (%), and basophils (%).

Statistical methods

Descriptive analysis was performed stratified by total sample, African American, Mexican American and White according to study variables. Continuous variables are presented as means ± standard deviation based on ANOVA and categorical variables as percent based on chi-square. Leukocyte telomere length was log-transformed by natural logarithm prior to modeling. Multivariate linear regression models were fitted to assess the relationship between LTL and each adiposity measure. We report the percentage change in the average value of telomere length for a one-unit change in a predictor variable based on the beta estimate for telomere length as the outcome. All regression models accommodated the complex sampling design of NHANES by incorporating strata and PSU indicators, as well as sample weights for the genetic subsample.[35] We first compared the association between LTL and each adiposity measures stratified by each race/ethnic group. We then stratified separately by sex according to

race/ethnic group. The models for stratified race/ethnic groups was adjusted for age, age^2, sex, PIR, hypertension status, type 2 diabetes status, CRP, GGT, white blood cells, lymphocytes, monocytes, neutrophils, eosinophils, and basophils. Sex, hypertension status and type 2 diabetes status were entered as categorical variables. Age, age^2, PIR, CRP, GGT and the characteristics of blood was entered as continuous variables. The use of age along with a age^2 term is important when analyzing LTL given the strength of its association with age and the potential for nonlinearity in this association. The models stratified by men and women according to race/ethnicity included the same adjustments as those for the race/ethnicity models – excluding sex.

To assess the moderating effect of race/ethnicity and sex, we entered an interaction term for each adiposity measure in a total aggregate model. We also examined moderating effects by assessing stratified models separately according to race/ethnicity and sex by comparing corresponding parameter estimate across race/ethnic groups and sex using *z*-test (African American versus White, African American versus Mexican American, White versus Mexican American, men versus women). A significant *z*-test suggest moderating effects of race/ethnicity and sex.[36] The mediating effect of each adverse behavior between adiposity measure and LTL was tested separately with a series of regression models using methodological extensions to accommodate categorical mediators.[37, 38] Models included confounding variables adjusted in the aggregate total model. We calculated Arioan test using standardized coefficients of the indirect effects of adiposity on LTL through smoking, drinking, physical activity, and diet. A significant Arioan *z* test suggests a significant indirect effect of adiposity measure and LTL via a candidate mediator. [38] We calculated the proportion of each of the mediators associated with

206 the individual adiposity measure and LTL.[39] We also fitted all 4 mediators as covariates in the
207 final regression model. The mathematical equation formula for Arioan *z* test is:

208 $$Z_{mediation} = \frac{Z_a Z_b}{\hat{\sigma}_{Z_{ab}}} = \frac{\frac{a}{Sa} \times \frac{b}{Sb}}{\sqrt{Z_a^2 + Z_b^2 + 1}}$$

209 All analyses were conducted using SAS version 9.3.[40] A two-tailed level of
210 significance was established as $P \leq .05$.

211 **Results**

212 Descriptive results in Table 1 reveal African Americans have longer mean LTL (1.13
213 T/S) compared to the total sample, Mexican Americans, and Whites (1.06, 1.04, 1.05 T/S,
214 respectively). The average mean age for the total sample and Whites was somewhat similar (46
215 versus 47 years) with younger age observed in African Americans and Mexican Americans (42
216 versus 38 years). The distribution of women and men was also comparable in the total sample
217 and among Whites (51% versus 49%). African Americans had a higher proportion of women; a
218 lower proportion was in Mexican Americans (53% versus 46%). The prevalence that lived
219 below poverty was lower in the aggregate sample and among Whites (18% and 14%) and a
220 higher prevalence was among African Americans and Mexican Americans (32% and 31%).
221 Mean body mass index and mean waist circumference was slightly higher among African
222 Americans (29kg/m^2 and 96cm) compared to the other groups; mean % total body fat was similar
223 across all groups. A lower prevalence of African Americans and Mexican Americans smoked 30-
224 ≥59 pack years of cigarettes (3.3% and 1.9%); prevalence of non-smokers was also higher in
225 these groups (61% and 62%). The prevalence of all groups smoking <30 pack years of cigarettes
226 was somewhat similar. A lower prevalence of African Americans were heavy drinkers (18%)
227 compared to a higher prevalence among Mexican Americans (33%). The prevalence of moderate
228 drinking was higher in the total sample and among Whites (50% and 53%). The prevalence of

