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Leukocyte telomere length and risks of incident coronary heart disease and mortality in a racially diverse population of post-menopausal women

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Abstract

Objective—Telomeres are regions at the ends of chromosomes that maintain chromosomal structural integrity and genomic stability. In studies of mainly older, white populations, shorter leukocyte telomere length (LTL) is associated with cardio-metabolic risk factors and increased risks of mortality and coronary heart disease (CHD). On average, African Americans (AfAm) have longer LTL than whites, but the LTL-CHD relationship in AfAm is unknown. We investigated the relationship of LTL with CHD and mortality among AfAm.

Approach and Results—Using a case-cohort design, 1,525 postmenopausal women (667 AfAm and 858 whites) from the Women's Health Initiative had LTL measured in baseline blood samples by Southern blotting. CHD or mortality hazards ratios were estimated using race-stratified and risk factor-adjusted Cox proportional hazards models. There were 367 incident CHD (226 mortality) events in whites, while AfAm experienced 269 incident CHD (216 mortality) events during median follow-up of 13 years. Shorter LTL was associated with older age, current smoking, and white race/ethnicity. In whites, each 1 kilobase decrease in LTL was associated with

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50% increased hazard of CHD, hazard ratio=1.50 (95%CI: 1.08–2.10), p=0.017. There was no association between CHD and LTL in AfAm. White women with shorter LTL had higher risks of mortality. In contrast, shorter LTL was weakly associated with decreased mortality hazard in AfAm.

Conclusions—As one of the largest prospective studies of LTL associations with incident CHD and mortality in a racially diverse sample, our study suggests differences in LTL associations with CHD and mortality between white and AfAm postmenopausal women.

Keywords

telomere length; incident coronary heart disease; mortality; women; African Americans

INTRODUCTION

Telomeres, protein-nucleotide complexes located at the ends of chromosomes, help maintain chromosomal structural integrity and genomic stability. In replicating somatic cells, progressive telomere shortening eventually induces cessation of cell division, termed replicative senescence.[1] This senescence has been implicated in aging and aging-related diseases including atherosclerosis.[2]

Telomere length in leukocytes (LTL) varies among individuals. Shorter LTL is associated with older age and with the presence of cardiometabolic risk factors such as male sex, smoking, insulin resistance, and sedentary lifestyle.[3, 4] Shortened LTL may be a marker of chronic vascular injury (oxidative stress, inflammation)[5, 6] and also reflect the diminished vascular repair capacity of hematopoietic stem cells.[7]

Several studies have reported associations between shorter LTL and increased risk of cardiovascular disease (CVD), other age-related diseases, and total mortality.[8–11] These data are derived largely from older, European-descent populations. African Americans (AfAm) tend to have longer LTL than whites, despite a greater burden of cardiovascular disease risk factors.[12] Because of these population differences, it is of interest whether LTL predicts mortality and outcomes related to vascular aging among AfAm. To address this question, we assessed the relationship of LTL with risks of incident CHD and mortality in white and AfAm post-menopausal women from the Women's Health Initiative, a large, multiethnic prospective study with extensive follow-up data on CHD and mortality outcomes.

MATERIALS AND METHODS

Detailed Materials and Methods are available in the online-only Data Supplement.

RESULTS

A total of 858 whites and 667 AfAm had baseline LTL measurements, which were normally distributed in both groups, mean (standard deviation [SD]) =6.79 (0.60)kb and mean(SD)=7.09 (0.61)kb, respectively. In whites, there were 367 CHD events and 226 deaths during a median follow-up of 13.3 years. AfAm experienced 269 incident CHD events and 218 deaths during a median follow-up of 12.7 years.

Baseline characteristics by race are shown in Table 1. At baseline, AfAm were younger, more likely to be obese, have lower SES, and higher prevalence of current smoking, treated diabetes, and hypertension, higher CRP and HDL levels, and higher eGFR compared to whites.

Cross-sectional baseline correlates of LTL in white and AfAm women

In models including all participants, age and race were independently associated with LTL. In age-adjusted analyses, AfAm had, on average, 175 bases [standard error *(SE)* 40] longer LTL compared to whites ($p < 0.001$). When adjusted for race, each 1 year increase in age was associated with average LTL decreases of 24 bases (*SE* 3; $p < .001$).

