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Title of Dissertation: Telomere Attrition and Age-related Cognitive Decline: Disparities by Poverty Status and Race

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# ABSTRACT

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| Title of Document: | TELOMERE ATTRITION AND AGE-RELATED COGNITIVE DECLINE: DISPARITIES BY POVERTY STATUS AND RACE |
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Telomere length (TL) is a marker of biological aging. However, evidence for relations between TL attrition and age-related cognitive decline is equivocal. Further, it is unknown whether historically disadvantaged sociodemographic groups (e.g., African Americans (AAs) and/or those living in poverty), are most vulnerable to cognitive decline associated with TL attrition. Therefore, the present study examined prospective interactive relations of TL change (ΔTL), poverty status, and race with age-related cognitive decline across multiple domains over five years. Participants were 323 urban-dwelling adults (baseline mean age = 48; 50.8% female; 52.0% AA; 50.2% below poverty) from the Healthy Aging in Neighborhoods of Diversity across the Life Span study. Cognitive tests included Digit Span Forward and Backward; California Verbal Learning Test-II (CVLT) total learning, short-delay free recall, and long-delay free recall subtests; Benton Visual Retention Test; Trail Making Test Parts A and B; and Animal Naming. TL was assayed from peripheral blood mononuclear cells using quantitative polymerase chain reaction. Linear mixed-effects models

examined prospective interactions of ΔTL, poverty status, race, and age (indexing time) with cognitive decline, adjusted for sex, high school-or-greater education, and baseline TL. Results revealed a significant four-way interaction of ΔTL×Poverty Status×Race×Age ($b$=-0.16, $p$=.023) such that greater TL attrition was associated with steeper decline in Digit Span Backward performance among Whites living in poverty and AAs living above poverty. Second, a significant three-way interaction of ΔTL×Race×Age ($b$=-0.15, $p$=.005) showed that greater TL attrition was associated with steeper decline in CVLT long-delay free recall performance among Whites. Third, a significant two-way interaction of ΔTL×Age ($b$ = 0.09, $p$ = .022) showed that, in the overall sample, greater TL attrition was associated with steeper decline in Animal Naming. Finally, sensitivity analyses showed that adjustment for hsCRP and the presence of cardiometabolic diseases (hypertension, diabetes mellitus, coronary artery disease, heart failure, myocardial infarction) did not cause attenuation of these effects. Findings suggest that associations between TL attrition and cognitive decline may be specific to working memory, delayed verbal memory, and verbal fluency, and vary by race and/or poverty status. Clarification of underlying mechanisms may ultimately support prevention and treatment of premature cognitive aging.

# TELOMERE ATTRITION AND AGE-RELATED COGNITIVE DECLINE: DISPARITIES BY POVERTY STATUS AND RACE

By

Daniel K. Leibel

Dissertation submitted to the Faculty of the Graduate School of the
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# Dedication

This work is dedicated to the memory of my father, John Karl Leibel, who was my greatest teacher. Thanks for encouraging me to keep my eyes on the prize. You show up in my life every day.

# Acknowledgments

My achievements to date are owed in large part to the tireless efforts of my family, friends, mentors, and colleagues who have supported me at every stage of my education. First and foremost, I would like to thank my wife, Kathleen Maltbie, for filling each day of my life with so much love. Thank you for the sacrifices you made to join me on this journey. I will always strive to do the same to support your pursuit of your dreams. Even after our many adventures together, I can promise you – this is just the beginning.

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# Table of Contents

# List of Tables

# List of Figures

In recent decades, telomere length (TL) has emerged as an important marker of human biological aging. Telomeres are DNA caps on the ends of eukaryotic chromosomes that shorten with advancing age in humans (Blackburn et al., 2015). TL shortening, also known as attrition, occurs in part as a consequence of mitosis (i.e., cellular division). As a result, telomeres experience progressive attrition over repeated cellular divisions throughout the lifespan of cells. Because of their crucial role in protecting the chromosomes, this gradual erosion of telomeres increases the risk of damage to genetic material. Cells with critically short telomeres cannot undergo further cellular divisions, in part, because the process could damage DNA. This state, known as replicative senescence (Campisi, 1997), leads to cellular dysfunction, and senescent cells may ultimately undergo apoptosis (i.e., programmed cell death). This overall decline in cellular health and functioning resulting from TL attrition is widely thought to contribute to primary biological aging.

Importantly, TL attrition and cellular aging more broadly have been linked to several age-related diseases and risk factors in humans, including systemic inflammation (Amsellem et al., 2011; Zhang et al., 2016), cardiovascular diseases (Haycock et al., 2014) and some cancers (Barthel et al., 2017), as well as all-cause mortality (Bakaysa et al., 2007; Mons et al., 2017). Researchers have also reported associations between TL and clinical and subclinical indicators of brain health (Forero et al., 2016; Valdes et al., 2010; Yaffe et al., 2011). In that regard, based on findings from human genetic studies, a potentially causal link between shortened TL and Alzheimer's disease (AD), the most prevalent cause of dementia, has been proposed (Zhan et al., 2015). Furthermore, TL has been linked to aspects of neurocognitive performance and decline among older adults without dementia (Valdes et al., 2010; Yaffe et al., 2011).

Despite recent advances in the area of TL and pre-dementia neurocognitive health, the literature lacks consensus, with some studies reporting null or counterintuitive results (e.g., Bendix et al., 2011; Liu et al., 2016). The equivocal evidence may result, at least in part, from methodological variability across studies. That is, studies in this area have been conducted in different populations, examined different cognitive domains and tests, and utilized different measures of TL. However, the prevention and management of cognitive decline and dementia are top public health priorities (Frankish & Horton, 2017), as is identifying potentially modifiable biological determinants of these conditions (Wright et al., 2009). Therefore, further clarification of whether and how TL attrition, a marker of cellular aging with far-reaching implications for health and longevity, is associated with cognitive decline is warranted.

In addition to the equivocal findings across studies, the available literature in the area of TL and cognitive functioning has several major limitations. First, most studies have used cross-sectional designs and have not examined prospective associations between concurrent TL attrition and age-related cognitive decline. This has greatly limited our understanding of how telomere compromise may contribute to cognitive aging. Second, many studies utilized measures of general cognitive ability or global cognitive status versus tests of distinct cognitive domains, which may mask important differences across domains of function. Third, to our knowledge, no previous studies have examined whether associations between TL attrition and cognitive decline vary as a function of poverty status (an indicator of socioeconomic status [SES]) and/or race, which are social identities implicated in neurocognitive health across the lifespan. Given that SES and self-identified race are social constructs that, via complex, multi-level mechanistic pathways, have robust negative associations with cognitive health and aging (Duncan & Magnuson, 2012; Glymour & Manly, 2008), it is possible that the association between TL

attrition and cognitive decline may be more pronounced among these groups. Finally, previous studies have not explored potential mediating effects of key medical risk factors with well-documented linkages to both TL and cognitive functioning, which greatly limits our knowledge of possible biological underpinnings. Clarification of these issues is necessary to further advance this area of research.

To address several of these limitations, the present study examined prospective associations between TL change and cognitive decline over approximately five years in a racially and socioeconomically diverse sample from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. This study expanded and improved upon the existing literature in several ways. First, instead of only examining baseline TL (as is the case in the majority of prospective studies; e.g., Devore et al., 2011; Yaffe et al., 2011) the present study concurrently examined TL attrition with cognitive decline. Second, given the importance of understanding trajectories of decline in different cognitive domains, this study examined prospective change in multiple domains of cognitive function including basic attention, psychomotor speed, verbal learning and memory, nonverbal immediate memory, and select subdomains of executive functioning (i.e., working memory, cognitive flexibility, and verbal fluency). Third, the present study examined whether associations between TL change and cognitive decline are more pronounced among members of marginalized groups, particularly African Americans living in poverty. Finally, sensitivity analyses were conducted to determine if significant findings attenuated with adjustment for potential biomedical mediators, namely a marker of global inflammation and the presence of one or more cardiometabolic diseases.

This dissertation first reviews the literature pertaining to TL attrition, cellular health, and aging. Next, there is an overview of the literature on relations of TL attrition to brain health,

including dementia, cognitive functioning, and cognitive decline, as well as poverty status and race as potential moderators of these associations. This is followed by a discussion of possible underlying biological mechanisms through which TL attrition may influence cognitive aging trajectories. After that, a summary of the problem, specific aims, hypotheses, methods, and data analytic procedures are introduced. Results are then presented and discussed, followed by strengths and limitations, future directions, implications, and conclusions.

## Literature Review

### *Telomere Length, Health, and Aging*

Telomeres are highly regulated regions at the ends of eukaryotic chromosomes that consist of a tract of tandemly repeated DNA (TTAGGG in vertebrates) and protective proteins (Blackburn et al., 2015). Telomeres protect genetic material through various mechanisms, such as preventing the ends of genomic DNA from being inappropriately recognized as damaged, thereby preventing DNA repair processes from inadvertently damaging the chromosomes. Telomeres also prevent the ends of chromosomes from inappropriately joining together, which causes genomic instability (Blackburn, 2001). Because DNA replication machinery cannot completely copy DNA sequences at the extreme ends of chromosomes, mitosis leads to gradual TL attrition over consecutive cellular divisions. When telomeres approach a critically short length, cells can no longer divide or replenish themselves (Campisi, 1997). Ultimately, this leads to replicative senescence and/or genomic instability, and may provoke apoptosis (Blackburn, 2001).

Importantly, an enzyme known as telomerase can partly compensate for attrition by adding telomeric sequences to chromosome ends (Blackburn et al., 2015). However, telomerase is unable to fully replenish telomere loss over time because its levels and/or activity are limited

in most somatic cells of adults. As a result, telomeres gradually shorten throughout the human lifespan until TL loss reaches a critical level, which has implications for health and aging.

TL attrition may have bidirectional associations with several age-related health endpoints. Findings from genetic studies in animals and humans demonstrate that shortened TL may potentiate age-related chronic diseases (Blackburn et al., 2015; von Zglinicki & Martin-Ruiz, 2005). In mice, experimentally deleting the RNA component responsible for promoting telomerase, an enzyme crucial for TL maintenance, has been shown to cause characteristic aging phenotypes after sufficient TL shortening occurs (H. W. Lee et al., 1998; Rudolph et al., 1999). This is particularly striking given that TL attrition is not thought to be the primary cause of senescence in mice under normal circumstances (Itahana et al., 2004).

In humans, the direct role of TL compromise in disease pathogenesis is perhaps best demonstrated by studies of individuals with inherited monogenetic disorders that influence TL maintenance. These single-gene inactivating mutations, also known as *inherited telomere syndromes*, are known in 11 human genes to date, and their impact on aging trajectories among individuals with these disorders is considerable (Blackburn et al., 2015). Because these mutations influence TL maintenance, individuals with inherited telomere syndromes experience earlier and more rapid TL attrition than their similarly aged counterparts without such mutations (Armanios & Blackburn, 2012; Savage & Bertuch, 2010). Consequently, humans with inherited telomere syndromes experience earlier onset of the diseases of aging, including cancer (Alter et al., 2009). People with telomere syndromes may also exhibit an earlier onset of other overt aging phenotypes, such as hair graying (Blackburn et al., 2015). Taken together, genetic studies in mice and humans suggest that shortened TL may potentiate age-related diseases.

Importantly, it is also well established that shortened TL may potentiate age-related diseases in humans without inherited telomere syndromes, at least in part via inflammatory mechanisms (Blackburn et al., 2015). However, as would be expected, disease onset is often later in the lifespan. In this body of literature, mean leukocyte TL (LTL) and peripheral blood mononuclear cell TL (PBMC TL) are considered particularly important biomarkers, as they are thought to reflect the overall health and functioning of circulating cells in the immune system and are implicated in the pathogenesis of many diseases (Blackburn et al., 2015). As a result, they are considered excellent models for overall cellular aging in humans and they are widely used to estimate the degree of cellular aging in immune cells and non-blood cells. Although LTL is more commonly utilized, PBMC TL, a subclass of LTL that was measured in the present study, is frequently used to estimate cellular aging in the literature (Lin et al., 2016).

Senescent immune cells with shortened TL are more likely to release pro-inflammatory cytokines, such interleukin-6 (IL-6; Rodier et al., 2009), which may hasten systemic inflammation and interfere with activities of cells in the body. Furthermore, increased inflammation resulting from shortened TL may promote diseases with inflammatory components (Blackburn et al., 2015). Indeed, individuals with shortened TL may have poorer immune functioning (Cohen et al., 2013), as well as higher prevalence of cancers (Barthel et al., 2017), diabetes (Zhao et al., 2013), and cardiovascular diseases (Haycock et al., 2014). Most notably, shortened TL is associated with all-cause mortality in humans (Bakaysa et al., 2007; Mons et al., 2017).

As noted previously, associations between TL attrition, age-related diseases, and associated risk factors are likely bidirectional. That is, while TL may potentiate several age-related diseases, such diseases may, in turn, further potentiate TL attrition via inflammation and

oxidative stress (Kordinas et al., 2016). In that regard, telomeres are especially vulnerable to pro-inflammatory cytokines and oxidative damage which promote TL shortening (Blackburn et al., 2015). However, as discussed, senescent cells with shortened TL also may release pro-inflammatory cytokines (e.g., IL-6; Rodier et al., 2009). In this way, shortened TL and increased inflammation and/or oxidative stress may continue to influence one another.

In summary, the literature indicates that TL attrition that occurs with aging may be involved in the pathogenesis of age-related diseases, perhaps through increased inflammation, although associations are highly complex and likely bidirectional. However, much less is known about the role of TL attrition in clinical and subclinical brain health outcomes such as dementia and age-related cognitive decline, factors of key importance to the functional status and well-being of older adults.

**Telomere Length and Brain Health.** Advancing age is the greatest risk factor for cognitive decline and dementia syndromes, such as AD (Corrada et al., 2010; Jorm & Jolley, 1998). Because the world's population is aging, the number of people living with these conditions has increased dramatically (Prince et al., 2015). The scope and severity of the problem is difficult to overstate. Nearly 50 million people currently have dementia globally, which is expected to increase to 132 million people by 2050, and nations vary widely in their level of preparedness (Prince et al., 2015). In addition to their economic and macro-level impact, cognitive impairment and dementia are among the leading causes of age-related disability and may negatively influence the wellbeing of patients and their caregivers (Frankish & Horton, 2017).

Unfortunately, research on efficacious treatments for dementia remains in its infancy. In the meantime, the prevention and management of dementia have been declared top public health

priorities (Frankish & Horton, 2017; Livingston et al., 2017). Identification of potentially modifiable biological risk factors for dementia will be important for future prevention and intervention efforts. TL, a marker of cellular health and an important factor in aging, may be a promising candidate.

