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.

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], 6131 [798] bp vs 6491 [881] bp), 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.

monary, and skin disorders. If TL is a surrogate marker for biological age, short TL is likely to predict risk of age-related diseases such as Alzheimer disease (AD) and mortality. Investigations to date have been inconsistent with respect to such relationships (eTable 1; http://www.archneurol.com). These investigations include our nested case-control study, other studies that showed shorter TL in elderly subjects developing dementia, and other studies that did not. Similarly, various studies have found an association of lifespan with shorter TL (eTable 1). We designed this large study to have reasonable power, using a multiethnic elderly epidemiologic population with follow-up as long as 16 years to test whether TL adjusted for age and sex is associated with dementia or mortality. We used a quantitative polymerase chain reaction (PCR) method that minimizes measurement variation.

METHODS

PARTICIPANTS AND SETTING

Participants are from the Washington Heights–Inwood Community Aging Project (WHICAP), a population-based study of aging and dementia in New York City. Of a total of 4308 participants recruited from 1992 and 1999 cohorts, blood samples were obtained from 3106 (72%), of whom 1838 (64%) had adequate DNA for TL measurement. We used DNA from the first available blood draw, regardless of whether the sample was obtained at baseline or a subsequent visit. Participants in the study undergo standardized assessments every 18 to 30 months, including medical history, functional status, and physical, neurological, and neuropsychological examinations. Ethnicity and race were self-identified by participants. Vital status was updated January 10, 2011, using Social Security Death Index data. The WHICAP study and this study of TL are approved by the institutional review boards of Columbia University Medical Center and the New York State Psychiatric Institute. Participants gave written informed consent for the WHICAP data collection and blood draws.

DEMENTIA CLASSIFICATION

Diagnosis at each assessment was made by consensus conference, based on Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) dementia criteria and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorder Association criteria for AD. Participants were considered non-demented if they did not meet criteria for dementia at their most recent visit. Participants who had dementia at the time of the blood draw were considered to have prevalent dementia, and those who developed dementia at a subsequent visit were considered to have incident dementia.

DNA PREPARATION AND APOLIPOPROTEIN E GENOTYPING

Leukocyte DNA was prepared from 5-mL samples of whole blood, using a non–phenol-based kit (Puregene; Gentra Systems). Apolipoprotein E (APOE) genotyping was performed by means of CfoI restriction analysis of whole-blood genomic DNA amplified by Taq PCR with APOE primers.

MEASUREMENTS OF TELOMERE LENGTH

Coded DNA samples were processed by laboratory personnel, blinded to participant characteristics. Average TL was determined using our modification of a method developed by Cawthon and colleagues. Real-time PCR was performed using a thermocycler (CFX384; Bio-rad). Assay method was optimized for use of telomere sequence and single-copy gene amplifications on the same 384-well plate, with reference standard DNA samples on each plate. Test DNA samples each underwent 2 triplicate PCR amplifications, with use of calibrator samples for correction of interplate variability. Amplification primers for telomeres included 5′-GGGTTTGGGTTGTTGGGTTTGGGTT-3′ forward and 5′-GGGTTTCCTTTACCCCTTAACCCCTTAACCCCTT ACCCT-3′ reverse; for single-copy genes (β globin chain), 5′-GGTTCTGACAACTGTGTTACATGC-3′ forward and 5′-CACCAACTCTCATCCAGTTCACC-3′ reverse. Thermocycling variables included activation for 10 minutes at 95°C, followed by 34 cycles for 15 seconds at 95°C and 120 seconds at 55°C. Our assay coefficient of variance ranged from 5% to 8%. The ratio of telomere sequence to single-copy gene sequence was converted to TL measured in base pairs (bp) by using the following linear regression formula: bp = (1585 × T:5 ratio) + 3582 (where T indicates telomere amplification and S, single-copy gene amplification), derived from coanalysis of selected DNA samples using PCR and terminal restriction fragment methods (nonradioactive TeloTAGGG TL assay, Roche Diagnostics) (correlation coefficient, r = 0.90).

