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

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## Abstract

**Objective—**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. We have hypothesized that shorter telomere length, as measured in human blood samples, is associated with the development of Alzheimer disease, and with mortality.

**Design/Setting—**Using data from a multiethnic community-based study of aging and dementia, we studied 1,983 subjects over age 65 yr, who had available stored leukocyte DNA. Mean age-at-blood-draw was 78.3 ± 6.9 yr. Mean age of death was 86.0 ± 7.4 yr. Median follow-up for mortality was 9.3 yr; 190 (9.6%) developed incident dementia. We used real-time PCR to determine mean telomere length (TL) in a modified telomere-sequence to single-copy-gene-sequence ratio method.

**Results—**TL was inversely related to age, and shorter in men than women. Persons dying during follow-up had shorter TL compared to survivors (6,218±819 vs. 6,491±881 basepairs, p<0.0001) even after adjustment for age, sex, education, and *APOE* genotype. Individuals who developed dementia had significantly shorter TL (6,131±798 for prevalent cases, and 6,315±817 for incident cases) compared with those remaining dementia-free (6,431±864). Cox-regression analyses showed that shorter TL was a risk for earlier onset of dementia (p=0.05), but stratified analyses for

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sex showed that this association of age-at-onset of dementia with shorter TL was significant in women, but not in men.

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

### Keywords

biological aging; Alzheimer's disease; apolipoprotein E; leukocyte; DNA

## Introduction

Telomeres are stretches of thousands of repeated TTAGGG hexanucleotide sequences located at the ends of each chromosome.[1] 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 cells than germline cells. In cultured cells, telomere shortening due to repeated cell divisions correlates with cellular aging or senescence. In cancer cells, telomeres may be longer, due 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,[2] but dispersion in TL due to normal variation prevents its use as a determinant of biological age. TL is likely influenced by both genetic factors (e.g. variants associated with telomerase RNA component, loci near *TERC* gene, or other loci identified from genome-wide studies[3-6]) and non-genetic factors. These latter may include smoking,[7] socioeconomic status or physical activity,[8] marine fatty-acid intake,[9] and psychological stressors,[10] and various cardiovascular,[2,11-14] diabetes,[15] chronic obstructive pulmonary,[16] and skin disorders.[17] If TL is a surrogate marker for biological age, short TL is likely to predict risk of age-related diseases such as Alzheimer's disease, and mortality. Investigations to date have been inconsistent with respect to such relationships (e-Table 1),[18-27]. These include our nested case-control study,[19] and others,[18,20,21, 22] which showed shorter TL in elders developing dementia, and other studies that have not.[23,24] Similarly, various studies have,[2,19,20,24,25] or have not,[23,26,27] found an association of lifespan with shorter TL (e-Table 1). We designed this large study, to have reasonable power, using a multiethnic elder epidemiologic population with up to 16 years followup, to test whether TL adjusted for age and sex, is associated with dementia or mortality. We used a quantitative PCR method which minimizes measurement variation.

## Materials and 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.[28-31] Of a total of 4,308 participants recruited from 1992 and 1999 cohorts, blood was obtained from 3,106 (72%), for whom 1983 (64%) had adequate DNA for TL measurement. DNA from the first available blood draw was utilized, regardless of whether this was from the baseline, or subsequent, visit. Participants in the study undergo standardized assessments every 18-30 months,[28] including medical history, functional status, 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 (IRB) of Columbia University Medical Center and the New York State Psychiatric Institute. Participant written informed consent was obtained for WHICAP data collection and blood draws.

## Dementia Classification

Diagnosis at each assessment was by consensus conference, based on DSM-IV-TR dementia criteria, and NINDS-ADRDA criteria for Alzheimer's disease.[28,30] Participants were considered "nondemented" if they did not meet criteria for dementia at their most recent visit. Participants who had dementia at time of 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 (APOE) Genotyping

Leukocyte DNA was prepared from 5 ml whole blood, using a non-phenol-based kit (Puregene™, Gentra Systems, Minneapolis, MN). Apolipoprotein E *(APOE)* genotyping was performed by *CfoI* restriction analysis of whole blood genomic DNA amplified by Taq PCR with *APOE* primers.[32]

