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## Leukocyte telomere length is associated with cognitive performance in healthy women

A.M. Valdes<sup>a,\*</sup>, I.J. Deary<sup>b</sup>, J. Gardner<sup>c</sup>, M. Kimura<sup>c</sup>, X. Lu<sup>c</sup>,  
T.D. Spector<sup>a</sup>, A. Aviv<sup>c</sup>, L.F. Cherkas<sup>a</sup>

<sup>a</sup> Twin Research & Genetic Epidemiology Unit, Kings College London, School of Medicine, UK

<sup>b</sup> MRC Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, UK

<sup>c</sup> Center of Human Development and Aging, New Jersey Medical School, USA

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### Abstract

**Background:** Age-related cognitive decline begins in mid-life and continues with advancing age. Leukocyte telomere length (LTL) shortens with age, and inflammation and oxidative stress enhance this process. Shorter LTL is associated with dementia.

**Methods:** The relationship between cognitive function and LTL was investigated in a cross-sectional study of 382 women (mean age 50.6 years, range 19–78), not diagnosed with any form of dementia or cognitive impairment, from the TwinsUK cohort using six tests from the Cambridge neuropsychological test automated battery (CANTAB).

**Results:** After adjusting for age and estimated prior intellectual ability, we observed significant correlations of LTL with episodic memory and associated learning (PAL,  $p = 0.032$ ), recognition memory for non-verbal patterns (DMS,  $p = 0.007$ ), and working memory capacity (SSP,  $p = 0.003$ ). In pairs of twins discordant for LTL the twin with longer telomeres also had significantly better DMS ( $p < 0.05$ ) and SSP ( $p < 0.013$ ) scores than their co-twin with shorter telomeres. The correlations between these two scores and LTL was significant both in women over the median mean age and in those below the median age, and remained significant after statistical adjustment for potential confounders.

**Conclusions:** Leukocyte telomere length correlates with a subset of measures of cognitive performance, suggesting that it might be a biomarker of cognitive aging in women before the onset of dementia.

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**Keywords:** Memory; Telomere length; Cognitive aging

### 1. Introduction

Age-related cognitive decline begins in mid-life and continues with advancing age (Park et al., 2002). However, there is high inter-individual variability associated with it (Foster, 2006). The variability in memory function in the aging population is likely due to both genetic and environmental factors. For example, measures of plasma cholesterol, inflammation and oxidative stress have all been negatively associated with memory and cognitive function in older individuals

(Engelhart et al., 2004; Rafnsson et al., 2007; Droge and Schipper, 2007). The presence of hypertension and of type 2 diabetes (T2D) are also associated with poorer cognitive performance (e.g. Korczyn and Vakhapova, 2007; Kumari and Marmot, 2005). In contrast, higher levels of physical activity are associated with better cognitive function (Lautenschlager and Almeida, 2006). Oxidative stress and inflammation offer possible common causes to aging and age-related memory impairment, which may help explain why physical and cognitive capabilities are highly correlated in old age (Rafnsson et al., 2007; Anstey et al., 2005; Peila and Launer, 2006; Lau et al., 2007). A possible index of the core concept of ‘common cause’ is leukocyte telomere length. Telomere length decreases with age and this is in large measure a record of the accruing burden of oxidative stress (von Zglinicki

\* Corresponding author at: Twin Research & Genetic Epidemiology Unit, King’s College London, St Thomas Hospital, Lambeth Palace Road, London SE1 7EH, UK. Tel.: +44 207 188 6765; fax: +44 207 188 6718.

E-mail address: ana.valdes@kcl.ac.uk (A.M. Valdes).

et al., 2000; von Zglinicki, 2002), and inflammation (Aviv, 2006).

Shortened telomere length has been implicated in a spectrum of aging related diseases, including cardiovascular disease (Benetos et al., 2004; Fitzpatrick et al., 2007; Brouillette et al., 2007; van der Harst et al., 2007) and other disorders, such as obesity (Valdes et al., 2005), osteoarthritis (Zhai et al., 2006), and osteoporosis (Valdes et al., 2007). Further, individuals with dementia display shortened telomere length (Panossian et al., 2003; Martin-Ruiz et al., 2006; von Zglinicki et al., 2000). Although a study of non-demented individuals aged 79 years ( $n = 190$ ) did not find any relationship between leukocyte telomere length and cognitive function (Harris et al., 2006), the relationship between telomere length and cognitive performance in a sample representative of the general adult population has not been investigated. In the present study we examined whether LTL was associated with cognitive function in 382 healthy (non-demented or cognitively impaired) women.