***Telomere Length and Dementia.*** Cellular health and cognitive functioning both decline with advancing age, but it is unclear whether and how these two processes are related. A growing body of research has examined associations between TL and neurocognitive aging, although the evidence is equivocal. With regard to clinical brain health endpoints, several studies have found that healthy controls have longer TL than patients with dementia syndromes, particularly AD, and mild cognitive impairment (MCI; Grodstein et al., 2008; Hochstrasser et al., 2012; Kume et al., 2012; Liu et al., 2016; Panossian et al., 2003; von Zglinicki et al., 2000). Further, there is some evidence that longer duration of AD may be associated with shorter TL, particularly in women and APOE-e4 non-carriers (Liu et al., 2016). Regarding dementia subtypes, one study found that patients with vascular dementia had shorter TL than age-matched participants with AD (von Zglinicki et al., 2000). However, in contrast, other studies have found null associations between TL and the presence of dementia or MCI diagnoses, the etiology or severity of dementia, or prospective change in dementia diagnostic status (Martin-Ruiz et al., 2005; Zekry, Herrmann, Irminger-Finger, Ortolan, et al., 2010; Zekry, Herrmann, Irminger-Finger, Graf, et al., 2010). Furthermore, other studies have reported counterintuitive findings. For example, one study found that shorter TL predicted better performance on the Mini-Mental State Examination (MMSE), a global cognitive screening measure, among patients with AD (Liu et al., 2016).

A recent meta-analysis (Forero et al., 2016) that included 13 primary studies examined differences in TL between patients with AD ($n$ = 860) and healthy controls ($n$ = 2,022). Overall,

the meta-analysis found consistent evidence that patients with AD had significantly shorter TL than healthy controls. Several possible explanations were considered. Given the role of inflammation in AD, shortened TL may influence how neurons respond to inflammation and oxidative stress, which may contribute to AD pathogenesis. In addition, senescent microglial cells, which are found throughout the central nervous system and are involved in immune functions, might contribute to inflammation in the brain and ultimately to AD.

Notably, a recent human genetic study proposed a causal link between TL and AD (Zhan et al., 2015). Using data from two genome-wide association studies, Zhan and colleagues (2015) examined associations between AD and seven single-nucleotide polymorphisms (SNPs) previously shown to have strong associations with TL. Of note, several of these SNPs are implicated in the monogenetic human telomere syndromes previously described. Findings revealed that two of the SNPs (*TERT* and *OBFC1*), as well as participants' overall genetic risk (accounting for all SNPs in the study) were significantly associated with shorter TL and higher risk for AD. Furthermore, using Mendelian randomization (i.e., utilizing specific SNPs with well-known functions as instrumental variables), the study's findings strongly suggested that shorter TL was causally associated with increased risk for AD, although more research is necessary to support this conclusion.

In summary, several studies have suggested an association between TL and dementia, particularly AD, although findings are not entirely consistent across the literature. However, even relatively mild, subclinical cognitive decline in the absence of dementia can negatively alter individuals' daily activities and reduce their quality of life (Pusswald et al., 2015). Given the importance of primary prevention and early detection of dementia, it is important to investigate whether and how TL attrition relates to subclinical cognitive decline prior to dementia onset.

***Telomere Length and Subclinical Cognitive Decline.*** In addition to clinical brain health endpoints, several cross-sectional and prospective studies have examined associations between TL and subclinical (i.e., prior to the onset of dementia) neurocognitive functioning and decline. This is an important research development, given that the prevention of dementia requires identification of modifiable risk factors prior to older adulthood, and even non-pathological cognitive decline may negatively impact quality of life. However, findings across cross-sectional and prospective studies have varied considerably. First, several cross-sectional and prospective studies have reported significant, positive associations between TL and scores on screening measures of global cognitive status (Ma et al., 2013; Martin-Ruiz et al., 2006; Yaffe et al., 2011), such as the MMSE, while others have not (Bendix et al., 2011; Harris et al., 2006). Findings from studies examining the relation between TL and general cognitive ability (as indicated by a composite of neuropsychological test scores) have also been equivocal. Although several cross-sectional studies have found that longer TL was associated with greater cognitive ability in older women (Devore et al., 2011; Harris et al., 2012), two other studies reported null associations (Bendix et al., 2011; Harris et al., 2016).

Studies that examined associations between TL and specific domains of cognitive functioning have also produced mixed results. Studies have reported associations between shorter TL and worse performance on measures of memory (Ma et al., 2013; Valdes et al., 2010), verbal fluency (Harris et al., 2006; Ma et al., 2013), and working memory (Valdes et al., 2010). However, it is important to note that these studies often have conflicting results, with some reporting null associations in the above domains (e.g., for memory, Harris et al., 2006).

In one of the few prospective studies to examine these trends in middle-aged adults, greater TL attrition from younger to middle adulthood was associated with poorer general

cognitive functioning (as indicated by a composite of five neuropsychological tests) during midlife (Cohen-Manheim et al., 2016). With regard to specific domains of function, greater TL attrition predicted poorer information processing speed, memory, and visuospatial functioning at follow-up; similar associations were present, but less pronounced for attention and executive function domains. As such, it is possible that TL attrition is more strongly related to cognitive decline during middle adulthood (versus older adulthood), although this likely varies across domains of function and more research is needed to support this hypothesis.

A recent meta-analytic study examined associations between baseline TL and general cognitive ability and decline by compiling unpublished data from four prospective, epidemiologic investigations in Sweden and the United States (Zhan et al., 2018). Following adjustment for age and sex, the study found weak, cross-sectional associations of longer baseline TL with greater concurrent general cognitive ability (as indicated by a composite of several neuropsychological tests). However, this association attenuated following adjustment for educational attainment. Furthermore, the study found a null longitudinal association between baseline TL and decline in general cognitive ability over time. Although this meta-analytic study represents a development in the area of TL-cognition associations, it did not examine specific cognitive domains and lacked TL measurement at multiple time points.

Overall, methodological differences distinguishing studies reporting significant effects (versus those reporting null effects) are not easily identified. That is, although studies varied considerably in design, sample composition, telomere assay methods, and cognitive tests administered, few patterns emerged that adequately explain the variability in findings. However, among the studies reporting few to no significant effects, all utilized older (i.e., $\geq$ 70 years of age), European samples (Bendix et al., 2011; Harris et al., 2006, 2016). This may be related to

findings demonstrating that TL has less utility as a predictor of morbidity and mortality in the oldest old, perhaps due to a higher degree of TL instability in this age group (Martin-Ruiz et al., 2005), as well as potential healthy survivor effects. This provides further justification for examining associations of TL with cognitive health at earlier periods in the adult lifespan.

There is also a nascent but growing literature examining neuroanatomical correlates of TL, which may underlie TL-cognition associations. A recent population-based study found that shorter TL was associated with smaller global and regional brain volumes (King et al., 2014). These associations appeared in both cortical and subcortical brain regions, indicating that immune cell senescence could have widespread effects on brain health. Another study found that shorter TL is associated with smaller hippocampal volumes (E. G. Jacobs et al., 2014), an area of the brain important for learning and memory. Importantly, the neuropsychological literature provides ample evidence to suggest that smaller neuroanatomical volumes predict poorer neurocognitive functioning across a range of domains (e.g., Haier et al., 2004). Therefore, although not examined in the present study, TL may influence neurocognitive functioning through its association with reduced neuroanatomical volumes.

In summary, findings from the literature on TL and clinical and subclinical brain health are equivocal. Studies reporting significant associations between TL and cognitive functioning lack consensus regarding which specific domains are implicated. As in other brain and cognitive health literatures, it may be important to identify relevant vulnerability and resilience factors that moderate these associations. Sociodemographic factors, particularly SES and race, have previously been found to be important factors in cognitive functioning (Duncan & Magnuson, 2012; Glymour & Manly, 2008). However, as discussed further below, no studies have examined

whether cognitive correlates of shortened TL vary as a function of SES or race, which may help to clarify the equivocal findings.

***Poverty Status and Self-identified Race as Potential Moderators***

SES is a multidimensional construct with robust relations to health and aging. Lower SES is associated with poorer cognitive performance across the lifespan (Lyu & Burr, 2016) and across a broad range of cognitive domains, including memory, language, visuospatial functioning, and executive functioning (Brewster et al., 2014; Farah et al., 2006; Noble et al., 2007). SES-related cognitive disparities are profound and persistent, and are thought to involve complex biopsychosocial mechanisms. Specifically, individuals of lower SES experience disproportionate exposure to risk factors that may negatively impact neurocognitive health. For example, individuals of lower SES have higher rates of cardiovascular risk factors and diseases, chronic stressors, neighborhood deprivation, and exposure to environmental toxins than their higher-SES counterparts (Baum et al., 1999; Hackman et al., 2010; Winkleby et al., 1992), all of which may influence brain and cognitive health in their own right.

It is increasingly recognized that lower SES earlier in the lifespan may have downstream effects on cognitive ability and decline later in life. For example, early childhood disadvantage is associated with poorer cognitive functioning in older age, independent of other risk factors (Lyu & Burr, 2016). Conversely, several other studies have demonstrated that higher SES is associated with lower risk of dementia and slower age-related cognitive decline. In that regard, theories of *cognitive reserve* (for a review, Stern, 2012) posit that socioeconomic privilege (e.g., greater educational attainment) is associated with greater cognitive resilience in the presence of dementia-related brain pathology (e.g., amyloid-β in AD). The cognitive reserve concept has been applied to pathological states other than dementia, such as traumatic brain injury (Kesler et

al., 2003). Therefore, it is conceivable that similar resilience may be seen in the face of other conditions implicated in cognitive functioning and impairment. This includes the possibility that those of lower SES will have increased susceptibility to the cognitive sequelae of shortened TL.

SES may refer to several indicators (e.g., income, education, or occupation) that estimate an individual's relative economic and/or social position. In the present study, dichotomous poverty status (based on adjusted household income; see Measures) was utilized as the primary indicator of SES. Although SES may be more nuanced that a dichotomy based on household income alone, the HANDLS parent study (see Participants and Parent Study Procedure) based its initial area probability recruitment on a stratification of household income at 125% of the 2004 Federal poverty threshold level (Evans et al., 2010). The aim of the stratification was to recruit roughly equivalent numbers of participants with household incomes below and above this threshold so that low and moderate incomes were well represented. Moreover, several studies have demonstrated that living in poverty specifically (as determined by income and/or financial hardship) is associated with poorer cognitive test performance, even after adjustment for other SES indicators (Mani et al., 2013; Zeki Al Hazzouri et al., 2017). Furthermore, because many HANDLS participants could not accurately estimate their annual incomes, a continuous measure of income was not a viable option for the present study. HANDLS investigators could not assess additional indicators of SES such as wealth or occupational status given that many HANDLS participants were unable to estimate their overall wealth and/or were only employed sporadically. Finally, high school-or-greater educational attainment (dichotomized as $<$ or $\geq$ high school diploma/GED), another important indicator of SES, was included as an adjustment variable in all analyses, given its potent influence on cognitive functioning across the lifespan (Lenehan et al., 2015) and overlapping variance with poverty status. Of note, given the

multidimensional nature of the construct, there is no universally accepted measure of SES in epidemiologic or health research. Indeed, SES measurement varies considerably across studies according to several factors, such as feasibility of measurement, the social group of interest, and dependent variables being examined (Braveman et al., 2005).

As with SES, race is social construct that influences health across the lifespan through complex, multilevel pathways. Importantly, research developments over the past several decades have discredited the previously widespread biological conceptualization of race (Williams, 1997). The overwhelming scientific consensus is that racial classifications – historically based on poorly defined variations in ancestry and physical traits – do not reflect genetic or biological homogeneity. Rather, the concept of race emerged from social, cultural, and political forces that sought to classify individuals into groups, which have since been used to justify oppression against those regarded as inferior (Williams, 1997). Hence, although "race-as-biology" has no scientific merit, race as a social construct continues to have enormous individual- and societal-level implications.

Unfortunately, in the United States, African Americans and other racial minorities continue to experience racial inequality, injustice, and discrimination. These racial disparities have implications for health and longevity. Indeed, compared to Whites, African Americans have higher rates of most causes of morbidity and mortality in the United States (National Academies of Sciences, Engineering, 2017). With respect to neurocognitive health, the literature has demonstrated race-related disparities in cognitive test performance, such that African Americans have poorer cognitive test performance than Whites across multiple domains of function (Schwartz et al., 2004). African Americans also experience faster rates of cognitive decline in older age than their White counterparts (H. B. Lee et al., 2012). Although mechanisms

underlying these unfortunate differences are not fully understood, as with SES, race-related disparities in cognitive functioning are thought to be highly complex and several hypotheses have been proposed. According to Glymour and Manly (2008), African American-White disparities in cognitive functioning and decline likely result from complex mediational pathways involving disproportionate exposure to several risk factors, including lower socioeconomic position, geographic segregation, poorer material conditions, inadequate nutrition, and interpersonal discrimination. Importantly, research has demonstrated profound racial differences in these risk factors across the lifespan, beginning in early childhood (Glymour & Manly, 2008). Indeed, some studies have demonstrated that racial differences in aspects of cognitive functioning may be reduced, or even eliminated, after statistical adjustment for life experience variables (e.g., Brewster et al., 2014). However, it should be acknowledged that our understanding of the measurement issues and mechanisms underlying racial disparities in cognitive test performance remains limited.

Several studies have examined whether TL itself varies as a function of SES and race, but overall findings have been equivocal. Although some cross-sectional studies have shown that African Americans have longer TL than Whites (Aviv et al., 2009; Brown et al., 2017; Hunt et al., 2008; Lynch et al., 2016; Zhu et al., 2011), others have found that African Americans have shorter TL than their White counterparts (Diez Roux et al., 2009), and still others have found no racial differences in TL (Pantesco et al., 2018). Two prospective studies reported that African Americans experience steeper TL attrition over time compared to Whites (Aviv et al., 2009; Rewak et al., 2014), but more research is needed in this area. Likewise, although some studies have found SES-related disparities in TL (Needham et al., 2014; Theall et al., 2013), many others

report nonsignificant associations (Cherkas et al., 2006; Needham et al., 2013; Steptoe et al., 2011).

Despite the inconsistent evidence for sociodemographic disparities in TL, it remains possible that the relations of shorter TL to cognitive function may vary among socioeconomic and racial groups. Specifically, it is plausible that shortened TL will have more profound influence on the neurocognitive health of those of living in poverty and African Americans, especially given the plethora of other negative vulnerability factors already experienced by these groups. Importantly, epidemiologists have previously urged examination of interactive relations between SES and race in health disparities research (Williams et al., 2010). Indeed, previous studies have demonstrated the interactive nature of SES and race on a broad range of health outcomes, including brain health (Waldstein et al., 2017), suggesting that examination of main effects alone may be insufficient. Therefore, the present study aimed to examine whether the interaction of Poverty Status × Race moderated prospective associations between TL attrition and age-related cognitive decline.