## Measurements of Telomere Length

Coded DNA samples were processed by laboratory personnel, blinded to participant characteristics. Average TL was determined by our modification of a method developed by Cawthon and colleagues.[2,33] Real-time PCR was performed using a CFX384 thermocycler (Biorad, Richmond, CA). Assay method was optimized for use of both telomere (T) and single copy gene (S) amplifications on the same 384-well plate, with reference standard DNA samples on each plate. Test DNA samples each underwent two triplicate PCR reactions, with use of "calibrator samples" for correction for inter-plate variability. Amplification primers for telomeres included $T_{for}$: 5′-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3′ and $T_{rev}$: 5′-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3′, and for single copy gene (beta-globin) $S_{for}$ 5′- GCTTCTGACACAACTGTGTTCACTAGC-3′ and $S_{rev}$ 5′-CACCAACTTCATCCACGTTCACC-3′. Thermocycling parameters were 95°C × 10min activation, followed by 34 cycles of 95°C × 15sec, and 55°C × 120sec. Our assay coefficient of variance was 5-8%. T/S ratio was converted to basepairs (bp) TL by use of a linear regression formula: bp=(1,585*T/S ratio)+3,582, derived from co-analysis of selected DNA samples using both PCR and terminal restriction fragment (non-radioactive *T*elo*TAGGG* Telomere Length, Roche Diagnostics, Mannheim, Germany) methods (correlation coefficient r=0.90).

## Statistical Analysis

We used $\chi^2$-tests, and analysis-of-variance (ANOVA) for comparisons. Cox proportional hazards were used to assess the relation of telomere length to cumulative percentage of mortality and dementia. Time-to-event variable was time from blood-draw to death or dementia. Statistical models were adjusted for age-at-blood-draw, sex, ethnic group, years-of-education, and presence of apolipoprotein E (*APOE*) ε4 alleles. Additional analyses examined effects of *APOE* ε2 alleles. Because *APOE* ε4 is associated both with risk of dementia,[34,35] and death,[36,37] we also examined the relation of TL to mortality within strata defined by the presence or absence of the *APOE* ε4 allele. Analyses were performed using IBM-SPSS Statistics version19 on Microsoft Windows–based systems.

## Results

### Group Characteristics (unadjusted analyses)

Subject demographics and other characteristics are shown in Tables 1 and 2. The mean age of the total group at time of blood draw was 78.3 years (range 66–101); 1355 (68.3%) were women. Ethnic distribution included 790 Hispanic (39.9%), 599 non-Hispanic African-Americans (30.3%), 564 non-Hispanic whites (28.3%), and 25 others (1.3%). The mean education level was 9.7±4.9 years (0–20). Mean follow-up time for mortality was 7.8±3.6 yr (0–16; median 9.3 yr, inter-quartile range 5.5).

Compared with participants who survived, participants who died were on average 4 years older at time of blood draw (80.7 vs. 76.4 yr; $p < 0.0001$), had about 1 year less education (9.3 vs. 10.0 yr; $p < 0.001$), were more likely to be men (35.6% vs. 28.6%; $p< 0.001$), were less likely to have dementia (no dementia 37.1% vs. 62.9%; $p<0.0001$), and had shorter telomeres (6,219±817 vs. 6,492±881; $p<0.0001$; Table 1). There was no difference between survivors and those who died, in distribution of ethnicity, or frequencies *of APOE* ε4 allele carrier status (27.9% vs. 25.8%), or *APOE* ε2 allele carrier status (15.4% 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 blood draw, 190 (9.6%) developed dementia during follow-up, while 1,469 (74.5%) participants remained dementia-free throughout the follow-up period. Of the 504 with dementia, 80% were classified as probable AD, 14% as possible AD, and only 5% were diagnosed with other dementias (not shown in tables). Participants remaining dementia-free had longer TL at blood draw than those with incident dementia, who in turn had longer TL than those with prevalent dementia (6,431±856 vs. 6,315±817 vs. 6,131±798; $p<0.0001$; Table 2). However, a similar rank-order was observed for demographic variables, in which those with no dementia, compared with incident dementia, compared with prevalent dementia, showed lower age-at-blood-draw, higher years-of-education, and greater frequency of men, non-Hispanic white ethnicity, and *APOE* ε4 non-carrier status (Table 2). Thus subsequent analyses were adjusted for these factors.

