Title: Social Disparities in Telomere Length among Older U.S. Adults: Differences by Race/Ethnicity, Gender, and Age

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Abstract

Telomeres are recognized as fundamental to the human aging process and telomere length (TL) is hypothesized to be a biomarker of aging. Prior research suggests shorter TL is associated with older age, male gender, and Caucasian race. However, little is known about differences in TL across race/ethnicity and gender or how differences vary by age in older adults. This study examines the social patterning of TL among older adults by simultaneously characterizing differences within and between race/ethnic and gender groups across age. Data are from the 2008 Health and Retirement Study. We found women and blacks have longer TL, yet black women maybe driving differences in TL by race/ethnicity and gender. Differences by race/ethnicity and gender did not vary across age, yet race/ethnic differences were greater among women than men across age. These findings suggest the importance of investigating disparities in TL using multiple dimensions of identity and social status.

Background

Telomeres are recognized as fundamental to the human aging process and telomere length (TL) is hypothesized to be a biomarker of aging. Telomeres are repeating DNA sequences that cap the ends of chromosomes and gradually shorten with age. TL, ideally, has the potential to estimate an individual's preclinical health and physiological function and thus may be a useful index of biological age that guides preventive or therapeutic interventions, as well as contribute to the understanding of disparities in the aging trajectory (Sanders et al., 2012). However, the research linking TL to health is mixed and dependent upon the outcome and study sample, thus it is unclear whether TL actually is a good biomarker of cellular age. Shortening in telomere length has been equivocally linked to oxidative stress, inflammation, chronic diseases, mortality, stress exposure, and cumulative disease burden (Bakaysa et al., 2007; Blackburn, 2000; Blackburn, 2005; Brouilette, Singh, Thompson, Goodall, & Samani, 2003; Ehrlenbach et al., 2009; Farzaneh-Far et al., 2008; Fitzpatrick et al., 2007; Needham et al., 2013; Sanders et al., 2012; Willeit et al., 2010). In addition, the research describing the social patterning of TL is inconsistent and further limits the application of TL as a biomarker of aging at the population level.

Evidence for gender and race/ethnic differences in TL is mixed. The majority of studies on gender differences in TL find that women have longer TL on average than men (Gardner et al., 2014). The reverse, however, has been reported in the Newcastle studies of older adults (Adams et al., 2007; Martin-Ruiz et al., 2011). Furthermore, several studies have found no gender differences in TL (Hunt et al., 2008; Needham et al., 2013; Shiels et al., 2011). Most studies that consider race differences in TL report longer TL in African Americans compared to whites (Adler et al., 2013; Hunt et al., 2008; Needham et al., 2013). At least two studies report shorter TL in African Americans. Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), Diez Roux and colleagues (2009) found that African Americans had shorter TL than whites, after adjusting for socioeconomic characteristics and health behaviors. Geronimus et al. (2010) also found shorter TL among African Americans compared to whites in a cohort of middle aged women. Only two TL studies, to our knowledge, have examined TL in Hispanics. One study found that Hispanics had shorter TL compared to whites (Diez Roux et al., 2009) while another found no differences (Needham et al., 2013).

Much of the prior research on gender and race/ethnic differences in TL is based on non-representative samples. Differences in study populations may account for some of the conflicting findings on differences in TL. Although one study has examined differences in TL in a national sample of U.S. adults ages 20-84, it did not focus specifically on differences among older adults. It remains unclear, therefore, how TL differs by gender and race/ethnicity in the older adult population. Finally, few studies have examined differences in TL by gender and race/ethnicity, though there is some evidence that gender differences vary by race/ethnicity (Hunt et al., 2008; Needham et al., 2013). The current study uses data from the nationally representative Health and Retirement Study (HRS) to examine gender and race/ethnic differences in TL among adults ages 54 and older.

Data and Measures

We use data from the nationally representative Health and Retirement Study (HRS). The HRS is an ongoing, biennial study of adults ages 50 and older that began in 1992 (Soldo, Hurd, Rodgers, & Wallace, 1997). In 2008, a random one half of sampled households were selected to receive an Enhanced Face-to-Face (EFTF) Interview that included collection of saliva from respondents. Of those selected for the EFTF, 5,808 respondents consented and provided saliva, representing an overall completion rate of 84% . Saliva was collected using an Oragene Collection Kit and TL assays were performed by Telomere Health (Telomere diagnostics.; Aviv et al., 2011; Cawthon, 2002).

