

# Association of Shorter Leukocyte Telomere Repeat Length With Dementia and Mortality

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**Background:** Shortening of chromosomal telomeres is a consequence of cell division and is a biological factor related to cellular aging and potentially to more rapid organismal biological aging.

**Objective:** To determine whether shorter telomere length (TL), as measured in human blood samples, is associated with the development of Alzheimer disease and mortality.

**Design:** We studied available stored leukocyte DNA from a community-based study of aging using real-time polymerase chain reaction analysis to determine mean TL in our modification of a method measuring the ratio of telomere sequence to single-copy gene sequence.

**Setting:** A multiethnic community-based study of aging and dementia.

**Participants:** One thousand nine hundred eighty-three subjects 65 years or older. Mean (SD) age at blood draw was 78.3 (6.9) years; at death, 86.0 (7.4) years.

Median follow-up for mortality was 9.3 years; 190 (9.6%) developed incident dementia.

**Results:** The TL was inversely related to age and shorter in men than women. Persons dying during follow-up had a shorter TL compared with survivors (mean [SD], 6218 [819] vs 6491 [881] base pairs [bp] [ $P < .001$ ]), even after adjustment for age, sex, education, and apolipoprotein E genotype. Individuals who developed dementia had significantly shorter TL (mean [SD], 6131 [798] bp for prevalent cases and 6315 [817] bp for incident cases) compared with those remaining dementia-free (6431 [864] bp). Cox-regression analyses showed that shorter TL was a risk for earlier onset of dementia ( $P = .05$ ), but stratified analyses for sex showed that this association of age at onset of dementia with shorter TL was significant in women only.

**Conclusion:** Our findings suggest that shortened leukocyte TL is associated with risks for dementia and mortality and may therefore be a marker of biological aging.

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**T**ELOMERES ARE STRETCHES OF thousands of repeated TTAGGG hexanucleotide sequences located at the ends of each chromosome.<sup>1</sup>

Telomeres provide an essential protective role for the genetic material, preventing DNA damage response and repair mechanisms from acting on the chromosomal ends with ensuing genome instability. However, telomere sequences, because of their end positions, are not fully replicated during DNA replication and thus become shorter with each cell division. A ribonucleoprotein enzyme complex known as telomerase can elongate or repair these sequences through a reverse transcriptase activity. Overall, telomeres are shorter in somatic than germline cells. In cultured cells, telomere shortening due to repeated cell divisions correlates with cellular aging, or se-

nescence. In cancer cells, telomeres may be longer, owing to increased telomerase activity. Successful aging may depend on a balance of adequate but not excessive telomerase activity.

Studies of blood cell telomeres have shown wide variation in telomere length (TL). Older individuals have shorter telomeres,<sup>2</sup> but dispersion in TL owing to normal variation prevents its use as a determinant of biological age. Telomere length is likely influenced by both genetic factors (eg, variants associated with telomerase RNA component, loci near the *TERC* gene, or other loci identified from genome-wide studies<sup>3-6</sup>) and nongenetic factors. Nongenetic factors may include smoking,<sup>7</sup> socioeconomic status or physical activity,<sup>8</sup> marine fatty acid intake,<sup>9</sup> psychological stressors,<sup>10</sup> and various cardiovascular,<sup>2,11-14</sup> diabetes,<sup>15</sup> chronic obstructive pul-