In race-stratified analyses, older age and current smoking were strongly associated with shorter LTL (Table 2). Geographic region of residence was additionally related to LTL among AfAm only, and lower HDL was associated with shorter LTL in whites. BMI, markers of socioeconomic status, prevalence of treated diabetes or hypertension, and lnCRP were not significantly associated with LTL in race-stratified analyses. In combined models, these variables also were not associated with LTL, and no significant interactions by race/ethnicity were observed.

LTL and incident CHD in white and AfAm women

In whites, each 1 kilobase (kb), or 1000 nucleotides, reduction in LTL was associated with 50% increased CHD hazard, HR (95%CI): 1.50 (1.08–2.10), p=0.017 (Table 3). In contrast, LTL was not associated with hazards of CHD in AfAm, p=0.68. Additional adjustment for blood biomarkers, available in subsets of 572 and 563 AfAm and white participants, did not appreciably affect the risk estimates in either race/ethnicity group. In models combining both whites and AfAm, the p-value for a difference in the relationship between LTL and CHD hazard by race/ethnicity was $p_{\text{interaction term}}=0.20$ (model 1) and $p_{\text{interaction term}}=0.04$ (model 2). To further test the relationship of LTL with CHD by race, we categorized LTL into quartiles. Among white women, those in the lowest quartile with the shortest LTL (LTL=5.24–6.37 kb) had a 1.95-fold increased hazard of CHD relative to those in the top quartile (LTL=7.18–8.73 kb) (Table 4) and the overall linear trend test for CHD risk was significant (p=0.008). In contrast, there were no significant differences in CHD hazard among AfAm women by LTL quartile, and the p-value for the overall trend test was 0.57.

LTL and risk of total mortality in white and AfAm women

Although not statistically significant, white women had a 41% increased all-cause mortality hazard, HR (95%CI): 1.41 (0.99–1.99), p=0.055 associated with each 1kb reduction in LTL (Table 3). When analyzed by quartiles, white women in the bottom LTL quartile (shorter LTL) had a 1.69-fold increased risk of mortality relative to those in the upper quartile (p=0.047) (Table 4). In contrast, AfAm women did not exhibit an increased risk of total mortality associated with shorter LTL, p=0.220; rather there was a non-significant trend among AfAm women toward decreased mortality (HR: 0.80) associated with shorter LTL (Table 3). In models combining both whites and AfAm, the p-value for a difference in the relationship between LTL and mortality by race/ethnicity was $p_{\text{interaction term}}=0.07$ (model 1) and $p_{\text{interaction term}}=0.02$ (model 2). When analyzing LTL by groups, AfAm individuals in

the second quartile (LTL=6.68–7.04 kb) had a reduced risk of mortality (p=0.025) compared to AfAm in the upper quartile (LTL=7.52–9.06 kb). Mortality hazards did not appreciably differ for the other quartiles. Nonetheless, overall, there was a significant linear trend of shorter LTL associations with decreased all-cause mortality in the AfAm women (p=0.035).

LTL and cause-specific mortality

In secondary analyses, we examined the LTL mortality relationship according to cause of death. Among the mortality cases, there were 82 CVD deaths, 102 cancer deaths and 108 deaths due to other causes in whites. In AfAm, there were 85 CVD, 97 cancer, and 83 other cause deaths. Shorter LTL was associated with a higher hazard of CVD death and deaths from other causes in whites, though only the latter reached statistical significance (Table 5). In AfAm, there was little evidence of association between LTL and either CVD death or death due to other causes. In both whites and AfAm, shorter LTL was associated with a trend toward decreased hazard of cancer deaths, though these associations were not statistically significant.

Sensitivity Analyses

HR from crude models only including adjustment for age were similar to risk factor-adjusted models, though as expected, some p-value differences were observed. For example, in whites, the LTL-mortality association p-value in Model 1 increased from p=0.007 to p=0.055 with risk factor adjustment.