We restrict our analyses to 5,392 respondents ages 54 and older. We also excluded 79 respondents who did not identify a white, black or Hispanic and 33 respondents with implausible values on TL (values greater than four standard deviations from the mean). Finally, 52 respondents were excluded because they had missing information on other covariates included in the analyses. The final analytic sample consisted of 5,228 community-dwelling adults ages 54 and older.

Telomere Length Ratio

Telomere length is measured from saliva, which has been shown to be highly correlated with blood leukocyte TL (r= 0.72) (Mitchell et al., 2014). Mean TL was assayed using quantitative PCR (qPCR) by comparing telomere sequence copy number in each patient's sample (T) to a single-copy gene copy number (S), resulting in a T/S ratio (Aviv et al., 2011; Cawthon, 2009).

Race/Ethnicity and Gender

Race/ethnicity was measured based on self-identified reports as white, black, or Hispanic. We then created six categories to identify respondents by their race/ethnicity and gender: white women, white men, black women, black men, Hispanic women and Hispanic men.

Covariates

We include sociodemographic and socioeconomic factors that might account for race/ethnic and gender differences in TL. Age is measured in years. Marital Status was categorized as married/partnered, divorced/separated, widowed, and never been married. Educational attainment was measured using number of years of completed education and categorized as less than 9 years, 9-11 years, 12 years, and 13 or more years. Employment status is a dichotomous variable indicating the respondent was currently employed. Total household income and wealth (assets minus debts) are self-reported. Both income and wealth were categorized into quartiles since they were not normally distributed.

Because some studies have found that TL is associated with obesity, physical activity, and smoking (Bekaert et al., 2007; Diez Roux et al., 2009; Fitzpatrick et al., 2007), and individual differences in health behaviors may account for gender and race/ethnic differences in TL, we include several health behavior measures. Obesity was calculated as a BMI>30 based on self-reported height and weight. We also measured physical inactivity using a dichotomous variable. Physical activity was

measured from reports of frequency of moderate or vigorous physical activity in the past 12 months. Those who did not engage in either vigorous or moderate physical activity more than once a week were considered inactive. Smoking status was categorized into never, former, or current smoker.

Analytic Strategy

Linear regression models were used to establish the bivariate intergroup age, gender, and race differences in TL. Model 1 included age, gender and race; model 2 further adjusted for demographics and SES measures including marital status, education, employment status, income, and wealth; and model 3 added adjustments for health behaviors including obesity, smoking status, and physical inactivity. Similarly, we then used linear regression modes with the same three model progression (M1: age; M2: add demographics and SES measures; M3: add health behaviors), but included each race/gender group separately in the models. After fitting these models we conducted pairwise comparisons of the margins between each race/gender group to estimate age adjusted race and gender intragroup differences. We used Stata's pwcompare command and determined differences in TL between groups where $p<.05$. All analyses were weighted to correct for differential probability of selection and non-response bias in the sample (using the respondent-level weight for the 2008 physical measures subsample). All regression models were adjusted for the plate numbers used in assaying TL based on the 6 different dilution factors. All analyses were performed using Stata software version 13.

Results

Table 1 describes the demographics and distribution of the covariates in the full sample and for each race/ethnic and gender group. On average whites were older, had higher education and higher levels of income and wealth relative to blacks and Hispanics. The proportion of obese, inactive and current smokers was higher among blacks and Hispanics compared to whites. Black women had the longest mean TL length (mean[SD]=1.5[0.4]), followed by Hispanic men (mean[SD]= 1.4[0.4]) and women (mean[SD]= 1.4[0.3]) and black men (mean[SD]= 1.4[0.5]). White men and women had the shortest mean TL (mean[SD]=1.3[0.4]).