STATISTICAL ANALYSIS

We used χ2 tests and analysis of variance for comparisons. Cox proportional hazards assessed the relation of TL to cumulative percentage of mortality and dementia. The time-to-event variable was time from the blood draw to death or onset of dementia. Statistical models were adjusted for age at blood draw, sex, ethnic group, years of education, and presence of APOE ε4 alleles. Additional analyses examined effects of APOE ε2 alleles. Because APOE ε4 is associated with the risks for dementia and death, we also examined the relation of TL to mortality within strata defined by the presence or absence of the APOE ε4 allele. We performed these analyses using commercially available software (IBM-SPSS Statistics, version 19 [SPSS Inc., on Microsoft Windows–based systems [Microsoft Corp.]]. Unless otherwise indicated, data are expressed as mean (SD).

RESULTS

GROUP CHARACTERISTICS (UNADJUSTED ANALYSES)

Subject demographics and other characteristics are shown in Table 1 and Table 2. The mean age of the total group at time of blood draw was 78.3 (range, 66-101) years; 1355 (68.3%) were women. Ethnic distribution included 790 Hispanic (39.9%), 599 non-Hispanic African American (30.3%), 564 non-Hispanic white (28.5%), and 25 other subjects (1.3%). The mean education level was 9.7 (±9 years) years. Mean follow-up time for mortality was 7.8 (range, 0-16; median, 9; 1st interquartile range, 5.5) years (data not shown in the Tables).

Compared with participants who survived, participants who died were on average 4 years older at the time of blood draw (80.7 years vs 76.4 years [P < .001])
Table 1. Demographic and Clinical Characteristics for Mortality Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants</th>
<th>Survived</th>
<th>Deceased</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of participants</td>
<td>1978 (100.0)</td>
<td>1115 (56.4)</td>
<td>863 (43.6)</td>
<td></td>
</tr>
<tr>
<td>TL, bp (SD)</td>
<td>6371 (864)</td>
<td>6491 (881)</td>
<td>6218 (819)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Range</td>
<td>4103-11447</td>
<td>4220-11447</td>
<td>4103-11405</td>
<td></td>
</tr>
<tr>
<td>Dementia at/after blood draw, No. (%)b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1469 (74.5)</td>
<td>930 (83.4)</td>
<td>539 (62.5)</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>Prevalent</td>
<td>314 (15.9)</td>
<td>92 (8.3)</td>
<td>222 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Incident</td>
<td>190 (9.6)</td>
<td>91 (8.2)</td>
<td>99 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Age at blood draw, y</td>
<td>78.3 (6.9)</td>
<td>76.4 (6.0)</td>
<td>80.7 (7.3)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Range</td>
<td>66-101</td>
<td>66-95</td>
<td>66-101</td>
<td></td>
</tr>
<tr>
<td>Age at death, y</td>
<td>81.1 (6.3)</td>
<td>86.0 (7.4)</td>
<td>67-111</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>628 (31.7)</td>
<td>319 (28.6)</td>
<td>309 (35.8)</td>
<td>.001c</td>
</tr>
<tr>
<td>Ethnic group, No. (%)</td>
<td>564 (28.5)</td>
<td>314 (28.2)</td>
<td>250 (29.0)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>599 (30.3)</td>
<td>236 (28.3)</td>
<td>283 (32.8)</td>
<td>.09c</td>
</tr>
<tr>
<td>Hispanic</td>
<td>790 (39.9)</td>
<td>470 (42.2)</td>
<td>320 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>25 (1.3)</td>
<td>15 (1.3)</td>
<td>10 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Education, yd</td>
<td>9.7 (4.9)</td>
<td>10.0 (4.9)</td>
<td>9.3 (4.8)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>APOE allele status, No. (%) with ≥1e</td>
<td>529 (27.1)</td>
<td>288 (26.2)</td>
<td>241 (28.3)</td>
<td>.33b</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; bp, base pairs; TL, telomere length.
a Compares values for survivors and deceased participants by means of analysis of variance.
b Five cases are missing data. Percentages have been rounded and might not total 100.
c Compares mortality for dementia status, sex, ethnicity, or APOE allele status using χ² test.
d Eight cases are missing data.
e Twenty-seven cases are missing data.