abstainers was higher among African Americans (44%). A higher prevalence of African Americans and Mexican Americans were below the recommended level of physical activity per week (56% and 53%). The aggregate sample and Whites had a higher prevalence that met/exceeded the recommended guidelines (61% and 65%). The mean HEI score was somewhat comparable across groups, except slightly lower in African Americans. However, the prevalence of hypertension was higher among African Americans and lower among Mexican Americans (33% versus15%) but comparable in the total sample and in Whites (25%). Mexican Americans as well as African Americans had a higher prevalence of type 2 diabetes (7% and 8%) compared to a comparable lower prevalence in Whites and the total sample (5%). Mean CRP and GGT was higher among African Americans (0.51mg/dL and 42U/L). White blood cell count was lower in African Americans and higher in Mexican Americans compared to the other groups (6.4µL versus 7.30µL). The % of lymphocytes, monocytes, and basophils was higher in African Americans (35%, 8.5%, .68%, respectively). However, percentages of neutrophils and eosinophils were higher among Whites and the total sample (59.3% and 2.7%).

Table 1: Total and race/ethnic specific weighted characteristics of study variables, NHANES[a] 1999-2002 (N=4919)

	Total (N=4919)		African American (N=919)		Mexican American (N=1262)		White (N=2738)		
	%	Mean(SD)[b]	%	Mean(SD)[b]	%	Mean(SD)[b]	%	Mean(SD)[b]	*P*-value
Leukocyte telomere length (T/S Ratio)		1.06(.01)		1.13(.02)		1.04(.02)		1.05(.02)	<.0001
Age, years (20-<85)		46.0(.42)		42.4(.48)		38.3(.56)		47.1(.46)	<.0001
Gender									.003
Women	50.8		53.6		45.8		50.9		
Men	49.2		46.4		54.2		49.1		
Poverty income ratio									<.0001
Below poverty	17.6		32.6		31.3		14.6		

Meet and above poverty	82.4		67.4		68.7	85.4	
Body mass index (kg/m^2)		27.9(.16)		29.5(.31)	28.2(.24)	27.6(.18)	<.0001
% Total body fat		33.7(.19)		33.1(.39)	33.6(.38)	33.8(.23)	<.0001
Waist circumference (cm)		95.6(.38)		96.2(.62)	94.7(.54)	95.6(.45)	<.0001
Pack years smoked							<.0001
30->=59	8.7		3.2		1.8	9.8	
<30	36.8		35.4		36.2	37.2	
0	54.5		61.2		62.0	53.0	
Drinking level per day							<.0001
Heavy	20.9		17.6		33.3	20.2	
Moderate	50.1		38.6		32.7	53.2	
Abstainer	29.0		43.8		34.0	26.6	
Physical activity recommendation level per week							<.0001
Below	38.5		56.4		53.4	35.0	
Meet / Exceed	61.4		43.5		46.6	64.0	
Healthy Eating Index Score (2005)		50.7 (.46)		48.2(.67)	51.5 (.45)	51.0 (.55)	<.0001
Hypertension	25.1		33.3		15.1	25.0	<.0001
Type 2 Diabetes	5.3		8.4		6.9	4.8	<.0001
CRP[c] (mg/dL)		.39(.01)		.51(0.04)	.43(.04)	.38(.01)	<.0001
GGT[d] (U/L)		30.7 (.70)		41.8 (2.7)	34.8 (1.2)	29.0 (.74)	<.0001
White blood cell count (SI)		7.1 (.06)		6.4 (.06)	7.3 (.06)	7.1 (.06)	<.0001
Lymphocyte (%)		29.8 (.21)		35.3 (.24)	30.5 (.21)	29.1 (.23)	<.0001
Monocyte (%)		8.1 (.04)		8.4 (.10)	7.7 (.10)	8.1 (.04)	<.0001
Neutrophils (%)		58.6 (.22)		52.8 (.29)	58.4 (.32)	59.3 (.24)	<.0001