### Telomere length in the total group: relation to age, sex, and ethnicity

Mean TL in the total group was 6,371±864 bp(4,103–11,447; Table 1). Individuals who were older at the time of blood draw had shorter telomeres (Figure 1). Linear regression analysis of TL by age-at-blood-draw reveals a least-squares line with slope of decline of 31.1±2.7 bp per year (95% CI: 25.7– 36.5; $r = -0.239$; $p<0.0000001$). Stratifying for sex, this was highly significant for both men ($r=-0.253$) and women ($r=-0.244$). However TL was significantly shorter in men than women; regression analysis performed by age and sex showed a difference of 128±41 bp (95%CI: 48– 209; $p=0.002$). TL also varied by ethnicity, being shortest in Hispanics (6,293±839, N=790) compared with blacks (6,417±860, N=599) or whites (6,427±902, N=564; ANOVA $F(3,1958)=3.93$, $p=0.008$). This relationship of TL with ethnicity persisted for those who remained free of dementia over the follow-up period: Hispanics (6,334±791, N=507) had shorter TL than blacks (6,499±867, N=449), or whites (6,460±927, N=492; ANOVA $F(3,1465)=3.68$, $p=0.012$).

### Shorter TL predicts mortality

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, quartile of TL as independent variable, years from time-of-blood-draw as the time-to-event variable, and age-at-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<0.0001). Since sex has effects on both 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).

### Shorter TL predicts dementia

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 of dementia. Because the presence of dementia might affect TL, survival analysis was performed based only upon those with incident dementia subsequent to the time-of-blood-draw (Table 3). The Cox regression model used incident dementia as the outcome, TL as independent variable, time-from-blood-draw to 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=0.05), indicating a 21% increased risk of dementia for each kilobasepair of decreased telomere length. Age, ethnicity, and years of education were significant covariates related to risk of dementia, but *APOE ε4* carrier status only showed a trend towards being a risk factor in this multiethnic population. Upon stratification for APOE ε4 carrier status, reduced numbers resulted in loss of statistical significance for effect of TL on dementia (data not shown). However, stratified analyses on sex, analyzing men and women separately (Figures 2B and 2C), showed a statistically robust effect of TL (HR=1.33 per kilobasepair TL; p=0.01) 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=0.06).

### Shorter TL predicts mortality independently of dementia or APOE status

Because dementia status and *APOE* are known to increase the likelihood of mortality, we performed stratified analyses examining effect of TL on mortality in those with differing dementia status and *APOE4* genotype. For those with prevalent or incident dementia, the shortest quartile TL remained a significant risk-factor for mortality (e-Table 2), although numbers in each group are small (ranging from 43–109). The effect of TL on mortality was independent of dementia, since in those without dementia significant risk was also present for each of the shorter quartile TL (e-Table 2). Similarly, the effect appeared independent of APOE genotype, since stratified analyses showed effects of TL on mortality for both those with and without *ε4* alleles (e-Table 3), although the smaller numbers attenuated statistical significance.

## Discussion

We examined the relation of TL to risk of dementia and mortality in a large multiethnic community-based cohort of elderly 65 years and older followed for up to 16 years. In this cross-sectional analysis, we found that blood leukocyte mean telomere length was shorter in those who were older at time of blood-draw, a finding in prior studies,[2,38] 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 lifespan, consistent with results from our earlier work with a small selected subsample of the

WHICAP population.[19] Several studies, of various sample sizes (see Table e-1) also have found that elders with shorter leukocyte TL have earlier mortality,[2,20,24] although some have not found an effect of TL on mortality.[23,26,27] Our study has the advantage of large size, broad age range from 66 to 101 years, thorough ascertainment of mortality, and use of the PCR method of TL measurement. We observed that the association of short TL with increased mortality was present in the presence or absence of dementia. The association of telomere length with mortality might indicate: (a) that shortened telomere length causes processes that lead to earlier mortality; (b) that other biological processes or preclinical disorders are causing telomere shortening; or (c) that some environmental or genetic influences are concomitantly both causing shortening of telomeres and increased 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.[19] A number of other prior studies (see Table e-1), have also shown a relationship between short TL and dementia[18,20-22] While some studies have not shown such an effect,[23,24] they were hampered by very small numbers of cases with dementia (Table e-1), and/or shorter followup. Other differences between studies, may relate to methodological variation with less reliable TL measurement, differences in study group demographics 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 owe to the small numbers of men with incident dementia (N=56) compared to 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 to 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 “age” per se, neither biological nor chronological. 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: (a) intrinsic, possibly genetic, differences in initial TL at birth; (b) intrinsic, possibly genetic, differences in rate of telomere attrition during life; (c) environmental influences affecting aging, including diet, exercise, infectious exposures; or (d) the presence of other diseases. There is evidence that telomere length is a heritable characteristic,[5,39,40] with varying estimates of heritability as high as 80%. It is likely that there are genes that affect the aging process in general. Similarly, given that telomere maintenance depends on telomerase, with both RNA and enzymatic protein subunit components, it is likely certain genes affect telomere length 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, it is probable that particular genes underlying telomere shortening or maintenance, or affecting the relationship of TL to aging will be identified.

