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Original Contribution

Leukocyte Telomere Length and Cardiovascular Disease in the Cardiovascular Health Study

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The telomere length of replicating somatic cells is inversely correlated with age and has been reported to be associated cross-sectionally with cardiovascular disease (CVD). Leukocyte telomere length, as expressed by mean terminal restriction fragment (TRF) length, was measured in 419 randomly selected participants from the Cardiovascular Health Study, comprising a community-dwelling cohort recruited in four US communities. The authors investigated associations between TRF length and selected measures of subclinical CVD/risk factors for CVD (data were collected at the 1992/1993 clinic visit) and incident CVD (ascertained through June 2002). In these participants (average age = 74.2 years (standard deviation, 5.2)), mean TRF length was 6.3 kilobase pairs (standard deviation, 0.62). Significant or borderline inverse associations were found between TRF length and diabetes, glucose, insulin, diastolic blood pressure, carotid intima-media thickness, and interleukin-6. Associations with body size and C-reactive protein were modified by gender and age, occurring only in men and in participants aged 73 years or younger. In younger (but not older) participants, each shortened kilobase pair of TRF corresponded with a threefold increased risk of myocardial infarction (hazard ratio = 3.08, 95% confidence interval: 1.22, 7.73) and stroke (hazard ratio = 3.22, 95% confidence interval: 1.29, 8.02). These results support the hypotheses that telomere attrition may be related to diseases of aging through mechanisms involving oxidative stress, inflammation, and progression to CVD.

cardiovascular diseases; inflammation; mortality; myocardial infarction; telomere

Abbreviations: CHS, Cardiovascular Health Study; CI, confidence interval; HR, hazard ratio; kb, kilobase pairs; SSC, sodium chloride/sodium citrate; TRF, terminal restriction fragment.

Telomeres cap and protect the ends of chromosomes. Their attrition, resulting from progressive rounds of cell division, is linked to replicative senescence of human somatic cells in culture (1, 2). In vivo, the telomere length of replicating somatic cells is inversely correlated with age and is associated with age-related disorders, including cardiovascular disease (3, 4). Associations with telomere length have been reported for essential hypertension (5, 6), diabetes (7),

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insulin resistance (8), obesity (9), atherosclerosis (10–12), vascular dementia (13), and mortality due to heart disease (14).

In a sample of older adults participating in the Cardiovascular Health Study (CHS), we examined associations between telomere length in leukocytes and indices of subclinical and clinical cardiovascular disease. Use of data from this large, well-documented cohort allowed evaluation of new measures of cardiovascular disease risk factors and subclinical cardiovascular disease not previously reported in relation to telomere length. In addition, using the extensive follow-up of CHS participants, we evaluated associations between leukocyte telomere length and subsequent cardiovascular outcomes, including myocardial infarction, angina pectoris, stroke, and peripheral vascular disease, as well as mortality. We tested the hypotheses that older adults with increased levels of cardiovascular disease risk factors and subclinical cardiovascular disease have relatively shorter leukocyte telomeres and are at increased risk of both cardiovascular events and death in comparison with their peers. We conducted this study to obtain effect size estimates of associations within this cohort as preliminary data for a larger study of telomere attrition in the CHS.

MATERIALS AND METHODS

The CHS cohort

The CHS is a multisite observational cohort study designed to investigate risk factors for cardiovascular disease in the elderly (15). In 1989/1990, CHS investigators recruited 5,201 participants from Medicare eligibility lists in four US communities: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania (16). In 1992/1993, an additional 687 African Americans were recruited into the study. Participants were aged 65 years or older at the baseline examination. Written informed consent was obtained at entry and at specified intervals during the course of the study. All procedures were conducted under institutionally approved protocols for use of human subjects.