**Table 1. Demographic and Clinical Characteristics for Mortality Analysis**

Characteristic	All Participants	Survived	Deceased	P Value
No. (%) of participants	1978 (100.0)	1115 (56.4)	863 (43.6)	
TL, bp				
Mean (SD)	6371 (864)	6491 (881)	6218 (819)	<.001 <sup>a</sup>
Range	4103-11 447	4220-11 447	4103-11 405	
Dementia at/after blood draw, No. (%) <sup>b</sup>				
None	1469 (74.5)	930 (83.4)	539 (62.5)	<.001 <sup>c</sup>
Prevalent	314 (15.9)	92 (8.3)	222 (25.7)	
Incident	190 (9.6)	91 (8.2)	99 (11.5)	
Age at blood draw, y				
Mean (SD)	78.3 (6.9)	76.4 (6.0)	80.7 (7.3)	<.001 <sup>a</sup>
Range	66-101	66-95	66-101	
Age at death, y				
Mean (SD)		81.1 (6.3)	86.0 (7.4)	
Range		66-103	67-111	
Sex, No. (%)				
Male	628 (31.7)	319 (28.6)	309 (35.8)	.001 <sup>c</sup>
Female	1350 (68.3)	796 (71.4)	554 (64.2)	
Ethnic group, No. (%)				
Non-Hispanic white	564 (28.5)	314 (28.2)	250 (29.0)	.09 <sup>c</sup>
Non-Hispanic African American	599 (30.3)	316 (28.3)	283 (32.8)	
Hispanic	790 (39.9)	470 (42.2)	320 (37.1)	
Other	25 (1.3)	15 (1.3)	10 (1.2)	
Education, y <sup>d</sup>				
Mean (SD)	9.7 (4.9)	10.0 (4.9)	9.3 (4.8)	<.001 <sup>a</sup>
Range	0-20	0-20	0-20	
<i>APOE</i> allele status, No. (%) with $\geq 1$ <sup>e</sup>				
$\epsilon 4$	529 (27.1)	288 (26.2)	241 (28.3)	.33 <sup>b</sup>
$\epsilon 2$	311 (15.9)	178 (16.2)	133 (15.6)	.76 <sup>b</sup>

Abbreviations: *APOE*, apolipoprotein E; bp, base pairs; TL, telomere length.

<sup>a</sup>Compares values for survivors and deceased participants by means of analysis of variance.

<sup>b</sup>Five cases are missing data. Percentages have been rounded and might not total 100.

<sup>c</sup>Compares mortality for dementia status, sex, ethnicity, or *APOE* allele status using  $\chi^2$  test.

<sup>d</sup>Eight cases are missing data.

<sup>e</sup>Twenty-seven cases are missing data.

**Table 2. Demographic and Clinical Characteristics for Dementia Analysis**

Characteristic	All Participants	No Dementia	Incident Dementia	Prevalent Dementia	P Value
No. (%) of participants	<b>1973</b> (100.0)	1469 (74.5)	190 (9.6)	314 (15.9)	
TL, mean (SD), bp	6372 (856)	6431 (864)	6315 (817)	6131 (798)	<.001 <sup>a</sup>
Age at blood draw, mean (SD), y	78.3 (6.9)	77.0 (6.3)	79.9 (6.5)	83.7 (7.3)	<.001 <sup>a</sup>
Age at death, mean (SD), y	86.0 (7.4)	84.3 (7.1)	88.2 (6.8)	89.2 (7.3)	<.001 <sup>a</sup>
Age of survivors, mean (SD), y	81.1 (6.3)	80.5 (6.1)	84.7 (6.1)	84.3 (6.4)	<.001 <sup>a</sup>
Sex, No. (%)					
Men	<b>627</b> (31.8)	489 (33.3)	56 (29.5)	82 (26.1)	.04 <sup>b</sup>
Women	<b>1346</b> (68.2)	980 (66.7)	134 (70.5)	232 (73.9)	
Ethnic group, No. (%) <sup>c</sup>					
Non-Hispanic white	565 (28.3)	492 (33.5)	34 (17.9)	37 (11.8)	<.001 <sup>a</sup>
Non-Hispanic African American	602 (30.2)	448 (30.5)	47 (24.7)	104 (33.1)	
Hispanic	801 (40.2)	507 (34.5)	107 (56.3)	172 (54.8)	
Education, mean (SD), y <sup>d</sup>	9.7 (4.9)	10.7 (4.6)	7.8 (4.6)	6.4 (4.4)	<.001 <sup>a</sup>
<i>APOE</i> allele status, No. (%) with $\geq 1$ <sup>e</sup>					
$\epsilon 4$	<b>529</b> (27.2)	368 (25.3)	51 (27.6)	110 (35.7)	.001 <sup>b</sup>
$\epsilon 2$	<b>311</b> (16.0)	230 (15.8)	45 (14.6)	36 (19.5)	.35 <sup>b</sup>

Abbreviations: *APOE*, apolipoprotein E; bp, base pairs; TL, telomere length.