Compared to prior studies, this study has strengths including large sample size, multiethnic group, population-based cohort, and the ability to thus adjust for age, sex, education, and other potential confounders when examining the relationship of telomere length to outcome variables. Weaknesses include that: (1) the study involves only those age 65 and older so we were unable to compare TL of younger individuals, (2) not all study participants had blood drawn, or DNA available; (3) the study population includes three ethnic groups and thus is likely heterogeneous. However, this is the only study that has examined a relatively large sample from different genetic and environmental backgrounds represented by three 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 either underestimation (due to superposed variability), or less likely overestimation (given adjustments) of the effect of TL on dementia and mortality. Telomere length shortening is associated with aging, male sex, dementia, and mortality. It is possible that short TL may cause more rapid aging, or alternatively that states of illness, including incipient dementia (since data suggests that AD pathology may precede clinical dementia symptoms by some 10-20 years), might cause short TL, or that some independent factor causes both 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 does suggest that very short telomeres are themselves deleterious, increasing errors in the cell division process, and possibly the development of cancer. While age is the strongest determinant of sporadic AD, there is very wide variation in age at onset, from fifth decade to tenth decade of life. It is increasingly clear that not only *APOE*, but a variety of other genes play a role in susceptibility to AD. It is possible that either 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 showing an association between shortened TL and mortality, and more specifically an association of shortened TL with Alzheimer's disease, 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 towards modifying TL shortening, by modestly increasing telomerase activity, might be helpful in decreasing the incidence of age-related dementia.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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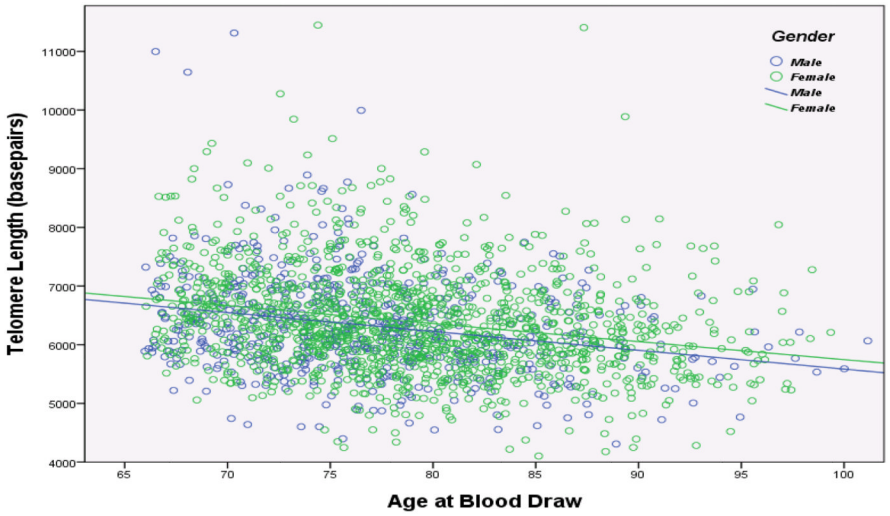


**Figure 1. Telomere length versus age-at-blood-draw**

A scatterplot of telomere length versus age-at-blood draw reveals that individuals who are older at the time of blood draw have shorter telomeres. Linear regression analysis of telomere length versus age-at-blood-draw, with sex as a covariate, reveals a least-squares decline of 31.1 ± 2.7 bp per year of age (95%CI: 25.7 – 36.5; $p < 0.0000001$), with shorter length in men compared to women by 128 ± 41 bp (95%CI: 48 – 208; $p = 0.002$).