## 2. Subjects and methods

### 2.1. Study participants

Participants were 382 women (aged 19–78) from the Twin-SUK cohort. All provided informed consent approved by The St Thomas' Hospital Research Ethics Committee.

Cognitive function was assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins et al., 1994).

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a series of computerised tests of cognition that run on a personal computer fitted with a touch sensitive screen. It has been standardised on a large sample of 787 normal elderly volunteers (Robbins et al., 1994) and test–retest reliability studies demonstrate correlations for individual test items range between 0.56 and 0.86 (Lowe and Rabbitt, 1998). Subjects were screened with a preliminary motor task to ascertain whether or not they were capable of performing the task and all of the participants passed. A practice run was not administered. Ten scores pertaining to six cognitive function measures were assessed in the original study (Singer et al., 2006). For this study we have used only one score from each cognitive function test as follows:

- (a) Delayed matching to sample (DMS) test. This test assesses forced choice recognition memory for non-verbal patterns. Subjects are presented with a pattern in a box and then – either simultaneously (with no delay) or a 12 s delay – shown four boxes and instructed to choose the pattern that had previously appeared. The total number of patterns correctly remembered was used in the subsequent analysis.
- (b) Paired associated learning (PAL). Six boxes appear and each opens in sequence showing up to 6 patterns. Subjects

were then shown a pattern in the middle of the screen and asked to choose the box the pattern previously appeared in. The total number of errors was used as a score.

- (c) Pattern recognition memory (PRM). Twelve patterns appear one after the other, none of which can be given a simple verbal label. Then, two choice boxes appear and the subject is instructed to choose which of the patterns they had already seen.
- (d) Simple reaction time (RTI) test. This test evaluates psychomotor retardation. Reaction time is measured by asking the subject to touch the screen immediately after a spot appears in the centre of the screen.
- (e) Space span (SSP) test. This test assesses working memory capacity. Many boxes appear and after presenting a sequence of opening boxes of different colours, the subject was asked to recall the order of the colours that appeared by pointing to the correct boxes in sequence. The total number of stages completed was used to score this test.
- (f) Spatial working memory (SWM) test. This is a self-ordered, searching task which is sensitive to fronto-subcortical dysfunction. Blue squares are hidden inside a subset of boxes on the left side of the screen. The subject is required to try to locate all the blue squares and transfer them to the right side of the screen without reopening a box that has previously been selected. The score recorded in this study is the total number of errors made.

The national adult reading test (NART) is a measure of an individual's ability to pronounce 50 irregular English words. It is widely used as a well-validated estimate of prior intellectual ability, as it is highly correlated with overall intelligence (Crawford et al., 2001; McGurn et al., 2004).

Current physical activity during leisure time was recorded on a 4-point scale; 1 = inactive, 2 = light, 3 = moderate and 4 = heavy. This classification system was significantly correlated with more detailed activity assessments reported in previous exercise research on a subset of these individuals several years earlier, based on the Allied Dunbar Health Survey (Cherkas et al., 2008).

Blood was collected for determination of leukocyte telomere length (LTL) and fasting glucose. LTL was derived from the mean length of the terminal restriction fragments, measured by Southern blot analysis (Benetos et al., 2001). The coefficient of variation of duplicates resolved on different gels and occasions was 1.48%. Fasting glucose was measured on Ektachem 700 multichannel analyzer, using an enzymatic colorimetric slide assay (Johnson and Johnson Clinical Diagnostic Systems, Amersham, UK). Diagnosis of T2D was based on history of hypoglycaemic treatment and/or confirmed fasting blood glucose >126 mg/dl (7.0 mmol/l). Blood pressure was measured with an Omron BP machine. Prior to measuring each study participant sat still for 3 min. Three readings were taken (1 min rest between readings). Diagnosis of hypertension was based on the presence of systolic blood pressure >140 mm Hg and/or diastolic blood pressure

>90 mm Hg and/or the use of anti-hypertensive medications. Serum homocysteine levels and vitamin D levels were measured as described elsewhere (Richards et al., 2007, 2008).