From baseline (1989/1990) until 1998/1999, study participants completed up to 10 annual clinic visits. Information collected at these examinations included data on vital signs, anthropometric factors, medical history and behaviors, and physical function, as well as results of psychosocial interviews (15). Blood was collected and stored during most years of the study (17). DNA was collected from participants providing consent to use genetic material (~85 percent of the cohort). Participants were evaluated for the prevalence of specific cardiovascular outcomes at baseline, including myocardial infarction, angina pectoris, and stroke (18). An extensive system for surveillance and collection of data on hospitalizations, mortality, and cardiovascular morbidity was developed and continues to be implemented (19).

Measurement of telomere length

For this study, 419 CHS participants completing the 1992/1993 clinic examination were randomly selected from 1,230 participants who consented to DNA preparation/use, had at least 12 μg of DNA available, and had stored leukocytes for additional DNA preparation. The integrity of the DNA was assessed through electrophoresis of 0.5 μg of DNA on 1.0 percent agarose gels (200 V for 2 hours) and staining with ethidium bromide. Telomere length was measured as the mean length of the terminal restriction fragments (TRFs) in peripheral leukocytes, using the Southern blot method as previously described (11, 20).

Briefly, DNA samples were digested overnight with the restriction enzymes *Hin*fI (10 U) and *Rsa*I (10 U; Roche Applied Science, Indianapolis, Indiana). Eighteen DNA samples (~5 μg each) and four DNA ladders (one kilobase pair (kb) DNA ladder plus λ DNA/*Hin*dIII fragments; Invitrogen, Carlsbad, California) were resolved on 0.5 percent agarose gel (20 cm × 20 cm) at 50 V (GNA-200 electrophoresis unit; GE Healthcare, Piscataway, New Jersey). After 16 hours, the DNA was depurinated for 30 minutes in 0.25 N hydrochloric acid, denatured for 30 minutes in 0.5 mol/liter sodium hydroxide/1.5 mol/liter sodium chloride, and neutralized for 30 minutes in 0.5 mol/liter Tris (pH 8)/1.5 mol/liter sodium chloride. The DNA was transferred for 1 hour to a positively charged nylon membrane (Roche Applied Science) with a vacuum blotter (Boekel Scientific, Feasterville, Pennsylvania). Membranes were hybridized at 65°C with the telomeric probe (digoxigenin 3′-end labeled 5′-$(CCCTAA)_3$) overnight in 5× sodium chloride/sodium citrate (SSC), 0.1 percent Sarkosyl, 0.02 percent sodium dodecyl sulfate, and 1 percent blocking reagent (Roche Applied Science). Membranes were washed three times at room temperature in 2× SSC, 0.1 percent sodium dodecyl sulfate each for 15 minutes and once in 2× SSC for 15 minutes. The digoxigenin-labeled probe was detected by means of the digoxigenin luminescent detection procedure (Roche Applied Science) and exposed on Hyperfilm (GE Healthcare).

We scanned all autoradiographs and digitized the TRF signal between molecular weights of 3 kb and 20 kb; background was fixed as the signal in a non-DNA-loaded region of the film. The optical density values versus DNA migration distances were converted to optical density (adjusted for background)/molecular weight versus molecular weight. The mean TRF length was then calculated accordingly (between the nadir and 20 kb). Each sample was analyzed twice for telomere length measurement (on different gels on different occasions), and the mean was used for statistical analyses. The Pearson correlation coefficient for the duplicates of this sample was 0.97, with an average coefficient of variation for pair sets of 1.5 percent. The laboratory conducting the TRF length measurements was completely blinded to all characteristics of participants.

Cardiovascular disease risk factors and subclinical cardiovascular disease

Data collection for all procedures followed a standardized protocol utilized across all sites (15). Hypertension status was defined as either not present (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg and no use of antihypertensive medication), borderline (systolic

TABLE 1. Characteristics of 419 participants from the Cardiovascular Health Study who provided DNA samples for measurement of telomere restriction fragment length, 1992–2002

