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Leukocyte Telomere Length and Cognitive Function in Older Adults

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Abstract

We evaluated the specific association between leukocyte telomere length (LTL) and cognitive function among a national sample of the broader U. S. older adult population. Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) were used to identify 1722 adults, between 60–85 years, with complete data on selected study variables. DNA was extracted from whole blood via the LTL assay, which is administered using quantitative polymerase chain reaction to measure telomere length relative to standard reference DNA (T/S ratio). Average telomere length was recorded with two to three assays performed to control for individual variability. The DSST (Digit Symbol Substitution Test) was used to assess participant executive cognitive functioning tasks of pairing and free recall. Individuals were excluded if they had been diagnosed with coronary artery disease, congestive heart failure, heart attack, or stroke at the baseline assessment. LTL was associated with higher cognitive performance, independent of gender, race-ethnicity, physical activity status, body mass index, and other covariates. In this sample, there was a strong association between LTL and cognition; for every 1 T/S ratio increase in LTL, there was a corresponding 9.9-unit increase in the DSST (β = 9.9; 95% CI: 5.6–14.2; p<0.001). However, this association was completely mediated by age, as after adding age into this model, LTL was no longer statistically significantly associated with DSST (β = 2.7; 95% CI:-1.4–6.8; p=0.18). There was a positive association between LTL and cognitive function, which was mediated age.

Keywords: Epidemiology, health promotion, immune function, mental health, physical activity

Öz

Yaşlılarda Lökosit Telomere Uzunluğu ve Bilişsel İşlev

Bu makalede, Amerika Birleşik Devletleri'de yaşayan ileri yaşlı nüfusun bir örneği üzerinde lökosit telomer uzunluğu ve bilişsel işlev arasındaki spesifik ilişkiyi değerlendirdik. 1999-2002 Ulusal Sağlık ve Beslenme İncelemesi Araştırması (NHANES) verilerinden seçilen çalışma değişkenleri hakkında eksiksiz veriler içeren 60–85 yaş arasındaki 1722 yetişkin tanımlandı. DNA, standart referans DNA'ya (T/S oranı) göre telomer uzunluğunu ölçmek için niceliksel polimeraz zincir reaksiyonu kullanılarak uygulanan lökosit telomer uzunluğu testi yoluyla tam kandan ekstre edildi. Ortalama telomer uzunluğu kaydedildi ve bireysel değişkenliği kontrol etmek için iki ila üç deney yapıldı. Eşleştirme ve ücretsiz geri çağırma ile ilgili katılımcıların yürütücü bilişsel görevlerini değerlendirmek için DSST (Rakamsal Sembol Değiştirme Testi) kullanıldı. Bireyler, başlangıç değerlendirmesinde koroner arter hastalığı, konjestif kalp yetmezliği, kalp krizi veya inme teşhisi konması durumunda dışlanmıştır. Lökosit telomer uzunluğu, cinsiyete, ırk-etnisiteye, fiziksel aktivite durumuna, vücut kütle indeksine ve diğer kovaryantlara bağlı olmaksızın yüksek bilişsel performans ile ilişkilendirildi. Bu örneklemde lökosit telomer uzunluğu ve biliş arasında kuvvetli bir ilişki vardı; lökosit telomer uzunluğundaki her 1 T/S oran artışı için DSST'de 9,9 birim artış vardı (β = 9,9; %95 CI: 5,6–14,2; p<0,001). Bununla birlikte, bu ilişki tamamen yaşla eşleştirildi ve bu modele yaş ekledikten sonra, lökosit telomer uzunluğu artık DSST ile istatistiksel olarak anlamlı bir ilişki göstermedi (β = 2,7; %95 CI: -1,4–6,8; p=0,18). Yaşla eşleştirildiğinde, lökosit telomer uzunluğu ve bilişsel işlev arasında pozitif bir ilişki vardı.