AfAm women with and without biomarkers were similar with respect to age and telomere length, though white women with biomarkers were younger and had longer LTL than those without biomarkers, on average. While the majority of AfAm (96%) and white (72%) women had biomarker data, we investigated whether minor differences in results between Models 1 and 2 may be due to sample differences rather than biomarker adjustment. In Model 1 analyses restricted to women with biomarkers, we observed a more robust association between continuous LTL and CHD in whites, HR=1.80 (95%CI:1.24–2.60), p=0.002, while the AfAm results changed little, HR=1.07 (95%CI:0.71–1.62), p=0.754. As expected, mortality estimates in AfAm women did not change, though the association in white women became statistically significant, HR=1.60 (95%CI: 1.03–2.48), p=0.036. P-values for the interaction terms in Model 1 testing for differences by race decreased to p=0.08 and p=0.02, respectively, lending further support to potential differences in the LTL-CHD and LTL-mortality relationships by race/ethnicity.

Approximately 24% of AfAm and all white women in this analysis were enrolled in the treatment or placebo arms of the WHI HT trial, at approximately equal proportions in each arm (Table 1). Given potential risk differences in trial participants, we stratified race-specific Cox proportional hazards models by HT treatment arm (and non-participation in AfAm), but did not observe any appreciable differences in the LTL-CHD or LTL-mortality results.

To further investigate differences in findings by race/ethnicity, we tested LTL associations using Model 1, but with adjustment for systolic and diastolic blood pressure instead of hypertension, which may combine both poorly- and well-controlled hypertensives into one

group. No changes in significance were observed in the LTL-CHD associations in AfAm (from p=0.68 to p=0.98) and whites (p=0.017 to p=0.009), but adjustment for blood pressures in the LTL-mortality models resulted in slightly more extreme and significant HR than the hypertension adjustment, from p=0.055 to p=0.036 in whites and p=0.22 to p=0.12 in AfAm.

DISCUSSION

In a large, prospective cohort of AfAm and white postmenopausal women, we found that AfAm women have significantly longer age-adjusted LTL than white women. Among white women, shorter LTL was significantly associated with increased incidence of CHD, independent of established cardiovascular risk factors. Similarly, white women in the lowest (shorter) LTL quartile had significantly higher risks of both mortality and CHD events compared with women in the upper (longest) LTL quartile. In AfAm women, we observed no association between LTL and incident CHD. Paradoxically, there was even some evidence that AfAm women with shorter LTL had a decreased risk of all-cause mortality (though non-significant). Mortality analyses conducted by cause of death suggested the possibility that the association of shorter LTL with decreased mortality in AfAm may be driven by cancer deaths.

Racial differences in LTL have been reported in US populations of various ages[13, 12, 14] and our findings for longer age-adjusted LTL in AfAm vs. white women are in agreement with these previous studies. The LTL-CHD and LTL-mortality associations in white postmenopausal women from WHI are also consistent with findings from the other prospective studies conducted to date[15,9] as well as with findings from two large meta-analyses including both prospective and retrospective designs and Asian study populations, which also found an inverse association between LTL and risk of CHD, independent of conventional vascular disease risk factors.[16, 17] However, these studies did not include large numbers of AfAm.

To our knowledge, our study is one of the first to specifically describe the relationship between LTL and CHD and mortality events in AfAm. Two other prospective studies of clinical outcomes in older adults, the Cardiovascular Health Study (CHS) and the Health ABC Study, have included AfAm participants. In CHS, shorter LTL was associated with increased risks of incident myocardial infarction[14] and mortality[18] in models which included small numbers of AfAm women and men. In the Health ABC study, which did include a sizeable AfAm sample in addition to whites and used a qPCR-based method to measure LTL, no association between LTL and mortality, and no LTL-mortality interaction by race/ethnicity were observed.[19]

There are several possible reasons for the varying LTL findings observed between AfAm and white women, including differences in cardiovascular risk factor burden. Consistent with prior observations that telomere length is a stronger indicator of cardiovascular risk factors in individuals with normal glucose tolerance,[6] we also found that LTL-CHD associations were more robust in whites without impaired fasting glucose (i.e. fasting glucose concentrations <100 mg/dL), data not shown. No differences were observed in