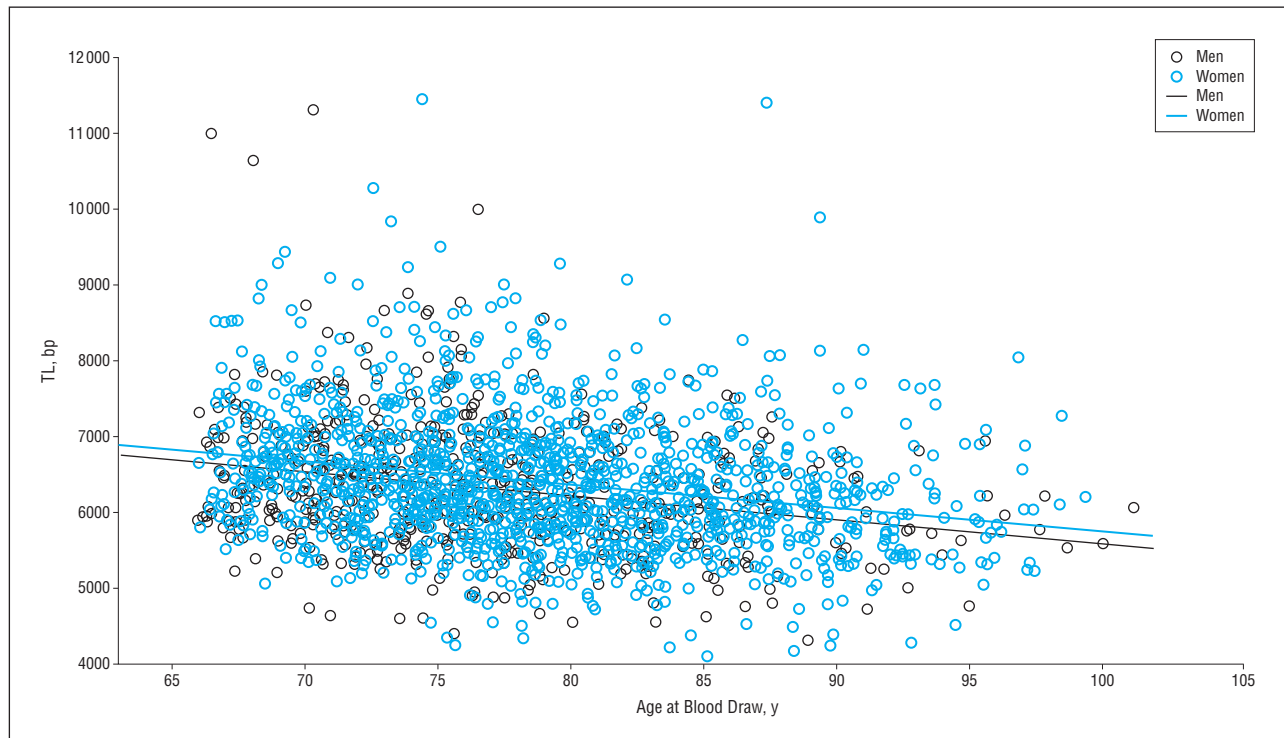
<sup>a</sup>Compares values for dementia status groups by analysis of variance.

<sup>b</sup>Compares dementia status for sex, ethnicity, or *APOE* allele status using  $\chi^2$  test.