Characteristic	Gender				Age category				Total ($n = 419$)	
	Female ($n = 247$)		Male ($n = 172$)		≤73 years ($n = 219$)		>73 years ($n = 200$)			
	No. or mean	% or SD†	No. or mean	% or SD	No. or mean	% or SD	No. or mean	% or SD	No. or mean	% or SD
Mean age (years)	74.0	5.0	74.4	5.5	70.3**	2.0	78.4	4.2	74.4	5.2
Race										
White	199	80.6	144	83.7	167*	76.3	176	88.0	343	81.9
Black	48	19.4	26	15.1	50	22.8	24	12.0	74	17.7
Other	0	0.0	2	1.2	2	0.9	0	0.0	2	0.4
Education										
Less than high school	69*	27.9	38	22.1	50	22.8	57	28.5	107	25.5
High school graduate	80	32.4	42	24.4	70	32.0	52	26.0	122	29.1
Some college	55	22.3	40	23.3	49	22.4	46	23.0	95	22.7
College graduate or more	43	17.4	52	30.2	50	22.8	45	22.5	95	22.7
History of coronary heart disease	40*	16.2	43	25.0	41*	18.7	42	21.0	83	19.8
Presence of diabetes‡										
Normal	176	73.3	117	70.9	154	72.0	139	72.8	293	72.3
Impaired fasting glucose	22	9.2	16	9.7	21	9.8	17	8.9	38	9.4
Diabetes	42	17.5	32	19.4	39	18.2	35	18.3	74	18.3
Presence of hypertension										
Normal	89*	36.6	79	46.7	95	44.0	73	37.2	168	40.8
Borderline	28	11.5	27	16.0	23	10.6	32	16.3	55	13.3
Hypertensive	126	51.9	63	37.3	98	45.4	91	46.4	189	45.9
Smoking status										
Never smoker	143**	59.1	53	31.2	106	49.3	90	45.7	196	47.6
Former smoker	78	32.2	94	55.3	84	39.1	88	44.7	172	41.7
Current smoker	21	8.7	23	13.5	25	11.6	19	9.6	44	10.7
Mean telomere restriction fragment length (kilobase pairs)	6.4*	0.6	6.2	0.6	6.4**	0.7	6.2	0.5	6.3	0.4

* $p < 0.05$; ** $p < 0.001$ (chi-squared t test).
† SD, standard deviation.
‡ American Diabetes Association criteria (21) were used.

pressure 140–159 mmHg or diastolic pressure 90–94 mmHg and no use of antihypertensive medication), or definite (systolic pressure ≥160 mmHg or diastolic pressure ≥95 mmHg or use of antihypertensive medication). Diabetes mellitus was classified using the American Diabetes Association criteria (21) as not present, impaired fasting glucose, or definite diabetes. Body mass index was calculated as weight (kg)/height $(m)^2$. Being overweight was defined as having a body mass index greater than or equal to 25 for women and greater than or equal to 27 for men. Self-reported smoking status was coded as never smoker, former smoker, or current smoker, and total pack-years of smoking was calculated from self-reported medical history information on average amount smoked and number of years of smoking. Measurements of intima-media thickness for both the common and internal carotid arteries were collected by B-mode carotid ultrasound. The ankle-brachial index was assessed by Doppler. An ankle-brachial index of less than 0.90 indicated peripheral arterial disease (22). Analyses of fasting insulin, glucose, C-reactive protein, and interleukin-6 were completed centrally (17, 23).

Mortality and clinical cardiovascular disease

The occurrence of death and incident cases of myocardial infarction, angina pectoris, stroke, and peripheral vascular disease were identified over the course of CHS follow-up from the 1992/1993 examination through June 2002, resulting in over 7 years of follow-up, on average, depending on outcome (from 7.4 years for angina to 7.9 years for peripheral vascular disease). Hospital and outpatient records, physician questionnaires, and interviews with participants/proxies

