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Leukocyte Telomere Length is Unrelated to Cognitive Performance among Non-Demented and Demented Persons: An Examination of Long Life Family Study Participants

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Abstract

Objective: Leukocyte telomere length (LTL) is a widely hypothesized biomarker of biological aging. Persons with shorter LTL may have a greater likelihood of developing dementia. We investigate whether LTL is associated with cognitive function, differently for individuals without cognitive impairment versus individuals with dementia or incipient dementia.

Method: Enrolled subjects belong to the Long Life Family Study (LLFS), a multi-generational cohort study, where enrollment was predicated upon exceptional family longevity. Included subjects had valid cognitive and telomere data at baseline. Exclusion criteria were age ≥ 60 years, outlying LTL, and missing sociodemographic/clinical information. Analyses were performed using linear regression with Generalized Estimating Equations, adjusting for sex, age, education, country, family, generation, and lymphocyte percentage.

Results: Older age and male gender were associated with shorter LTL, and LTL was significantly longer in family members than spouse-controls ($p < 0.005$). LTL was not associated with working or episodic memory, semantic processing, and information processing speed for 1,613 cognitively unimpaired individuals as well as 597 individuals with dementia or incipient dementia ($p < 0.005$), who scored significantly lower on all cognitive domains ($p < 0.005$).

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Conclusions: Within this unique LLFS cohort, a group of families assembled on the basis of exceptional survival, LTL is unrelated to cognitive ability for individuals with and without cognitive impairment. LTL does not change in the context of degenerative disease for these individuals who are biologically younger than the general population.

Keywords

Telomere Shortening; Cognitive Aging; Cognitive Decline; Cognitive Function; Cognitive Tests; Cognition; Dementia and Longevity

INTRODUCTION

Telomeres are repetitive TTAGGG hexanucleotide sequences that cap the ends of linear chromosomal DNA, preventing genomic instability during cell replication (Hochstrasser, T., Marksteiner, J., & Humpel, C., 2012; Honig, L., Kang, M., Schupf, N., Lee, J., & Mayeux, R., 2012; Moverare-Skrtic et al., 2011; Wikgren et al., 2012). Telomeres are maintained by telomerase, a ribonucleoprotein enzyme complex, which elongates and repairs these hexanucleotide repeats, alleviating some of the telomere shortening that otherwise occurs with each cell division due to the inherent incapability of the genomic replication machinery to replicate the full-length of the chromosome. Telomere length is most often measured in DNA extracted from leukocytes. Leukocyte telomere length (LTL) decreases with increasing human age (Honig, L., Schupf, N. L., Tang, M., & Mayeux, R., 2006; Martin-Ruiz et al., 2006; Honig et al., 2012; Wikgren et al., 2012). LTL may be a marker for the construct of “biological age” since inter-individual variation can arise from genetic, lifestyle and disease factors among people of the same chronological age (Herrmann, M., Pusceddu, I., Marz, W., & Herrmann, W., 2018; Cai, Z., Yan, L., & Ratka, A., 2013; Grodstein et al., 2008; Honig et al., 2006; Eitan, E., Hutchison, E., & Mattson, M., 2014; Honig et al., 2012). Studies have indicated that LTL may reflect cumulative damage from cellular stress and heightened inflammatory responses, which allow it to serve as an indicator of biological or cellular aging (Chang et al., 2018). Persons with longer average LTL may be biologically “younger” than those with shorter average LTL. Men exhibit shorter average LTL than women, consistent with sex-specific differences in lifespan (Honig et al., 2012).

Extant literature further demonstrates how shorter LTL may be associated with mortality and several age-related diseases like cancer, cardiovascular disease (CVD), type II diabetes, and neurodegenerative disorders such as Parkinson’s Disease, Huntington’s Disease, and Alzheimer’s Disease (AD) (Herrmann et al., 2018; Cai et al., 2013; Honig et al., 2012; Wikgren et al., 2014; Insel, K., Merkle, C., Hsiao, C.-P., & Vidrine, A., 2012; Scarabino, D., Broggio, E., Gambina, G., & Corbo, R., 2017; Degerman et al., 2014; Forero et al., 2016; Ma et al., 2013). Some studies have also found relationships between LTL with neuropsychiatric disorders such as depression, anxiety-related disorders, schizophrenia and other psychotic disorders, as well as bipolar disorder (Richard, E., Reitz, C., Honig, L., Schupf, N., & Tang, M. X., 2013; Chang et al., 2018; Czepielewski et al., 2018; Nieratschker et al., 2013; Powell, T., Dima, D., Frangou, S., & Breen, G., 2018; Vasconcelos-Moreno et al., 2017; Wang et al., 2017; Colpo, G., Leffa, D. K., Quevedo, J., &

Carvalho, A., 2015). Such aging-, metabolic-, psychiatric- and inflammation-related conditions have all been associated with cognitive outcomes (Cohen-Manheim et al., 2016).

Age-related cognitive decline is caused by oxidative stress triggering neuroinflammation, and subsequent neurodegeneration and cell apoptosis (Ma et al, 2013). In this way, it relates to telomere attrition, which can arise from the cumulative burden of inflammation and oxidative stress through the lifecourse (Ma et al, 2013; Rask et al, 2016). Yet, the extent to which LTL relates to typical and/or pathologic cognitive aging is still largely unknown; it is uncertain whether shortened telomeres are a cause, consequence or both for deteriorating cognitive ability (Hagg et al., 2017). The literature is limited and inconsistent in that some studies have observed LTL being associated with cognitive decline, whereas others have not (Honig et al., 2006; Martin-Ruiz et al., 2006; Devore, E., Prescott, J., De Vivo, I., & Grodstein, F., 2011; Moverare-Skrtic et al., 2011; Valdes et al., 2010; Yaffe et al., 2011; Harris et al., 2010; Mather et al., 2010; Cohen-Manheim et al., 2016; Hagg et al., 2017; Zekry et al., 2010). Differences in study findings may be attributed to methodological differences in the measurement of LTL, use of varying cognitive assessment tools, diverse sociodemographic and clinical characteristics, and distinct study designs (e.g. cross-sectional vs. cohort). For example, not all studies have conducted their investigation in an aging cohort or distinguished whether some individuals in their sample may be cognitively impaired. Since several papers have already shown a relationship between shorter average LTL and the risk of dementia or AD (Honig et al., 2006; Honig et al., 2012; Hochstrasser et al., 2012; Grodstein et al., 2008; Martin-Ruiz et al., 2006; Roberts et al., 2014), the extent to which telomere length is related to cognitive function may be dependent on whether or not there are individuals within a given study who show evidence of cognitive impairment.