Subjects completed a questionnaire detailing the age at which they finished education and their own and their partner's occupation. The grouping of occupations was based on Goldthorpe and Hope (1974) and classifications based on the National Statistics Socio-Economic Classification (NS-SEC, 2002).

Subjects were then assigned to a socio-economic status (SES) I, II, IIN, IIM, IV or V (as used routinely in UK studies (Marmot, 2004)), based on the higher occupational level of either the twin or their partner, in accordance with the new UK NS-social-economic measure. According to this system, I = professional occupations, II = managers & administrators and associate professional & technical workers, IIN = clerical and secretarial non-manual skilled occupations, IIM = crafts & manual related skilled occupations, IV = partly skilled occupations and V = unskilled occupations (Cherkas et al., 2006).

## 2.2. Statistical analysis

Using standard linear regression, leukocyte telomere length was regressed on age and NART and the Pearson's correlation coefficients between the multiply-adjusted leukocyte telomere length and cognitive test variables were computed. Because twin-pair data are not independent observations, we examined the correlation between LTL versus the various factors using a linear mixed effects model which included twin-pair of origin as a random effect and any other independent variables as fixed effects. Analyses of covariance were used to compute the multiple adjusted leukocyte telomere length means of the top (T1) and bottom (T3) tertiles of the cognitive trait distributions.

In addition, correlation coefficients between all six CANTAB scores and LTL and various potential confounders were computed adjusting only for age. The potential confounders tested were: diastolic blood pressure, fasting serum glucose, body mass index, smoking status (never, ex-smoker and current), serum levels of homocysteine, serum concentration of vitamin D, levels of physical activity, age at which the individual finished education and socio-economic status.

We examined within twin pair CANTAB score differences for 40 pairs of twins discordant for telomere length (above vs. below the median of age adjusted LTL). All such twins were non-identical. This mean and standard error of within pair CANTAB score difference were calculated and a paired *t*-test was carried to assess statistical significance. S-Plus 6.0 (Insightful Corp., WA) was used for all analyses.

## 3. Results

Characteristics of the study participants are shown in Table 1. Leukocyte telomere length was negatively associ-

ated with age (Pearson's correlation coefficient  $r = -0.342$ ,  $p < .001$ ). In this cohort the mean extrapolated telomere length shortening rate was 18.2 base pairs/year (S.E. 2.6 base pairs) and appeared to be constant with age, with no significant difference in rates of loss between various age ranges (not shown).

The mean NART-estimated IQ score for all the women of Twins UK is 113.6 (S.D. = 7.5) ( $n = 1379$ ) (range 85–129). The mean LTL for the 3200 women measured is 7.05 kilobases (S.D. = 0.68), and their mean age is 48.6 (S.D. = 13.6), with an annual rate of telomere loss of 19.1 base pairs/year. Therefore, the present report's subsample of 382 women is representative of the whole cohort with regards to these traits.

The estimate of prior intelligence used here, the NART score, was not significantly correlated with LTL (Supplementary Table 1). Five of the six CANTAB scores (all except RTI) were significantly correlated with the NART score, with better CANTAB subtest scores being associated with a higher NART score (Supplementary Table 1). We first assessed the correlation between the six cognitive performance measures and telomere length, adjusting for age and NART score. For clarity, we note that a higher PAL, SWM or RTI score indicated a worse performance whereas a higher PRM, DMS or SSP score indicated a better performance. Better performance on all six CANTAB scores was positively correlated with longer LTL (Table 1). The correlations were statistically significant for PAL, RTI, DMS and SSP, but not for PRM or SWM. For five of the six cognitive function scores studied, individuals in the highest performance tertiles had longer LTL than those with the lowest performance tertile. This was not observed for the PRM, which showed no significant association with leukocyte telomere length (Fig. 1). However, the difference was statistically significant only for SSP and DMS. Women with the highest (T1) tertile of SSP had on average 304 bp leukocyte telomere length than those in the lowest (T3) tertile ( $p < 0.001$ ), while women in the highest tertile for DMS had 190 bp longer leukocyte telomere length than those in the worst tertile ( $p = 0.020$ ) (Fig. 1).