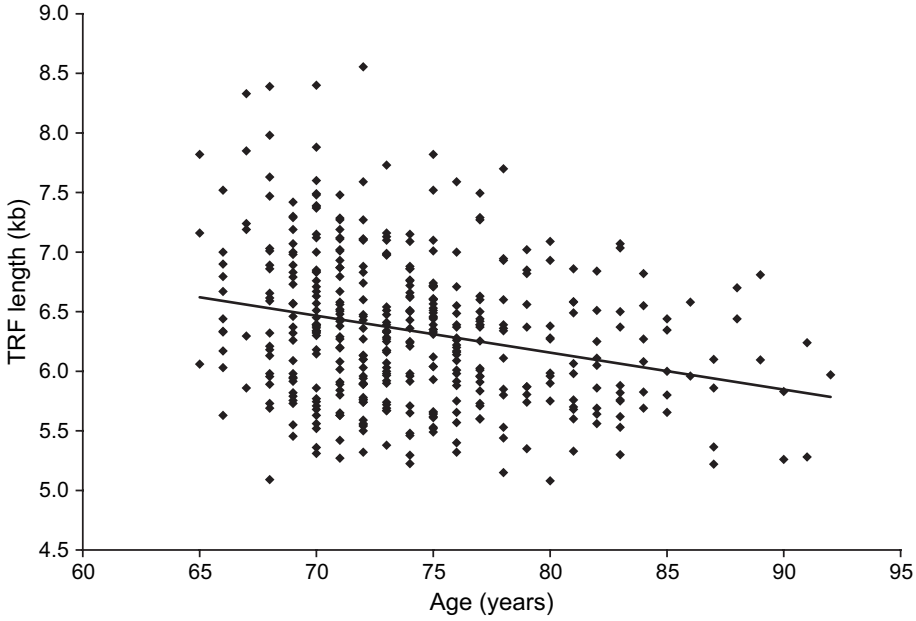

FIGURE 1. Association between mean telomere restriction fragment (TRF) length and age in 419 participants from the Cardiovascular Health Study (mean age = 74 years), 1992–2002. Unadjusted linear regression coefficient = −0.031; standard error, 0.006; $p < 0.001$; linear $R^2 = 0.068$. kb, kilobase pairs.

were used to document self-reported conditions. Classification of events was determined by a review committee of physicians making up the CHS cardiac adjudication committee (19).

Statistical analyses

Selected characteristics of the study sample were determined bivariately by gender and age category (under ($\leq$) and over ($>$) the median age of 73 years). Numbers and percentages were calculated for categorical variables, and means and standard deviations were calculated for continuous variables. Multiple linear regression was used to evaluate cross-sectional associations between TRF length and cardiovascular disease risk factors and measures of subclinical disease. While leukocyte telomere length is unlikely to cause aging or diseases of aging in the general population, it may be a biomarker for these processes. For consistency in reporting results, TRF length was considered the dependent variable in these models. Regression coefficients, standard errors, and *p* values were calculated. Cox proportional hazards regression was used to estimate the associations between TRF length (measured at baseline in 1992/1993) and time to death and to the incidence of specific clinical diseases. Incident diseases evaluated included myocardial infarction, angina pectoris, stroke, and peripheral vascular disease. Participants with prevalent disease and procedure-related events were excluded from each specific model. Effect modification was assessed by gender and age; stratified models were used if effect modification was suggested by either significant interactions or observation of differences in stratified associations. Hazard ratios and 95 percent confidence intervals were estimated for associations, with adjustment for age, race, and gender. All analyses were carried out using SPSS, version 12.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

The mean age of this sample was 74.2 years (standard deviation, 5.2). The sample comprised 58.9 percent females and 81.9 percent Whites (table 1). Males in this sample were more educated and had a higher prevalence of coronary heart disease, while females had a higher rate of hypertension and more had never smoked cigarettes. Almost half of the sample had never smoked, and only about 11 percent currently smoked tobacco. Persons over age 73 years were more likely to be White and to have a history of coronary heart disease. The 419 participants included in this analysis represented 7 percent of the entire CHS cohort. No differences in gender, race, education, smoking, or the prevalence of coronary heart disease, hypertension, or diabetes were found between persons selected for this sample and other CHS participants ($p > 0.10$; data not shown). There was, however, a significant difference in age (mean age at baseline = 71.7 years for this sample vs. 72.9 years for nonsampled participants). This difference most likely reflects the survival of this sample, as 625 cohort members (12.0 percent) recruited in 1989/1990 either died or did not attend the 1992/1993 clinic examination at which blood for this study was collected.