In this investigation, we explored whether LTL relates to cognitive performance among family members and spouse controls enrolled in the Long Life Family Study (LLFS). This LLFS cohort is unique because it consists of families who were selected based on collective survival exceptionalism, and previous work has shown that family members have both longer telomeres and higher cognitive functioning than spouse controls. Specifically, Honig et al. (2015) demonstrated that LTL is highly heritable across generations within this cohort, and that first degree offspring of long lived probands had longer average LTL than second degree relatives (i.e., nieces and nephews), who in turn had longer LTL than unrelated spouses, supporting a genetic underpinning for telomere length (Honig et al., 2015). Prior studies with this population have also shown that relatives in the offspring generation demonstrate higher cognitive functioning than spouse controls, that genetic variants might influence cognitive ability, and that exceptional cognitive ability may contribute to exceptional longevity in these families (Barral et al., 2012; Barral et al., 2013; Barral et al., 2017).

The purpose of this study was to elucidate the significance of LTL across the cognitive continuum between normal aging and dementia. We examined whether LTL is associated with individual differences in various cognitive functions, including episodic memory, semantic processing, working memory, and information processing speed, for aging members of the LLFS cohort, separately for non-demented individuals and individuals with dementia or incipient dementia. Lack of an association between LTL and cognitive ability in the non-demented group may suggest that the association between telomere length and

cognitive function relates to the presence of degenerative disorders such as Alzheimer's and Lewy Body disease. This explanation would be strengthened if, in juxtaposition, an association was present between LTL and cognitive function for the group with cognitive impairment.

METHODS

Participant Recruitment

The Long Life Family Study is a multi-generational cohort study that enrolled individuals with exceptional survival phenotypes for an examination of several key indicators of longevity, including major chronic diseases, risk factors, physical and cognitive function. Families were recruited from field centers located in the US (Boston, New York, or Pittsburgh) and Denmark. Eligible families in the US had to meet the following criteria: 1) have at least two living siblings above 80 years of age, including the proband; 2) have at least one living offspring from one of the two living siblings; 3) have one living spouse of the offspring generation to serve as a control; and 4) demonstrate exceptional survival through a Family Longevity Selection Score (FLoSS) of seven or higher for members of the proband generation. FLoSS is a summary measure of the survival experience for probands and their siblings relative to what would be expected based on birth cohort specific life tables and the availability of living subjects for the study (Sebastiani et al., 2009). In Denmark, the same criteria were used to select eligible families initially identified from the Danish National Register of Persons. First, individuals who had an age of 90 and above were identified; then, parish registers from regional archives were searched for place of birth and names to locate the parents of the elderly individuals and to identify sibships. Detailed characteristics of the unique LLFS cohort have been published elsewhere (Barral et al., 2012; Barral et al., 2013; Cosentino et al., 2013; Newman et al., 2011). There are 4,559 participants from 552 different families that have been followed since recruitment. Recruitment, informed consent and study procedures were approved by the Institutional Review Boards of all participating sites, including Columbia University, Boston University, University of Pittsburgh and University of Southern Denmark.

Cognitive Assessment

All participants underwent cognitive assessment at baseline. Episodic memory in the form of immediate and delayed memory were evaluated with the Logical Memory subset of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987), where subjects had to recall one paragraph at immediate and delayed intervals. Working memory was measured with Digit Span Forward and Backward, where each subject was required to repeat number sequences of increasing length, both forward and backward. Semantic processing was assessed by asking subjects to name as many animals and vegetables as possible in two separate one minute trials. The Digit Symbol subtest (DSST) of the Wechsler Adult Intelligence Scales-Revised (WAIS-R) was used to measure information processing speed. This test consisted of digit-symbol pairs, followed by a grid with digits only. Participants were required to place the corresponding symbol below each digit as fast as possible. Higher scores for all assessments indicated better cognitive performance. Unadjusted z-scores were computed for the seven cognitive test scores using the mean and standard deviation of the

Since the purpose of the study was to observe the relationship between telomere length and cognitive function among the aging population, participants aged 60 and below at the time of enrollment were excluded. Of the 2,783 individuals who stayed, including members of the proband generation (proband and their siblings) and the offspring generation (sons, daughters, nieces, and nephews of the probands), 428 individuals were excluded because they had missing information on a previously published dementia algorithm variable (Cosentino et al., 2013). This algorithm variable distinguished between individuals with mild AD and cognitively normal older adults in the National Alzheimer's Coordinating Center (NACC) sample on the basis of demographic and cognitive attributes. Using the dementia algorithm variable, participants meeting criteria for cognitive impairment in the LLFS sample were separated from those who were cognitively normal. An additional 75 individuals with missing information on white blood cell/leukocyte counts and 3 individuals with a missing score on at least one cognitive test were removed to ensure complete case analysis. Also, 67 individuals who demonstrated severely impaired attention or working memory in the absence of other cognitive impairment were excluded (operationalized as digit span forward < 4, digit span backward < 3 or immediate memory < 6). Performance in this range of each test would, for example, fall at or below the 7th percentile for a 90 year old with a high school education, or be to the 3rd percentile for an 80 year old with a college education. Among the 2,210 individuals who remained in the final analytic sample, 597 study participants had dementia or incipient dementia, while 1,613 study participants had no evident cognitive impairment. The final analytic sample spanned both proband and offspring generations and included both relatives and spouses. Using partners of long-lived subjects and their offspring as comparison groups avoided potential cofounders, since it is likely that they had a similar distribution of birth cohort, socioeconomic, and geographical backgrounds.