Eosinophils (%)	2.7 (.02)	2.7 (.06)	2.6 (.10)	2.7 (.03)	<.0001
Basophils (%)	.66(.02)	.68(.01)	.61(.01)	.66(.02)	<.0001

[a]NHANES, National Health and Nutrition Examination Survey

[b]SD, standard deviation

[c]CRP, C-reactive protein

[d]GGT, gamma glutamyltransferase

Adiposity and LTL according to each race/ethnic group

The results for the adjusted association comparing adiposity measures and LTL differences according to each race/ethnic group are presented in Table 2. Findings reveal LTL significantly decreased 28% and 11% for each unit increase in BMI and waist circumference in African Americans, respectively. LTL significantly decreased 33% in Mexican Americans due to increasing % total body fat. Whites experienced a significant 19%, 23%, and .08% decrease in LTL associated with increasing BMI, % total body fat, and waist circumference, respectively. There was no significant association between LTL and % total body fat in African Americans or BMI and waist circumference in Mexican Americans.

Table 2: Adjusted ordinary least squares regression of log-transformed LTL[a] (T/S ratio) on adiposity stratified by individual race/ethnic group, NHANES[b]1999-2002

	African American[c]		Mexican American[c]		White[c]	
Adiposity	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
BMI	-.0028 (-.0053, -.0004)	.02	-.0012 (-.0044,.0019)	.43	-.0019 (-.0037,.000003)	.05
% total body fat	-.0023 (-.0049, 0.0002)	.07	-.0033 (-.0066, -0.0001)	.04	-.0023 (-.0037, -.0008)	.003
Waist circumference	-.0011 (-.0020, -.0001)	.03	-.0003 (-.0015,.0009)	.59	-.0008 (-.0016, -.0001)	.02

[a]LTL, Leukocyte telomere length

[b]NHANES, National Health and Nutrition Examination Survey

[c]Adjusted for age, age^2, sex, PIR, hypertension, type 2 diabetes, CRP, GGT, white blood cells, lymphocytes, monocytes, neutrophils, eosinophils, basophils.

Adiposity and LTL by sex specific race/ethnicity

Findings comparing differences in the association of LTL and adiposity measures according to sex specific race/ethnic groups are presented in Table 3. There was no association between any of the adiposity measures and LTL in African American and Mexican American men. Only White men experienced a 26% significant decrease in LTL associated with increasing BMI and increasing waist circumference was marginally associated with a 11% decrease in LTL. African American women experienced a significant 41%, 44%, and 16% decrease in LTL due increasing in BMI, % total body fat and waist circumference, respectively. Increasing % total body fat resulted in a significant 29% decrease in LTL in White women. There was no association with any of the adiposity measures in Mexican American women.

Table 3: Adjusted ordinary least squares regression of log-transformed LTL[a] (T/S ratio) on adiposity comparing race/ethnic group stratified by sex, NHANES[b] 1999-2002

	Men[c]					
	African American[c]		Mexican American[c]		White[c]	
Adiposity	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
BMI	-.0016 (-.0060, .0028)	.46	-.0025 (-.0079, .0029)	.34	-.0026 (-.0053,.0001)	.05
% total body fat	-.0012 (-.0055,.0032)	.58	-.0041 (-.0092,.0011)	.11	-.0018 (-.0042,.0005)	.12
Waist circumference	-.0008 (-.0025,.0010)	.37	-.0009 (-.0029,.0011)	.36	-.0011 (-.0022, .0001)	.06

	Women[c]					
	African American[c]		Mexican American[c]		White[c]	
Adiposity	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
BMI	-.0041 (-.0070, -.0012)	.007	-.0003 (-.0037,.0031)	.85	-.0017 (-.0039,.0005)	.12
% total body fat	-.0044 (-.0081, -.0007)	.02	-.0028 (-.0069,.0012)	.16	-.0029 (-.0048, -.0009)	.006
Waist circumference	-.0016 (-.0031, -.0001)	.04	.0003 (-.0015,.0020)	.77	-.0007 (-.0017, .0004)	.19

[a]LTL, leukocyte telomere length

[b]NHANES, National Health and Nutrition Examination Survey

[c]Adjusted for age, age^2, PIR, hypertension, type 2 diabetes, CRP, GGT, white blood cells, lymphocytes, monocytes, neutrophils, eosinophils, basophils.