Table 2 shows results from multivariate models of mean TL by age, gender, and race/ethnicity. Model 1 presents coefficients without adjustment for other characteristics. TL decreased by 0.004 (SE=0.00) with every one year increase in age. Women had longer TL than men ($\beta=0.03$, SE=0.01). Additionally, both blacks ($\beta=0.12$, SE=0.02; $p<0.001$) and Hispanics ($\beta=0.04$, SE=0.02; $p<0.10$) had longer TL than whites, though the difference was smaller and only marginally statistically significant for Hispanics. Model 2 shows these differences remained after adjusting for marital status, education, employment status, income, and wealth. Model 3 shows the differences after further adjusting for health behaviors (smoking, obesity, physical inactivity). Age and black-white differences remained, but gender and Hispanic-white differences were no longer statistically significant.

We further explored race/ethnic and gender differences in TL in Table 3 using pairwise comparisons of all groups. Model 1 shows age-adjusted differences

between groups. Blacks had longer telomeres compared to whites and black women had longer telomeres than all other groups. White men had the shortest TL than any other race/ethnic and gender group, though the difference with Hispanic men was not statistically significant. Both white and black women had longer telomeres than their male counterparts, however there were no significant gender differences in telomere length among blacks. Yet, health behaviors (Table 3, model 3) accounted for the difference between white men and women, while sociodemographic and SES measures (Table 3, model2) accounted for the difference between Hispanic women and white men. Neither health behaviors, sociodemographic or SES measures accounted for other differences in telomere length by race/gender groups.

Finally, we estimated how race/ethnic and gender differences in TL vary with age. Figure 1 shows the mean T/S ratio by race/ethnicity across age for women and men separately. Both black women and men have the highest TL across all ages relative to Hispanic and white men and women. Additionally, race/ethnic differences in TL are greater among women than men across age.

Discussion

The purpose of this study was to examine the interactive effects of race/ethnicity and gender on TL by age in a racially and socioeconomically diverse population based sample of older adults. We found that women had longer TL than men, which is consistent with most of the literature examining gender differences in TL (Gardner et al., 2014). However, two prior studies using Newcastle data, one in adults 50 years of age and the other in 85+, found that men had longer TL than women (Adams et al., 2007; Martin-Ruiz et al., 2011). These findings may differ from ours due to the age differences in the samples. We also found that Blacks had longer TL than whites. This is consistent with data from NHANES (Needham et al., 2013), ABC (Adler et al., 2013), and the Family Heart Study (Hunt et al., 2008) that examined race differences in older adults. Further, our results show that Hispanics had longer TL than whites, however this difference disappeared after accounting for sociodemographic and SES measures. This finding is consistent with NHANES, who found no difference in TL between Hispanics and whites in a representative sample of adults ages 20-84.

When examining race and gender differences simultaneously, we don't find a gender difference among blacks unlike Needham et al. (2013). However, we do find that white women have longer TL than white men, until we adjust for demographic and SES measures. Further, black women had the longest TL than all groups except black men. This is in contrast to Geronimus et al. (2010) who found that black women had shorter TL than white women in a very select sample of middle aged women 49-55. Moreover, differences between black women and other race/ethnic and gender groups were largely unaffected after accounting for health behaviors, sociodemographic and SES measures. Thus, it may not be the case that women and blacks have longer TL, as prior studies have reported, but that black women have much longer TL compared to other groups. In addition, we found that black women had consistently higher TL across age relative to both white and Hispanic women.

Our findings also demonstrated that significantly shorter telomeres were independently linked to the very old, males, and whites. Demographic and SES

measures accounted for the race differences between Hispanic women and white men, while health behaviors (smoking, obesity, physical inactivity) accounted for the for the gender difference between white men and women. Thus, the health advantage for women is largely accounted for by the differences in social roles, SES, and health behaviors between men and women.

Theoretical and empirical evidence suggest that black women experience accelerated aging and thus would reflect biological weathering in TL in later life. Yet, in this study we found that black women show an advantage with respect to TL while research has generally found black women to have worse health. One hypothesis that may explain why findings show that black women appear to have longer TL is a result of selection effects (e.g. greater mortality among black women than other groups), a common issue in socioeconomically and ethnically diverse population studies of older adults. Thus, the black women remaining in the HRS at older ages may be healthier or unrepresentative of all black women. Another potential hypothesis is that black women are born with longer TL and remain longer over the life course. Prior research has fairly consistently demonstrated that females are born with longer telomeres reflecting the known health advantage associated with the female gender (Aubert, Hills, & Lansdorp, 2012). Yet, blacks have equivocally been shown to have longer TL at birth (Okuda et al., 2002; Rewak et al., 2014) and the observed black advantage in TL at birth remains largely understudied. Additional research has shown that girls and blacks maintain longer TL into adolescence (Zhu et al., 2011), thus our findings extend prior research showing longer TL for black women continues into older adulthood.