Statistical Analyses

The sociodemographic and clinical characteristics of LLFS family members were compared with spouse controls using Chi-squared tests and Analysis of Variance (ANOVA) to assess statistically significant differences between categorical and continuous variables, respectively. To address the question of whether LTL was related to cognitive function among older adults in the LLFS cohort, separately for individuals who lacked cognitive impairment versus individuals whose performance was consistent with mild cognitive impairment (MCI) or dementia, we used linear regression with General Estimating Equations (GEE). The GEE method adjusted for the relatedness of the LLFS sample by treating family membership as a cluster without assuming joint distribution of the whole family and allowing for differences in family size. It, therefore, allowed for the possibility that the characteristics of family members are correlated by both shared genetics and shared environment.

All regression analyses were adjusted for potential confounders such as sex (male vs. female), age (in years), education (less than college, some college, or post college), country (US or Denmark), generation (proband vs. offspring), and lymphocyte percentage. Since different leukocyte subpopulations have varying replicative histories, and may thus differ in telomere length, we wanted to account for variations in leukocyte differential counts (Fagan

et al., 2017). Lymphocytes are generally longer-lived than neutrophils, eosinophils, basophils, or monocytes. Therefore, we adjusted for the percentage of lymphocytes as a fraction of the total WBC count, analogous to what was done previously by Fagan et al. (2017) in this LLFS cohort. SPSS version 25.0 (IBM Corp., 2017) was used to perform all the descriptive and regression analyses. Since we assessed the relationship between LTL and 11 different cognitive measures, some of which were composites of the individual cognitive tests, we corrected for multiple testing using a Bonferroni-adjusted p-value of 0.005 ($\alpha = 0.05/11$) to determine if findings were significant. Scatterplots, depicting the relationship between LTL and cognitive ability, were created using adjusted z-scores for the independent and dependent variables in R software (R Core Team, 2014). Post-hoc power calculations were conducted for both non-demented and cognitively impaired samples using G*Power software (Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G., 2009).

RESULTS

Participant Characteristics

As non-demented individuals of the aging LLFS cohort were separated from subjects with MCI or dementia, those in the former group ($n = 1,613$) had significantly ($p < 0.005$) higher mean cognitive scores across all domains compared to those in the latter group ($n = 597$) (Table 1). The non-demented sub-sample had the following mean (SD) raw scores for each cognitive test: *immediate memory* = 13.1 (3.5), *delayed memory* = 11.6 (3.8), *digit forward* = 8.4 (2.1), *digit backward* = 6.6 (2.1), *animal fluency* = 21.0 (5.8), *vegetable fluency* = 14.3 (4.3), and *DSST* = 45.0 (12.7). In contrast, subjects with MCI or dementia averaged cognitive scores that were up to 74.1% lower than their non-demented counterparts: *immediate memory* = 5.7 (3.3), *delayed memory* = 3.0 (2.5), *digit forward* = 7.3 (2.2), *digit backward* = 5.0 (1.9), *animal fluency* = 13.0 (4.8), *vegetable fluency* = 9.1 (3.6), and *DSST* = 25.4 (11.3).

Shorter LTL was correlated with older age in both groups (demented: $r = -0.110$, $p = 0.007$; non-demented: $r = -0.213$, $p < 0.005$). Males, on average, had shorter LTL than females for the cognitively impaired (mean (SD): 5,133 (361) vs. 5,197 (360) bp, $t = -2.164$, $p = 0.031$) and unimpaired groups (mean (SD): 5,253 (401) vs. 5,277 (386) bp, $t = -1.208$, $p = 0.227$), albeit the differences were insignificant. Individuals with MCI or dementia were also significantly older (mean (SD): 88.0 (9.3) vs. 73.0 (10.3) years) and more likely to be members of the proband generation (82.2% vs. 26.2%) than those without evident dementia, consistent with an overall shorter average LTL (mean (SD): 5,163 (362) vs. 5,266 (393) bp) ($p < 0.005$). Additionally, they were significantly less educated, more likely to be male and reside in the US than non-demented subjects ($p < 0.005$). Over half of LLFS participants without evident dementia had some college education (56.0%) as their highest level of study, whereas over half of subjects with dementia had no post-secondary education (54.4%). The ratio of US to Danish subjects was approximately 2:1 in the former group, but 4:1 in the latter group. Lastly, study subjects with cognitive impairment had a slightly lower lymphocyte percentage in their white blood cell count than non-demented individuals ($p < 0.005$).

In the non-demented sample, there were nearly three times more family members ($n = 1,221$) than spouse controls ($n = 392$) (Table 1). Relatives were more likely to be female (56.3% vs. 48.0%), members of the proband generation (28.2% vs. 19.9%) and older (mean (SD): 73.6 (10.8) vs. 70.8 (8.1) years), as well as from the US (73.1% vs. 52.6%) when compared to spouse controls ($p < 0.005$). LTL was, on average, longer in family members than their spouses (mean (SD): 5,281 (398) vs. 5,218 (375) bp, $p < 0.005$) (Table 1). With respect to cognitive function, relatives, on average, had higher digit span forward and backward mean scores, but a lower animal fluency mean score than spouse controls ($p < 0.005$).

Leukocyte Telomere Length and Cognitive Function in Individuals without Evident Dementia

No significant associations were detected between LTL and any of the cognitive tests within the non-demented subsample of the aging LLFS cohort, after adjusting for sex, age, education, country, generation and lymphocyte percentage ($p > 0.005$) (Table 2). The relationship between LTL and each cognitive measure in the regression analyses, were as follows: *global cognitive function* = β : -0.011 (SE: 0.0301), *working memory* = β : -0.028 (SE: 0.0497), *digit forward* = β : -0.009 (SE: 0.0549), *digit backward* = β : 0.064 (SE: 0.0605), *episodic memory* = β : -0.031 (SE: 0.0626), *immediate memory* = β : -0.057 (SE: 0.0641), *delayed memory* = β : -0.004 (SE: 0.0661), *semantic processing* = β : -0.033 (SE: 0.0445), *animal fluency* = β : -0.041 (SE: 0.0529), *vegetable fluency* = β : -0.019 (SE: 0.0583), and *DSST* = β : 0.005 (SE: 0.0519). Subsequent sensitivity analyses revealed that not adjusting for education in the regression model, in case it may overcorrect and bias the associations of interest towards the null, did not alter these insignificant findings (Supplementary Table S1). Inclusion of those subjects who were initially excluded because they had severely impaired attention/working memory, but did not necessarily classify as having dementia (by the NACC-algorithm), into the analytic sample again also did not change the null results (Supplementary Table S2).