Anahtar Kelimeler: Epidemiyoloji, sağlık indirimi, bağışıklık fonksiyonu, akıl sağlığı, fiziksel aktivite

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INTRODUCTION

The field of neuroscience is centralized on illuminating the mechanisms underlying the complex physiology of the human brain (Dikranian, 2015). Extending the knowledge of neural function allows for great strides to be made in the treatment and prevention of disease and for health promotion efforts to be grounded in clinical significance with respect to a variety of special populations. Comprised of billions of neurons, these avenues of cognitive connectivity are highly susceptible to attacks by free radicals, or by-products of oxidative metabolism (Entringer et al., 2011). An aggregation of damaging metabolites is antecedent to cognitive impairment (Keller et al., 2005), and neurodegeneration (Barnham, Masters, & Bush, 2004). Neurodegeneration may emerge when biological processes are upregulated. Specifically, telomeres, protein-bound complexes instrumental in DNA replication, naturally shorten during mitosis (Greider & Blackburn, 1989). This shortening is advantageous to human health, as it protects against unregulated cellular neoplasms. Therefore, telomere regulation is vital in the control of cell growth and turnover (Jacobs et al., 2011). If telomeres are subject to either uncontrolled mitosis, or the abrupt senescence of replication, age-associated development of disease and early-mortality may be accelerated (Entringer et al., 2011; Jaskelioff et al., 2011).

Telomeric biology has also been linked to adverse health outcomes during intrauterine development. Thus, telomere length may be compromised prior to birth, initiating a cascade of unfavorable health outcomes in adulthood (Entringer et al., 2011). The consequent negative impact of maternal stress during pregnancy may be translated to impact leukocyte telomere length (LTL) of newborns. A number of biological pathways are posited to exert this noteworthy influence on uterine LTL, including augmented cortisol concentrations (Choi, Fauce, & Effros, 2008) and proinflammatory cytokines, such as IL-6 (Carrero et al., 2008) which have been found to decrease telomerase activity. These biomarkers have also been implicated as risk factors for reduced quality of life (Lupien et al., 1999) as well as markers of diminished neuroplasticity and cognitive dysfunction in learning and memory domains (McAfoose & Baune, 2009).

Previous work has indicated increased telomerase activity following intensive meditation programs designed to counteract stress (Harris et al., 2006). Research has also shown that dietary modification, counseling, and stress management interventions may be useful in catalyzing the enzymatic reaction prompting telomerase to add length to existing telomeres (Ornish et al., 2008). Both aging and stress are characteristic predecessors of biological aging (Edwards & Loprinzi, 2017; Lopez-Otin, Blasco, Partridge, Serrano, & Kroemer, 2013). However, to our knowledge, research has yet to address the potential for LTL to influence cognition independent of the cellular aging process. Thus, the purpose of this study was to examine the potential for LTL to be utilized as biomarker for cognition, in addition to evaluating the plausibility for age to mediate this relationship.

METHODS

Study Design

Data from the 1999–2002 NHANES were used. NHANES is an ongoing survey conducted by the National Center for Health Statistics, a major section of the Centers for Disease Control and Prevention. NHANES evaluates a representative sample of non-institutionalized U. S. civilians, selected by a complex, multistage probability design. All procedures for data collection were approved by the National Center for Health Statistics ethics review board, and all participants provided written informed consent prior to data collection.

Participants

Participants were excluded if they had missing data on the study variables or if they self-reported having coronary artery disease, congestive heart failure, stroke or a heart attack. The analyzed sample included 1.722 older adults between 60 and 85 years.