Overall, TRF length ranged from 5.1 kb to 8.6 kb, with a mean of 6.3 kb (standard deviation, 0.62) and a median of 6.32 kb. An inverse association with age was found (figure 1).

TABLE 2. Associations between telomere restriction fraction length (kilobase pairs), cardiovascular disease risk factors, and subclinical cardiovascular disease in 419 participants from the Cardiovascular Health Study, 1992–2002

Risk factor or subclinical disease	Unstandardized β coefficient*	Standard error	*t* statistic	*p* value
Body mass index†	−0.010	0.007	−1.529	0.13
Waist circumference (cm)	−0.004	0.002	−1.537	0.12
Overweight‡	−0.117	0.06	−1.857	0.06
Diabetes status§				
Impaired fasting glucose	0.092	00.10	0.898	0.37
Definite diabetes	−0.16	0.08	−2.138	0.03
Fasting glucose level (mg/dl)	−0.0015	0.001	−1.878	0.06
Fasting insulin level¶ (mg/dl)	−0.010	0.004	−2.616	0.009
Hypertension status				
Borderline	−0.095	0.09	−1.027	0.30
Definite	−0.015	0.06	−0.23	0.82
Systolic blood pressure# (mmHg)	−0.0034	0.002	−1.460	0.15
Diastolic blood pressure# (mmHg)	−0.0083	0.004	−1.922	0.06
Smoking status				
Former smoker	−0.088	0.06	−1.374	0.17
Current smoker	−0.092	0.10	−0.92	0.36
Pack-years of smoking	−0.002	0.001	−1.097	0.27
Common carotid intima-media thickness (mm)	−0.26	0.16	−1.674	0.10
Internal carotid intima-media thickness (mm)	−0.11	0.06	−1.806	0.07
Ankle-brachial index	0.27	0.16	1.677	0.09
Interleukin-6 level** (pg/ml)	−0.050	0.023	−2.204	0.03
C-reactive protein level (mg/liter)	−0.059	0.003	−2.352	0.02

* Adjusted for age, race, and gender using multiple linear regression.
† Weight (kg)/height $(m)^2$.
‡ Defined as body mass index $\geq$25 for women and $\geq$27 for men.
§ American Diabetes Association criteria (21) were used.
¶ Persons with diabetes were excluded, leaving $n = 293$.
# Persons taking antihypertensive medication were excluded, leaving $n = 197$.
** Interleukin-6 was measured at participants' baseline (1989/1990 for the original cohort and 1992/1993 for the African-American cohort).

Unadjusted linear regression showed TRF length to be 0.031 kb shorter for each increasing year of age (regression coefficient $= -0.031$; standard error, 0.006; $p < 0.001$).

Of the cardiovascular disease risk factors measured (table 2), inverse associations were found between TRF length and definite diabetes, fasting insulin, interleukin-6, and C-reactive protein. Relations with the presence of overweight, fasting glucose, diastolic blood pressure, carotid intima-media thickness of both the common and internal arteries, and ankle-brachial index approached significance. All associations pointed in the direction one would expect if longer telomeres corresponded with a better health status.

Gender and age modified the associations between TRF and body size and C-reactive protein (table 3). Associations between leukocyte TRF length, being overweight, and C-reactive protein were found in men but not in women (p values for interaction were 0.07 and 0.005 for overweight and C-reactive protein, respectively) and in participants below the median age of the sample ($\leq$73 years) but not in older participants (p values for interaction were 0.008 and 0.06, respectively). Overweight men were found to have TRFs approximately 0.25 kb shorter than nonobese men, while this was not found in women. In persons aged 73 years or younger, being overweight was associated with a reduction in TRF length of 0.19 kb. In men, each 1-mg/liter increase in C-reactive protein was associated with a 0.02-kb reduction in telomere length. In men aged 73 years or younger, each additional mg/liter of C-reactive protein was associated with a reduction in TRF length of 0.01 kb. C-reactive protein remained associated with TRF length within these strata even after adjustment for body size. No age $\times$ gender or three-way interactions were found.

