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Leukocyte Telomere Length and Cardiovascular Risk Scores for Prediction of Cardiovascular Mortality

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To the Editor

Leukocyte telomere length is considered a biomarker of cellular aging and shorter telomere length is a putative cardiovascular disease (CVD) risk factor.[1,2] A recent study reported no association between leukocyte telomere length and CVD mortality.[3] However, that analysis is uncertain because a) stroke deaths were excluded from the CVD endpoint and b) dichotomized risk factors were used to partition CVD risk. Whereas the dichotomous risk factor approach assumes risk equivalence across sex, race, and comorbidities, current CVD risk formulations optimally discriminate risk by considering risk factors simultaneously within sex and race-specific models.[4] These risk scores are more sensitive and valid compared to multiple binary risk factors considered individually.[4] The purpose of this study was to re-examine the association between leukocyte telomere length and CVD mortality[3] including stroke in the CVD endpoint and additionally using more precise 10-year atherosclerotic CVD risk scores.[4]

We analyzed the 1999-2002 National Health and Nutrition Examination Surveys (NHANES), a probability sample of US residents.[5] We restricted analyses to examined participants 40-79 years of age (N=5329) who had laboratory assessments for atherosclerotic CVD risk calculations (N=4780) and genomic analysis of stored blood samples (N=4262). All participants provided informed consent and their vital status was ascertained via the National Death Index through the end of 2011 (median=10.7 years; IQR 9.8-11.7). Non-CVD deaths (N=610) were censored, leaving 3652 for analysis. The study was approved by the National Center for Health Statistics Ethical Review Board.

Telomere assays have been described elsewhere. [3] Leukocyte telomere length was calculated as the ratio of telomere repeat copy number (T) to single gene copy number (S), the T/S

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ratio. The interassay coefficient of variation was 6.5%. Using attained age as the time scale [6] we estimated the association between standardized leukocyte telomere length with CVD mortality before and after controlling for 10-year atherosclerotic CVD risk. Cox regression analyses incorporated the complex survey design and were stratified on 5-year age cohorts to satisfy proportional hazards assumptions (see eAppendix for annotated code). We analyzed data with StataMP 13.1 (Stata Corp, College Station, TX).

Participant characteristics are presented in the Table. During follow up there were 198 CVD deaths (148 due to diseases of heart [ICD-10 codes I00-I09, I11, I13, I20-I51]; 50 due to cerebrovascular diseases [ICD-10 codes I60-I69]). Leukocyte telomere length was not predictive of CVD mortality in a model with age, sex and race/ethnicity (HR=0.93, 95%CI 0.74-1.2), nor when adjusted for only atherosclerotic CVD risk risk (HR=0.92, 95%CI 0.73-1.2). The latter model produced similar hazards when restricting analyses to those free of diagnosed CVD at baseline (N=3274; 118 events; HR=0.92; 95%CI 0.72-1.2).

In a representative sample of US adults, leukocyte telomere length was not associated with CVD mortality either before or after entering the 10-year atherosclerotic CVD risk score. This research corroborates a recent analysis of CVD mortality in NHANES [3] and extends it to show that the null association between leukocyte telomere length and CVD mortality persists when including stroke in the CVD endpoint and when using currently recommended atherosclerotic CVD risk scores. [4] Our study was limited by a lack of nonfatal endpoints and the use of atherosclerotic CVD risk scores across the full sample, despite it being developed for use in persons initially free of known atherosclerotic disease. These concerns are mitigated by the consistency of findings among participants free of established CVD, the fact that atherosclerotic deaths comprise roughly 70% of events in our CVD definition, and that atherosclerotic CVD risk scores are calibrated to optimally discriminate risk in this population.[4] In combination with prior work, [3,7] this study casts doubt upon the statistical association between leukocyte telomere length and CVD death. Leukocyte telomere length may be prognostic in combination with skeletal-muscle telomere length.[1]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table

Participant Characteristics, 1999-2002 NHANES

	Cardiovascular death at follow up			
	No (N = 3454)		Yes (N = 198)	
	Percent	95% CI	Percent	95% CI
Age, weighted mean, y	54	(53-54)	65	(63-68)
Female sex, %	52	(51-54)	35	(27-44)
Race/ethnicity, %				
Mexican American	5	(3-7)	4	(2-7)
Other Hispanic	5	(3-9)	4	(1-12)
White (non-Hispanic)	78	(74-82)	79	(70-85)
Black (non-Hispanic)	8	(6-10)	12	(8-17)
Other race	4	(3-5)	2	(0-11)
Education level				
<9th grade	6	(5-8)	15	(10-23)
9-11 no diploma	12	(11-14)	19	(12-29)
High school diploma	25	(23-27)	20	(13-30)
Some college	27	(25-30)	28	(19-39)
College graduate or higher	29	(25-33)	18	(10-29)
Existing CVD, %[a]	8	(6-9)	37	(31-45)
ASCVD risk, %	8	(7-8)	20	(18-22)
Telomere length (T/S), mean[b]	1.0	(0.98,1.1)	0.93	(0.88,0.98)

Abbreviations: NHANES, National Health and Nutrition Examination Survey; ASCVD, atherosclerotic cardiovascular disease, 10-year percent risk; T/S, telomere length divided by standard reference DNA. All values are weighted to represent the civilian noninstitutionalized US population aged 40-79 years.

[a] Diagnosed heart attack, coronary heart disease, congestive heart failure or stroke.

[b] To convert to base pairs multiply the T/S ratio by 2413 and then add 3274.