Cognitive Function

The Digit Symbol Substitution Test (DSST) (Wechsler, 1958) was used to assess cognitive function among older adults 60+ years of age. The DSST, a component of the Wechsler Adult Intelligence Test and a test of visuospatial and motor speed-of-processing, has a considerable executive function component and is frequently used as a sensitive measure of frontal lobe executive functions (Parkin & Java, 1999; Vilkki & Holst, 1991). The DSST was used to assess participant cognitive function tasks of pairing (each digit from 1 to 9 has a symbol associated with it) and free recall (allowing participants to draw many figures in the limited time due to remembering pairs). Participants were

asked to draw as many symbols as possible that were paired with numbers within 2 min following the standard scoring method; one point is given for each correctly drawn and matched symbol, and one point is subtracted for each incorrectly drawn and matched symbol, with a maximum score of 133.

Leukocyte Telomere Length

Detailed methodology of the NHANES procedures for assessing LTL has been previously reported (Needham et al., 2013; Roig et al., 2016). Briefly, DNA was extracted from whole blood with the LTL assay performed using quantitative polymerase chain reaction to measure telomere length relative to standard reference DNA (T/S ratio) (Cawthon, 2002; Lin et al., 2010; Needham et al., 2013). Each sample was assessed at least twice, and among samples with a T/S ratio within 7% variability, the average value was used; a third assay was run for samples with a variability greater than 7%, and in this case, the average of the two closest T/S values was used.

Measurement of Covariates

Covariates included: age (continuous; yrs), gender, race-ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, other), measured body mass index (continuous; kg/m^2), C-reactive protein (continuous; mg/dL; marker of inflammation), self-reported smoking status (current, former, never), self-reported diabetes status (yes/no), measured mean arterial pressure (continuous; mmHg; average of 4 blood pressure measurements), self-reported physical activity (meeting guidelines vs. not; based on ≥2000 MET-min-month (Loprinzi & Kane, 2015)). Notably, when we added in other covariates such as education status, results were unchanged.

Analysis

All statistical analyses were computed in Stata (v.12) and accounted for the complex survey design employed in NHANES. Multivariable linear regression analyses were computed that examined the association between LTL and cognitive function (outcome variable). The first model included all the covariates with the exception of age followed by a subsequent model that added age into the model. This tiered approach was used to see if potential relationship between LTL and cognition was completely driven by age-induced effects. Statistical significance was set at an alpha of 0.05.

RESULTS

Table 1 displays the weighted characteristics of the study variables. Participants, on average, were 69.8 years, the mean DSST was 48.9, and the mean LTL was 0.91.

In a multivariable linear regression model adjusting for all covariates with the exception of age, there was a strong association between LTL and cognition; for every 1 T/S ratio increase in LTL, there was a corresponding 9.9-unit increase in the DSST (β = 9.9; 95% CI: 5.6–14.2; p<0.001). However, this association was completely mediated by age as after adding age into this model, LTL was no longer statistically significantly associated with DSST (β = 2.7; 95% CI: -1.4–6.8; p=0.18).

Results were similar when considering LTL as a binary variable dichotomized at the median level (1.02 T/S ratio). After adjusting for all covariates with the exception of age, those above the median LTL had a DSST score 3.9 units higher than those below the median LTL (β = 3.9; 95% CI: 1.61–6.32; p=0.002). However, after including age into this model the results were attenuated and no longer significant (β = 1.1; 95% CI: -1.08–3.36; p=0.30).

Results were similar when creating quartiles for LTL. After adjusting for all covariates with the exception of age, and compared to those in the lowest LTL quartile, those in the 2nd, 3rd, and 4th quartiles respectively, had a DSST score 2.7 (β = 2.7; 95% CI: 0.07–5.45; p=0.04), 3.8 (β = 3.8; 95% CI: 1.31–6.41; p=0.004), and 6.6 (β = 6.6; 95% CI: 3.34–10.04; p<0.001) units higher. When adding age into this model results were attenuated, and no longer significant; compared to those in the bottom quartile, those in the 2nd, 3rd, and 4th quartiles respectively had a DSST score 0.31 (β = 0.31; 95% CI: -2.30–2.94; p=0.80), 1.2

Table 1: Weighted characteristics of the analyzed sample (N=1,722)