In prospective survival analyses (table 4), age appeared to modify the associations between TRF length and incident

TABLE 3. Associations between telomere restriction fragment length (kilobase pairs), overweight status, and C-reactive protein level in 419 participants from the Cardiovascular Health Study, by gender and age category, 1992–2002

	No. of participants	Unstandardized β coefficient*	Standard error	*p* value
Overweight†				
Men	165	−0.249	0.094	0.009
Women	235	−0.016	0.084	0.85
Age ≤73 years	212	−0.188	0.095	0.05
Age >73 years	188	−0.037	0.082	0.65
C-reactive protein (mg/liter)				
Men	164	−0.024	0.007	0.001
Women	237	−0.003	0.003	0.21
Age ≤73 years	212	−0.010	0.004	0.01
Age >73 years	189	−0.002	0.003	0.47

* Results were obtained from multiple linear regression. Models stratified by gender were adjusted for age and race; models stratified by age were adjusted for gender and race.

† Defined as body mass index (weight (kg)/height (m)^2) ≥25 for women and ≥27 for men.

TABLE 4. Risk of incident cardiovascular disease and total mortality by shorter telomere restriction fragment length* in 419 participants from the Cardiovascular Health Study, 1992–2002

	No. of cases	No. of participants	Adjusted hazard ratio†	95% confidence interval	*p* value
Myocardial infarction					
Total (all ages)	36	388	1.55	0.85, 2.83	0.15
Age ≤73 years	17	203	3.08	1.22, 7.73	0.02
Age >73 years	19	185	0.83	0.36, 1.90	0.66
Stroke					
Total (all ages)	42	399	2.09	1.17, 3.74	0.01
Age ≤73 years	17	208	3.22	1.29, 8.02	0.01
Age >73 years	25	191	1.46	0.68, 3.17	0.34
Angina	52	345	0.84	0.53, 1.32	0.45
Peripheral vascular disease	22	409	1.30	0.60, 2.81	0.51
Total mortality	156	419	1.22	0.91, 1.63	0.19

* Telomere restriction fragment length (kilobase pairs) was multiplied by −1 in order to rank the measurements from longest to shortest.

† Adjusted for age, race, and gender using Cox proportional hazards regression.

myocardial infarction and stroke, although the interaction was significant only for myocardial infarction (*p* values for interaction with age were 0.02 for myocardial infarction and 0.27 for stroke). In persons aged 73 years or younger, after adjustment for age, gender, and race, a threefold increased risk of myocardial infarction was found for each 1-kb decrease in TRF length (hazard ratio (HR) = 3.08, 95 percent confidence interval (CI):1.22, 7.73). Similarly, a reduction of 1 kb in TRF length was found to increase the risk of stroke more than three times in this age group (HR = 3.22, 95 percent CI: 1.29, 8.02). These relations were not found in persons over age 73 years. While the risk of death was increased prior to adjustment (HR = 1.61, 95 percent CI: 1.22, 2.13; data not shown), the association was attenuated when results were adjusted for age, race, and gender (HR = 1.22, 95 percent CI: 0.91, 1.63). Length of telomeres was not associated with incident angina or peripheral vascular disease, and age did not modify the associations between TRF length and mortality, angina, or peripheral vascular disease.

DISCUSSION

In this study of 419 older adults from the CHS, we observed inverse associations between leukocyte TRF length and factors traditionally related to cardiovascular disease. We found significant or borderline associations between TRF length and diabetes, fasting glucose and insulin, diastolic blood pressure, internal carotid intima-media thickness, ankle-brachial index, and interleukin-6. Associations between body size and chronic inflammation as indicated by C-reactive protein level were found only in men and in the ''younger'' elderly. Furthermore, TRF length was associated with a threefold increased risk of incident myocardial infarction and stroke in the younger half of the sample. These results, in a sample of well-characterized older adults, provide new evidence of the relation between shortened leukocyte telomeres and vascular disease in both cross-sectional and longitudinal associations.