***Potential Biomedical Mediating Factors***

As discussed, TL attrition is associated with age-related diseases and risk factors, among them systemic inflammation (Zhang et al., 2016) and cardiovascular and metabolic diseases (hereafter referred to as cardiometabolic diseases; Wang et al., 2016; Yeh & Wang, 2016). In addition, increased burden of these factors is known to negatively influence cognitive aging trajectories and may contribute to both vascular-related cognitive impairment and AD (Breteler et al., 1994; Knopman et al., 2001; Newman et al., 2005). It is plausible that TL influences cognitive functioning, at least in part, through its contributions to risk factors and diseases with known associations with cognitive aging. Therefore, the present study examined whether certain

factors attenuate significant associations between TL attrition and cognitive decline, namely (a) high sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation, and (b) the presence of one or more cardiometabolic diseases, namely hypertension, diabetes, coronary artery disease, heart failure, and myocardial infarction. Of note, cardiometabolic diseases was represented with a dichotomous variable indicating the absence (0) or presence (1) of one or more of these diseases. The variable was dichotomized because the literature suggests that cardiometabolic diseases often co-occur within persons and share overlapping risk factors (Cannon, 2007; Kendir et al., 2018; Robbins et al., 2005). These factors confer risk for age-related cognitive decline, and therefore were examined as candidate mediators in the present study. In that regard, these candidate mediators were added to models with significant interaction or main effects using hierarchical entry, such that hsCRP was entered first, followed by cardiometabolic diseases. The purpose of the sensitivity analyses was to examine whether controlling for hsCRP and/or cardiometabolic diseases leads previously significant effects to attenuate and become nonsignificant, which could indicate potential mediation (see Data Analytic Plan). Literature linking the candidate mediators with TL and cognitive functioning is described below.

**Inflammation.** Increased systemic inflammation and TL attrition are highly interrelated processes that occur with aging (Zhang et al., 2016). Specifically, the inflammatory marker that was used in this study, hsCRP, is a plasma protein involved in the systemic response to inflammation, such that its concentrations increase during inflammatory states (Black et al., 2004). Due to these factors, hsCRP has enjoyed widespread use as a marker of inflammation for both clinical and research purposes. Under normal conditions, inflammation is a protective immune response to injury, infection, or other somatic insults; however, chronic inflammation

can lead to tissue damage (Franceschi & Campisi, 2014). Previous studies have specifically linked several inflammatory markers, such as greater hsCRP and IL-6 concentrations, with shorter TL (Mazidi et al., 2018; Solorio et al., 2011), although there has been some inconsistency in the literature (O'Donovan et al., 2011). As discussed, at the cellular level, TL attrition eventually leads to replicative senescence and dysfunction. Cells undergoing senescence have been observed to produce and secrete proinflammatory cytokines, a process that likely serves important signaling and protective functions, but may also interfere with activities of other cells, thereby causing tissue damage over the long-term (Kordinas et al., 2016). This inflammatory response, while initially confined to local tissues, may develop into systemic, chronic inflammation, and ultimately contribute to chronic diseases with inflammatory components.

Converging evidence in the literature suggests that age-related increases in systemic inflammation may contribute to concurrent age-related neurocognitive decline. Although circulating proinflammatory cytokines serve key communicative functions between the immune and central nervous systems (CNS), over time increased inflammation (both peripheral and neuroinflammation) may adversely influence brain and cognitive health (Marsland, 2015). Indeed, neuroinflammation has also been linked to increased incidence of AD and other dementias (Heneka et al., 2015). Furthermore, in adults without dementia, findings from human studies have shown inverse associations between concentrations of systemic inflammatory markers (e.g., IL-6) and cognitive test performance, particularly on measures of learning and memory, working memory, and executive functioning (Marsland, 2015). These associations may be explained, at least in part, by reductions in gray matter volumes in the hippocampus and prefrontal cortex, which have also been observed with higher levels of systemic inflammation (Marsland et al., 2008). Finally, it is well documented that systemic inflammation is associated

with age-related cardiometabolic diseases and risk factors that also have inverse associations with cognitive functioning (Haffner, 2006).

In brief, the literature suggests that shortened TL is associated with systemic inflammation, which in turn is associated with clinical and subclinical brain health outcomes. However, to our knowledge, previous research has not examined whether inflammatory markers mediate associations between TL attrition and age-related cognitive decline. Therefore, a marker of systemic inflammation, hsCRP, was examined as a candidate mediator in the present study.

**Cardiometabolic Diseases.** As with systemic inflammation, risk for cardiometabolic diseases (e.g., hypertension, coronary artery disease, heart failure, and diabetes) increases with advancing age (Jousilahti et al., 1999). These diseases are among the leading causes of morbidity and mortality in the United States (Centers for Disease Control and Prevention, 2017). Of note, these diseases often co-occur, suggesting a shared underlying pathophysiology (Kendir et al., 2018; Robbins et al., 2005). For example, the literature indicates that particular behavioral and lifestyle risk factors, such a tobacco smoking, unhealthy diet, and low physical activity, may increase risk for several cardiometabolic diseases (Cannon, 2007). Furthermore, a growing literature suggests an association between shortened TL and all of these disorders (for reviews, see Tellechea & Pirola, 2017; Wang et al., 2016; Yeh & Wang, 2016). Although associations are likely bidirectional, shortened TL may contribute to development of cardiometabolic diseases through cellular senescence and dysfunction. For example, the literature suggests that shortened TL may lead to senescence in endothelial cells, vascular smooth muscle cells, and myocytes, which may in turn contribute to the development of atherosclerosis, hypertension, and heart failure (Yeh & Wang, 2016). Similarly, shortened TL may be associated with premature senescence of β-cells in the pancreas, which secrete insulin, thereby contributing to glucose

intolerance that is a characteristic symptom of diabetes (Elks & Scott, 2014). Finally, increased inflammation, which as discussed may be a consequence of immune cell senescence, is implicated in cardiometabolic disease pathogenesis (Haffner, 2006), further suggesting a link between TL and such diseases.

Cardiometabolic diseases are also risk factors for clinical and subclinical brain disorders. Indeed, it is well-documented that these diseases are associated with substantially elevated risk for ischemic and hemorrhagic stroke, vascular dementia, and AD (Gorelick et al., 2011). Furthermore, prior to onset of clinical brain disorders, cardiometabolic diseases and associated risk factors are associated with more subtle, but still significant, neurocognitive deficits. Although executive functioning is the cognitive domain most frequently linked to vascular diseases and risk factors in the literature (e.g., Falkowski et al., 2014), deficits in multiple cognitive domains have been observed. For example, in addition to executive functioning, cardiometabolic diseases are also associated with lower test performance in the domains of learning and memory, attention, and psychomotor speed (Waldstein & Wendell, 2010).

In summary, previous studies suggest that TL attrition may contribute to cardiometabolic diseases, which are among the leading risk factors for stroke, dementia, and subclinical cognitive decline. Therefore, it is plausible that cardiometabolic diseases mediate prospective relations of TL attrition and age-related cognitive decline, although to our knowledge previous researchers have not explored this question. As such, the present study examined the potential mediating effect of cardiometabolic diseases.

**Alternative Mechanisms.** The present study conceptualized TL attrition as a primary determinant of cognitive aging, due to previous literature demonstrating its contributions to biological aging and age-related diseases that may influence cognitive functioning. Furthermore,

as described, this study conceptualized its sensitivity variables as candidate mediators. However, it is important to note that TL attrition may be related to cognitive decline via alternative pathways than those proposed. First, as discussed, associations between TL attrition and inflammation and/or cardiometabolic diseases may be bidirectional. Therefore, if the present study's findings suggested significant interrelations among TL, inflammation, and cardiometabolic diseases and cognitive decline, future research would be necessary to clarify the nature and directionality of these associations. Second, previous literature has shown that TL attrition may interact with other primary risk factors to influence disease expression, progression, and outcomes. That is, in some cases, TL attrition may act as a moderator, rather than the primary cause, of disease and aging trajectories (Blackburn et al., 2015). Hence, it is possible that shortened TL moderates associations between other primary risk factors (e.g., cardiometabolic disease) for cognitive aging. Finally, it remains possible that TL attrition and cognitive decline each reflect a biological aging process dictated by other factors, thereby reflecting a shared, but not causally linked, pathophysiology. For example, oxidative stress, which increases with advancing age, could plausibly contribute to TL attrition and age-related cognitive decline. With consideration of these alternative mechanisms, the present study's hypotheses considered (a) TL attrition as a potential determinant of cognitive decline, and (b) inflammation and cardiometabolic diseases as potential mediators of this association, based on previous literature suggesting these patterns are biologically plausible.

***Covariate Rationale***

In the present study, biological sex, high school-or-greater educational attainment, and baseline TL were included as covariates in all analyses, given their potential confounding effects with TL and cognitive test performance. Regarding TL, overall the literature suggests that

women have longer TL than men, but such differences are not universal across studies (for a meta-analytic review, see Gardner et al., 2014). With regard to cognitive functioning, on average, women tend to outperform men on tests of episodic memory and verbal abilities, whereas men tend to outperform women on tests of visuospatial abilities (Herlitz et al., 1997; Hyde & Linn, 1988; Voyer et al., 1995). Furthermore, sex differences in these domains of function remain stable with increased age (de Frias et al., 2006). However, it should be noted that meta-analyses have revealed that such differences, while statistically significant, are small in magnitude (Hyde, 1981). In light of previous research, biological sex was included as a covariate in all present analyses.

Recent cross-sectional studies have also demonstrated that greater educational attainment is associated with longer TL (Adler et al., 2013; Steptoe et al., 2011; Surtees et al., 2012). Furthermore, educational attainment is one of the strongest correlates to cognitive test performance across the lifespan (Lenehan et al., 2015). Greater educational attainment has also been linked to lower incidence of dementia among older adults (Stern et al., 1994). As such, it is critical to adjust for education effects in all studies utilizing cognitive test outcomes. In light of these findings, the present study included high school-or-greater educational attainment as a covariate in all analyses.

Finally, previous research has also shown that rates of TL attrition are associated with baseline TL. Specifically, longer baseline TL is typically associated with greater TL attrition over time (Aviv et al., 2009; Nordfjäll et al., 2009), although this association is reduced considerably after statistical adjustment for regression to the mean (Verhulst et al., 2013). Given these prior findings, all analyses in the present study adjusted for baseline TL (i.e., TL at wave 1).

## Present Study

### *Statement of the Problem*

The prevention and management of age-related cognitive impairment and dementia are top public health priorities (Frankish & Horton, 2017). Indeed, cognitive impairment and dementia are increasing in prevalence worldwide (Prince et al., 2015), and are among the leading causes of disability and reduced quality of life in older adults (Frankish & Horton, 2017). In order to prevent the onset of clinical-level cognitive impairment, it is imperative to identify potentially modifiable risk factors and biomarkers for subclinical age-related cognitive decline (Wright et al., 2009).

TL, an important biomarker of human aging, may be a promising candidate. A growing literature indicates that TL may be associated with clinical and subclinical neurocognitive aging. Several studies have demonstrated that shortened TL is associated with risk for dementia, particularly AD, and genetic studies are highly suggestive of a causal association. Importantly, in individuals without dementia, TL attrition has also been associated with poorer performance on measures of general cognitive ability and across multiple domains of cognitive function. However, as discussed, findings are equivocal overall, with other studies reporting null or even counterintuitive results.

Furthermore, the existing literature on TL and cognitive functioning has several limitations. First, the vast majority of studies utilized cross-sectional designs, and most prospective studies did not examine both TL and cognitive functioning at more than one time point. Indeed, to our knowledge, only one previous study (Harris et al., 2016) has examined concurrent change in TL with change in cognitive test performance in a European sample of older adults (≥ 70 years). As such, no previous studies have examined concurrent TL attrition

and cognitive decline during midlife in a racially and socioeconomically diverse sample. Second, many previous studies utilized brief global cognitive status and/or dementia screening measures, such as the MMSE, or examined a composite score from tests of multiple cognitive domains to estimate general cognitive ability. Although it is important to examine global measures of cognitive functioning, TL and/or attrition may not be associated with all cognitive domains equally. As a result, examining only global cognitive estimates may mask domain-specific cognitive changes. Third, the vast majority of research in this area has focused on samples of older adults, and less is known about associations between TL and cognitive functioning at earlier periods in the lifespan. This is problematic in light of the importance of early detection in the prevention of age-related diseases, as well as evidence that TL is highly unstable among older adults, possibly reducing its predictive utility (Martin-Ruiz et al., 2005). Fourth, although some studies in this area have adjusted for related medical comorbidities, to our knowledge, none have measured their potential mediating effects through individual entry in sensitivity analyses. Finally, researchers have yet to examine whether associations between TL and cognitive functioning vary by SES and race, which have robust associations with cognitive test performance.

### *Study Objectives*

The objective of this study was to examine prospective interactive relations of TL attrition, poverty status, and race with age-related cognitive decline over a period of approximately five years. Furthermore, the study aimed to address several of the limitations described previously by (a) examining concurrent changes in TL attrition and cognitive test performance, (b) utilizing an extensive battery of neurocognitive tests examining multiple domains of function, (c) ascertaining potential mediating effects of systemic inflammation and

cardiometabolic diseases through sensitivity analyses, (d) utilizing a racially and socioeconomically diverse sample of middle-aged to young-old adults, and (e) directly testing moderating effects of poverty status and race, which are social identities associated with cognitive functioning and exposure to risk factors for poor cognitive health. With regard to the latter point, the present study hypothesized that Africans Americans living in poverty would be most vulnerable to the cognitive sequelae of TL attrition, given the potential for synergistic influences of racial and socioeconomic disadvantage.

### *Specific Aims and Hypotheses*

The following specific aims and hypotheses were previously proposed:

**Aim 1.** Examine potential interactive relations of TL change, poverty status, race, and age (indexing time) with decline in cognitive test performance over approximately five years and across multiple domains of function.

***Hypothesis 1*.** TL change, poverty status, and race will interact with age (indexing time) to significantly predict decline in cognitive test performance across multiple domains (i.e., a significant four-way interaction of TL Change × Poverty Status × Race × Age). Specifically, following adjustment for sex, high school-or-greater educational attainment, and baseline TL, greater TL attrition will be associated with the most pronounced age-related cognitive decline among African Americans living in poverty.

**Aim 2.** Examine potential mediating effects of a marker of systemic inflammation (hsCRP) and/or the presence of one or more cardiometabolic diseases (hypertension, diabetes mellitus, coronary artery disease, myocardial infarction, and/or heart failure) on the interaction of TL Change × Poverty Status × Race × Age with decline in cognitive

test performance over approximately five years. This aim was achieved through sensitivity analyses using hierarchical entry.