AfAm however, and thus our data do not provide sufficient evidence that the LTL-CHD association in AfAm is obscured by poor glycemic control, a major risk factor for CHD. Differences in CHD pathogenesis or severity between whites and AfAm could reflect different mechanisms of LTL involvement. AfAm women in our sample were slightly less likely than white women to undergo revascularization procedures during follow-up, though this difference was not significant (p=0.25). AfAm typically experience a lower burden of coronary atherosclerosis (as defined by coronary artery calcification) but a higher burden of hypertension and left ventricular hypertrophy (LVH) compared to whites.[20] In bi-racial studies of coronary artery calcification (CAC), associations between LTL and CAC were weaker in AfAm than in whites, though AfAm sample sizes were smaller.[21, 22] These and other results suggesting that longer LTL is associated with LVH[23] along with the higher LVH prevalence in AfAm might account for the lack of an association between shorter LTL and CHD in AfAm. The observed differences in LTL-CHD relationships may also be due to differing genetic architecture underlying LTL and its regulation in AfAm vs. whites. For example, activity levels of a key enzyme regulating LTL were observed to be higher in adult male AfAm than in whites, and were also associated with CVD risk factors: lower socioeconomic status, higher C-reactive protein levels, smoking and increased coronary artery calcium.[24] Finally, the lack of association between LTL with CHD in AfAm from WHI could simply be due to chance (type 2 error). Additional studies that include even larger numbers of AfAm with incident CHD may be required to resolve this question.

The majority of deaths in our sample were due to CVD and cancer causes. Prior studies have found that LTL associations with cancer are somewhat complex and cancer-specific. For example, LTL displays a U-shaped association with colorectal and breast cancers in that extremely short and long LTL are both associated with increased risk.[25,26] Other studies have found associations between longer LTL and increased cancer risk.[27, 28] While limited in numbers of events, our cause-specific mortality analyses similarly suggest that shorter LTL may be associated with decreased risk of cancer mortality in whites and AfAm women.

Some strengths and limitations of our analysis deserve mention. With our large sample sizes and prospectively collected, adjudicated outcomes, we have reasonable power (>80%) to detect changes in risk of ≥35% in AfAm and ≥30% in whites associated with 1kb differences in LTL, but may lack sufficient power to detect smaller changes in risk. While we included a race/ethnicity diverse, well-characterized sample in our analyses, our findings are based on postmenopausal women, and may not be generalizable to men or younger women.

Atherosclerosis and other health consequences of aging are increasingly recognized to reflect an imbalance between tissue injury and tissue repair. Chronic oxidative stress and inflammation, which lead to vascular injury, also lead to telomere shortening in human cells.[29] As a possible chronic disease biomarker, LTL has some advantages over currently used biomarkers—it may reflect the cumulative burden of oxidative stress and aging of the immune system[30], unlike many blood biomarkers which reflect only current exposure or status at the time of blood draw. Additionally LTL is a heritable trait, reflecting a genetic predisposition to cellular senescence.[31, 32] Relatively short telomeres in somatic tissues, as expressed in a shorter LTL, may signal diminished somatic cellular repair capacity.

Diminished repair capacity is implicated in aging and atherosclerosis[2] suggesting a potential mechanism underlying LTL associations with CHD and mortality. The notion of LTL as a causal determinant, rather than simply a biomarker, of atherosclerotic heart disease is supported by a recent genome-wide analysis that revealed an association between genetic variants associated with shortened LTL and an increased risk of CHD.[33] Similarly, genetic variants linked with telomere length in either direction (shorter or longer) were also associated with specific cancers. [33]

We report and have hypothesized several possible explanations for the observed differences in CHD and mortality risk between whites and AfAm, but ultimately our findings require validation in other large AfAm populations, as well as further investigation into the mechanisms that may underlie these differences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations

LTL	leukocyte telomere length
AfAm	African Americans, CHD, coronary heart disease
CVD	cardiovascular disease
kb	kilobases

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SIGNIFICANCE

Telomere length in leukocytes (LTL) varies between individuals and is a putative biomarker of cellular aging and vascular injury. Shorter LTL is associated with cardio-metabolic risk factors, such as smoking, and increased risks of mortality and coronary heart disease (CHD), a leading cause of death for African American (AfAm) and white women. On average, AfAm have longer LTL than whites, but whether LTL is associated with CHD and mortality in AfAm is unknown. Using prospectively collected data from the Women's Health Initiative, we found differences in LTL relationships with mortality and CHD by race/ethnicity. Shorter LTL was associated with increased risks of subsequent CHD and mortality in white women. In contrast, shorter LTL was weakly associated with decreased mortality and was not associated with CHD in AfAm women. We propose potential hypotheses to explain these observed differences, but further studies are needed to confirm our findings and investigate underlying mechanisms.