With a sample size of 1,613 subjects, a post-hoc power analysis indicated a 96.0% chance of detecting a small effect size ($f^2 = 0.02$ or 2% of the variance of Y) if there was one at the 0.5% level of Bonferroni-adjusted significance (Cohen, 1988). While the association between LTL and cognitive function was null, significant associations were observed between each of the cognitive domains with sex, age, generation, education and country, as expected (Supplementary Table S3). For example, significantly worse global cognitive function ($p < 0.005$) was observed in males as opposed to females (β : -0.186; SE: 0.0262), with increasing age (β : -0.016; SE: 0.0022), among individuals who had less education (less than college vs. post college - β : -0.441; SE: 0.0380; some college vs. post college - β : -0.232; SE: 0.0315), and for members of the proband versus the offspring generation (β : -0.226; SE: 0.0331).

After stratifying by LLFS family member status, the relative and spousal control groups independently displayed null findings ($p > 0.005$) (Table 2). Also, when the sample was divided by sex, neither males nor females demonstrated an association between LTL and cognitive function across all domains (Figure 2, Supplementary Table S4).

Leukocyte Telomere Length and Cognitive Function in Individuals with Alzheimer's Disease, Dementia or Incipient Dementia

The group of aging LLFS individuals who had MCI or dementia ($n = 597$) constituted of 525 relatives and 72 spousal controls. With this sample size, there was a 37.8% chance of detecting a small effect size ($f^2 = 0.02$) and a 100.0% chance of detecting a medium effect size ($f^2 = 0.15$) if there was one at the 0.5% level of Bonferroni-adjusted significance (Cohen, 1988). Similar to the non-demented group, null findings were detected between LTL and all of the cognitive tests, after adjusting for sex, age, education, country, generation and lymphocyte percentage ($p > 0.005$) (Figure 3). More specifically, the relationship between LTL and each cognitive measure in the regression analyses were as follows: *global cognitive function* = β : 0.006 (SE: 0.0654), *working memory* = β : 0.149 (SE: 0.0890), *digit forward* = β : 0.017 (SE: 0.0970), *digit backward* = β : 0.258 (SE: 0.1095), *episodic memory* = β : -0.073 (SE: 0.0958), *immediate memory* = β : -0.133 (SE: 0.1072), *delayed memory* = β : -0.013 (SE: 0.1050), *semantic processing* = β : -0.045 (SE: 0.0982), *animal fluency* = β : 0.020 (SE: 0.1022), *vegetable fluency* = β : -0.111 (SE: 0.1163), and *DSST* = β : 0.028 (SE: 0.1023).

Upon stratification by sex, neither males nor females demonstrated an association between LTL and cognitive function across all domains ($p > 0.005$). However, significant findings for some of the other covariates, similar to what was described in the non-demented sample, were observed between sex, age, education, country and lymphocyte percentage with each of the cognitive domains in this group of individuals with dementia or incipient dementia (Supplementary Table S5).

DISCUSSION

Overall, within this Long Life Family Study sample, null associations were detected between LTL and working memory, episodic memory, semantic processing, and information processing speed for 1,613 aging, non-demented individuals and 597 aging individuals with dementia or incipient dementia ($p > 0.005$). Very few other studies have investigated the relationship between LTL and cognitive function in older adult populations and distinguished whether subjects were unimpaired at baseline. Harris et al. (2006) studied 550 Scottish 79 year olds in the Lothian Birth Cohort 1921 (LBC1921), who were without evident dementia, as determined by the Mini-Mental State Examination (MMSE) to be a total score of 24 or higher. The mean telomere length of the LBC1921 was longer than that of the non-demented LLFS individuals (6.63 (SD=1.70) kbp vs. 5.27 (SD=0.40) kbp), despite the fact that the aging LLFS participants were, on average, younger (72 years old). Aside from a small negative correlation between telomere length and verbal fluency $r = -0.16$, $p = 0.027$, Harris et al. (2006) found that telomere length was not cross-sectionally associated with test scores on the Raven's standard progressive matrices (used to measure verbal reasoning), the Moray House Test (MHT) (used to measure mental ability, including following directions, word classification, analogies, practical items, reasoning, arithmetic, and spatial items), and the Logical Memory test ($p > 0.05$).

Harris et al. (2012) then further replicated these null findings in another larger cross-sectional study of 1,091 non-demented members of the Lothian Birth Cohort 1936

(LBC1936). At age 70, there were no significant correlations in their overall sample between telomere length and general cognitive ability (derived from matrix reasoning, letter number sequencing, block design, symbol search, digit span backwards, and digit symbol subtests on the Wechsler Adult Intelligence Scale-III (WAIS-III)), general processing speed (derived from a set of mental speed measures: symbol search, digit symbol, simple reaction time mean, choice reaction time mean, inspection time), or general memory (derived from subtests of the Wechsler Memory Scale-III (WMS III) and WAIS-III, including Logical Memory I and II, spatial span forward and backward, Verbal Paired Associates I and II, letter-number sequencing, and digit span backwards) ($p>0.05$). In their most recent study, Harris et al. (2016) additionally found no association between change in telomere length and change in general cognitive ability in either of these two Scottish cohorts, LBC1921 or LBC1936. All these findings coincide with the null associations we detected between LTL and several cognitive domains in the non-demented LLFS subsample.