***Hypothesis 2*.** The significant interaction of TL Change × Poverty Status × Race × Age with decline in cognitive test performance over approximately five years will become nonsignificant following further adjustment for hsCRP and cardiometabolic diseases.

**Exploratory Aims.** The present study utilized a model deconstruction approach to data analysis. That is, significant, higher-order interactions were retained as nonsignificant interactions were removed from the linear mixed-effects regression models in a stepwise fashion (see Data Analytic Plan). Therefore, Hypothesis 1 specifically focused on the highest-order interaction term being tested (i.e., the four-way interaction of TL Change × Poverty Status × Race × Age), but if this interaction was nonsignificant, exploratory analyses aimed to examine all lower-order interactions and main effects nested beneath it, until the highest-order effect(s) for each cognitive outcome were identified. These effects were then probed and interpreted, and sensitivity analyses (analogous to those outlined in Aim 2) were then run to examine the potential mediating effects of hsCRP and cardiometabolic diseases.

## Methods

### Participants and Parent Study Procedure

All participants were enrolled in the Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS) study, a longitudinal, epidemiologic investigation (for more information about the design and implementation of HANDLS, see Evans et al., 2010). Briefly, HANDLS is an ongoing longitudinal study of health disparities attributable to race and SES.

Participants are a fixed cohort of urban-dwelling adults who were recruited from one of 13 neighborhoods in the city of Baltimore, Maryland. Neighborhoods were pre-selected for their probability of yielding equal proportions of individuals who were African American and White, men and women, and with adjusted household incomes above and below 125% of the 2004 federal poverty level. All HANDLS participants self-identified their race as either African American or White and were 30–64 years old at baseline. Participants are assessed approximately every four to five years for various psychological, cognitive, and physiological factors. The present study utilized data from HANDLS baseline (Wave 1; occurred 2004–2009) and the first follow-up period with complete data collection, approximately five years later (Wave 3; occurred 2009–2013).

After initial selection, potential participants were excluded from HANDLS if they met any of the following criteria at baseline: (1) outside of the age range of 30–64 years, (2) currently pregnant, (3) within six months of active cancer treatment (i.e., chemotherapy, radiation, or biological treatments), (4) diagnosed with AIDS, (5) unable to provide informed consent, (6) unable to provide data for at least five measures, and (7) unable to provide valid government-issued identification or were currently without a verifiable address. There were two phases of data collection at HANDLS baseline. Phase 1 occurred within participants' homes and consisted of recruitment, written informed consent, and an interview and survey. Phase 2 occurred on mobile medical research vehicles (MRVs) parked within participants' neighborhoods, and consisted of a medical history assessment, physical examination, and other psychological, physiological, and neurocognitive assessments. Altogether, 3,720 participants met criteria for the HANDLS study, of whom 2,707 (57.7% African American, 42.3% White) completed both phases of data collection. Of those participants, all but 39 consented to genetic analyses. African

Americans (versus Whites) were significantly more likely to consent to genetic analyses (OR = 2.6, $p < .05$), whereas age, sex, and poverty status were not associated with likelihood of consenting to genetic testing. Subsequently, 360 participants with DNA in the biorepository from Waves 1 and 3 of HANDLS were randomly selected for telomere assays from a cross of race, sex, and baseline age (median-split).

Participants were excluded from the present analyses if they self-reported a history of AD or other form of dementia, brain cancer, stroke, multiple sclerosis, Parkinson's disease, or epilepsy at either measurement wave ($n = 24$). Participants were also excluded if they were missing data for any relevant predictor variables (i.e., TL, race, poverty status, age, sex, high school-or-greater educational attainment, hsCRP, or cardiometabolic diseases) and/or at least one cognitive test at a given wave. If participants had complete data at only one wave, their data for that wave was included in the analysis. After exclusion criteria were applied, the present study's sample consisted of 323 participants (see Results and Table 1 for sample characteristics) with data for TL, all relevant sociodemographic variables (i.e., age, sex, race, poverty status, and high school-or-greater educational attainment), sensitivity variables, and at least one cognitive test at baseline and/or follow-up. Analysis-specific sample sizes varied slightly due to unequal missing data across all cognitive tests (see *N*'s in Tables 3-14). Sample sizes for the sensitivity analyses also varied slightly due to missing data on the sensitivity variables.

## Measures

### *Predictor Variables*

**Telomere Length Assay.** TL was measured at both time points in PBMCs via quantitative polymerase chain reaction (qPCR), as was previously described (see Cawthon, 2002). Briefly, 10 ng of DNA isolated from PBMCs was used in each PCR reaction, and

triplicate reactions were performed per sample. From each triplicate set, the average cycle threshold (Ct) values of T and S were calculated to generate the average T/S ratio value. TL from 130 samples was measured by both qPCR and the Southern method and the resulting conversion equation was used to calculate TL in kb from the T/S ratio value. TL change over five years was determined by calculating the difference between TL values at both measurement waves.

**Sociodemographic Moderators.** At the time of recruitment, participants reported their age, self-identified race (coded as 0 = White, 1 = African American), and annual household income. Poverty status was assessed via participants' household income (adjusted for household size) and was then dichotomized using the 2004 Federal poverty threshold level (e.g., $18,850 per year for a family of four; see Evans et al., 2010). Participants with adjusted household incomes ≥ 125% of the poverty threshold were classified as *living above poverty* (coded as 0). In contrast, those with adjusted household incomes < 125% of the poverty threshold were classified as *living in poverty* (coded as 1).

**Covariate Measures.** Participants reported their biological sex (coded as 0 = female, 1 = male) and educational attainment at the time of recruitment, and these variables were included as covariates in all analyses. Education level was dichotomized into high school-or-greater educational attainment (coded as 0 = high school diploma/GED or greater, 1 = less than high school diploma/GED). Baseline TL was also included as a covariate measure in all analyses.

**Sensitivity Variables.** As described previously, the present study examined whether adding two candidate mediators, namely hsCRP (a marker of systemic inflammation) and the presence of one of more cardiometabolic diseases (hypertension, diabetes mellitus, coronary artery disease, myocardial infarction, and/or heart failure), into the models attenuated significant associations between TL attrition and cognitive decline. First, hsCRP measured systemic

inflammation in the present study. Blood testing was conducted during the physical examination on the MRVs. Following an overnight fast, blood samples were obtained from an antecubital vein. hsCRP levels were measured from these blood samples by immunoassay at the National Institute on Aging or Quest Diagnostics (Chantilly, VA; http://www.questdiagnostics.com) using similar procedures and equipment.

Second, a dichotomous variable was used to indicate whether participants had a history of one or more cardiometabolic diseases (coded as 0 = none, 1 = one or more diseases), namely hypertension, diabetes mellitus, coronary artery disease, myocardial infarction, and/or heart failure. These data were collected during the physical examination and medical history interview on the MRVs. Participants were diagnosed with hypertension if they (a) self-reported diagnosed hypertension, (b) self-reported use of antihypertensive medications (diuretics, blockers, angiotensin inhibitors, and/or vasodilators), and/or (c) had resting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Next, participants were diagnosed with diabetes if they (a) self-reported a previous diagnosis of diabetes, (b) self-reported use of diabetes medications, and/or (c) had blood glucose ≥ 126 mg/DL (7 mmol/liter). Finally, during the medical history interviews, participants self-reported historical and/or current diagnoses of coronary artery disease, myocardial infarction, and heart failure.

***Cognitive Test Outcome Variables***

Participants completed a neurocognitive test battery at both measurement waves on the MRVs. Cognitive tests were used in the present study to estimate the domains of basic attention, psychomotor speed, verbal learning and memory, nonverbal immediate memory, and select domains of executive functioning (i.e., working memory, cognitive flexibility, and verbal

fluency). In total, nine outcome measures were examined. Test scores were used as outcome variables and are described in detail below.

**Attention and Working Memory.**

***Digit Span Forward and Backward.*** Digit Span Forward and Backward are subtests from the Wechsler Adult Intelligence Scale-Revised (for the manual, see Wechsler, 1981). For DSF, participants listened to a span of numbers read aloud by the examiner, beginning with three digits, and were asked to repeat the numbers back in the same order immediately. After two trials of a specific span length, the span increased by one digit, and continued to increase through nine digits. The test ended when participants could not successfully complete two trials of the same span length. Digit Span Backward was administered similarly, except participants were instructed to repeat the span of digits aloud in reverse order. In addition, Digit Span Backward started with two-digit spans and continued through eight digits. In the present study, total scores from Digit Span Forward were used to measure basic auditory attention. Total scores from Digit Span Backward were used to measure working memory as a subdomain of executive functioning.

Digit Span Forward and Backward both require auditory attention and short-term retention capacity, but otherwise require different mental activities (Lezak et al., 2012). Indeed, Digit Span Forward is primarily a test of attention, whereas Digit Span Backward is a purer test of working memory and is more sensitive to brain damage and neurological disorders (Lezak et al., 2012). Digit span tests have strong test-retest reliability (Matarazzo & Herman, 1984; Snow et al., 1989) and internal consistency (Strauss et al., 2006).

**Learning and Memory.**

***California Verbal Learning Test-II.*** The California Verbal Learning Test-II (CVLT) is a multi-trial word list learning task and a commonly administered measure of verbal learning and memory (Lezak et al., 2012). The HANDLS protocol was adapted from the original manual administration (for the manual, see Delis et al., 2000). Administration began with three trials (versus five trials in standard administration) of a 16-word list (List A), during which participants were instructed to learn the list and immediately recall the words. Correct responses across the three learning trials for List A were summed to measure participants' verbal learning ability (hereafter referred to as CVLT total learning). After the initial three trials for List A, another word list (List B) was administered once for the purpose of interference. Participants were asked to recall as many words from List B as possible. Immediately following the recall of List B, participants were again asked to recall as many words from List A as possible, which represented their CVLT short-delay free recall score. Participants were then given four category cues (i.e., categories that match words from List A), and asked to recall as many words from List A that fit into each category as they could. Later, after a 20- to 25-minute delay during which other cognitive tests were administered, participants were asked to recall as many words from List A as they could, which represented their CVLT long delay free recall score.

All components of the CVLT have been shown to have high internal consistency ($\alpha$ = .82; Strauss et al., 2006) and test-retest reliability ($r$ = .76 over one year; Paolo et al., 1997). Results of factor analyses have revealed that the 19 scores available from standard administration of the CVLT load onto six factors, namely general verbal learning, response discrimination, primacy-recency effects, organization strategies, recall efficiency, and acquisition rate (Strauss et al., 2006). In the present study, CVLT total learning, short delay free recall, and long delay free

recall scores were used as outcome measures of verbal learning, short-term verbal memory, and delayed verbal memory, respectively.

***Benton Visual Retention Test.*** The Benton Visual Retention Test (BVRT) is a widely used test of visual perception, visual constructive abilities, and visual memory (Sivan, 1992). Participants were presented with ten designs, one at a time, for five seconds. The first two designs contained one geometric shape, whereas the latter eight designs contained two larger figures and one smaller figure. After the five-second presentation, the designs were withdrawn, and the participants were then instructed to draw them from memory. Figures were scored according to the manual instructions, and two examiners independently scored the figures to ensure interrater agreement. Errors in the drawings were coded as omissions, distortions, perseverations, rotations, misplacements, and incorrect size. In the present study, total number of errors across the ten figures was used to measure nonverbal immediate memory.

Previous studies of the BVRT have reported high internal consistency ($\alpha$ = .71–.82; Strauss et al., 2006). Interrater reliability of the BVRT was found to be very high in two large-scale epidemiologic studies ($r$ = .96 for total correct, $r$ = .97 for error codes; Swan et al., 1990). The BVRT has been shown to differentiate acute stroke patients from healthy controls (Messinis et al., 2009). Greater age and lower educational attainment are associated with poorer BVRT performance (Youngjohn et al., 1993). Finally, a factor analysis of several cognitive tests found that the BVRT loaded most heavily on a visuospatial factor (.55), as well as memory (.45) and concentration (.42) factors (Larrabee et al., 1985).

**Psychomotor Speed and Cognitive Flexibility.**

***Trail Making Test Parts A and B.*** The Trail Making Test was originally included within the Army Individual Test Battery in 1944 and has since been adapted as a standalone test of

divided attention, speed, and mental flexibility (Strauss et al., 2006). The Trail Making Test consists of two sections: (1) Part A, a measure of psychomotor speed and visual scanning, and (2) Part B, a measure of cognitive flexibility through set-shifting. Standard test administration procedures were followed. Participants first completed the Trail Making Test Part A practice sample, which consisted of a page of circles that each contained a number. The examiner instructed participants to begin at number 1, then continue onto number 2, and continue in order until they reached the end at number 8. Participants then completed the Trail Making Test Part A test, which follows the same instructions as the sample and continues on through number 25. If participants made an error, the examiner instructed them to return to the last circle and correct the error. Time to completion, in seconds, and the number of errors made during the task were recorded. In the present study, the time to completion of Trail Making Test Part A was used to measure psychomotor speed.

Administration of the Trail Making Test Part B followed similar procedures, with administration of a sample followed by the actual test. However, the circles on the Trail Making Test Part B contained either a number or a letter. The Trail Making Test Part B test consisted on 25 circles (numbers 1–13 and letters A–L) and continued through number 13. The examiner instructed participants to begin at number 1 and draw a line to letter A, then continue onto number 2, and continue alternating numbers and letters (1 to A, A to 2, 2 to B, etc.). As with the Part A, if participants made an error on Part B they were instructed to return to the last circle and correct the error. Time to completion, in seconds, and the number of errors made during the task were recorded. In the present study, the time to completion of Trail Making Test Part B in seconds was used to measure cognitive flexibility as a subdomain of executive functioning.

The Trail Making Test Parts A and B are commonly administered by neuropsychologists in research and practice (Strauss et al., 2006). Age accounts for approximately 34% and 38% of the variance on the Trail Making Test Parts A and B, respectively, such that older adults perform more slowly and produce more errors than their younger counterparts (Tombaugh, 2004). Greater educational attainment is also associated with faster performance on the Trail Making Test Parts A and B, with no reported gender effects (Tombaugh, 2004). The Trail Making Test Parts A and B are moderately correlated, suggesting that they measure similar, but distinct, functions (Corrigan & Hinkeldey, 1987). Test-retest reliability is low to moderate for the Trail Making Test Part A, but adequate for the Trail Making Test Part B, whereas alternate form reliability is high for both measures (Strauss et al., 2006). The Trail Making Test Part B is sensitive to cognitive flexibility, as compared to perseverative errors on the Wisconsin Card Sorting Test (Kortte et al., 2002). The Trail Making Test Part B scores also correlate to other tests of set shifting, attention, and processing speed (Strauss et al., 2006).