Forty pairs of twins discordant for LTL were identified. The twins with the higher LTL had a better mean DMS score (17.6, S.D. = 1.9) than their co-twins with lower LTL (16.6, S.D. = 2.3) ( $p < 0.05$ ). Similarly women in the top half of LTL had a higher mean SSP score (5.7, S.D. = 1.3) than their co-twin with low LTL (5.1, S.D. = 1.1) ( $p < 0.013$ ). The difference in the other scores between twins discordant for telomere length were not statistically significant with  $p$  values  $> 0.15$ .

Because twins share to a large extent the same environmental (education, socio-economic status) and genetic background these data suggested to us that the associations between SSP and LTL and between DMS and LTL were the most likely to be robust to confounding effects and thus they were further investigated.

We next explored the role of a number of potential confounders for the observed associations in the whole set of women with LTL and CANTAB data regardless of their discordant or concordant twin status (see Supplementary

Table 1  
Descriptive statistics of the study cohort

Trait	Count or percentage			
Sample size	382			
Hypertension (%)	21.1			
Ex-smokers (%)	34.0			
Current smokers (%)	18.2			
T2D (%)	0.8			
Post-menopausal (%)	65.4			
	Mean	S.D.	Q1–Q3	
LTL (kb)	7.04	0.66	6.56–7.51	
Age (years)	50.65	12.34	42.8–60.1	
BMI (kg/m <sup>2</sup> )	25.15	4.27	22.12–26.96	
Physical activity <sup>a</sup>	2.6	0.6	2–3	
National average reading test (NART)	113.7	7.9	109.0–119.8	
Finished education (years)	17.6	4.9	15–18	
Socio economic status <sup>b</sup>	2.3	1.1	2–3	
CANTAB scores <sup>c</sup>	Mean	S.D.	Q1–Q3	Correlation with LTL adjusted for age + NART <sup>d</sup>
Delayed matching to Sample (DMS)	17.2	1.9	16.0–19.0	$r = +0.14, p < 0.006$
Paired associates learning (PAL)	23.8	26.8	9.0–29.0	$r = -0.12, p < 0.013$
Pattern recognition memory (PRM)	20.8	2.4	19.0–23.0	$r = +0.04, p < 0.47$
Reaction time test (RTI)	357.8	65.5	314.0–392	$r = -0.12, p < 0.032$
Space span (SSP)	5.5	1.2	5.0–7.0	$r = +0.15, p < 0.003$
Spatial working memory (SWM)	30.7	19.7	15.0–46.0	$r = -0.08, p < 0.10$

S.D. = standard deviation; Q1–Q3, interquartile range; LTL = leukocyte telomere length.

<sup>a</sup> Categories of physical activity 1 = inactive, 2 = light, 3 = moderate and 4 = heavy.

<sup>b</sup> Categories of SES 1 = I, 2 = II, 3 = III, 4 = IIIM and 5 = IV and V.

<sup>c</sup> DMS = delayed matching to sample, total number of patterns correctly remembered; PAL = paired associates learning, total number of errors made; PRM = pattern recognition memory, total number of patterns correctly remembered; RTI = reaction time test simple reaction time in seconds; SSP = space span, total stages completed; SWM = spatial working memory, total number of errors made.

<sup>d</sup> Pearson's correlation coefficient adjusted for age and NART.

Table 2

Correlation between multiply adjusted leukocyte telomere length and delayed match to sample (DMS) and space span (SSP) scores stratified by median age

CANTAB test	Age < 50.6 <sup>a</sup> (n = 192)	Age ≥ 50.6 <sup>a</sup> (n = 190)	Total sample multiply adjusted <sup>a</sup> (n = 382)
DMS	$r = 0.21, p < 0.002$	$r = 0.14, p < 0.035$	$r = 0.16, p < 0.002$
SSP	$r = 0.18, p < 0.026$	$r = 0.13, p < 0.048$	$r = 0.16, p < 0.002$

<sup>a</sup> Pearson's correlation coefficient and corresponding *p*-value adjusted for age, NART, non-independence between twins, hypertension, type 2 diabetes, SES, education, physical exercise, smoking, BMI, menopausal status, serum vitamin D, and homocysteine levels.