Moderating and mediator effects

The moderating effect of race/ethnicity and sex was not associated with adiposity measures and LTL as evidenced by non-significant *z* scores. The *z* score for BMI is $z_{\text{African American vs White}} = .03$, $P = .97$, $z_{\text{African American vs Mexican Americans}} = -.33$, $P = .74$, $z_{\text{White vs Mexican American}} = -.37$, $P = .70$. The *z* score for % total body fat is $z_{\text{African American vs White}} = .97$, $P = .32$, $z_{\text{African American vs Mexican Americans}} = 1.02$, $P = .30$, $z_{\text{White vs Mexican American}} = .20$, $P = .83$. The *z* score for waist circumference is $z_{\text{African American vs White}} = .22$, $P = .82$, $z_{\text{African American vs Mexican Americans}} = -.39$, $P = .69$, $z_{\text{White vs Mexican American}} = -.64$, $P = .52$. For sex the *z* score for BMI is $z_{\text{men vs women}} = -.51$, $P = .60$, for % total body fat $z_{\text{men vs women}} = .14$, $P = .88$, and for waist circumference $z_{\text{men vs women}} = -.49$, $P = .61$. There was also no significant interaction for race/ethnicity and sex in the aggregate model (data not presented). Therefore, the test of mediation for health behaviors associated with LTL and adiposity measures was performed on the full sample due to the lack of moderating effects. Table 4 presents the combined results associated with separate linear regression analysis without

311 adjustment for mediators, with adjustment for mediators, and separate test of mediation for each
312 health behavior contributing to the relationship between adiposity measure and LTL. Results
313 revealed BMI and waist circumference were associated with relatively similar significant
314 relationships with decreased LTL after adjustment for mediators as indicated by the *p* values in
315 model 1 and model 2. However, the association between LTL and % total body fat disappeared
316 after adjustment for mediators ($p = .07$).

317 **Table 4**: Adjusted ordinary least squares regression of log-transformed LTL (T/S ratio) on adiposity for the total
318 sample without mediators, with mediator effects and the effect of mediators between adiposity and LTL, NHANES
319 1999-2002
320

	Model 1[a]		Model 2[b]				
Adiposity	β (95% CI)	*P*-value	β (95% CI)	*P*-value			
BMI	-.0018 (-.0032, -.0004)	.01	-.0015 (-.0030, -.0002)	.02			
% Total Body Fat	-.0022 (-.0034, -.0010)	.001	-.0019 (-.0033, -.0005)	.07			
Waist Circumference	-.0007 (-.0013, -.0002)	.007	-.0006 (-.0011, -.0001)	.02			
Adiposity/Mediator			β (95% CI)	*P*-value	MP[c]	$Z_{mediation}$	*P*-value
BMI							
Pack Years Smoked							
30->=59	*	*	-.0379 (-.0734, -.0023)	.03	.04	-.45	.65
<30	*	*	.0065 (-.0123, .0255)	.48	.01	.11	.90
0	*	*	Reference	*	*	*	*
Drinking Level per Day							
Heavy	*	*	.0232 (-.0110, .0573)	.17	.09	-1.05	.29

Moderate	*	*	.0098 (-.0148, .0344)	.42	.13	-.94	.34
Abstainer	*	*	Reference	*	*	*	*
Physical Activity Level per Week							
Below	*	*	-.0128 (-.0259, .0004)	.05	.35	-1.93	.05
Meet / Exceed	*	*	Reference	*	*	*	*
Healthy Eating Index	*	*	.0011 (.0004, .0018)	.003	.28	-1.84	.06
% Total Body Fat							
Pack Years Smoked							
30->=59	*	*	-.0386 (-.0742, -.0030)	.03	.21	2.10	.03
<30	*	*	.0055 (-.0138, .0248)	.56	.02	.26	.79
0	*	*	Reference	*	*	*	*
Drinking Level per Day							
Heavy	*	*	.0227 (-.0114, .0568)	.18	.08	-1.17	.24
Moderate	*	*	.0099 (-.0144,.0343)	.41	.07	-.93	.35
Abstainer	*	*	Reference	*	*	*	*
Physical Activity Level per Week							
Below	*	*	-.0115 (-.0247, .0016)	.08	.29	-1.87	.06
Meet / Exceed	*	*	Reference	*	*	*	*
Healthy Eating Index	*	*	.0011 (.0004, .0018)	.004	.25	-2.33	.01
Waist Circumference							
Pack Years Smoked							
30->=59	*	*	-.0367 (-.0724, -.0011)	.04	.15	-1.55	.11