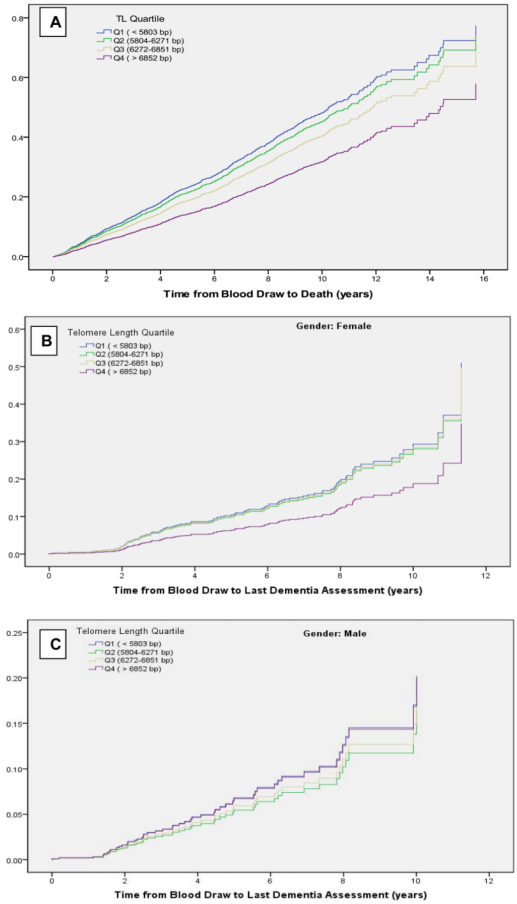


**Figure 2. Survival analyses of mortality and dementia for participants with different telomere lengths**

Cox regression models shows effects of telomere quartile length, on outcomes of mortality or dementia over time (in years), with adjustment for covariates. Panel A shows analysis for outcome measure of mortality. Compared to longest quartile TL (Q4), hazard ratios for shorter quartiles were for Q1 HR = 1.72 (95%CI 1.40 - 2.11; $p < 0.000001$), Q2 HR = 1.57 (95%CI 1.28 - 1.94; $p < 0.0002$), and Q3 HR = 1.35 (95%CI 1.09 - 1.67; $p = 0.005$). Covariates, with their effect significance, included age-at-blood-draw ($p < 0.00001$), gender ($p < 0.00001$), ethnicity ($p = 0.06$ for Hispanic), education ($p = 0.08$), and APOE ε4 (ns) carrier status. Panels B and C show outcome measures of dementia, with separate analyses for women (B) and men (C) as described in the text. 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 women participants (B) show a significant effect of shorter TL (Q1, Q2, and Q3) on shorter time-to-dementia compared to those with longer TL (Q4).

## Table 1

Subject Demographics and Clinical Characteristics – Mortality Analysis.

| | Total Group | Survived | Deceased | p |
|---|---|---|---|---|
| Number of subjects, N (% total) | 1,978 | 1,115 (56%) | 863 (44%) | |
| Telomere Length, basepairs | 6,371 ± 864 | 6,491 ± 881 | 6,218 ± 819 | <0.0001 * |
| Dementia (at/after blood draw) | | | | <0.0001 # |
| *No dementia* | 1,469 (74.5%) | 930(83.4%) | 539 (62.5%) | |
| *Prevalent dementia* | 314 (15.9%) | 92 (8.3%) | 222 (25.7%) | |
| *Incident dementia* | 190 (9.6%) | 91 (8.2%) | 99 (11.5%) | |
| Age-at-blood-draw, yr | 78.3 ± 6.9 | 76.4 ± 6.0 | 80.7 ± 7.3 | <0.0001 * |
| Age-at-survival/death, yr | | 81.1±6.3(66-103) | 86.0±7.4(67-111) | |
| Men, N (%) | 628 (31.7%) | 319 (28.6%) | 309 (35.8%) | 0.001 # |
| Women, N (%) | 1,350 (68.3%) | 796 (71.4%) | 554 (64.2%) | |
| Ethnic Group, N (%) | | | | ns # |
| *Non-Hispanic white* | 564(28.5%) | 314 (28.2%) | 250 (29.0%) | |
| *Non-Hispanic black* | 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, yr (mean ± SD) | 9.7±4.9 (0-20) | 10.0±4.9 (0-20) | 9.3 ± 4.8 (0-20) | <0.001 * |
| *APOE* ≥ 1 ε4 allele N (%ε4+) | 529 (27.1%) | 288 (26.2%) | 241 (28.3%) | ns # |
| *APOE* ≥ 1 ε2 allele N (%ε2+) | 311 (15.9%) | 178 (16.2%) | 133 (15.6%) | ns # |

Some cases are missing dementia status (5), education (8), or *APOE* (27), or have ethnicity of "other", not listed here (25). For basepairs and years, means ± standard deviation (and range) are listed.

* p compares values for survivors and deceased by ANOVA;

# p compares mortality for dementia status, sex, ethnicity, or APOE allelic status using chi-square

ns = not significant at 0.05 level.