Table 1). In this sample of 382 women from the TwinsUK cohort none of these potential confounders is associated with both LTL and CANTAB scores – which would normally be required before a variable may be classed as a possible confounder – so, for the initial exploratory part of the analysis, these factors were not included. However, having observed a robust correlation between SSP and LTL, and between DMS and LTL, we investigated the effect of including the additional factors in the analysis. We further adjusted for those factors which have been previously implicated with either LTL (Richards et al., 2007, 2008; Aviv et al., 2006) or with cognitive function, including BMI, smoking, menopausal status, presence of T2D, hypertension, level of education, socio-economic status, homocysteine and vitamin D serum levels, and levels of physical activity. The correlations with LTL remained statistically significant for both SSP and DMS (Table 2).

Because age is a major determinant of both telomere length and cognitive functions we also explored whether the association between LTL and SSP and DMS remained statistically significant stratifying by median age. The results (Table 2) indicate that a similar correlation between these two CANTAB scores and telomere length is found among the younger half as among the older half of the study cohort, and although the correlations appear slightly stronger in the younger half the difference is not statistically significant.

#### 4. Discussion

The central finding of this work was that cognitive performance, notably SSP and DMS, correlated significantly with LTL among healthy (non-demented) women within a broad

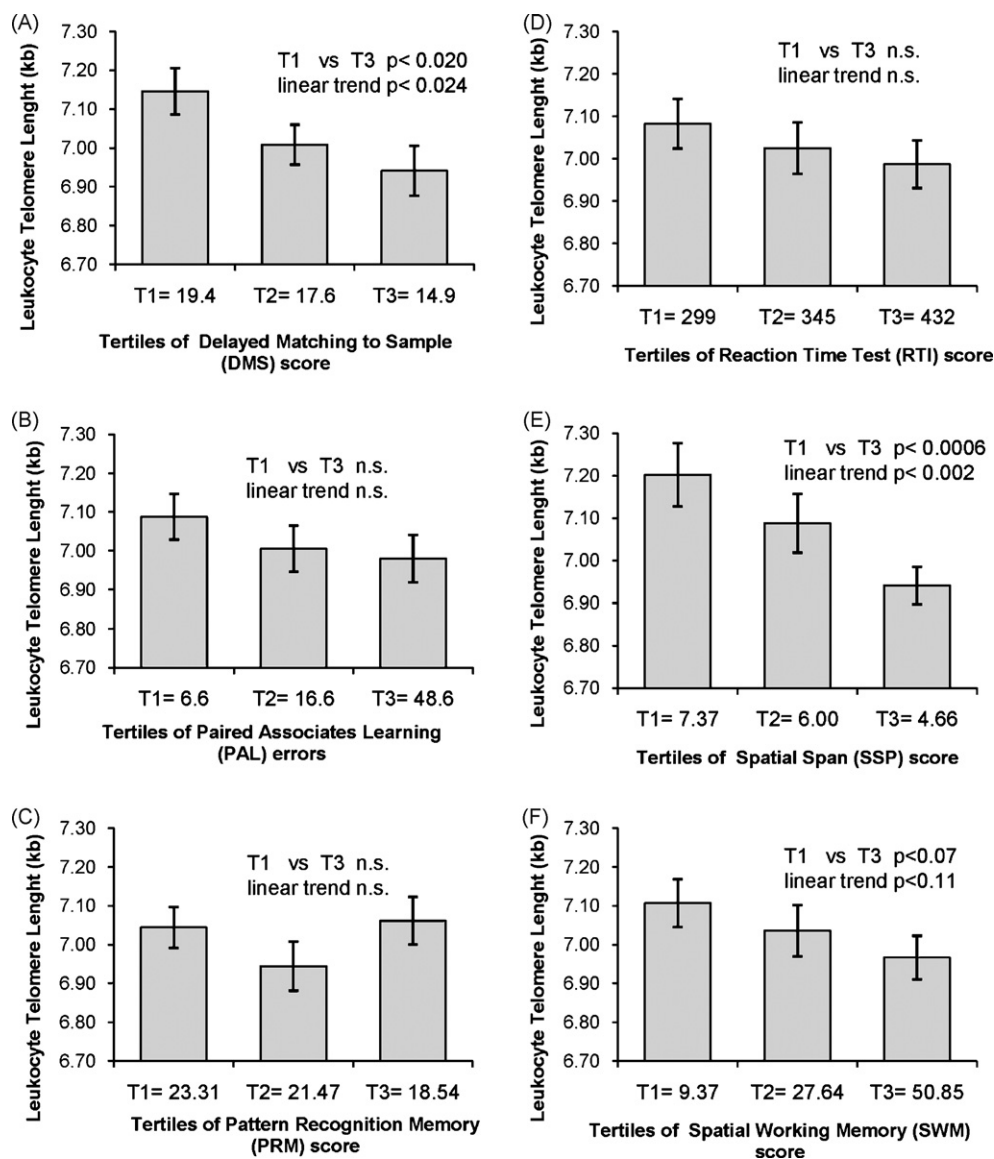


Fig. 1. Adjusted mean leukocyte telomere length adjusted for tertiles of six CANTAB scores. For all CANTAB scores T1, indicates the tertile with the best performance; T2, the middle tertile; and T3, the tertile with the worst performance. For PAL, RTI and SWM the best tertile (T1) is the tertile with the lowest scores, for DMS, PRM and SSP the best tertile (T1) is the tertile with the highest value. The mean score value for each tertile is shown. Results are adjusted for NART score, and age.

age-range. LTL accounted for up to 2.3% of the variance in cognitive ability. Previous work found that telomere length was predictive of better outcomes and better cognitive performance among stroke survivors and among demented subjects (Martin-Ruiz et al., 2006; Honig et al., 2006), suggesting that oxidative stress and inflammation might be the common thread linking LTL shortening with cognitive decline and dementia.

LTL has been previously noted to be heritable (familial) based on twin and family studies (Jeanclous et al., 2000; Nawrot et al., 2004). Therefore, genetics could be a confounder of the relationship observed. From a previous study – of which the current sample is a subgroup – we estimated heritability to be around 36% (95% CI 18–48%) (Andrew et al.,