<30	*	*	.0068 (-.0121, .0257)	.46	.004	.08	.94
0	*	*	Reference	*	*	*	*
Drinking Level per Day							
Heavy	*	*	.0236 (-.0101, .0573)	.16	.06	-.91	.36
Moderate	*	*	.0101 (-.0141, .0343)	.40	.09	-.95	.34
Abstainer	*	*	Reference	*	*	*	*
Physical Activity Level per Week							
Below	*	*	-.0126 (-.0258, .0007)	.06	.32	-1.95	.05
Meet / Exceed	*	*	Reference	*	*	*	*
Healthy Eating Index	*	*	.0011 (.0004, .0018)	.003	.28	-2.14	.03

[a]Adjusted for race, age, age^2, sex, PIR, Hypertension, Type 2 diabetes, CRP, GGT, white blood cells, Lymphocytes, monocytes, neutrophils, eosinophils, basophils.

[b]Additionally adjusted for mediators - pack years smoked, drinking level per day, physical activity level per week, diet based on Healthy Eating Index.

[c]MP**,** mediated proportion.

Findings regarding the mediation effects of adverse health behaviors reveal that 30-=>59 pack years smoked was associated with about a 4% decrease in LTL for each unit increase in BMI (p =.03); however, it was not a significant mediator ($z_{30\text{-=>}59 \text{ pack years}}$ = -.45, p= .65). Alcohol consumption per day was also not a significant mediator between LTL and BMI. On the other hand, physical activity below the recommended guidelines was associated with a 1.28% decrease in LTL and BMI (p =.05) and accounted for 35% of the relationship ($z_{\text{physical activity}}$ = -1.92, p =.05). Diet as measured by HEI was associated with a 11% increase in LTL for each unit

increase in BMI (p=.003); however, it was marginally associated with the correlation (z_{HEI} = -1.83, p = .06).

Smoking 30-=>59 pack years was associated with a 4% decrease in LTL and increasing % total body fat (p=.03) and was a significant mediator contributing 21% of the association ($z_{30-=>59\ pack\ years}$ = -2.52, p = .03). Physical activity below recommended guideline was marginally correlated with 1.15% decrease in LTL for each unit increase in % total body fat (p=.08) and was a marginal mediating factor ($z_{physical\ activity}$ = -1.86, p = .06). Diet based HEI resulted in a 11% increase in LTL due to increasing % total body fat (p=.004) and was responsible for 25% of the relationship (z_{HEI} = -2.32, p =.01).

30-=>59 pack years smoked was associated with a 4% decrease in LTL for each unit increase in waist circumference (p =.04); however, it was not a significant mechanism between the association ($z_{30-=>59\ pack\ years}$ = -1.55, p=.11) Physical activity below the recommended guidelines resulted in a 1.26% marginal decrease in LTL and waist circumference (p=.06) but was a mediating effect responsible for 32% of the relationship ($z_{physical\ activity}$ =-1.95, p = .05). Diet measured by HEI was associated with a 11% increase in LTL and waist circumference (p=.003) and significantly contributed 28% to the mechanism between the association (z_{HEI} = -2.14, p = .03).

Discussion

The objective of our study was to assess the association between adiposity measures and LTL in a representative US sample population comprised of major racial/ethnic groups and demonstrate mediation effects based on adverse health behaviors. As a group, African Americans experienced shorter telomere length associated with BMI and waist circumference. Whites, on the other hand, experienced shorter telomere length for each of the measures. Only % total body

fat correlated with shorter telomere length in Mexican Americans. This finding may reflect how adiposity is concentrated in Mexican Americans. We observed a steeper decline in telomere length associated with BMI in African Americans compared to Whites. It has been demonstrated that regional and whole-body adiposity, including skeletal muscle and bone, differ by race/ethnicity and may not adequately reflect adiposity measures when comparing one race/ethnic group to another.[41] Our stratified findings may support this theory.