Martin-Ruiz et al. (2006) also evaluated the relationship between LTL and cognitive function prospectively in 195 non-demented stroke survivors from the UK, above age 75, who had MMSE total scores greater than 24 at baseline. The mean age of participants (80 years) and the baseline average telomere length (6.17 (SD=0.57) kbp) in their sample were both higher than our non-demented LLFS sample. The authors found that telomere length at baseline was inversely associated to cognitive decline ($p=0.04$), as measured by changes in the MMSE score, for the 145 individuals who survived to 2 years. By year two, however, many of these participants had cognitive impairment (MMSE scores <24) and 20 were even diagnosed with dementia. This result contrasts with our own study finding that LTL is unrelated to cognitive ability when the sample includes individuals with MCI or dementia. This dissimilarity may be attributed to differing study designs between our study and theirs (cross-sectional vs. cohort).

Contrary to our study findings, Valdes et al. (2010) evaluated a non-demented, healthy group of 382 women, aged 19 to 78 years, from the TwinsUK cohort cross-sectionally. After adjusting for age and prior intellectual ability, they found that LTL was associated with episodic memory and associative learning (via the Paired Associates Learning (PAL) test), working memory capacity (via the Space Span (SSP) test) and recognition memory for non-verbal patterns (via the Delayed Matching to Sample (DMS) test). They further discovered that among pairs of twins discordant for LTL, twins with longer telomeres had significantly better SSP and DMS scores compared to their siblings ($p < 0.05$). Similarly, Yaffe et al. (2011) found that among 2,741 non-demented, multi-ethnic elders, aged 70–79 years in the US, those with longer telomere lengths exhibited better baseline attention, psychomotor speed and executive function via the Digit Symbol Substitution Test (DSST). They also found that longer telomere length was associated with slower global cognitive decline (MMSE) over seven years when compared to short and medium telomere lengths within the older population (–1.7 points vs. –2.5 and –2.9, $p=0.01$). The reason for the discrepancy in findings between the study by Valdes et al. (2010) and our own study may be attributed to differences in the age range of the two cohorts. Valdes et al. (2010) studied individuals from a broader and younger age group than our LLFS aging analytic sample. The association of LTL with age related cognitive decline will change according to the timing of telomere analysis and age at cognitive assessment (Mather et al., 2011). Further, LTL changes may

depend on different factors that vary across the lifespan (Rask et al., 2016). Divergent findings between the Yaffe et al. (2011) study and our own investigation may be a consequence of differing study designs and the fact that the former comprises of an ethnically diverse population of community residents while the latter comprises of individuals solely of European ancestry, who were selected based on exceptional survival attributes.

Studies that were comprised of older individuals across the full spectrum of cognitive function, including those who may have MCI or dementia, reported mainly positive findings. Mather et al. (2010) examined two cohorts of Australian middle-aged ($n = 351$, 44–49 years) and older ($n = 295$, 64–70 years) adults. While cross-sectional analyses showed no significant relationships between LTL and cognitive function in the middle-aged cohort, a positive association was detected within the older cohort between telomere length and the Symbol Digit Modalities Test (SDMT), which measured processing speed and attention. This association with SDMT remained significant among men only, after stratification by sex. In another cross-sectional study, Ma et al. (2013) studied 976 Chinese men, aged 65–91 years, and observed significant correlations between telomere length with episodic memory ($r = 0.086$, $p=0.007$) and executive function ($r = -0.053$, $p=0.048$), assessed through a three-item recall and verbal fluency test, respectively. Additionally, Devore et al. (2011) detected a modest association ($p=0.04$) between longer telomere length and slower cognitive decline, as measured by the Telephone Interview for Cognitive Status (TICS), within a 10-year time span among ~2,000 participants in the Nurses' Health Study, over 70 years old.

Our own study makes a valuable contribution to the literature on LTL and cognitive ability in that we are able to examine this potential relationship in a large, unique cohort with exceptional cognitive function and survival attributes. We previously established that members of long lived families evidence longer telomere length (Honig et al., 2015) and a cognitive advantage as compared with spouse controls (Barral et al., 2012; Cosentino et al., 2013), and we observed these same findings in the current sample of LLFS participants. It should be noted that variations in the specific cognitive test scores, which differed across relatives and spousal controls, likely indicate differences in the specific individuals included in the analysis. A key strength of our study is that we evaluated cognitive function and identified cognitive impairment through a wide array of age-sensitive cognitive tests. We also adjusted for sex and age, both of which are well-established predictors of telomere length, along with education, country, family generation, and lymphocyte percentage. While the subjects in our study are not independent observations, we did adjust for familial clustering through robust regression methods so that it would not bias the levels of significance. Furthermore, our sample size was large and had sufficient power to detect an association between LTL and cognitive function, if there was one, for both the non-demented group ($n = 1,613$) and the group with dementia or incipient dementia ($n = 597$).

Our study had several limitations as well. Dementia status was not clinically ascertained; we used a dementia algorithm variable to separate cognitively impaired individuals from unimpaired individuals. We examined the relationship between LTL and cognitive function cross-sectionally. It may be that cross-sectional measurements of both variables are less informative than longitudinal change scores in capturing a potential association. As the

pathology underlying cognitive impairment arises decades before detectable symptoms appear, measuring LTL change prior to assessment of cognitive change may be necessary, and may be most clinically relevant for informing the extent to which telomere length influences, initiates, or corresponds with the onset or rate of cognitive decline. However, the previously mentioned study by Harris and colleagues (2016) found no link between change in LTL and change in cognitive ability. Additionally, the current findings are not generalizable to different ethnic populations, given the homogenous demographic and geographic characteristics of our study cohort. This highly selected sample of exceptional LLFS families further constrain the external validity of the observed findings. For example, the non-significant associations observed between LTL and cognitive function in our study, even among the group of individuals with dementia or incipient dementia, may be a consequence of the LLFS participants being “biologically younger” than the general population.