2006). Our discordant twin analysis confirmed that the two cognitive scores significantly associated with telomere length were also significantly different between twins from the same pair discordant for telomere length. Such results confirm that the associations observed between memory scores and telomere lengths are robust to age and some possible confounding factors.

Indices of oxidative damage and inflammation increase during normal brain aging concomitantly with decline in cognitive and motor performance; these changes take place even in the absence of neurodegenerative diseases (Rafnsson et al., 2007; Peila and Launer, 2006; Lau et al., 2007). Leukocyte telomere length is associated with indices of oxidative stress (Demissie et al., 2006; Epel et al., 2004) and inflammation

(Fitzpatrick et al., 2007; Bekaert et al., 2007) and in this same cohort, shorter telomeres are associated with higher levels of c-reactive protein, a marker of inflammation (Valdes et al., 2007). Oxidative stress enhances telomere erosion (Saretzki and Von Zglinicki, 2002) with each cell division, while inflammation entails increased leukocyte turnover, which would further heighten telomere erosion. Leukocyte telomere length might hence register, at least in part, the cumulative burden of oxidative stress and inflammation during the individual's lifetime.

We note some potential study limitations. The sample consisted of twins rather than singletons, but participants of the TwinsUK cohort are comparable to age-matched population singletons in terms of disease-related and lifestyle characteristics (Andrew et al., 2001). Twins are also related and not independent observations, which could bias the levels of significance, but we have adjusted for this using robust regression methods and, the discordant twin analysis confirmed results from the whole cohort. Another limitation is a relatively modest sample size ( $n=382$ ) although this sample is larger than any previous study investigating the relationship between leukocyte telomere length and cognitive function in a healthy population. Finally, our results are derived from cross-sectional and not longitudinal observations, thus no direct inference about the role that shorter telomeres may have on cognitive decline can be made.

Our data support the hypothesis that oxidative stress and inflammation and perhaps other factors that contribute to cognitive performance also influence leukocyte telomere length and the differences in telomere length relating to cognitive performance can be detected before the onset of any signs of dementia, as all the women in our sample were healthy. Thus, telomere length may represent a potential biomarker to help identify individuals at risk of cognitive decline although this is an avenue that would need to be explored in a prospective study setting.

### Conflict of interest

None.

### Acknowledgements

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2008.07.012.

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