Table 1

Baseline characteristics of participants

Baseline Characteristic*	African Americans (n=667)	Whites (n=858)
Age in years	62.6 ± 7.2	65.8 ± 6.8
BMI Category		
normal†	84 (12.7)	255 (29.9)
overweight	210 (31.8)	279 (32.8)
obese	366 (55.5)	318 (37.3)
Current smoker	117 (17.8)	107 (12.6)
Treated type 2 diabetes	119 (17.9)	61 (7.1)
Hypertension	440 (66.0)	410 (47.8)
History of cancer	64 (9.6)	27 (3.2)
Lipid-lowering medication use	71 (10.6)	85 (9.9)
Highest education level		
Less than high school diploma	95 (14.4)	43 (5.1)
High school diploma	101 (15.3)	187 (22.0)
Some vocational/college	256 (38.9)	347 (40.7)
College degree/graduate training	207 (31.4)	275 (32.3)
Income		
<$10,000	84 (13.6)	27 (3.3)
$10,000 to $19,999	121 (19.6)	165 (20.3)
$20,000 to $34,999	155 (25.2)	254 (31.2)
$35,000 to $49,999	108 (17.5)	154 (18.9)
$50,000 to $74,999	90 (14.6)	132 (16.2)
≥$75,000	58 (9.4)	81 (10.0)
Residential latitude		
Southern : < 35° North	214 (32.1)	193 (22.5)
Middle : 35–40° North	238 (35.7)	223 (26.0)
Northern : > 40° North	215 (32.2)	442 (51.5)
Hormone Trial Arm Participation		
E-alone	44 (6.6)	195 (22.7)
E-alone placebo	41 (6.2)	188 (21.9)
E + P	32 (4.8)	246 (28.7)
E + P placebo	43 (6.5)	229 (26.7)
ln(CRP) ‡	1.34 ± 1.14	0.84 ± 1.05
HDL in mg/dL‡	53.4 ± 13.5	50.4 ± 12.1
LDL in mg/dL ‡	153.2 ± 42.6	157.0 ± 35.5
ln(TRI) ‡	4.7 ± 0.5	4.9 ± 0.5
eGFR in mL/min/1.73m^2 ‡	90.7 ± 23.4	81.2 ± 16.5

*Expressed as mean ± SD or n(%) where percentage reflects proportion of women with non-missing data, by race

†Four underweight women with BMI>17.3kg/m^2 were included in the normal category

‡Available on a subset (n=1135) of the total 1525 participants

Table 2

Telomere length associations with baseline CHD and mortality risk factors

	African Americans		Whites	
Baseline Risk Factor*	**Beta ± SE†**	**P-value**	**Beta ± SE†**	**P-value**
Age in years	−28.1 ± 4.3	1.4e-10	−22.9 ± 3.6	2.2e-10
BMI category	−80.1 ± 41.4	0.053	−25.0 ± 30.5	0.410
Current smoker (no/yes)	−146.2 ± 73.3	0.047	−237.9 ± 67.9	4.8e-4
Treated type 2 diabetes (no/yes)	113.7 ± 81.9	0.170	−7.0 ± 86.3	0.940
Hypertension (no/yes)	40.1 ± 65.1	0.540	13.9 ± 52.9	0.790
History of cancer (no/yes)	−50.2 ± 101.4	0.620	−25.1 ± 92.6	0.790
Lipid-lowering medication use, n(%)	71.4 ± 86.9	0.410	77.6 ± 102.0	0.450
Highest education level category	−33.9 ± 31.7	0.280	44.1 ± 27.2	0.110
Income category	9.0 ± 20.4	0.660	32.2 ± 18.4	0.080
Residential latitude		0.036‡		0.655‡
Southern : <35° N	*reference*		*reference*	
Middle : 35–40° N	−9.6 ± 76.3	0.900	62.3 ± 70.1	0.370
Northern : >40° N	−174.2 ± 76.8	0.024	45.3 ± 62.1	0.470
ln(CRP)	−17.9 ± 27.0	0.510	−42.7 ± 28.1	0.130
HDL in mg/dL	−0.8 ± 2.1	0.720	5.6 ± 2.6	0.029
LDL in mg/dL	0.1 ± 0.7	0.900	0.3 ± 0.8	0.720
ln(TRI)	−22.2 ± 74.6	0.770	−8.8 ± 65.2	0.890
eGFR in mL/min/1.73m^2	0.4 ± 1.3	0.740	−1.9 ± 2.0	0.330