**Verbal Fluency.**

***Animal Naming.*** Participants completed a verbal fluency test in which they were instructed to name as many animals as they could within one minute. Perseverations and errors were not counted in the total score.

In the present study, the total score on this task was the sum of all admissible words (i.e., accurate names of animals), and was used to measure verbal fluency as a subdomain of executive functioning.

Verbal fluency tasks are frequently administered to measure executive functioning, but also correlate highly with semantic memory (Strauss et al., 2006). Poorer verbal fluency performance is associated with greater age and lesser education (Tombaugh et al., 1999). Racial

disparities in sematic fluency performance are thought to partially reflect differences in quality of education, which may vary according to geographic region (Fillenbaum et al., 2001). Semantic verbal fluency tests show high internal consistency and test-retest reliability (Strauss et al., 2006).

## Data Analysis

### *Power Estimate*

There is not a universally accepted method for accurately predicting statistical power for linear mixed-effects models, in part due to the complexities and variations of such designs. However, power analyses for multiple linear regression (as conducted herein, see below) may be presumed to underestimate the actual likelihood of rejecting a false null hypothesis in prospective studies, given that increasing the number of data points relevant to sample size is associated with enhanced statistical power. Therefore, a power analysis was run using the multiple linear regression formula within the G*Power software (version 3.1; for more information, see Faul et al., 2007). Based on a sample size of 323 participants (i.e., those who met inclusion criteria at waves 1 and/or 3; see Participants and Parent Study Procedure), the power analysis revealed that a model with 19 predictors (i.e., all two-, three-, and four-way interactions, main effects, sensitivity variables, and covariates) at conventional levels of $\alpha$ (.05) was adequately powered (1 - $\beta$ = .80) to detect a small $f^2$ effect size of .02. This demonstrated adequate power to detect small (or larger) effects in this study. As described, analysis-specific sample sizes varied due to unequal missing data across the cognitive tests. However, further analysis revealed that the range of sample sizes caused little to no change in the power estimate.

### *Data Analytic Plan*

**Preliminary Analyses.** Prior to any analyses, descriptive statistics among all outcome variables were requested. All variables were evaluated for normality, skewness, outliers, and multicollinearity. Variable distributions were visualized through histograms and Q-Q plots. Logarithmic transformations were conducted to normalize skewed distributions of any outcome variables. After all variables were examined for normality, preliminary correlation tables were generated to examine zero-order correlations among all predictors, sensitivity variables, covariates, and outcomes. All preliminary analyses were run with the Statistical Package for the Social Sciences (SPPS; version 25) and R (version 3.6.1; R Core Team, 2019).

**Linear Mixed-Effects Regression Model Analyses.** Linear mixed-effects regression models were used to test Hypothesis 1, regarding prospective interactive relations among TL change, poverty status, race, and age with cognitive decline across multiple domains of functioning. This statistical approach is highly recommended for testing hypotheses in prospective studies (Gueorguieva & Krystal, 2004; Zonderman et al., 2020). Linear mixed-effects regression analyses were run using the 'lmer' function within the *lmerTest* (version 3.0-1; Kuznetsova et al., 2017) and *lme4* (version 1.1-18-1; Bates et al., 2015) packages for R (version 3.6.1; R Core Team, 2019).

Parallel linear mixed-effects regression models were run for each cognitive test outcome. As discussed, the present study utilized a model deconstruction approach to data analysis. That is, analyses began with fully adjusted models containing all interactions, main effects, and covariates. Specifically, the fully adjusted models contained the highest-order, four-way interaction of TL Change × Poverty Status × Race × Age, all lower-order interactions and main effects nested beneath it, and sex, high school-or-greater educational attainment, and baseline TL

as covariates. If the four-way interaction was significant (i.e., $p < .05$), the fully adjusted model was retained. Conversely, if the four-way interaction was nonsignificant, it was removed from the model, and the analysis was rerun. Nonsignificant, higher-order interactions continued to be removed from the model in a stepwise fashion until the highest-order significant effect(s) were identified, at which point that model was retained. After arriving at the final model for each of the cognitive tests, the highest-order significant effects were probed and plotted to assist with interpretation. Of note, significant lower-order interactions and main effects nested beneath higher-order interactions were not interpreted.

***Sensitivity Analyses.*** Sensitivity analyses were run to test Hypothesis 2, regarding the potential mediating effects of hsCRP and cardiometabolic diseases. Specifically, hsCRP and cardiometabolic diseases were added sequentially to all final models that revealed significant interactions and/or main effects. Hierarchical entry was employed, such that hsCRP was added to the models first, followed by the dichotomous cardiometabolic disease variable. Across the different iterations of the models, the interaction and/or main effect(s) under examination were monitored for attenuation to nonsignificance (i.e., $p \geq .05$). In addition, likelihood ratio tests were run to compare goodness-of-fit across the different model iterations, using the 'anova' function within the *stats* package for R (version 3.6.1; R Core Team, 2019). When the likelihood ratio test revealed a significant change in model fit between iterations (i.e., $p < .05$), the Akaike Information Criterion (AIC) was used to judge the magnitude of the change in model fit. Potential mediation effects were considered if adding one or both candidate mediators resulted in (a) the interaction or main effect in question becoming nonsignificant, and (b) significantly improved model fit.

***Model Specifications.*** Each of the nine cognitive outcome variables was entered as a dependent variable in separate models as time-varying fixed effects. The intercept was modeled as a random effect. Age was used to index change within participants over time, as seen in prior studies with similar designs (Waldstein et al., 2008; Wendell et al., 2009). TL change, age, hsCRP, and cardiometabolic diseases were modeled as time-varying fixed effects, whereas poverty status and race were modeled as time-invariant fixed effects. Interactions among TL attrition, poverty status, race, and age were also be modeled as fixed effects. Sex, high school-or-greater educational attainment, and baseline TL were modeled as time-invariant, fixed effect covariates.

## Results

### Sample Descriptives

Table 1 contains sample characteristics at baseline (wave 1) and follow-up (wave 3). The final sample ($N$ = 323) consisted of participants with complete data for all main predictors, sensitivity variables, and at least one cognitive test outcome at baseline ($n$ = 266) and/or follow-up ($n$ = 304). Participants were aged 30–64 years at baseline ($M$ baseline age= 48.0, $SD$ = 8.9; $M$ follow-up age = 52.6, $SD$ = 9.0). The overall sample was 50.8% female, 52.0% African American, 50.2% living in poverty, and 34.1% with less than a high school education or GED. Approximately 45.5% and 57.2% of the sample had one or more cardiometabolic diseases (i.e., hypertension, diabetes, coronary artery disease, myocardial infarction, or heart failure) at baseline and follow-up, respectively. A correlation matrix of all study variables is presented in Table 2.

There were no concerning violations of statistical assumptions for all outcome variables except the Trail Making Test Parts A and B and the BVRT, which had non-normally distributed

residuals (i.e., distributions were positively skewed). Therefore, these variables were log-transformed for all analyses. Transformations resolved the skewed residual distributions.

### *Comparison of Variables of Interest across Sociodemographic Groups*

Predictors of interest were compared between race/poverty status subgroups at baseline and follow-up through independent samples *t*-tests and $\chi^2$ tests of independence (see Table 1). Compared to those living above poverty, those living in poverty were significantly more likely to have less than a high school education or GED (at baseline and follow-up, *p*'s < .01) and had significantly higher levels of hsCRP (at follow-up only, $p < .01$). There were no other race- or poverty-related differences in predictors of interest at baseline or follow-up.

## Main Analyses

### *Aim 1*

**Four-way Interactions.** There was a four-way interaction of TL Change × Poverty Status × Race × Age with change in Digit Span Backward, $b = -0.16$, $p = .023$ (Table 3). As shown in Figure 1, among (a) Whites living below poverty, $b = -0.09$, $p = .025$, and (b) African Americans living above poverty, $b = -0.08$, $p = .020$, greater decline in TL was associated with significant decline in Digit Span Backward. There were no further four-way interaction effects.

**Three-way Interactions.** There was a significant three-way interaction of TL Change × Race × Age with the CVLT long delay free recall, $b = -0.15$, $p = .005$ (Table 4). As shown in Figure 2, among Whites, decline in TL was significantly associated with decline in CVLT long delay free recall, $b = -0.28$, $p < .001$. Next, also among Whites, stable TL between time points was significantly associated with age-related decline in CVLT long-delay free recall performance, though to a lesser degree than decline in TL, $b = -0.17$, $p < .001$. Conversely, among Whites, positive TL change was not significantly associated with age-related decline in

CVLT long-delay free recall performance, $b$ = -0.06, $p$ = .229. In contrast to the associations among Whites, TL change did not moderate rates of decline in CVLT long delay free recall performance among African Americans (all $p$'s < .05; see Figure 2).

There was also a cross-sectional three-way interaction of TL Change × Poverty Status × Race with CVLT long-delay free recall, $b$ = 2.58, $p$ = 0.10 (see Table 4). Probing the interaction did not reveal significant simple effects of TL Change with CVLT long-delay free recall performance among any race/poverty status subgroups ($p$'s ≥ .05). Therefore, this effect was not interpreted further. There were no additional three-way interaction effects.

**Two-way Interactions.** There was a significant two-way interaction of TL Change × Age with Animal Naming, $b$ = 0.09, $p$ = .022 (Table 5). As shown in Figure 3, there was significant age-related decline in Animal Naming among those with decline in TL, $b$ = -0.22, $p$ < .001, and stable TL, $b$ = -0.15, $p$ = .003, with the steepest declines among those with negative TL change. In contrast, those who experienced positive TL change did not experience significant age-related decline in Animal Naming, $b$ = -0.08, $p$ = .124. There were no further two-way interaction effects.

**Main Effects.** There were no significant main effects of TL change with decline in any of the remaining cognitive tests (all $p$'s ≥ .05; see Tables 6-11 for primary linear mixed-effects regression models of all remaining cognitive tests).

***Aim 2***

As described in the Methods, potential mediating effects of hsCRP and cardiometabolic diseases were examined by adding these variables into models that yielded significant effects of TL change on cognitive test performance and/or decline. These hierarchical analyses did not result in any of the aforementioned significant effects attenuating to nonsignificance (i.e., all

effects remained significant at the $p < .05$ level; see Tables 12-14). For the model with CVLT long delay free recall as the outcome, likelihood ratio tests indicated significantly improved fit with additional adjustment for hsCRP, $p = .013$, and subsequently cardiometabolic diseases, $p = .022$. Additional adjustment for these sensitivity variables did not result in improved fit for any other models ($p$'s $\geq .05$).

## Discussion

The current study examined prospective interactive relations among TL change, poverty status, and race with age-related decline across multiple domains of cognitive function over approximately five years. For the first aim, it was hypothesized that significant four-way interactions of TL Change × Poverty Status × Race × Age would demonstrate relations of greater TL attrition with the most pronounced age-related cognitive decline among African Americans living in poverty. For the second aim, it was hypothesized that significant four-way interactions of TL Change × Poverty Status × Race × Age with cognitive decline would become nonsignificant following further adjustment for a marker of systemic inflammation (i.e., hsCRP) and the presence of one or more cardiometabolic diseases (i.e., hypertension, diabetes mellitus, coronary artery disease, myocardial infarction, and/or heart failure). Finally, for analyses in which the aforementioned four-way interaction was nonsignificant, exploratory aims examined lower-order interactions and main effects among TL change, poverty status, race, and age (via a backward elimination process), as well as the influence of adjusting for hsCRP and cardiometabolic diseases on the significance of such effects.

Results did not support any of the proposed hypotheses. However, there were several significant interactions observed among TL change, poverty status, race, and age, albeit not in the hypothesized patterns. First, a significant four-way interaction among TL Change × Poverty

Status × Race × Age with Digit Span Backward (i.e., working memory) performance demonstrated that greater TL attrition was associated with steeper age-related decline on this measure among Whites living in poverty and African Americans living above poverty. Next, a significant three-way interaction among TL Change × Race × Age with CVLT long-delay free recall (i.e., delayed verbal memory) performance demonstrated that greater TL attrition was associated with steeper age-related decline on this measure among Whites, but not African Americans. Finally, a significant two-way interaction of TL Change × Age with Animal Naming (i.e., verbal fluency) demonstrated that, irrespective of poverty status or race, greater TL attrition was associated with steeper age-related decline on this measure. Findings also revealed a significant three-way interaction among TL Change × Poverty Status × Race with CVLT long delay free recall performance. However, upon probing the interaction, no significant simple effects were noted, hence this interaction was not interpreted further. Unexpectedly, there were no significant associations of TL change or its interaction with race or poverty status for a test of basic attention (Digit Span Forward), psychomotor speed (Trail Making Test Part A), cognitive flexibility (Trail Making Test Part B), verbal learning (CVLT total learning), short-term verbal memory (CVLT short delay free recall), or nonverbal immediate memory (BVRT). Lastly, subsequent adjustment for hsCRP and the presence of one or more cardiometabolic diseases did not cause any significant interactions to attenuate to nonsignificance. The following sections will discuss these findings in the context of the primary and exploratory aims and hypotheses and previous literature.

**Interactive Relations among TL Change, Age, Poverty Status, and/or Race (Aim 1)**

To this researcher's knowledge, this was the first study to examine potential interactive relations among TL change, poverty status, and race with age-related cognitive decline.

Although this is a novel research question, significant four-way interactions among TL Change × Poverty Status × Race × Age were hypothesized for a wide range of cognitive measures in light of prior related literature. Briefly, previous studies have shown significant associations between shorter TL and worse performance and/or greater decline on a range of cognitive outcomes (e.g., Cohen-Manheim et al., 2016; Devore et al., 2011; Valdes et al., 2010; Yaffe et al., 2011). Further, given the multitude of vulnerability factors for accelerated cognitive aging among African Americans living in poverty (Glymour & Manly, 2008), it was expected that the most pronounced associations between TL attrition and cognitive decline would be observed among this group.

As noted above, results did not confirm this hypothesis. Indeed, a significant four-way interaction of TL Change × Poverty Status × Race × Age was only found for one of the nine cognitive outcomes examined herein – Digit Span Backward, a measure of working memory. Contrary to expectations, greater TL attrition was associated with steeper decline on this measure among Whites living in poverty and African Americans living above poverty, whereas the effect of TL attrition for African Americans living in poverty was nonsignificant. Four-way interactions among TL change, poverty status, race, and age were nonsignificant for all other cognitive tests. Following the backward elimination procedure, results further revealed a significant three-way interaction of TL Change × Race × Age with CVLT long-delay free recall (i.e., delayed verbal memory), such that greater TL attrition was associated with decline on this measure among Whites, but not African Americans. Lastly, findings revealed a significant two-way interaction of TL Change × Age with Animal Naming (i.e., verbal fluency), such that greater TL attrition was significantly associated with steeper decline on this measure among the overall sample. Thus, although greater TL attrition was associated with more pronounced age-

related decline on measures of working memory, delayed verbal memory, and verbal fluency, a different pattern of sociodemographic variation (or lack thereof) was found for each outcome. In addition, there were no significant independent or interactive relations of TL change with poverty status and/or race for tests of basic attention (Digit Span Forward), psychomotor speed (Trail Making Test Part A), cognitive flexibility (Trail Making Test Part B), verbal learning (CVLT total learning), short-term verbal memory (CVLT short delay free recall), or nonverbal immediate memory (BVRT).