When analyzed separately by sex, we found no association with any of the adiposity measures and telomere length in African American or Mexican American men. African American and Mexican American men tend to be leaner compared to African American and Hispanic American women. [42] Only BMI was associated with shorter telomere length in White men. The fact that only one adiposity measure was correlated with shorter telomere length is consistent with this group having a lower overall prevalence of obesity.[42]

We observed opposite findings for women. For instance, African American women experienced shorter telomere length related to increases in each of the adiposity measures. This finding is not surprising given African American women have the highest prevalence of obesity compared to men and women in other racial/ethnic groups.[42] One theory suggests African American women are a unique group susceptible to obesity due to mechanisms associated with dietary preferences and early childbearing.[43] It may also be due to differences in metabolism and perceptions about an ideal body.[44] As with Mexican American men, we found no correlation in Mexican American women associated with any of the exposure measures and telomere length. We were surprise to find the lack of association in Mexican American women given the high prevalence of obesity in Hispanic women.[42, 45] National prevalence rates are generally based on aggregate data of Hispanics in general and does not consider ethnic

differences within Hispanics. Our findings on Mexican American women may reflect such heterogeneity and may not be indicative of obesity status in Mexican American women. Only % total body fat was correlated with shorter telomere length in White women. This is not a unique finding given White women have an overall lower prevalence of obesity. [42] The difference in the association by sex that we observed may be due to several factors – including environmental and hormonal.[11, 19]

Our findings regarding adverse health behaviors as mediators revealed physical activity per week below the recommended guideline was a mechanism associated with the relationship between BMI and shorter telomere length. 30-=>59 pack years smoked was a pathway between % total body fat and shorter telomere length while an improvement in diet was associated with an increase in telomere length and % total body fat. Inadequate weekly physical activity was also a causal pathway between waist circumference and shorter telomere. An improvement in diet was a mechanism between longer telomere length and waist circumference. Level of drinking per day was not a mediator between any of the adiposity indices and telomere length.

There are conflicting findings regarding the relationship between adiposity and telomere length in the literature.[26] Lee and colleagues, for instance, studied 345 White individuals in the greater Dayton, Ohio and demonstrated individuals with higher total and abdominal adiposity have shorter telomere length.[12] Findings from two studies using national NHANES data similarly revealed an increase in BMI, waist circumference and % total body fat was associated with a decrease in LTL in the aggregate sample which reflect our findings.[14, 15] An investigation of the Cardiovascular Health Study, on the other hand, found no association between telomere length and BMI and waist circumference.[16] A study by Maceneay et al of 67 middle-aged and older adults also revealed no correlation between normal and

406 overweight/obese BMI parameters with telomere length.[18] A study of 322 postmenopausal
407 women residing in Seattle, Washington revealed no association with BMI and % body fat.[19]
408 Few studies have compared the association between adiposity and telomere length
409 according to race/ethnicity and concomitant sex. We could find only one study of 317 White and
410 African American adults residing in South Carolina.[17] The investigators found no relationship
411 between BMI and visceral fat in Whites, African Americans or by sex.

412 Other studies with a racial/ethnic homogenous sample population also produced mixed
413 results. A Swedish study show selective adiposity measures were associated with a decrease in
414 telomere length only in women.[46] An investigation in Denmark revealed an inverse association
415 between BMI and telomere length.[47] A recent study found obesity was related to shorter
416 telomere length in Latina women.[48] However, a study sample of Koreans showed waist
417 circumference was negatively associated with telomere length.[49] These conflicting findings
418 between adiposity and cellular aging as measured by telomere length may be due to several
419 factors -including study design, participant characteristics, a small study sample and other
420 limitations.