In conclusion, this study suggests that among individuals whose cognitive abilities are broadly intact and who have longer telomeres and higher cognitive function, on average, than the general population, a single measure of telomere length is not directly associated with episodic memory, semantic processing, working memory and information processing speed. Likewise, for LLFS individuals with cognitive impairment, LTL is unrelated to cognitive function. Future studies should evaluate this association prospectively to determine whether LTL attrition across the lifespan plays a potential causal role in cognitive decline. Researchers should also seek to explore the association between LTL and cognitive ability in a sample that is more representative of the general population and/or with clinically verified dementia diagnoses. It is critically important to identify biomarkers of cognitive change for early treatment and detection of neurodegenerative diseases. The relative advantage of investigating telomere length as a potential biomarker for cognitive function is that it can be measured through minimally invasive, readily available, and inexpensive methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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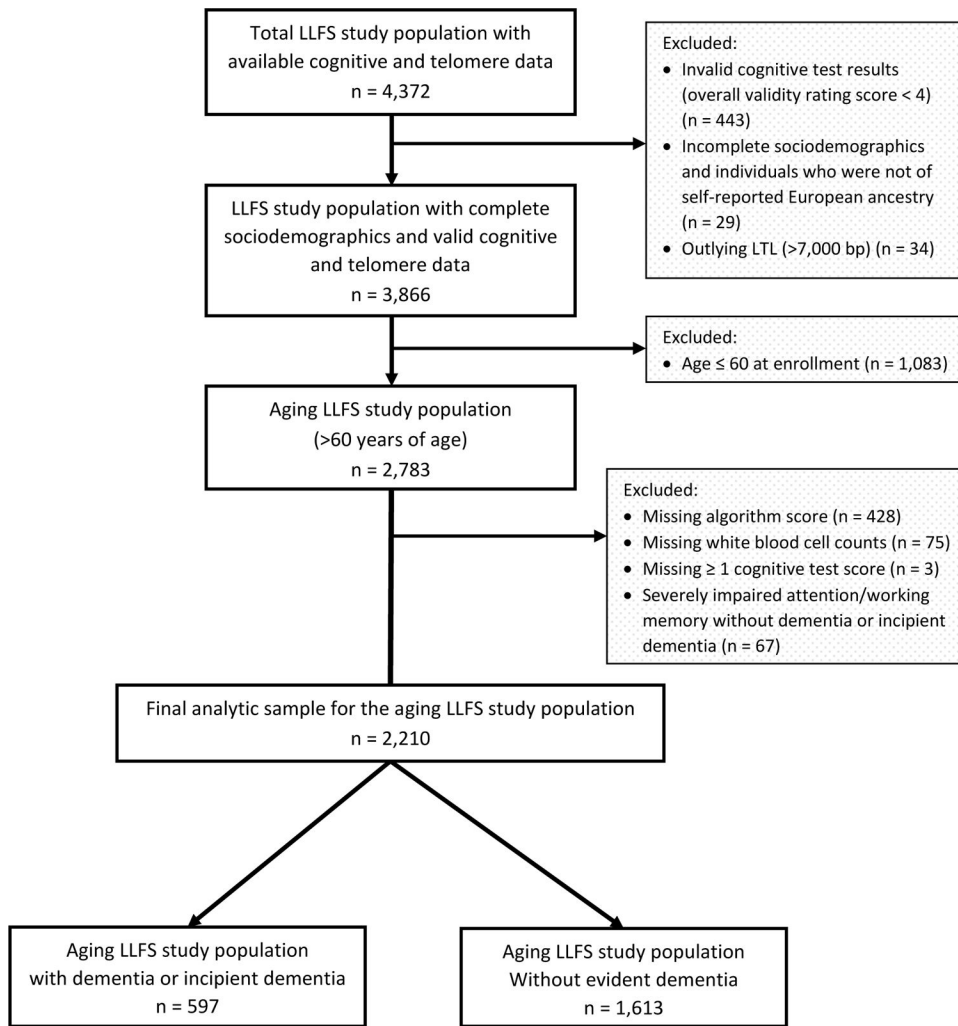


Figure 1. Non-demented vs. Demented Persons of the Long Life Family Study (LLFS). 2,210 individuals, of which 1,613 were cognitively unimpaired and 597 had dementia or incipient dementia, fulfilled the inclusion and exclusion criteria (had available and valid cognitive and telomere data, complete sociodemographic information, fulfilled the age restriction, and had no missing data).