In the following section, the present study's findings will be integrated with prior literature on TL and cognitive function. Given that previous studies have not examined race- and poverty-related variation in TL-cognition associations, the present pattern of cognitive findings will first be discussed in the context of the available TL-cognition literature, followed by a discussion of potential factors underlying their sociodemographic variation.

***Cognitive Patterns***

The present findings revealed that greater TL attrition is associated with steeper declines in subdomains of executive functioning (i.e., working memory [Digit Span Backward] and verbal fluency [Animal Naming]) and delayed verbal memory (CVLT long delay free recall), albeit for different groups of participants. These cognitive patterns partly overlap with findings from several previous prospective and cross-sectional studies that examined TL or attrition in relation to these or similar cognitive domains (Cohen-Manheim et al., 2016; Devore et al., 2011; Harris et al., 2006; Valdes et al., 2010), and are further supported by other studies that found broader associations between TL/attrition and performance or decline on measures of general cognitive ability and global cognitive status (Harris et al., 2012; Martin-Ruiz et al., 2006; Yaffe et al., 2011). However, these patterns are also inconsistent with other prior studies, which is

perhaps unsurprising given the equivocal literature on TL-cognition associations. Highly variable methodological approaches, including differences in study design, sample composition, and measurement of cognition and TL, have likely contributed to the mixed findings in this literature.

Findings revealed that greater TL attrition is associated with steeper declines in working memory (among Whites living in poverty and African Americans living above poverty) and verbal fluency (among all participants). Working memory and verbal fluency are nested within the broader domain of the executive functions (Strauss et al., 2006), which are higher-order cognitive processes that are involved in the "orchestration of basic cognitive processes during goal-oriented problem-solving" (Roth et al., 2015, p. 105). Importantly, patients with focal frontal lobe lesions have shown impairments on working memory and verbal fluency tests (Lezak et al., 2012), suggesting some overlap across these measures. However, it is unclear why associations were not found between TL attrition or its interaction with poverty status and/or race with change in cognitive flexibility (as measured by the Trail Making Test B), which is also considered a subdomain of the executive functions (Strauss et al., 2006). One possibility is that not all executive functioning subdomains are equally associated with TL attrition, given that this domain is highly heterogeneous. Therefore, it is plausible that TL attrition is associated with working memory and verbal fluency, but not cognitive flexibility and perhaps other executive function subdomains that were not assessed in the present investigation (e.g., abstract reasoning). Another possibility is that the Trail Making Test Part B is highly dependent on psychomotor speed – a domain that was not related to TL change in the present study (as indicated by the Trail Making Test Part A) – whereas Digit Span Backward and Animal Naming are not as strongly dependent on speed or motor functions (Lezak et al., 2012). As such, it is plausible that associations between TL attrition and executive functioning may be stronger for non-speeded,

nonmotor tasks. However, these hypotheses are entirely speculative and require further examination, especially given that executive function subdomains tend to correlate moderately with one another (McCabe et al., 2010).

It is also notable that an association was found between TL attrition and decline on Digit Span Backward (among select subgroups), but not decline on Digit Span Forward. Both of these tasks require auditory attention and short-term retention capacity and have been found to load onto a single factor (Mirsky, 1989). However, Digit Span Backward (versus Digit Span Forward) is considered the purer test of working memory, requires use of mental imagery, and is more commonly impacted by the presence of neuropathology (Lezak et al., 2012). For these reasons, Digit Span Backward may be more sensitive to TL attrition than Digit Span Forward. Further examination of this hypothesis is warranted.

Beyond executive functioning, findings revealed a significant association between TL attrition and decline in CVLT long delay free recall performance, a widely administered measure of delayed verbal memory, among Whites. Conversely, associations between change in TL and decline in CVLT total learning or short-delay free recall performance were nonsignificant. These patterns suggest that changes in retention of verbal information associated with TL attrition may emerge with longer time lapses following exposure to stimuli. In addition, participants may have more effectively utilized semantic clustering strategies (widely recognized as beneficial on the CVLT; Lezak et al., 2012) during the learning and short delay free recall trials (versus the long delay free recall trial) of the CVLT, given that the shorter time lapses following presentation of the word list might have aided retention of relevant semantic categories. These key differences might explain, at least in part, the variable associations with TL attrition observed across CVLT tasks. Findings also revealed a nonsignificant association between TL change and decline on a

measure of nonverbal immediate memory, the BVRT. Although the BVRT is widely considered a test of nonverbal immediate memory (Sivan, 1992), other cognitive skills are also involved, such as visual-spatial processing and psychomotor response (Lezak et al., 2012), that may not be associated with TL attrition. Further, as with the CVLT total learning and short-delay free recall subtests, the BVRT is an immediate memory task and does not include a measure of delayed nonverbal memory, which may be more sensitive to TL attrition given the longer time lapse following presentation of the stimulus. Further investigation and replication of these patterns will be critical to determine their validity.

Notably, there are a paucity of published prospective studies, highly variable methodological approaches, and equivocal findings within the literature on TL/attrition and cognitive function or decline. Nonetheless, the cognitive patterns observed in the current investigation are at least partly consistent with those reported in several previous studies. Most notably, the present investigation partially overlapped with findings from the only previous prospective study of TL-cognition associations to examine multiple cognitive domains (Cohen-Manheim et al., 2016). In this prior study, greater TL attrition from younger to middle adulthood (i.e., TL measured at two time points) was associated with lower levels of general cognitive ability, memory, and executive functioning, as well as information processing speed, attention, and visuospatial functioning, on the NeuroTrax computerized cognitive battery at subsequent follow-up. Next, the present study's delayed verbal memory pattern was generally consistent with a previous investigation among older women, which found that shorter baseline TL predicted significantly greater four-year decline on a verbal memory composite (without comparing immediate and delayed memory measures), as well as a general cognitive ability composite and a measure of global cognitive status (Devore et al., 2011). Finally, although other

prospective studies did not examine the domains of executive functioning and memory, two others reported significant associations of shorter baseline TL with decline in global cognitive status (e.g., on the MMSE; Martin-Ruiz et al., 2006; Yaffe et al., 2011), potentially supporting broad relations between TL and age-related cognitive decline. Of note, one of these latter studies also reported a nonsignificant association of baseline TL and change on a measure of psychomotor speed (Digit Symbol Modalities Test), which is generally consistent with the null association between TL change and decline on the Trail Making Test Part A in the present study.

Several previous cross-sectional studies have also reported significant associations between TL and cognitive performance on a range of outcomes. Although not directly applicable to the present prospective work, these prior findings are among the reasons why a broad range of cognitive domains were expected to relate to TL attrition in the present study. First, the present study's cognitive patterns are highly consistent with two previous studies reporting associations between shorter TL and lower levels of performance on tests of working memory (Valdes et al., 2010) and verbal fluency (Harris et al., 2006). In the former study, there was also a significant association between shorter TL and worse delayed recognition memory for nonverbal patterns (Valdes et al., 2010). Although delayed verbal memory was not assessed, this finding may provide further support for a relation of TL to delayed memory more broadly. Additionally, two other cross-sectional studies reported significant associations of shorter TL with (a) lower levels of general cognitive ability among older women (but not older men; Harris et al., 2012) and (b) impairment, but not continuous scores, on a Cantonese cognitive screening measure akin to the MMSE among older Chinese adults (Ma et al., 2013), potentially indicative of broad relations of TL to cognitive functioning within select sociodemographic groups. Additional analyses in the latter study revealed significant relations of baseline TL with three-word recall and verbal

fluency items on the cognitive screening measure, which is consistent with the present study's prospective patterns between TL attrition and decline in verbal memory and verbal fluency.

While the present study's findings are generally consistent with those from the studies described above, the overall literature on TL-cognition associations is highly equivocal. Therefore, it is perhaps unsurprising that the present study's results are, in part, inconsistent with other published findings. For instance, a recent meta-analysis of previously unpublished data from four population-based longitudinal investigations found (a) a weak, cross-sectional association of shorter baseline TL with lower scores on a general cognitive ability composite, which attenuated following adjustment for educational attainment, and (b) null associations between baseline TL and decline in general cognitive ability over time (Zhan et al., 2018). Likewise, a separate original empirical article reported null associations between concurrent change in TL and general cognitive ability (comprising tests of verbal fluency, verbal declarative memory, and nonverbal reasoning) among older European adults (Harris et al., 2016). Although these prospective findings do not support the broad TL-cognitive decline associations reported by other aforementioned studies (e.g., Cohen-Manheim et al., 2016; Devore et al., 2011; Martin-Ruiz et al., 2006; Yaffe et al., 2011), their lack of examination of specific cognitive domains limits direct comparisons to the current study's cognitive patterns.

There are also notable inconsistencies between the present findings and those from prior cross-sectional studies. One study reported null associations between TL and a memory composite among older Scottish adults (Harris et al., 2012), which is inconsistent with the present study's association between greater TL attrition and delayed verbal memory decline among White participants. However, given that the memory composite comprised multiple, heterogenous measures (e.g., immediate and delayed memory; verbal and visual stimuli), direct

comparisons cannot be made to the present study's analyses that measured learning and memory subdomains with individual test outcomes. Similarly, Bendix and colleagues (2011) reported null associations between TL and performance on the MMSE and a general cognitive composite, but did not examine individual cognitive domains, thereby limiting comparisons to the present work. However, it should be noted that the general cognitive composite used in that study comprised several identical or highly similar measures to those used in the present study (i.e., immediate and delayed word list memory, verbal fluency, and digit span forward and backward).

Perhaps most relevantly, this researcher was a co-first author on a recently published cross-sectional investigation of TL-cognition associations (the final results of which were not available prior to proposal of the present study; Leibel et al., 2020). Results of this study, which utilized the same sample of HANDLS participants, found that shorter TL was associated with poorer performance on (a) Digit Span Forward and Backward among Whites living in poverty, and (b) the Trail Making Test Part B and the BVRT among those living in poverty irrespective of race. The previous study's association between TL and Digit Span Backward performance, a measure of working memory, was similar to the prospective patterns between TL attrition and the same subtest in the present work. Similarly, psychomotor speed (Trail Making Test Part A), verbal learning (CVLT total learning) and short-term verbal memory (CVLT short delay free recall) were not related to TL or attrition across either study, suggesting some degree of overlap across the two investigations. However, several discrepancies between the previous cross-sectional work and the present investigation were also noted. Specifically, the previous study linked shorter TL to worse performance on Digit Span Forward, the Trail Making Test Part B, and the BVRT (among different subgroups); however, none of these measures were associated with greater TL attrition in any of the present prospective analyses. Likewise, in the present

study, findings linked greater TL attrition to steeper decline on CVLT long delay free recall (among Whites) and Animal Naming, whereas these measures were not associated with shortened TL in the previous cross-sectional work. Factors underlying these discrepant patterns are unclear. It is possible that some cross-sectional associations reflected an unassessed third-variable process, by which participants in poverty, particularly Whites, had shared risk factors influencing shorter TL and worse executive function and nonverbal memory performance (e.g., circulating pro-inflammatory cytokines; cardiometabolic burden). These discrepancies demonstrate the importance of examining TL-cognition associations prospectively, given that cross-sectional studies cannot capture cognitive trajectories with implications for future health and functioning. However, despite the lack of specific overlap for several tests, it should be noted that subdomains that were related to TL/attrition across both studies (albeit in different subgroups) were all subsumed within the broader domains of executive functioning and memory.

Several methodological considerations may have contributed to noted consistencies and inconsistencies between this investigation's findings and prior literature. As described, the present investigation measured concurrent change in TL and cognitive functioning across two time points, which may explain, at least in part, its unique findings compared to prior prospective and cross-sectional studies that examined TL and/or cognition at only one time point (Bendix et al., 2011; Cohen-Manheim et al., 2016; Devore et al., 2011; Harris et al., 2006, 2012; Leibel et al., 2020; Ma et al., 2013; Martin-Ruiz et al., 2006; Valdes et al., 2010; Yaffe et al., 2011; Zhan et al., 2018). In fact, only one previous study, which reported null effects, measured both TL and cognition at more than one time point; however, this study only examined general cognitive ability and not individual cognitive domains, thereby limiting comparisons to the present work (Harris et al., 2016). Regarding differences in sample composition, most previous studies utilized

samples of European or majority-White United States participants (Bendix et al., 2011; Devore et al., 2011; Harris et al., 2006, 2012, 2016; Martin-Ruiz et al., 2006), whereas the present study's sample consisted of nearly equal representation of African Americans and Whites. Although some previous studies utilized socioeconomically diverse samples (e.g., Yaffe et al., 2011; Cohen-Manheim et al., 2016), others did not and none utilized poverty status in their population-based recruitment stratification, a strategy that HANDLS employed (Evans et al., 2010). Of note, the present study's length of follow-up was approximately five years, which is shorter than most previous prospective studies that measured cognitive functioning at more than one time point, most of which had follow-up periods of seven years or more (Cohen-Manheim et al., 2016; Devore et al., 2011; Harris et al., 2016; Yaffe et al., 2011), with one notable exception being a two-year follow-up in a study that only examined a cognitive screening measure (Martin-Ruiz et al., 2006). Given the mixed findings and other varying aspects of methodology in studies with longer follow-up periods, it is unclear whether and how extending the length of follow-up of the present investigation might have influenced the results.

Across the relevant literature, there has been extensive variability in the measurement of cognitive functioning. Several of the cognitive tests used in the present work have not been utilized in previous studies of TL-cognition associations (with the exception of the cross-sectional investigation that preceded this work, Leibel et al., 2020). That is, to this researcher's knowledge, none of the aforementioned studies utilized the Trail Making Test Parts A or B, CVLT, or the BVRT, greatly limiting comparisons between the present work and previous literature with respect to patterns of outcomes involving these measures. In contrast, Animal Naming and Digit Span Backward (or very similar tasks) have been utilized in select previous investigations, which may explain consistencies in some, but not all, patterns involving working

memory and verbal fluency measures and composite variables that included these tests (Devore et al., 2011; Harris et al., 2006; Leibel et al., 2020; Ma et al., 2013; Valdes et al., 2010). Next, of the prior studies that analyzed at least one individual cognitive domain (as opposed to only general cognitive ability and/or global cognitive status), some used composite variables comprised of multiple tests (e.g., Devore et al., 2011; Harris et al., 2012), whereas other used individual tests as outcomes (e.g., Cohen-Manheim et al., 2016; Valdes et al., 2010). Given that comparisons between individual tests and cognitive composites have not been tested, it is unclear whether and how the use of composite variables would have impacted the present study's cognitive patterns.