Table 2. Demographic and Clinical Characteristics for Dementia Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants</th>
<th>No Dementia</th>
<th>Incident Dementia</th>
<th>Prevalent Dementia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of participants</td>
<td>1973 (100.0)</td>
<td>1469 (74.5)</td>
<td>314 (15.9)</td>
<td>341 (32.0)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>TL, mean (SD), bp</td>
<td>6372 (856)</td>
<td>6431 (866)</td>
<td>6315 (817)</td>
<td>6131 (798)</td>
<td></td>
</tr>
<tr>
<td>Age at blood draw, mean (SD), y</td>
<td>78.3 (6.9)</td>
<td>77.0 (6.3)</td>
<td>79.9 (6.5)</td>
<td>83.7 (7.3)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Age at death, mean (SD), y</td>
<td>86.0 (7.4)</td>
<td>84.3 (7.1)</td>
<td>88.2 (6.8)</td>
<td>89.2 (7.3)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Age of survivors, mean (SD), y</td>
<td>81.1 (6.3)</td>
<td>80.5 (6.1)</td>
<td>84.7 (6.1)</td>
<td>84.3 (6.4)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>627 (31.8)</td>
<td>489 (33.3)</td>
<td>56 (29.5)</td>
<td>82 (26.1)</td>
<td></td>
</tr>
<tr>
<td>Ethnic group, No. (%)</td>
<td>1346 (68.2)</td>
<td>980 (66.7)</td>
<td>134 (70.5)</td>
<td>232 (73.9)</td>
<td>.04b</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>565 (28.3)</td>
<td>492 (33.5)</td>
<td>34 (17.9)</td>
<td>37 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic African American</td>
<td>602 (30.2)</td>
<td>448 (30.5)</td>
<td>47 (24.7)</td>
<td>104 (33.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>801 (40.2)</td>
<td>507 (34.5)</td>
<td>107 (56.3)</td>
<td>172 (54.8)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Education, mean (SD), y d</td>
<td>9.7 (4.9)</td>
<td>10.7 (4.6)</td>
<td>7.8 (4.6)</td>
<td>6.4 (4.4)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>APOE allele status, No. (%) with ≥1e</td>
<td>529 (27.2)</td>
<td>368 (25.3)</td>
<td>51 (27.6)</td>
<td>110 (35.7)</td>
<td>.001b</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; bp, base pairs; TL, telomere length.
a Compares values for dementia status groups by analysis of variance.
b Compares dementia status for sex, ethnicity, or APOE allele status using χ² test.
c Twenty-five cases classified as other are missing; percentages do not total 100.
d Eight cases are missing data.
e Twenty-seven cases are missing data.
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 \(\text{APOE}\) \(\varepsilon 4\) (28.3% vs 26.2%) or \(\varepsilon 2\) 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 \(\text{APOE}\) \(\varepsilon 4\) 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, 4103-11 447]) bp (Table 1). Individuals who were older at the time of blood draw had shorter TL (Figure 1). Linear regression analysis of TL vs age at blood draw revealed a least-squares linear regression analysis of TL by age at blood draw with sex as a covariate revealing 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; \(P = .002\)).

#### 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; \(P = .002\)).

### 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-
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 ε4 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 ε4 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 ε4 carrier status only showed a trend toward being a risk factor in this multiethnic population. On stratification for APOE ε4 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 ε4 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 ε4 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 ε4 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, 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. Several studies of various sample sizes (see eTable 1) also have found that elderly subjects with shorter leukocyte TL have earlier mortality, although some studies have not found an effect of TL on mortality. 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. A number of prior studies (see Table 1) have also found a relationship between short TL and dementia. Although some studies have not shown such an effect, they were hampered by very small numbers of cases with dementia 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 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, 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 may play a role in susceptibility to AD. The amount of β-amyloid deposition or the development of β-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 shorted 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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REFERENCES