<sup>c</sup>Twenty-five cases classified as other are missing; percentages do not total 100.

<sup>d</sup>Eight cases are missing data.

<sup>e</sup>Twenty-seven cases are missing data.



**Figure 1.** A scatterplot of telomere length (TL) vs age at blood draw reveals that individuals who are older at the time of blood draw have shorter TL. Linear regression analysis of TL vs age at blood draw with sex as a covariate reveals a mean (SD) least-squares decline of 31.1 (2.7) base pairs (bp) per year of age (95% CI, 25.7-36.5;  $P < .001$ ), with shorter length in men compared with women by a mean (SD) of 128 (41) bp (95% CI, 48-208;  $P = .002$ ).

had about 1 year less education (9.3 vs 10.0 years [ $P < .001$ ]), were more likely to be men (35.8% vs 28.6% [ $P = .001$ ]), were more likely to have dementia (37.4% vs 16.6% [ $P < .001$ ]), and had shorter mean TL (6218 [819] vs 6491 [881] bp [ $P < .001$ ]) (Table 1). We found no difference between survivors and those who died in distribution of ethnicity or frequencies of APOE  $\epsilon 4$  (28.3% vs 26.2%) or  $\epsilon 2$  allele carrier status (15.6% vs 16.2%).

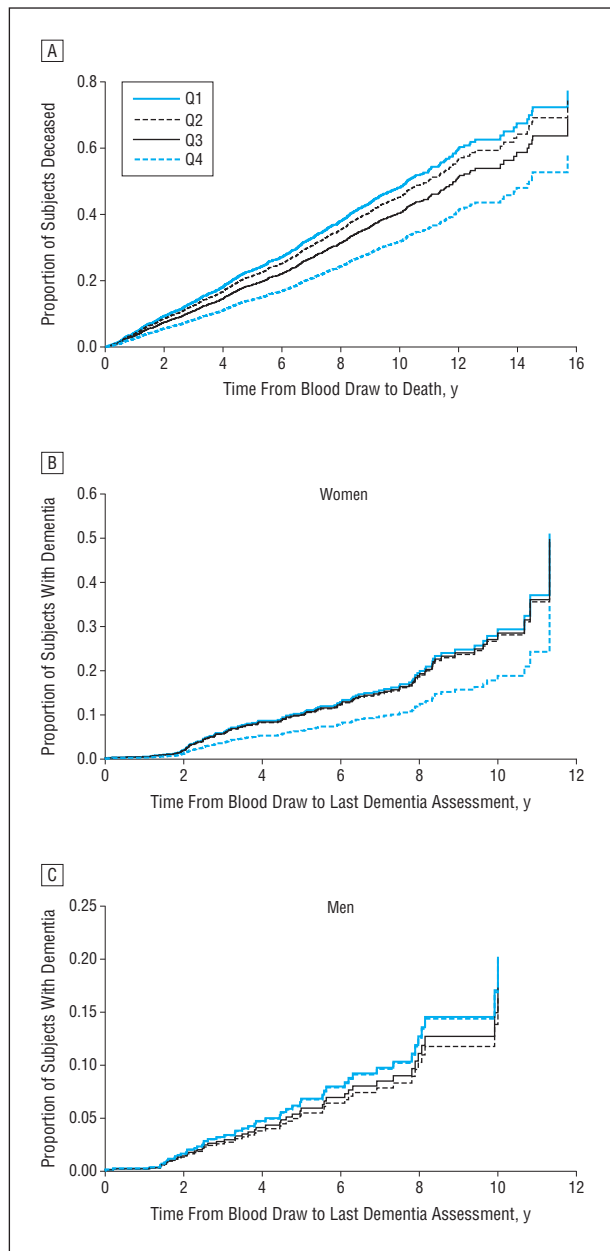
Table 2 provides the demographic and clinical characteristics of those with and without dementia. At the time of the blood draw, 314 participants (15.9%) had prevalent dementia; subsequent to the blood draw, 190 (9.6%) developed dementia during follow-up, whereas 1469 (74.5%) remained dementia free throughout the follow-up period. Of the 504 participants with dementia, 79.6% were classified as having probable AD, 13.9% as having possible AD, and only 6.5% as having other dementias (not shown in the Tables). Participants remaining dementia free had longer TL at the blood draw than those with incident dementia, who in turn had longer TL than those with prevalent dementia (6431 [864], 6315 [817], and 6131 [798], respectively [ $P < .001$ ]) (Table 2). However, a similar rank order was observed for demographic variables, in which those with no dementia, compared with incident and prevalent dementia, were younger at the blood draw, had more years of education, were more likely to be male and non-Hispanic white, and have APOE  $\epsilon 4$  noncarrier status (Table 2). Thus, subsequent analyses were adjusted for these factors.