Although the current and most prior investigations used examiner-administered, paper-and-pencil cognitive tests, two previous investigations utilized the computer-administered NeuroTrax battery (a prospective study by Cohen-Manheim et al., 2016) and the Cambridge Neuropsychological Test Automated Battery (CANTAB; a cross-sectional study by Valdes et al., 2010). Although several of the measures within these computerized batteries were based on traditional neuropsychological measures used in the present study (e.g., the BVRT), other computerized measures did not overlap with the present study's tests (e.g., inclusion of a Stroop task to measure executive functioning). Likewise, several tests used in the present study had no analogous measure in either NeuroTrax or CANTAB; for instance, there were no digit span, word list memory, or verbal fluency tasks in either battery, which were tests/domains significantly associated with TL change in the present study. In addition, NeuroTrax characterizes and scores cognitive functioning through a combination of accuracy and reaction time. This degree of precision may have allowed for better detection of TL attrition-cognition associations across the five domains examined by Cohen-Manheim and colleagues (2016).

Conversely, traditional cognitive tests used in the current investigation are less precise, which may have limited the ability to capture associations between concurrent change in TL and psychomotor speed, cognitive flexibility, basic attention, verbal learning, short-term verbal memory, and nonverbal immediate memory. This hypothesis may be supported by the far less extensive TL-cognition associations observed in studies that used traditional cognitive measures, but also the study that used CANTAB, which does not parse reaction time in its characterization of cognitive functioning (Valdes et al., 2010).

Other studies have relied solely on general cognitive ability and global cognitive status measures and/or used batteries of individual tests that were less comprehensive than those used in the current investigation (Devore et al., 2011; Harris et al., 2006; Yaffe et al., 2011; Zhan et al., 2018). For example, one study relied exclusively on verbal measures and did not assess several nonverbal domains such as nonverbal memory, psychomotor speed, and/or cognitive flexibility (Devore et al., 2011), thereby limiting comparisons to the present study's patterns in such domains. Some prior investigations provided incomplete information regarding the specific tests administered. For instance, in the meta-analysis of unpublished data by Zhan and colleagues (2018), specific tests administered were not named for two of the four prospective cohort studies used in the analysis. In another study by Harris and colleagues (2016), a measure of verbal fluency was included in a general cognitive ability composite, though without further details about the task (e.g., letter versus semantic fluency; specific prompt/instructions). Therefore, it is unclear whether this task was identical or similar to Animal Naming, the verbal fluency measure used in the present study.

Variability in TL measurement may also have further contributed to equivocal findings in the literature. Most of the aforementioned studies assayed TL in leukocytes (a heterogenous

group of immune blood cells) whereas the present study and its preceding cross-sectional investigation assayed TL in PBMCs (a subtype of leukocytes that consists of lymphocytes and monocytes). Each leukocyte subtype divides at different rates, which in turn influences rates of TL attrition. As such, differences in cell subtypes assayed across studies might have influenced discrepancies between the present work and previous literature. However, given that TL across different PBMC subtypes are correlated (Lin et al., 2016), the extent to which the specific cells assayed would influence the findings is unclear.

In summary, the present study's cognitive patterns indicate that greater TL attrition is associated with steeper declines on non-motor/non-speeded aspects of executive functioning, namely working memory and verbal fluency, as well as delayed verbal memory (among varying subgroups of participants). Although findings in the literature are highly equivocal, these patterns are consistent with select prior studies demonstrating associations between TL/attrition and executive functioning and memory, as well as general cognitive ability, global cognitive status, and in some cases, additional domains of cognitive functioning. As such, it is possible that memory and executive functioning may be particularly impacted by the deleterious effects of cellular aging, though broader cognitive patterns are possible. Replication of the present study's findings in a unique sample will be necessary to determine if these domain-specific patterns are reliable. Methodological differences across the TL-cognition literature have likely contributed to equivocal patterns of cognitive outcomes, as well as discrepancies between the present study's findings and those from prior studies. Efforts to address the high degree of heterogeneity in research methodology may help to elucidate factors underlying these inconsistencies in the literature. In the following section, potential explanations for sociodemographic variability in the present study's patterns of cognitive outcomes are explored.

### *Sociodemographic Patterns*

The first aim of the present investigation, and subsequent exploratory analyses, hypothesized sociodemographic moderation of prospective TL-cognition associations. Specifically, African Americans living in poverty were hypothesized to have the most pronounced associations between TL change and cognitive decline given a multitude of relevant biopsychosocial risk factors. As described, results were not consistent with this hypothesis. Rather, findings revealed that as a function of greater TL attrition, (a) Whites living in poverty and African Americans living above poverty experienced significantly steeper working memory decline (Digit Span Backward), (b) Whites experienced steeper delayed verbal memory decline (CVLT long delay free recall), and (c) all participants, irrespective of race or poverty status, experienced steeper verbal fluency decline (Animal Naming). Although, to our knowledge, no prior studies have examined race and poverty status as moderators of TL-cognition associations, these sociodemographic patterns are generally inconsistent with prior related literature demonstrating that individuals of lower SES and African Americans are at greater risk for poor brain and cognitive health outcomes than those of higher SES and Whites, respectively. Indeed, lower SES and self-identified African American race have been associated with increased risk for stroke (Addo et al., 2012; Benjamin et al., 2019; Cox et al., 2006), dementia (Chen & Zissimopoulos, 2018; Goldbourt et al., 2007; Harwood & Ownby, 2000), and subclinical brain pathology and cognitive decline (Butterworth et al., n.d.; Glymour & Manly, 2008; Nyquist et al., 2014; Turrell et al., 2002). Other research has demonstrated that lower SES portends greater risk for African Americans than Whites with regard to brain health. For example, a previous study of a subset of HANDLS participants with neuroimaging data (i.e., HANDLS SCAN) revealed that African American participants of lower SES had significantly greater white matter

lesion volumes than White participants with lower SES (Waldstein et al., 2017). For these reasons, African Americans with lower SES were expected to be at greater risk than other race/poverty status subgroups for cognitive decline associated with TL attrition in the present study. Despite these prior findings, the present study's sociodemographic patterns may indeed be consistent with other related theoretical literature on intersectionality and related empirical literature on sociodemographic variation in health risks, as will be discussed below.

**Four-way Interaction.** As described, the findings demonstrating that Whites living in poverty and African Americans living above poverty experienced steeper working memory decline associated with TL attrition may be consistent with previous intersectionality literature. Intersectionality is a theoretical framework that outlines how a multitude of social identity dimensions (e.g., self-identified race, SES, sex, gender identity, sexual orientation, age, and religion, among myriad others) interact at the micro-level of the individual to reflect macro-level systems of privilege and oppression (Bowleg, 2012; Else-Quest & Hyde, 2016). Although intersectionality certainly emphasizes the deleterious effects of occupying multiple disadvantaged social statuses, this perspective does not necessitate that all identities confer disadvantage equally (Bowleg, 2012). Indeed, one of intersectionality's noteworthy contributions to public health and epidemiology is the *intersectionality paradox*, which suggests that simultaneously occupying privileged and oppressed social statuses may also portend adverse health outcomes. Consistent with this theory, Whites living in poverty and African Americans living above poverty – identified as potentially vulnerable groups in the present study – concurrently occupy both privileged and historically disadvantaged social identities. Although these groups may share select underlying risk factors, intersectional perspectives would suggest

that unique factors may be driving increased vulnerability among these groups in the present study.

Regarding the significant relation of TL attrition to working memory decline among lower-SES Whites, recent epidemiologic studies demonstrated that lower-SES Whites in the United States are experiencing increased risk for morbidity and mortality during midlife (Case & Deaton, 2015). Case and Deaton (2017) observed that Whites with a high school degree or less have experienced an increase in midlife mortality rates since the turn of the twenty-first century, while rates have fallen for other racial/ethnic groups in the United States during the same period. These trends have emerged rapidly and appear to transcend geographic regions within the United States. The increased midlife mortality rates among lower-SES Whites have been referred to as "deaths of despair" (DOD), given parallel declines in self-reported physical and mental health and daily functioning, as well as concurrent increases in chronic pain, inability to work, misuse/abuse of opioid medications, and deteriorating liver function (often related to alcohol and substance misuse). These alarming trends in morbidity and mortality among lower-SES Whites have been confirmed by subsequent investigations and appear to be persisting over time (Stein et al., 2017).

Several factors hypothesized to contribute to declining health among working class Whites, particularly substance misuse, worsening mental health, and economic disadvantage, may influence both TL and cognitive functioning in some contexts (e.g., Bruijnen et al., 2019; Bunce et al., 2008; Mani et al., 2013; Needham et al., 2014; Vakonaki et al., 2018; Yang et al., 2013). Importantly, however, recent research suggests that the popularization of the DOD construct may have led researchers and policy-makers to ignore increases in premature deaths due to cardiovascular diseases and non-lung cancers – diseases that may be partially mediated by

chronic stress suggestive of weathering – among working class Whites (particularly White women) as well as African Americans (Geronimus et al., 2019). Indeed, chronic stress associated with economic hardship is associated with sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis, which has been linked to wear-and-tear on organ systems, a concept known as allostatic load (Mcewen & Gianaros, 2010). As such, overall burden of stress-mediated diseases and risk factors and maladaptive coping strategies (e.g., substance misuse), which may impact cognitive functioning in their own right, might increase the vulnerability of lower-SES Whites to the negative effects of TL attrition on age-related cognitive decline.

Our findings among African Americans living above poverty are also consistent with the intersectionality paradox. Previous literature has documented larger racial health disparities at higher levels of socioeconomic position (such that higher-SES African Americans are at greater risk than Whites) for a range of poor health outcomes, such as coronary artery disease (Diez-Roux et al., 1995), childhood obesity (Assari, 2018c), overall burden of chronic disease (Assari, 2018b), self-rated health (Diez-Roux et al., 1995; Farmer & Ferraro, 2005), and all-cause mortality (Gornick et al., 1996; Lankarani & Assari, 2017). Further, a previous investigation of HANDLS participants found that African Americans living above poverty had higher body mass index and waist circumference and lower high-density lipoprotein cholesterol than their African American counterparts living in poverty (Waldstein et al., 2016). These *diminishing returns* are thought to reflect, in part, select negative social consequences of economic progress for higher-SES African Americans. In particular, African Americans of higher SES are more likely than those of lower SES to encounter social spaces occupied by Whites. In this way, higher SES may expose African Americans to experiences of interpersonal discrimination, a chronic stressor can chronically activate stress pathways (e.g., the HPA axis) that in turn may negatively impact their

health and longevity (Bowleg, 2012; Clark et al., 1999). Indeed, previous research has demonstrated linkages between experiences of discrimination (e.g., racial discrimination) and adverse health outcomes such as elevated blood pressure and cardiovascular disease (Dolezsar et al., 2014; Panza et al., 2019). With regard to cellular aging, this researcher was a co-author of a previous work within a similar subset of HANDLS participants which revealed that greater experiences of racial and other forms of discrimination among African American women of higher SES (as measured by a composite of poverty status and high school-or-greater educational attainment) are associated with shorter TL (Beatty Moody et al., 2019). Therefore, it is plausible that experiences of discrimination among higher-SES African Americans also increase their vulnerability to the negative health effects of greater TL attrition, including cognitive decline.

As such, the aforementioned theoretical and empirical literature supports the possibility of relative vulnerability among Whites living in poverty and African Americans living above poverty. However, it should be noted that cognitive decline associated with TL attrition among these subgroups was only observed for one of nine measures, thus this finding may be spurious. Future replication studies will help to determine the validity of these patterns.

**Three-way Interaction.** Additional analyses explored lower-order interactions among TL change, race, poverty status, and/or age for all cognitive trajectories that yielded nonsignificant four-way interactions. Elimination of the nonsignificant four-way interaction revealed a significant three-way interaction of TL Change × Race × Age with CVLT long-delay free recall performance, a measure of delayed verbal memory. Probing the interaction revealed that greater TL attrition was associated with steeper decline in this measure among Whites, but not African Americans. As described, this pattern is inconsistent with previous research that has shown extensively that African Americans are at greater risk for adverse brain health outcomes

than Whites (e.g., Benjamin et al., 2019; Chen & Zissimopoulos, 2018; Glymour & Manly, 2008; Harwood & Ownby, 2000; Nyquist et al., 2014).

Notably, however, the troubling trends in morbidity and mortality among lower-SES Whites described above might have contributed to the delayed verbal memory decline noted among all Whites in the present study. Stein and colleagues (2017) recently demonstrated that premature death rates – and ostensibly worsening health and despair – among Whites are perhaps more widespread than previously thought, with potential implications for Whites living in Baltimore City. From 1999–2015, the researchers found significant increases in premature death rates for all Whites aged 2564 years living in small/medium metropolitan areas (i.e., Baltimore City's classification, per the National Center for Health Statistics), particularly for those under the age of 54. Premature death rates increased at an even faster rate for Whites living in rural areas, while they decreased and did not change for Whites in large urban areas and suburban areas, respectively. These mortality trends were mostly explained by increases in suicide, accidental poisonings, and liver disease, consistent with the DOD concept proposed by previous investigators (Case & Deaton, 2015, 2017). Meanwhile, premature death rates decreased for Black and Hispanic middle-aged adults during the same period, regardless of geographic urbanicity (although Blacks had the highest absolute rates of death overall; Stein et al., 2017). Although this previous work did not adjust for individual-level socioeconomic position (e.g., education or income), these findings and the aforementioned literature suggest that middle-aged Whites living outside of the largest population centers are experiencing a health and mortality crisis that may be, at least in part, explained by social and/or economic stagnation. One possibility raised by Stein and colleagues (2017) is that Whites living outside of the largest population centers are likely to have lower lifetime earnings than their parents, whereas this is

not true for the current generation of Blacks and Hispanics overall. Therefore, Whites living in at-risk geographic areas who simultaneously occupy a privileged racial group while facing economic hardship may tend to engage in upward social comparisons, shown elsewhere to negatively influence mental health (Wetherall et al., 2019), which may in turn contribute to maladaptive coping behaviors and chronic disease. In this context, it is plausible that Whites living in small/medium metropolitan areas such as Baltimore City, irrespective of individual-level poverty status, could be increasingly vulnerable to delayed memory decline associated with greater TL attrition.