This paper has a number of strengths that differentiate our findings from other studies. First, we use a nationally representative study of older adults with a strong study design. This allowed us to examine TL in an ethnically and socioeconomically diverse sample of whites, blacks and Hispanics. Second, our study looks strictly at an older adult age range when indicators of biological age would be most relevant and visible. Lastly, we had a sample size large enough to look at both race and gender differences simultaneously, which likely inhibited similar analyses in other studies.

This study has several limitations. First, we used cross-sectional data and thus cannot study change or age dependent shortening across age. While our findings suggest that race/ethnic differences did no vary across age, recent population based studies observed that TL was longer in blacks, but age-dependent TL shortening was faster than in whites (Aviv, Shay, Christensen, & Wright, 2005; Hunt et al., 2008). Further, both the Bogalusa Heart and NHLBI study found that longer TL in blacks was age dependent; middle-aged blacks were advantaged relative to whites, but that advantage disappeared in older adults (Aviv et al., 2005; Chen et al., 2009; Hunt et al., 2008). Thus, it may be that the slope or rate of change is more important than the length.

Second, even though we had a large sample of older adults, we did not have enough participants to do age specific models in the oldest old (80+), and sample sizes are significantly reduced in the oldest black and Hispanic populations. Thus, our results may not be representative in older subgroups of the sample. Third, method specific biases have been shown to matter for gender and race differences

(Elbers et al., 2014; Gardner et al., 2014). For example, southern blot is the only method that has shown unequivocal sex differences where women have longer TL than men. This analysis uses qPCR which has been inconsistent in showing these differences, thus this study may underestimate gender differences (Gardner et al., 2014). Lastly, it may be that the association between race/ethnicity and gender in TL varies by cell type. For example, in adults, lymphocytes have been shown to have shorter TL than granulocytes (Aviv et al., 2005). However, as previously mentioned, saliva has been shown to be highly and significantly correlated with blood leukocyte TL (Mitchell et al., 2014)and thus maybe appropriate for cross study comparisons. Empirically, there are still questions on whether TL is a biomarker of aging for a whole organism or a biomarker of aging for specific tissues (Gardner et al., 2014).

Conclusion

In summary, our findings suggest that women and blacks have longer TL, yet black women may be driving distinct differences in TL by race/ethnicity and, to a lesser degree, gender. Differences by race/ethnicity and gender did not vary across age, yet race/ethnic differences in TL were greater among women than men across age. Thus, important differences in the social patterning of TL may be masked if TL is examined separately by gender, race/ethnicity, and age.

Is telomere length a good indicator of biological aging? Our findings suggest that TL may be useful in characterizing gender and race differences in health outcomes specific to aging populations. TL may be one way in which clinicians, researchers and health professionals are able to identify preclinical biological risk and group based health disparities in older adult populations. The broader public health impact of our findings suggest the importance of investigating social disparities in TL using multiple dimensions of identity and social status in understanding population variation. It is not enough to look at only gender differences or only race differences in TL since our findings suggest both have important distinctions for TL in older adults. In future analyses, longitudinal data are needed to determine whether there are gender and ethnic differences in the intra-individual rate of change in TL over time, and whether it is the shorter TL or the slope of change that is most significant in determining biological aging.

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Table 1. Sample Characteristics by Race/Gender, Health and Retirement Study (N=5,228)