#### TL IN THE TOTAL GROUP: RELATION TO AGE, SEX, AND ETHNICITY

Mean TL in the total group was 6371 (864 [range, 4103-11447]) bp (Table 1). Individuals who were older at the time of blood draw had shorter TL (**Figure 1**). Linear regression analysis of TL by age at blood draw revealed a least-squares line with slope of decline of 31.1 (2.7 [95% CI, 25.7-36.5] bp/y;  $r = -0.24$  [ $P < .001$ ]). Stratifying for sex, this finding was highly significant for men ( $r = -0.25$ ) and women ( $r = -0.24$ ). However, TL was significantly shorter in men than women; regression analysis performed by age and sex showed a difference of 128 (41 [95% CI, 48-209] bp [ $P = .002$ ]). The TL also varied by ethnicity, being shortest in Hispanic (6293 [839] bp;  $n = 790$ ) compared with African American (6417 [860] bp;  $n = 599$ ) or white subjects (6427 [902] bp;  $n = 564$ ) (analysis of variance,  $F_{3,1958} = 3.93$  [ $P = .008$ ]). This relationship of TL with ethnicity persisted for those who remained free of dementia during the follow-up period: Hispanic subjects (6334 [791] bp;  $n = 507$ ) had shorter TL than African American (6499 [867] bp;  $n = 449$ ) or white subjects (6460 [927] bp;  $n = 492$ ) (analysis of variance,  $F_{3,1465} = 3.68$  [ $P = .01$ ]).

#### PREDICTION OF MORTALITY BY SHORTER TL

The TL was shorter in those who died during follow-up than in survivors (Table 1). However, age, sex, and education were also factors affecting mortality. We performed a survival analysis using a Cox regression model (see **Figure 2A**) with mortality as the outcome, quar-



**Figure 2.** Survival analyses of mortality and dementia for participants with different telomere lengths (TLs). Cox regression models show the effects of TL quartile on outcomes of mortality or dementia over time, with adjustment for covariates. A, Analysis for the outcome measure of mortality. Compared with the longest quartile TL (quartile 4 [Q4]), the following hazard ratios (HRs) for shorter quartiles were found: 1.72 (95% CI, 1.40-2.11;  $P < .001$ ) for Q1, 1.57 (95% CI, 1.28-1.94;  $P < .001$ ) for Q2, and 1.35 (95% CI, 1.09-1.67;  $P = .005$ ) for Q3. Covariates, with their effect significance, included age at blood draw ( $P < .001$ ), sex ( $P < .001$ ), ethnicity ( $P = .06$  for Hispanic), education ( $P = .08$ ), and apolipoprotein E  $\epsilon 4$  carrier status ( $P = .25$ ). B, Outcome measures of dementia for women. C, Outcome measures of dementia for men. When stratified by sex in this fashion, the numbers are small, particularly for men, of whom 56 had incident dementia, compared with women, of whom 134 had incident dementia. Only female participants show a significant effect of shorter TL (Q1, Q2, and Q3) on shorter time to dementia compared with those with longer TL (Q4). Bp indicates base pair; Q1, 5803 bp or less; Q2, 5804 to 6271 bp; Q3, 6272 to 6851 bp; and Q4, 6852 bp or more.