Variable	*Point Estimate*	*SE*
DSST (mean)	48.9	0.6
Age (mean years)	69.8	0.3
Female (%)	57.7	
White (%)	83.8	
BMI (mean kg/m^2)	28.0	0.1
CRP (mean mg/dL)	0.49	0.02
MAP (mean mmHg)	93.3	0.5
Diabetes (%)	11.6	
Smoker (%)	11.6	
Active (%)	37.8	
Telomere length (mean T/S ratio)	0.91	0.01

(β = 1.2; 95% CI: -1.33–3.75; p=0.34), and 2.0 (β = 2.0; 95% CI: -1.37–5.37; p=0.23) units higher. Collectively, these findings suggest that LTL is not independently associated with cognition, but rather that age completely mediates the relationship between LTL and cognition.

DISCUSSION

A large body of evidence presents age as a highly associative hallmark of both LTL and cognition (Barnham et al., 2004; Edwards & Loprinzi, 2017; Entringer et al., 2011; Jaskelioff et al., 2011; Lopez-Otin et al., 2013); although stress and inflammation have also been suggested to play a impactful role on cellular telomerase reactivity (Carrero et al., 2008; Entringer et al., 2011; Epel et al., 2004) providing plausibility for LTL to manifest concomitantly, or even independently of human aging. Less investigated is the potential for LTL to exert age-independent effects on cognition which was the purpose of this study. The main finding of our study was that, among elderly individuals, longer LTL was associated with higher performance on a test of executive cognitive functioning; although after controlling for participant age, results were attenuated and no longer significantly associated with higher scores on the DSST.

This is a novel finding, as emerging work suggests that there might be a unique and compounded effect of diverse biomarkers on telomere length. Increased adiposity, sedentary behaviors, cardiovascular complications, inflammatory cytokines, and stress-associated influences on LTL have been observed (Dankel, Loenneke, & Loprinzi, 2016; Edwards & Loprinzi, 2017; Loprinzi, 2015a, 2015b; Loprinzi & Loenneke, 2016; Loprinzi, Loenneke, & Blackburn, 2015; Loprinzi & Sng, 2016; Lupien et al., 1999; McAfoose & Baune, 2009). If age is in fact a profound mediator, the associated implications of these negative health risks would place the older adult population in a position of extreme vulnerability to cognitive decline linked with LTL. In addition to the scientific importance of our study, the significance of our objective analysis of telomere length relative to standard reference DNA demonstrates that, for every 1 T/S ratio increase in LTL, there was a corresponding 9.9-unit increase in the DSST. This strong relationship was statistically significantly attenuated when age was computed in the model. Although LTL is a classic biomarker of aging, this investigation of LTL on cognition is a valuable addition to existing research, as past work has demonstrated LTL is associated with morbidity and mortality, even independent of age (Marioni et al., 2016). Although our findings fail to reinforce this postulation, it remains unclear whether LTL shortening plays a causal role in influencing mental health, morbidity and mortality, or whether LTL shortening is an adverse outcome which may be linked to poor health in elderly populations. Subsequent research should overcome the limitations of our cross-sectional study design by targeting elderly participants using longitudinal interventions which will address the ambiguity of reverse causation more comprehensively.

Our null age-independent association between LTL and cognition aligns with other work from The VA Normative Aging Study showing that, after controlling for age, LTL was not independently associated with cognitive function (Colicino et al., 2017). Notably, however, other work demonstrates that, after adjusting for age, lifestyle interventions may be more effective in enhancing cognitive function among those with shorter LTLs (Sindi et al., 2017). This underscores the importance of implementing lifestyle intervention especially to high-risk individuals.

In conclusion, this study highlights the independent association between LTL and cognition within the broader U. S. older adult population. Specifically, our findings demonstrated that extended telomere length was associated with higher cognition, but LTL was not independently associated with cognition after adjusting for age. We found that age may mediate the relationship between LTL and cognition.

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