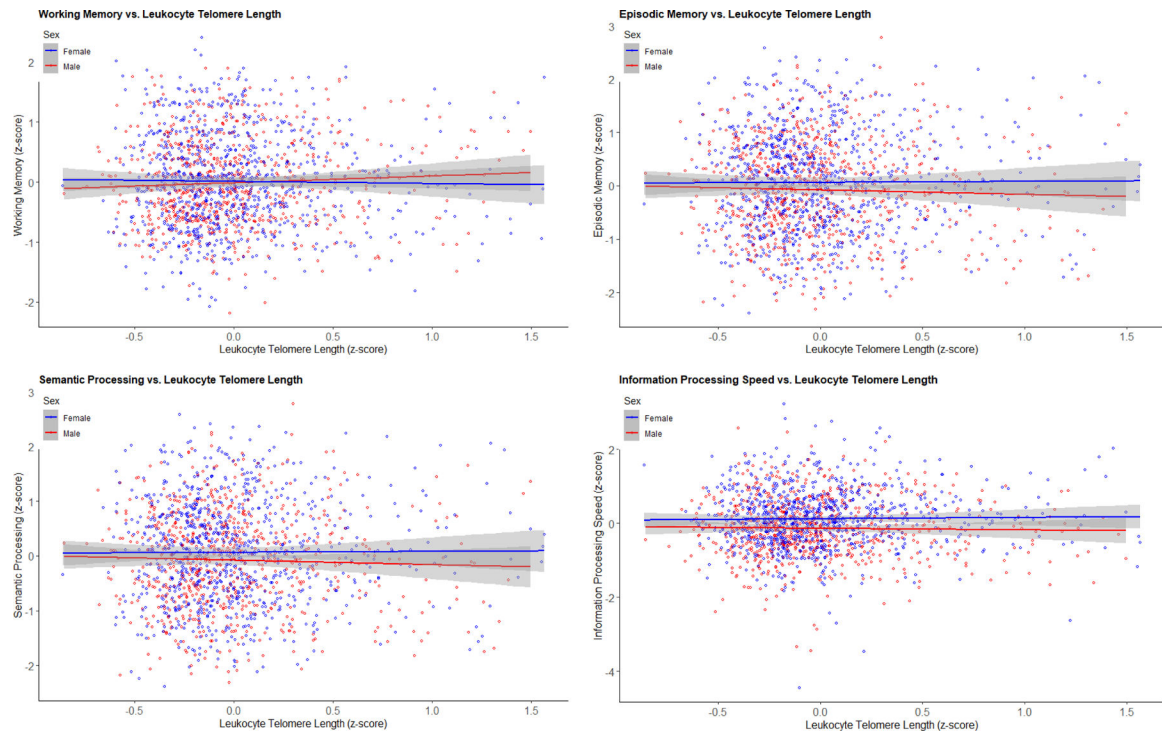


Figure 2. Scatterplots between leukocyte telomere length and the cognitive performance, stratified by sex.

A linear relationship and the corresponding 99.5% confidence interval (shaded region) is modeled to depict the association between z-scores for leukocyte telomere length and working memory, episodic memory, semantic processing, and information processing speed, separately for aging LLFS males ($n = 752$) and females ($n = 883$) in the cognitively unimpaired group ($n = 1,613$). The z-score computed for each cognitive domain adjusts for age, generation, education, and country, while the z-score for leukocyte telomere length adjusts for the aforementioned in addition to lymphocyte percentage.

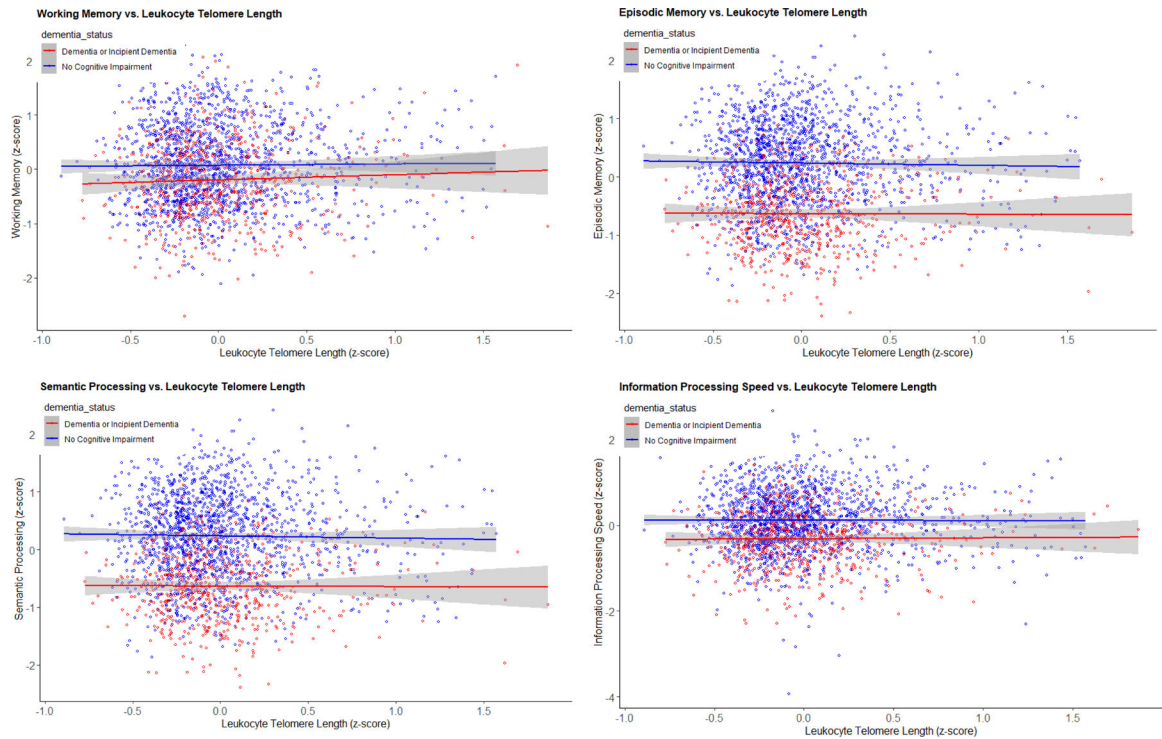


Figure 3. Scatterplots between leukocyte telomere length and the cognitive performance, stratified by dementia status.

A linear relationship and the corresponding 99.5% confidence interval (shaded region) is modeled to depict the association between z-scores for leukocyte telomere length and working memory, episodic memory, semantic processing, and information processing speed, separately for those with ($n = 597$) and without cognitive impairment ($n = 1,613$). The z-score computed for each cognitive domain adjusts for age, generation, education, and country, while the z-score for leukocyte telomere length adjusts for the aforementioned in addition to lymphocyte percentage.

Table 1. Sociodemographic and clinical characteristics among individuals of the aging Long Life Family Study cohort (n = 2,210).