tile of TL as the independent variable, years from the time of the blood draw as the time-to-event variable, and age at the blood draw, sex, ethnicity, education, and *APOE*

$\epsilon 4$  carrier status as covariates. The risk of mortality for individuals with the shortest TL was 1.72 (95% CI, 1.40-2.11;  $P < .001$ ). Because sex has effects on TL and mortality, stratified analyses were performed for men and women; for both sexes, mortality risk was greater in those with shorter TL (data not shown in the Tables or Figures).

#### PREDICTION OF MORTALITY BY SHORTER TL

The TL was shorter in those with dementia, whether prevalent or incident, than in those without dementia during the follow-up period (Table 2). However, age, sex, education, ethnicity, and *APOE* genotype were also factors affecting risk for dementia. Because the presence of dementia might affect TL, survival analysis was performed only for those with incident dementia subsequent to the time of the blood draw (Table 3). The Cox regression model used incident dementia as the outcome, TL as the independent variable, and the time from the blood draw to the last diagnostic visit as the time variable, and was adjusted for age at blood draw, sex, ethnicity, education, and *APOE*  $\epsilon 4$  carrier status. Results displayed in Table 3 show that shorter TL (as a continuous variable) was a risk for dementia (hazard ratio [HR], 1.21 [95% CI, 1.00-1.46;  $P = .05$ ]), indicating a 21% increased risk for dementia for each kilobase pair (kb) of decreased TL. Age, ethnicity, and years of education were significant covariates related to risk of dementia, but *APOE*  $\epsilon 4$  carrier status only showed a trend toward being a risk factor in this multiethnic population. On stratification for *APOE*  $\epsilon 4$  carrier status, reduced numbers resulted in loss of statistical significance for the effect of TL on dementia (data not shown). However, stratified analyses on sex, analyzing men and women separately (Figure 2B-C), showed a statistically robust effect of TL (HR, 1.33 per kb of TL [ $P = .01$ ]) on dementia only in women ( $n = 134$ ), with no evident effect in men ( $n = 56$ ). For the women, those same covariates that were significant in the cohort as a whole were also significant factors (age at blood draw, Hispanic ethnicity, and education), and *APOE*  $\epsilon 4$  carrier status showed a trend (HR, 1.46 [ $P = .06$ ]).

#### PREDICTION OF MORTALITY INDEPENDENT OF DEMENTIA OR *APOE* STATUS BY SHORTER TL

Because dementia and *APOE* status are known to increase the likelihood of mortality, we performed stratified analyses examining the effect of TL on mortality in those with differing dementia status and *APOE*  $\epsilon 4$  genotype. For those with prevalent or incident dementia, the shortest quartile TL remained a significant risk factor for mortality (eTable 2), although numbers in each group are small (ranging from 43 to 109). The effect of TL on mortality was independent of dementia, because in those study participants without dementia, significant risk was also present for each of the shorter quartile TL (eTable 2). Similarly, the effect appeared independent of *APOE* genotype, because stratified analyses showed effects of TL on mortality for those with and without  $\epsilon 4$  alleles (eTable 3), although the smaller numbers attenuated statistical significance.

We examined the relation of TL to the risk for dementia and mortality in a large multiethnic community-based cohort 65 years or older followed up for as long as 16 years. In this cross-sectional analysis, we found that blood leukocyte mean TL was shorter in those who were older at the time of blood draw, a finding in prior studies,<sup>2,39</sup> and presumably reflecting loss of telomeres during the cell divisions undergone by the leukocytes during life. Our results also confirm that men had shorter TL than women, for which the cell biological explanation is unclear. However, this effect of sex is consonant with the biological impression that men are on average “biologically older” than women.