**Table 2**

Subject Demographics and Clinical Characteristics – Dementia Analysis.

| | Total Group | No Dementia | Incident Dementia | Prevalent Dementia | p |
|---|---|---|---|---|---|
| Subjects, N (%total) | 1,973 | 1,469 (74.5%) | 190 (9.6%) | 314 (15.9%) | |
| Telomere Length (bp) | 6,372 ± 856 | 6,431 ± 864 | 6,315 ± 817 | 6,131 ± 798 | <0.0001 * |
| Age-at-blood-draw, yr | 78.3 ± 6.9 | 77.0 ± 6.3 | 79.9 ± 6.5 | 83.7 ± 7.3 | <0.0001 * |
| Age at death, yr | 86.0 ± 7.4 | 84.3 ± 7.1 | 88.2 ± 6.8 | 89.2 ± 7.3 | <0.0001 * |
| Age of survivor, yr | 81.1 ± 6.3 | 80.5 ± 6.1 | 84.7 ± 6.1 | 84.3 ± 6.4 | <0.0001 * |
| Men, N (%) | 627 (31.8%) | 489 (33.3%) | 56 (29.5%) | 82 (26.1%) | 0.04 # |
| Women, N (%) | 1,346 (68.2%) | 980 (66.7%) | 134 (70.5%) | 232 (73.9%) | |
| Ethnic Group, N (%) | | | | | <0.0001 * |
| *Non-Hispanic white* | 565 (28.3%) | 492 (33.5%) | 34 (17.9%) | 37 (11.8%) | |
| *Non-Hispanic black* | 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, yr | 9.7 ± 4.9 | 10.7 ± 4.6 | 7.8 ± 4.6 | 6.4 ± 4.4 | <0.0001 * |
| *APOE* ≥1 ε4, N (%ε4+) | 529 (27.2%) | 368 (25.3%) | 51 (27.6%) | 110 (35.7%) | 0.001 # |
| *APOE* ≥ 1 ε2, N (%ε2+) | 311 (16.0%) | 230 (15.8%) | 45 (14.6%) | 36 (19.5%) | ns # |

Some cases are missing education (8), or *APOE* (27), or have ethnicity of "other", not listed here (25). For basepairs and years, means ± standard deviation (and range) are listed.

* p compares values for dementia status groups by ANOVA;

# p compares dementia status for sex, ethnicity, or APOE allelic status using chi-square.

ns = not significant at 0.05 level.

## Table 3

Association of Telomere Length with Incident Dementia after Blood Draw.

| **ALL** | **HR** | **95%CI** | **p** |
|---|---|---|---|
| N = 1,559; Incident Dementia n = 190 | | | |
| Shorter Telomere Length (kbp) | 1.21 | 1.00 - 1.46 | 0.05 |
| Men | 1.19 | 0.86 - 1.64 | ns |
| Ethnicity (Hispanic) | 2.02 | 1.25 - 3.27 | 0.004 |
| Education (yr) | 0.92 | 0.89 - 0.96 | 0.0001 |
| *APOE* ≥1 *ε4* | 1.36 | 0.97 - 1.89 | 0.07 |
| Age-at-blood-draw (yr) | 1.12 | 1.10 - 1.15 | <0.0000001 |
| Men | | | |
| N = 545; Incident Dementia n = 56 | | | |
| Shorter Telomere Length (kbp) | 0.94 | 0.65 - 1.35 | ns |
| Ethnicity (Hispanic) | 3.40 | 1.37 - 8.42 | 0.01 |
| Education (yr) | 0.91 | 0.85 - 0.98 | 0.02 |
| *APOE* ≥1 *ε4* | 1.01 | 0.54 - 1.89 | ns |
| Age-at-blood-draw (yr) | 1.12 | 1.07 - 1.17 | 0.00001 |
| Women | | | |
| N = 1,114; Incident Dementia n = 134 | | | |
| Shorter Telomere Length (kbp) | 1.33 | 1.06 – 1.68 | 0.01 |
| Ethnicity (Hispanic) | 1.78 | 1.00 - 3.16 | 0.05 |
| Education (yr) | 0.93 | 0.89 - 0.98 | 0.01 |
| *APOE* ≥1 *ε4* | 1.46 | 0.99 - 2.17 | 0.06 |
| Age-at-blood-draw (yr) | 1.13 | 1.09 - 1.16 | <0.0000001 |

Cox regression model of telomere length on outcome of incident dementia, with covariates age-at-blood-draw, gender, ethnicity (Hispanic compared with non-Hispanic whites), education, and *APOE ε4* carrier status. Shorter TL, on a continuous basis, relates to shorter time to dementia, but only clearly so in women. Covariates also are associated with incident dementia, as shown in this table.