Variables	Full Sample	White		Black		Hispanic	
		Women (n=2,256)	Men (n=1,744)	Women (n=441)	Men (n=262)	Women (n=313)	Men (n=212)
Age, years	66.9(9.8)	68.1(10.2)	66.8(9.5)	65.6(9.5)	63.7(8.5)	64.4(9.0)	63.1(8.2)
Female (%)	53.2	--	--	--	--	--	--
Race/Ethnicity (%)							
White	83.0	--	--	--	--	--	--
Black	9.1	--	--	--	--	--	--
Hispanic	7.9	--	--	--	--	--	--
Education (%)							
< High School	17.0	12.7	11.4	28.9	29.4	56.0	51.5
High School Diploma	34.1	40.4	30.4	28.7	31.0	24.6	19.2
Some College	24.4	25.8	24.8	24.1	20.1	14.5	20.6
≥ College Degree	24.6	21.2	33.4	18.4	19.6	5.0	8.8
Marital Status (%)							
Married	65.4	57.2	79.4	31.1	60.4	52.4	82.9
Divorced/Separated	13.8	14.4	9.3	31.9	22.1	21.8	11.5
Widowed	17.1	25.6	7.6	27.6	9.6	22.2	3.5
Never Married	3.7	2.8	3.6	9.5	7.9	3.6	2.0
Employment Status (%)	42.2	37.4	48.7	39.4	46.1	29.7	45.3
HH Income, dollars	10.6(1.4)	10.6(1.2)	10.9(1.1)	9.7(1.8)	10.3(1.7)	9.7(2.1)	10.0(2.0)
HH Wealth, dollars	11.1(3.5)	11.4(3.1)	11.9(2.8)	7.8(5.0)	9.0(4.5)	9.3(4.3)	9.4(4.3)
Obese (%)	32.6	31.1	31.0	51.5	34.2	36.4	35.4
Smoking Status (%)							
Never Smoked	42.1	49.7	33.8	48.8	32.1	57.0	24.1
Former Smoker	43.3	37.6	51.4	32.4	46.6	27.5	56.3
Current Smoker	14.3	12.6	14.5	18.7	20.7	14.3	19.6
Physically Inactive, %	40.8	42.0	36.2	56.8	44.9	46.1	43.9
T/S Ratio	1.3(0.4)	1.3(0.4)	1.3(0.4)	1.5(0.4)	1.4(0.5)	1.4(0.3)	1.4(0.4)

Numbers represent weighted means, with standard deviations in parentheses, and weighted percentages.

Table 2. Linear regression models of TL on age, gender, and race/ethnicity (n=5,228)

	Model 1			Model 2 (+demographics, SES)			Model 3 (+health behaviors)		
	β		SE	β		SE	β		SE
Constant	1.60	***	(0.04)	1.69	***	(0.10)	1.72	***	(0.10)
Age	-0.004	***	(0.00)	-0.005	***	(0.00)	-0.005	***	(0.00)
Female	0.03	*	(0.01)	0.03	*	(0.01)	0.02	+	(0.01)
Race/Ethnicity (ref=White)									
Black	0.12	***	(0.02)	0.12	***	(0.02)	0.12	***	(0.02)
Hispanic	0.04	+	(0.02)	0.04		(0.02)	0.04		(0.02)

Model 2 adjusted for marital status, education, employment status, income, wealth
Model 3 adjusted for marital status, education, employment status, income, wealth, BMI, smoking, physical inactivity
***p<.001, **p<.01, *p<.05, +p<.10

Table 3. Predicted mean telomere length by race/ethnicity and gender groups (n=5,228)

	Model 1		Model 2 (+demographics, SES)		Model 3 (+health behaviors)	
	Mean	CI	Mean	CI	Mean	CI
White Women	1.34	(1.33, 1.36)	1.34	(1.33, 1.36)	1.34	(1.32, 1.36)
White Men	1.31a	(1.29, 1.34)	1.31a	(1.29, 1.33)	1.32	(1.29, 1.34)
Black Women	1.46a,b	(1.42, 1.51)	1.47a,b	(1.42, 1.52)	1.46a,b	(1.41, 1.51)
Black Men	1.43a,b	(1.35, 1.51)	1.44a,b	(1.36, 1.52)	1.44a,b	(1.36, 1.52)
Hispanic Women	1.37b,c	(1.32, 1.41)	1.37c	(1.32, 1.42)	1.36c	(1.31, 1.41)
Hispanic Men	1.37c	(1.31, 1.43)	1.37c	(1.30, 1.44)	1.37c	(1.31, 1.44)

[a] different from white women ($p<.05$)

[b] different from white men ($p<.05$)

[c] different from black women ($p<.05$)

Model 1 adjusted for age. Model 2 adds marital status, education, occupational status, income, and wealth. Model 3 further adds BMI, smoking, physical activity.