We found that decreased leukocyte TL was associated with mortality, or decreased life span, consistent with results from our earlier work with a small selected subsample of the WHICAP population.<sup>19</sup> Several studies of various sample sizes (see eTable 1) also have found that elderly subjects with shorter leukocyte TL have earlier mortality,<sup>2,20,24</sup> although some studies have not found an effect of TL on mortality.<sup>23,26,27</sup> Our study has the advantage of a large size, a broad age range from 66 to 101 years, thorough ascertainment of mortality, and use of the PCR method of TL measurement. We observed an association of short TL with increased mortality in the presence or absence of dementia. The association of TL with mortality might indicate (1) that shortened TL causes processes that lead to earlier mortality; (2) that other biological processes or preclinical disorders are causing TL shortening; or (3) that some environmental or genetic influences are concomitantly both causing shortening of TL and increasing mortality.

An association, albeit modest, between shorter TL and risk for dementia was also evident in this population, taking into account age differences, and confirming our earlier results from a selected case-control subsample of this cohort.<sup>19</sup> A number of prior studies (see Table 1) have also shown a relationship between short TL and dementia.<sup>18,20-22</sup> Although some studies have not shown such an effect,<sup>23,24</sup> they were hampered by very small numbers of cases with dementia (eTable 1) and/or shorter follow-up. Other differences between studies may relate to methodological variation with less reliable TL measurement, differences in study group demographic age and ethnic distributions, and differences in dementia ascertainment or incidence. An effect of TL on dementia risk may simply reflect the effect of biological aging. Alternatively, TL and AD may share a common set of genes or other determinants. The association of TL with dementia was, after stratification, only significant in women, not men, and this might be owing to the small numbers of men with incident dementia (n = 56) compared with women (n = 134), leading to reduced power, to increased variability in TL in men, or to increased numbers of confounders/concomitant medical disorders in men compared with women.

Our study shows that TL has a wide variation between individuals even within the same age stratum. Indeed, the variation between individuals within age groups

**Table 3. Association of TL With Incident Dementia After Blood Draw<sup>a</sup>**

	HR (95% CI)	P Value
<b>All Participants (N = 1659)</b>		
Incident dementia (n = 190)		
Shorter TL, kb	1.21 (1.00-1.46)	.05
Men	1.19 (0.86-1.64)	.30
Ethnicity, Hispanic	2.02 (1.25-3.27)	.004
Education, y	0.92 (0.89-0.96)	<.001
<i>APOE</i> ε4 allele, ≥1	1.36 (0.97-1.89)	.07
Age at blood draw, y	1.12 (1.10-1.15)	<.001
<b>Men (n = 545)</b>		
Incident dementia (n = 56)		
Shorter TL, kb	0.94 (0.65-1.35)	.74
Ethnicity, Hispanic	3.40 (1.37-8.42)	.01
Education, y	0.91 (0.85-0.98)	.02
<i>APOE</i> ε4 allele, ≥1	1.01 (0.54-1.89)	.98
Age at blood draw, y	1.12 (1.07-1.17)	<.001
<b>Women (n = 1114)</b>		
Incident dementia (n = 134)		
Shorter TL, kb	1.33 (1.06-1.68)	.01
Ethnicity, Hispanic	1.78 (1.00-3.16)	.05
Education, y	0.93 (0.89-0.98)	.01
<i>APOE</i> ε4 allele, ≥1	1.46 (0.99-2.17)	.06
Age at blood draw, y	1.13 (1.09-1.16)	<.001

Abbreviations: *APOE*, apolipoprotein E; HR, hazard ratio; kb, kilobase pair; TL, telomere length.