421 Obesity is a major risk factor for chronic morbidities and is due, in large part, to adverse
422 modifiable lifestyle factors.[5] The predominant mechanism through which obesity may shorten
423 telomere length and increase risk of aging-related diseases include increased oxidative stress,
424 which increase telomere erosion, inflammation and accelerates leukocyte turnover.[9-11] A non-
425 biological mechanism contributing to telomere attrition may also include adverse behaviors
426 factors.[26] Several studies have established a parallel relationship between adverse lifestyle
427 factors and telomere length. Patel el al, for instance, found lack of physical activity resulted in
428 shorter telomere length among US adults.[24] A national sample of US women likewise found

smoking, unhealthy diet and lower physical activity was correlated with telomere attrition.[25] Other investigations fail to establish a correlation.[19, 21, 22] None have assessed the relationship associated with adverse lifestyle between obesity and telomere length. Our investigation was designed to examine health behaviors as mediators between adiposity and telomere length. Findings demonstrate selective lifestyle behavior factors as a potential causal pathway. Such a relationship suggest improvements in lifestyle may reduce biological aging and prevent telomere cell senescence due to obesity.

Limitations

There are some caveats to our study that require consideration. First, we do not know the direction of the relationship between adiposity and LTL. Some researchers argue that selective adoption may be a causal factor related to telomere length.[50] Selective adoption could occur either because telomere length directly affects behavior or because behavior affects telomere length, or both are affected by a third variable – such as exposure to early-life adversity. In addition, telomere senescence occurs overtime and may present in some cases with a U-shaped pattern.[51] The NHANES is a cross-sectional survey and changes in LTL may come before exposure. Therefore, the correlations we observed should not be interpreted as causal. One way to address these important issues is to design longitudinal analysis to measure the bi-directional effect of differences in LTL and adiposity overtime before obesity event. Second, although we adjusted for potential confounders – other unmeasured confounding factors may exist resulting in "omitted variable bias" such as heritability, ancestry, menopausal status, adiposity biomarkers (i.e. leptin and adiponectin) and sex-hormones that may affect our findings. Third, we measured telomere length only in leukocytes. Whether our findings can be extrapolated to other tissues is unclear. However, studies have demonstrated robust correlations between LTL and telomere

length in other tissues.[52, 53] Fourth, our mediation measures are subject to measurement error even though they have been validated and proven to be accurate in other studies.[54-56]

Despite, these limitations, our study has many strengths. It is comprised of a representative major racial/ethnic sample of US adults from which findings can be extrapolated. It is among the largest and first study to investigate the association of adiposity and telomere length according to race/ethnicity and sex specific race/ethnicity. Finally, we investigated the causal pathway between adiposity and telomere length based on potential modifiable lifestyle behavioral factors. Our detailed measurements of lifestyle and dietary factors enabled us to make categories that were consistent with current guideline on lifestyle and diet which can subsequently be translated into public health intervention messages.

Conclusion

Telomere length is a measure of biological and cellular aging.[11] Obesity is increasing at an epidemic rate and is associated with several age-related health conditions.[5, 57] Several studies have investigated the relationship between adiposity and telomere length.[12-19] Ours is the first to assess such a relationship in a US representative sample according to race/ethnicity and corresponding sex. Our findings reveal that African Americans and Whites have a worse overall profile regarding the association between collective adiposity measures and telomere length. White men experienced decreased telomere length due to increasing BMI and there was no relationship observed in African American and Mexican American men. White women only experienced shorter telomere length due to increasing % total body fat. African American women experienced shorter telomere length associated with increases in each of the adiposity measures and have a more deleterious health profile based on sex. Our findings also reveal selective adverse lifestyle factors as a mechanism underlying the relationship between adiposity

and LTL which portend modifying such factors may result in improvements in cellular and biological aging due to obesity among US adults.

Author Contributions

Conceptualization, design, acquisition of data: Sharon K. Davis

Statistical analysis: Ruihua Xu and Sharon K. Davis

Interpretation of data: Sharon K. Davis, Ruihua Xu, Rumana J. Khan, Amadou Gaye, Yie Liu

Writing first draft: Sharon K. Davis

Writing, review and editing: Sharon K. Davis, Ruihua Xu, Rumana J. Khan, Amadou Gaye, Yie Liu

All authors approved the final version of the manuscript to be published and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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