Characteristics	Non-Demented Individuals				p-value	
	Individuals with Dementia or Incipient Dementia (n = 597)	All (n = 1,613)	Relatives (n = 1,221)	Spouse Controls (n = 392)		Cognitively Impaired vs. Non-Demented
Generation, No. (%)						
Proband	491 (82.2%)	422 (26.2%)	344 (28.2%)	78 (19.9%)		
Offspring	106 (17.8%)	1,191 (73.8%)	877 (71.8%)	314 (80.1%)	<0.005	<0.005
Country, No. (%)						
US	488 (81.7%)	1,098 (68.1%)	892 (73.1%)	206 (52.6%)		
Denmark	109 (18.3%)	515 (31.9%)	329 (26.9%)	186 (47.4%)	<0.005	<0.005
Sex, No. (%)						
Male	317 (53.1%)	738 (45.8%)	534 (43.7%)	204 (52.0%)		
Female	280 (46.9%)	875 (54.2%)	687 (56.3%)	188 (48.0%)	<0.005	<0.005
Age (years), mean (SD)	88.0 (9.3)	73.0 (10.3)	73.6 (10.8)	70.8 (8.1)	<0.005	<0.005
Education, No. (%)						
Less than college	325 (54.4%)	326 (20.2%)	243 (19.9%)	83 (21.2%)		
Some college	223 (37.4%)	904 (56.0%)	679 (55.6%)	225 (57.4%)	<0.005	0.455
Post college	49 (8.2%)	383 (23.7%)	299 (24.5%)	84 (21.4%)		
Leukocyte Telomere Length (base pairs)						
Mean (SD)	5,162.9 (361.6)	5,265.9 (393.2)	5,281.2 (397.7)	5,218.2 (375.3)		
Range	4,450 – 6,959	4,303 – 6,973	4,546 – 6,973	4,303 – 6,934	<0.005	0.006
Lymphocyte Percentage, mean (SD)	27.8 (10.9)	31.3 (10.1)	31.2 (10.0)	31.7 (10.5)	<0.005	0.404
Cognitive Domain, mean (SD)						

Characteristics	Non-Demented Individuals				p-value
	Individuals with Dementia or Incipient Dementia (n = 597)	All (n = 1,613)	Relatives (n = 1,221)	Spouse Controls (n = 392)	
Immediate Memory	5.7 (3.3)	13.1 (3.5)	13.1 (3.5)	13.1 (3.6)	<0.005
Delayed Memory	3.0 (2.5)	11.6 (3.8)	11.6 (3.8)	11.7 (3.8)	<0.005
Digit Forward	7.3 (2.2)	8.4 (2.1)	8.5 (2.1)	8.0 (2.1)	<0.005
Digit Backward	5.0 (1.9)	6.6 (2.1)	6.7 (2.2)	6.2 (2.0)	<0.005
Animal Fluency	13.0 (4.8)	21.0 (5.8)	20.7 (5.7)	21.8 (5.8)	<0.005
Vegetable Fluency	9.1 (3.6)	14.3 (4.3)	14.3 (4.3)	14.3 (4.2)	<0.005
Information Processing Speed	25.4 (11.3)	45.0 (12.7)	45.1 (12.9)	44.6 (11.7)	<0.005

Comparisons for categorical variables used Chi-Squared tests and comparisons for continuous variables used Analysis of Variance (ANOVA).

Association between leukocyte telomere length (per 1,000 base pairs) and cognitive domain z-scores among individuals of the aging Long Life Family Study cohort without evident dementia.

Table 2.

Cognitive Domain z-scores	All (n = 1,613)		Relatives (n = 1,221)		Spouse Controls (n = 392)	
	EST [†]	SE	EST [†]	SE	EST [†]	SE
Global Cognitive Function	-0.011	0.0301	0.007	0.0358	-0.086	0.0629
Working Memory	0.028	0.0497	0.077	0.0582	-0.172	0.0956
Digit Forward	-0.009	0.0549	0.043	0.0643	-0.213	0.1217
Digit Backward	0.064	0.0605	0.111	0.0699	-0.136	0.1042
Episodic Memory	-0.031	0.0626	0.015	0.0730	-0.197	0.1302
Immediate Memory	-0.057	0.0641	-0.017	0.0757	-0.207	0.1296
Delayed Memory	-0.004	0.0661	0.047	0.0757	-0.179	0.1405
Semantic Processing	-0.033	0.0445	-0.064	0.0512	0.057	0.1011
Animal Fluency	-0.041	0.0529	-0.076	0.0590	0.060	0.1272
Vegetable Fluency	-0.019	0.0583	-0.038	0.0678	0.054	0.1239
Information Processing Speed	0.005	0.0519	-0.003	0.0585	0.030	0.1010

Leukocyte telomere length is expressed as kilo base-pairs, while cognitive scores are unadjusted z-scores. The significance of the association between the two are evaluated using the Wald Chi-Square Test. Abbreviations: EST, beta estimate; SE, standard error.

[†] Analysis adjusted for sex (males vs. females), generation (proband vs. offspring), country (US vs. Denmark), education (less than college, some college or post college), age (in years), and lymphocyte percentage.

P-values are denoted as follows:

* p<0.005

Association between leukocyte telomere length (per 1,000 base pairs) and cognitive domain z-scores among individuals of the aging Long Life Family Study cohort with dementia or incipient dementia.

Table 3.

Cognitive Domain z-scores	All (n = 597)		Males (n = 317)		Females (n = 280)	
	EST†	SE	EST†	SE	EST†	SE
Global Cognitive Function	0.006	0.0654	0.026	0.0988	-0.033	0.0960
Working Memory	0.149	0.0890	0.168	0.1531	0.041	0.1188
Digit Forward	0.017	0.0970	0.036	0.1461	-0.047	0.1352
Digit Backward	0.258	0.1095	0.268	0.1766	0.155	0.1417
Episodic Memory	-0.073	0.0958	-0.022	0.1462	-0.132	0.1370
Immediate Memory	-0.133	0.1072	-0.073	0.1671	-0.196	0.1405
Delayed Memory	-0.013	0.1050	0.023	0.1519	-0.067	0.1571
Semantic Processing	-0.045	0.0982	-0.115	0.1394	0.037	0.1453
Animal Fluency	0.020	0.1022	-0.045	0.1545	0.050	0.1484
Vegetable Fluency	-0.111	0.1163	-0.185	0.1611	-0.010	0.1696
Information Processing Speed	0.028	0.1023	0.201	0.1237	-0.185	0.1556

Leukocyte telomere length is expressed as kilo base-pairs, while cognitive scores are unadjusted z-scores. The significance of the association between the two are evaluated using the Wald Chi-Square Test. Abbreviations: EST, beta estimate; SE, standard error.

†Analysis adjusted for sex (males vs. females), generation (proband vs. offspring), country (US vs. Denmark), education (less than college, some college or post college), age (in years), and lymphocyte percentage.

P-values are denoted as follows:

* p<0.005