<sup>a</sup>Among 1659 participants without prevalent dementia, 190 had incident dementia (56 of 545 men and 134 of 1114 women). The data presented are the results of a Cox regression model of TL on outcome of incident dementia, with the following covariates: age at blood draw, sex, ethnicity (Hispanic compared with non-Hispanic white), education, and *APOE* ε4 allele carrier status. Shorter TL, on a continuous basis, relates to a shorter time to dementia, but only clearly so in women. Covariates also are associated with incident dementia, as shown herein.

is larger than the effect of many years of aging. For this reason, TL cannot be used as a measure of biological or chronological age per se. However, the combination of TL and chronological age is likely to be more informative than either one alone. Reasons for the wide variation in TL may include (1) intrinsic, possibly genetic, differences in initial TL at birth; (2) intrinsic, possibly genetic, differences in the rate of telomere attrition during life; (3) environmental influences affecting aging, including diet, exercise, and infectious exposures; or (4) the presence of other diseases. Evidence suggests that TL is a heritable characteristic,<sup>5,40,41</sup> with varying estimates of heritability as high as 80%. Genes likely affect the aging process in general. Similarly, given that telomere maintenance depends on telomerase, with RNA and enzymatic protein subunit components, certain genes likely affect TL and its rate of decline. In our previous smaller case-control study, we reported a relationship between TL and *APOE* genotype, but not in this study. With the increasing ability to perform large-scale genetic analyses, particular genes underlying TL shortening or maintenance or affecting the relationship of TL to aging will probably be identified.

Compared with prior studies, this study's strengths include the large sample size, multiethnic group, population-based cohort, and ability to thus adjust for age, sex, education, and other potential confounders when examining

the relationship of TL to outcome variables. Weaknesses include the following: (1) the study involves only those 65 years or older, so we were unable to compare TL from younger individuals; (2) not all study participants had blood drawn or DNA available; and (3) the study population includes 3 ethnic groups and thus is likely heterogeneous. However, to our knowledge this study is the only one to examine a relatively large sample from different genetic and environmental backgrounds represented by 3 ethnic groups, thereby allowing examination of a greater range of risk factors using a single assay with good laboratory reproducibility. Incomplete DNA availability should not have any differential effects on TL, and thus is unlikely to affect the interpretation of this study, but it is possible that the ethnically heterogeneous population leads to underestimation (owing to superposed variability) or less likely overestimation (given adjustments) of the effect of TL on dementia and mortality. Shortening of TL is associated with aging, male sex, dementia, and mortality. Short TL may cause more rapid aging, or alternatively states of illness, including incipient dementia (because data suggest that AD pathology may precede clinical dementia symptoms by some 10 to 20 years), might cause short TL, or some independent factor might cause shortened telomeres and aging and dementia. Our studies do not imply the direction of causation, and telomeres may simply be a marker of aging, rather than a determinant of the aging process. Evidence from cell culture and from animal models suggests that very short telomeres are themselves deleterious, increasing errors in the cell division process and possibly the development of cancer. Although age is the strongest determinant of sporadic AD, very wide variation exists in age at onset, from the fifth to the tenth decades of life. In addition to *APOE*, a variety of other genes plays a role in susceptibility to AD. The amount of  $\beta$ -amyloid deposition or the development of  $\beta$ -amyloid-induced nervous system injury may relate not simply to chronological age, but also to other factors such as biological age. Our results show an association between shortened TL and mortality, and more specifically an association of shortened TL with AD, and are consistent with but not indicative of the possibility that TL may be a factor indicative of biological age. If TL was a determinant rather than a marker of aging, one could speculate that therapies directed toward modifying TL shortening, by modestly increasing telomerase activity, might be helpful in decreasing the incidence of age-related dementia.

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*of the manuscript for important intellectual content:* Honig, Kang, Schupf, and Mayeux. *Statistical analysis:* Honig, Kang, Schupf, and Lee. *Obtained funding:* Honig and Mayeux. *Administrative, technical, and material support:* Honig, Kang, and Mayeux. *Study supervision:* Honig.

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**Online-Only Material:** The eTables are available at <http://www.archneur.com>.

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