Pvalue< 0.05 based on pairwise comparison

Figure 1a. Predicted mean telomere length by age in women*

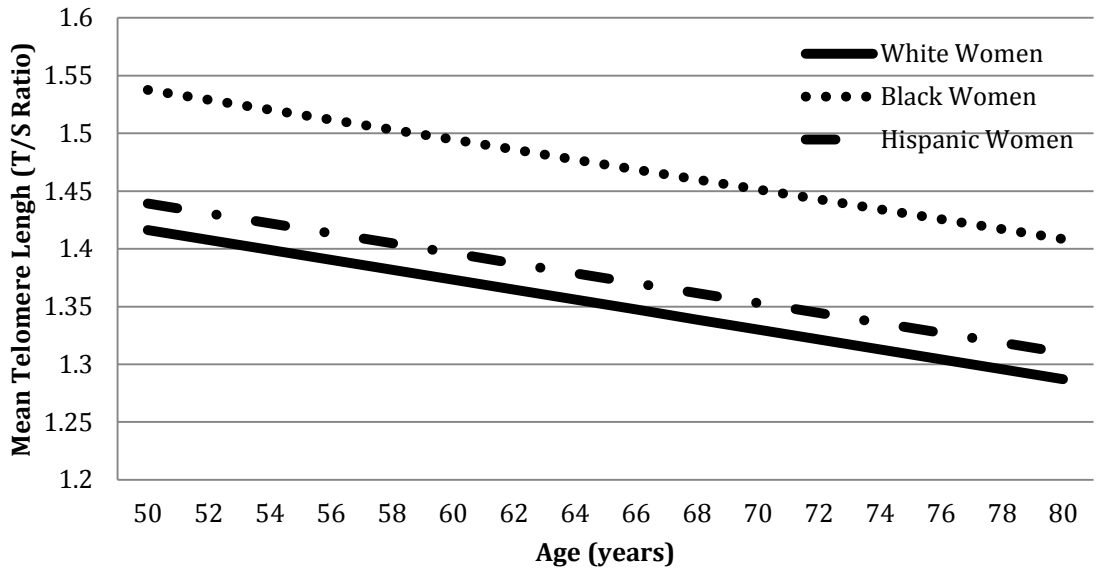
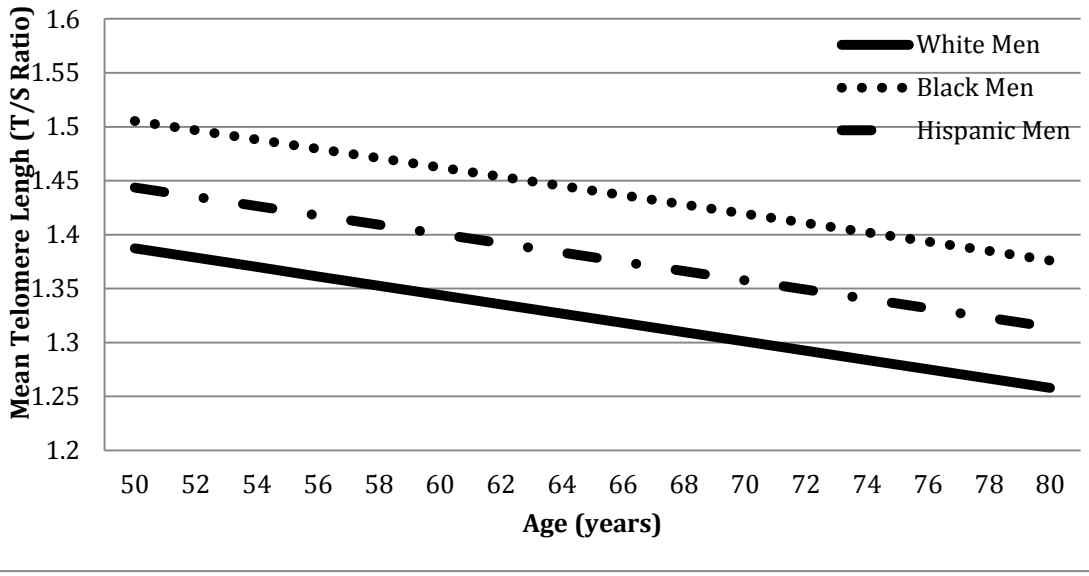


Figure 1b. Predicited mean telomere length by age in men*



*Means are weighted