*Race-stratified, weighted, univariate models include only adjustment for age

†Beta from age-adjusted models reflects the change in telomere length (in nucleotides) for the presence of the risk factor (yes vs. no), or each one unit or ordinal category increase of the risk factor

‡Global test of significance for the latitude variable

Table 3

Associations between shorter LTL and incident CHD or all-cause mortality

		African Americans			Whites		
Outcome*	**Model†**	**N/N cases‡**	**HR(95% CI)**	**P-value**	**N/N cases‡**	**HR(95% CI)**	**P-value**
CHD	1	598/242	1.09 (0.72–1.64)	0.678	796/344	1.50 (1.08–2.10)	0.017
	2	572/232	0.94 (0.62–1.43)	0.760	563/260	1.68 (1.16–2.42)	0.006
All-Cause Mortality	1	598/190	0.80 (0.57–1.14)	0.220	796/212	1.41 (0.99–1.99)	0.055
	2	572/186	0.76 (0.54–1.08)	0.121	563/138	1.51 (0.97–2.36)	0.067

*Models reflect the change in hazard of the outcome associated with each 1kb lower LTL

†Model 1 is adjusted for age, current smoking, BMI category, diabetes status, geographic region, hypertension, education, and income; Model 2 includes Model 1 adjustment factors and additionally the biomarkers: ln(CRP), HDL, LDL, ln(TRI) and for mortality models, eGFR

‡Unweighted numbers are shown

Table 4

Associations between LTL quartiles and CHD and mortality outcomes

	African Americans			Whites		
Outcome*	**LTL Quartile**	**HR(95% CI)**	**P-value**	**LTL Quartile**	**HR(95% CI)**	**P-value**
CHD	5.57–6.67 kb	0.97 (0.50–1.90)	0.930	5.24–6.37 kb	1.95 (1.17–3.24)	0.011
	6.68–7.04 kb	0.76 (0.39–1.51)	0.437	6.38–6.77 kb	1.11 (0.65–1.88)	0.698
	7.05–7.51 kb	1.24 (0.66–2.35)	0.503	6.78–7.17 kb	1.02 (0.61–1.71)	0.938
	7.52–9.06 kb	1.0 (reference)	0.571†	7.18–8.73 kb	1.0 (reference)	0.008†
All-Cause Mortality	5.57–6.67 kb	0.64 (0.36–1.13)	0.126	5.24–6.37 kb	1.69 (1.01–2.83)	0.047
	6.68–7.04 kb	0.52 (0.29–0.92)	0.025	6.38–6.77 kb	1.00 (0.59–1.69)	0.990
	7.05–7.51 kb	0.99 (0.59–1.67)	0.977	6.78–7.17 kb	1.13 (0.69–1.87)	0.622
	7.52–9.06 kb	1.0 (reference)	0.035†	7.18–8.73 kb	1.0 (reference)	0.068†

*Model 1 results using race-specific LTL quartiles with quartile boundaries shown

†P-value for the test for linear trend

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Table 5

LTL Associations with cause-specific mortality

		African Americans		Whites	
Outcome*	**Model†**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
CVD Death	1	1.03 (0.60–1.76)	0.922	1.54 (0.86–2.75)	0.144
	2	0.81 (0.47–1.39)	0.447	1.84 (0.98–3.46)	0.060
Cancer Death	1	0.69 (0.41–1.18)	0.176	0.76 (0.50–1.18)	0.219
	2	0.68 (0.41–1.13)	0.135	0.81 (0.47–1.39)	0.444
Other Death	1	1.18 (0.68–2.02)	0.559	2.03 (1.07–3.86)	0.030
	2	1.10 (0.63–1.92)	0.737	2.30 (0.95–5.54)	0.065

*Models reflect the change in hazard of the outcome associated with each 1kb lower LTL

†Model 1 is adjusted for age, current smoking, BMI category, diabetes status, geographic region, hypertension, education, and income; Model 2 includes Model 1 adjustment factors and additionally the biomarkers: ln(CRP), HDL, LDL, ln(TRI) and for mortality models, eGFR

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