Although the processes of aging are extremely complex, these relations suggest that factors related to the progression of cardiovascular disease could be involved. While the genetic and environmental factors that shape human leukocyte telomere length in vivo are poorly understood, there is evidence that chronic inflammation enhances leukocyte turnover and therefore may accelerate leukocyte telomere attrition. Inflammation is considered a major player in human aging (24–26) and longevity (27), and leukocyte telomere dynamics may capture in part the effect of this process.

Our results demonstrating associations of telomere length with some risk factors for cardiovascular disease, including diabetes, indices of glucose regulation (fasting insulin and glucose), and inflammation, confirm previous findings (8, 28–30). They also corroborate that telomeres in persons with type 2 diabetes are shorter than those in nondiabetics (28, 29), and our findings regarding serum insulin and glucose correspond to those of studies examining insulin resistance (8, 30). Gardner et al. (8) went one step further in their longitudinal analysis, which showed increases in insulin resistance to correlate with escalated telomere attrition. Aviv et al. (30) recently reported that associations between TRF length, insulin resistance, and C-reactive protein were modified by menopausal status in that associations were found in premenopausal women but not in

postmenopausal women. Although we did not have premenopausal women in our sample, we found that age modified the association between TRF and C-reactive protein and that, similarly to Aviv et al.'s (30) finding, associations were present in younger participants but not older participants. We did not find associations between cigarette smoking, body mass index, and TRF length as had another study of younger women (31). However, the advanced age of the CHS cohort may explain these differences, especially since age was found to modify obesity in this study. The small number of smokers (<11 percent) in the CHS may also have affected the discrepancy in smoking. Our findings, however, do corroborate other reports of cross-sectional associations between telomere length, atherosclerosis, and blood pressure (reviewed in the paper by Ferrano and Andres (4)). We did not find a significant association between length of telomeres and mortality as previously reported (14).

The effect modification by age of associations between TRF length and incident myocardial infarction and stroke found here may help explain the findings of several studies reporting lack of associations with morbidity and mortality in the oldest old (32, 33). As humans reach advanced ages, a survival effect may modify associations with leukocyte telomere length. Investigation into cellular mechanisms involved in telomere attrition across age groups may ultimately shed light on this important matter.

Leukocytes were selected for TRF measurement primarily because of the availability of stored blood in the CHS repository. However, telomere length across tissues is partially synchronized (34, 35). Persons endowed with relatively long (or short) telomeres in one type of tissue exhibit relatively long (or short) telomeres in other tissues, regardless of the different proliferative rates of the different tissues. While our results may only be generalized to leukocyte TRF length, we speculate that telomeres from other tissues may be similarly affected.

We acknowledge several limitations of this study. Because it was a pilot study, the sample size was restricted, and larger studies are needed to confirm these results. Related to this, we cannot rule out the possibility of chance in overall associations or in the effect modification that was found. In addition, while the CHS had extensive follow-up for ascertainment of cardiovascular disease, only cross-sectional data were available for most of the subclinical cardiovascular disease measures and risk factors in the study. In addition, a number of factors that may have affected telomere attrition in the elderly were not considered in these analyses, including medications taken for treatment of cardiovascular disease and related conditions, as well as lifestyle and other health behaviors. Finally, while the pathophysiologic mechanisms that connect shortened telomeres and chronic disease states cannot be determined from these data, results of new associations and effect modification may help generate hypotheses to further elucidate related processes.

It has been shown that oxidative stress accelerates telomere erosion by increasing telomeric loss per replication of cultured somatic cells (36). Both inflammation (37) and oxidative stress (38) are related to the initiation and progression of age-related cardiovascular disease. It is reasonable, therefore, to propose that leukocyte telomere dynamics may chronicle the lifelong burden of inflammation and oxidative stress, two major determinants in a number of disease states or perhaps aging itself. Longitudinal assessment of telomere dynamics in large cohorts will provide valuable information about the relations between chronic diseases of aging, inflammation, and leukocyte telomere dynamics.

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Conflict of interest: none declared.

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