In contrast, the finding that African Americans with greater TL attrition did not experience steeper decline in CVLT long-delay free recall performance or other measures is discordant with the present study's first hypothesis, which predicted that African Americans (specifically those living in poverty) would experience steeper decline across all domains with greater TL attrition. This pattern is unexpected given the multitude of vulnerability factors experienced by African Americans across the lifespan (Glymour & Manly, 2008). Indeed, while the morbidity and mortality crisis among lower-SES Whites has received disproportionate research and media attention (for related commentary, see Brown & Tucker-Seeley, 2018), African Americans continue to have higher rates of most age-related chronic diseases and shorter average lifespans than Whites overall (Stein et al., 2017). However, through centuries of living with social adversity, African Americans may have developed sources of resilience that serve to mitigate the negative effects of risk factors (Assari, 2018a). For example, in previous studies Africans Americans have reported higher levels of social support, positive affect, and spirituality than their White counterparts (Utsey et al., 2007), all of which may be health-promoting in some

contexts. Future research is necessary to confirm this finding and provide support for this hypothesis.

Although these race-related patterns may be supported by recent empirical literature on health disparities, it is unclear why delayed verbal memory was the only cognitive outcome associated with TL attrition among Whites in the present study. Given that no other similar three-way interactions were observed, this finding may be spurious. Replication studies will help establish the validity of this finding. If confirmed, future mediational research will help to uncover the biopsychosocial factors underlying these trends among Whites.

**Two-way Interaction.** Finally, exploratory analyses revealed that greater TL attrition was associated with steeper decline in verbal fluency among all participants (i.e., a significant two-way interaction of TL Change × Age), regardless of their race and poverty status. Although sociodemographic moderation was hypothesized for all cognitive tests and was observed for two other outcomes, TL attrition may predict certain aspects of cognitive decline equally across populations. Notably, no previous studies on TL-cognition associations examined race- or poverty-related moderation of such effects (with the exception of Leibel et al., 2020), and two studies reported significant associations between shorter TL and worse verbal fluency in their entire samples (Harris et al., 2006; Ma et al., 2013). In addition, it is possible that verbal fluency is an especially vulnerable aspect of cognitive functioning associated with TL attrition across people, perhaps due to its dependence on both frontal systems involved in word retrieval and temporal systems that store semantic knowledge (Lezak et al., 2012; Strauss et al., 2006). Together, these considerations could explain the uniform associations with TL attrition across sociodemographic groups in the present study.

However, as with the aforementioned sociodemographic patterns for working memory and delayed verbal memory, it is notable that a significant two-way interaction of TL Change × Age was only observed for one of nine cognitive outcomes, verbal fluency. This discrepancy across cognitive outcomes indicates that this pattern may be spurious. Therefore, this finding should be interpreted with caution pending replication in a unique sample.

**The Role of Systemic Inflammation and Cardiometabolic Diseases (Aim 2)**

The second hypothesis predicted that interactive relations among TL change, poverty status, and race with age (indexing time) would attenuate to nonsignificance following additional adjustment for hsCRP and cardiometabolic diseases. Results did not confirm this hypothesis. Rather additional adjustment for hsCRP and cardiometabolic diseases did not result in any of the significant interactions becoming nonsignificant. Contrary to expectations, these findings suggest that hsCRP and the presence of cardiometabolic diseases, as assessed herein, are unlikely to mediate significant associations between TL attrition and cognitive test performance in the present sample. The possibility that inflammatory and cardiometabolic pathways are independent of those linking TL attrition and cognitive decline is further supported by the observation that adding hsCRP and cardiometabolic diseases each separately improved overall fit for the model with CVLT long delay free recall.

To this researcher's knowledge, this was the first study to examine whether associations between TL attrition and cognitive decline and/or performance attenuated following adjustment for two potential mediators, a marker of systemic inflammation or burden of cardiometabolic diseases. Although these questions have not been investigated previously, inflammatory and cardiometabolic risk factors were hypothesized as potential mediators of these associations in light of previous literature separately linking shorter TL to inflammation and cardiometabolic

risk (Wang et al., 2016; Yeh & Wang, 2016; Zhang et al., 2016), and associating these latter factors to cognitive performance (Falkowski et al., 2014; Marsland, 2015; Waldstein et al., 2010). In that regard, associations between shortened TL with systemic inflammation is well-documented in the literature. Specifically, elevated levels of inflammatory markers, including hsCRP, have been linked to shorter TL (Mazidi et al., 2018; Solorio et al., 2011). Senescent cells with shortened TL may secrete pro-inflammatory cytokines, thereby interfering with functioning of other cells and tissues and potentially developing into chronic inflammatory states (von Zglinicki, 2002). Regarding cognitive functioning, converging evidence suggests that systemic inflammation and neuroinflammation may contribute to age-related cognitive outcomes, including AD and other dementias (Heneka et al., 2015). Further, in individuals without dementia, elevated inflammatory markers have been linked to poorer performance on measures of learning and memory, working memory, and other aspects of executive functioning (Marsland, 2015), which are cognitive domains that were linked with TL attrition among different subgroups in the present study.

Given this prior literature separately linking TL attrition to inflammation, and inflammation to cognitive decline, the current lack of attenuation of noted TL attrition-cognitive function relations with adjustment for hsCRP was somewhat unexpected, but not unprecedented. Although select studies have linked hsCRP specifically to shortened TL, others have reported nonsignificant associations (O'Donovan et al., 2011). Further, a review of the literature reveals that associations have more consistently been found between shortened TL and IL-6, a pro-inflammatory cytokine that is critical to the immune response (Mazidi et al., 2018; O'Donovan et al., 2011; Solorio et al., 2011; Zhang et al., 2016). Adjustment for circulating IL-6 levels, or other pro-inflammatory cytokines, may have attenuated associations between TL attrition and

cognitive decline in the present study. Unfortunately, IL-6 was not available for examination as a potential mediator in the present investigation.

Like inflammation, age-related cardiometabolic diseases have been linked to shortened TL in previous studies (for reviews, see Tellechea & Pirola, 2017; Wang et al., 2016; Yeh & Wang, 2016). Previous research suggests that these associations are bidirectional, but that shortened TL may contribute to the pathogenesis of cardiometabolic diseases through cellular senescence and dysfunction (Elks & Scott, 2014; Yeh & Wang, 2016). This may be highly relevant to brain health, given that cardiometabolic diseases are among the most impactful risk factors for subclinical neurocognitive decline, vascular dementia, and AD (Gorelick et al., 2011). Indeed, several of the cardiometabolic risk factors examined in the present study (e.g., hypertension, diabetes) are among the strongest predictors of memory and executive functioning decline (Waldstein et al., 2010). Therefore, it was hypothesized that associations between TL attrition and cognitive decline would attenuate with adjustment for cardiometabolic diseases in the present study, which would signal potential mediation via cardiometabolic pathways. However, as described, significant associations between TL change and executive functioning and memory outcomes across race and poverty status groups remained significant following adjustment for the presence of one or more cardiometabolic diseases. This suggests that the presence of one or more cardiometabolic diseases does not explain associations between TL change and the cognitive domains implicated in the present study. However, it remains plausible that the severity of cardiometabolic disease burden (e.g., number of disorders; whether conditions are well-controlled) plays a more significant role in these associations. Although using a dichotomous variable to identify the presence or absence of cardiometabolic diseases was appropriate for an exploratory study, more comprehensive and direct assessment of clinical and

subclinical cardiovascular disease and its biomedical risk factors may have produced different results. In that regard, it is important to consider the possibility of residual confounding with respect to this study's measure of cardiometabolic risk, particularly given that several of the diseases were self-reported. Further, a dichotomous variable may have not fully adjusted for unique (or cumulative) contributions of these five diseases to TL attrition-cognitive decline associations.

***Alternative Mechanisms***

Additional mechanisms beyond inflammatory and cardiometabolic disease risk factors may underly the findings in the present study. As reviewed previously, a growing number of studies have examined whether shorter TL is associated with increased risk for dementia, although findings to date are mixed (e.g., Grodstein et al., 2008; Hochstrasser et al., 2012; Kume et al., 2012; Martin-Ruiz et al., 2005; Panossian et al., 2003; Zekry, Herrmann, Irminger-Finger, Graf, et al., 2010; Zekry, Herrmann, Irminger-Finger, Ortolan, et al., 2010). Overall, however, the evidence appears to be converging on a significant association between shortened TL and increased dementia risk, particularly for AD. For example, a recent meta-analysis of 13 studies found that AD patients had significantly shorter TL than healthy controls (most studies assayed leukocytes, though others assayed PBMCs, lymphocytes, buccal cells, or brain tissue; Forero et al., 2016). Most studies included in the meta-analysis assayed TL in leukocytes, whereas others assayed TL in PBMCs, lymphocytes, buccal cells, or brain tissue. Other studies have examined shared genetic contributors to shorter TL and AD, with one study proposing a causal link between SNPs with well-known associations with shortened TL and increased risk for AD (Zhan et al., 2015). Although mechanistic research will be necessary, it is plausible that PBMC TL attrition relates to age-related cognitive trajectories, at least in part, through increasing

vulnerability to AD pathogenesis, and possibly via increased inflammatory signaling. Importantly, memory and executive functioning may decline in preclinical Alzheimer's disease (Bäckman et al., 2005). Although entirely speculative, it is plausible that associations between TL attrition and worsening performance in these domains are related to early AD pathology (i.e., prior to the onset of clinical-level AD criteria). AD is a slowly progressing illness, such that markers of AD pathology (e.g., amyloid-β) are present up to decades prior to the onset of clinical-level cognitive impairment.

Research on neuroanatomical correlates of blood cell TL (i.e., leukocytes or PBMCs) is in its nascent stage. A recent population-based study found associations between TL and global and regional brain volumes (King et al., 2014). Following adjustment for sociodemographic factors and total cranial volume, shorter TL was associated with smaller volumes across a number of cortical and subcortical neuroanatomical subregions (i.e., parietal, temporal, frontal, and occipital lobes, as well as deep nuclei, cingulate gyrus, and insula). Most notably, the researchers noted that shorter TL was associated with smaller volumes in regions implicated in AD, namely the hippocampus, amygdala, parietal cortex, temporal cortex, precuneus, and posterior cingulate, although several other regions not thought to be primarily related to AD pathology were also associated with shorter TL. Given the current study's findings, future work should examine if certain sociodemographic subgroups are particularly susceptible to the TL-brain relations observed by King and colleagues (2014). Further, in light of our findings, future research should specifically examine associations between TL and neural subregions implicated in verbal memory and aspects of executive functioning, such as the hippocampus and prefrontal cortex.

Relatedly, TL attrition is associated with markers of oxidative stress (Houben et al., 2008; von Zglinicki, 2002), which were not measured in the present study but have been found to be associated with cognitive health (Hajjar et al., 2018; Revel et al., 2015). Previous research has shown that telomeres are particularly vulnerable to oxidative damage, which is a major cause of TL attrition (von Zglinicki, 2002). The strength of this association has led some researchers to suggest that TL in leukocytes or PBMCs are markers for cumulative oxidative stress (Houben et al., 2008). This is relevant for neurocognitive health, given that oxidative stress may be implicated in AD pathogenesis (Huang et al., 2016) and has been linked to cognitive decline, particularly for executive functioning (Hajjar et al., 2018; Revel et al., 2015). Oxidative stress has been proposed as a potential contributing factor in TL-brain health associations (King et al., 2014), although this has not been directly examined in previous literature. Future studies should consider the potential triangulations among oxidative stress, TL attrition, and cognitive decline, as well as the directionality of these associations.

Finally, the role of telomerase in TL-brain health associations has not been previously studied. As described, telomerase is an enzyme that repairs and elongates damaged telomeres (Chan & Blackburn, 2004). Lower telomerase concentrations and activity have been associated with more rapid TL attrition and aging phenotypes (Blackburn et al., 2015). Interestingly, however, telomerase concentrations are very low in most somatic cells; only germline and stem cells maintain high concentrations of telomerase indefinitely (Blackburn et al., 2015). Although associations between blood cell TL (i.e., leukocytes or PBMCs) and telomerase activity in the brain have not been previously examined, King and colleagues (2014) proposed that associations between TL attrition and cognitive decline may reflect lower proliferative potential of neural stem cells, which are clustered in the dentate gyrus of the hippocampus and subventricular zone.

Future research is necessary to determine whether telomerase activity in the brain is driving associations between TL attrition and neurocognitive health.

**Strengths and Limitations**

The current study has several notable strengths. This was among the first studies to examine prospective associations between concurrent age-related change in TL and cognitive functioning. Relatedly, the use of an extensive neuropsychological test battery allowed this study to examine multiple domains of cognitive functioning, thereby expanding on previous literature which has been overly reliant on global cognitive screening measures and general cognitive composites. Relatedly, to our knowledge, this was the first investigation to examine whether associations between TL change and cognitive trajectories are moderated by poverty status and race, which are key sociodemographic factors associated with cognitive performance across the lifespan. Our sample had comparable distributions of African Americans and Whites across poverty statuses, as well as roughly equal representation of men and women. Participants were mostly middle-aged at baseline and had no known cognitive impairment, allowing for examination of pre-clinical cognitive decline trajectories.

The current study also has several limitations. Given the inconsistent sociodemographic variation noted among findings in the present work, it is plausible that the results are spurious. Therefore, findings should be considered preliminary pending replication in a unique sample. Replication is necessary to determine the validity of the findings and their generalizability to the broader population. Relatedly, given that Whites were significantly more likely than African Americans to consent to genetic assays, these findings might not even generalize to the overall HANDLS sample. There may be key differences between African Americans who consented to genetic assays and those who did not that could have influenced the findings (e.g., lack of

associations between TL change and delayed verbal memory among African Americans). Poverty status was characterized as a dichotomous variable which greatly restricted the full of range of income in the sample, which may have been more informative. TL was assayed from PBMCs, which comprise subtypes that may experience different rates of TL attrition (Lin et al., 2016; Montpetit et al., 2014). Although research suggests that TL of PBMCs and leukocytes more broadly are highly correlated (Lin et al., 2016), the heterogeneity of PBMC subtypes calls into question the comparability and reliability of TL measurement across participants and time points. Finally, across analyses, unstandardized regression coefficients for age suggest that declines in cognitive test performance over five years were minimal in the overall sample (see Tables 3–11). Therefore, it is unclear whether substantive cognitive decline associated with TL attrition should be expected in a primarily middle-aged cohort with only five years between measurement waves.

**Future Directions**

Future studies are necessary to better understand associations between TL change and age-related cognitive trajectories across domains of function. Most importantly, although the present study has several methodological strengths, it does not clarify the overwhelming ambiguity in the literature regarding associations between TL/attrition and cognitive functioning and decline. In addition, as described, the inconsistent sociodemographic patterns observed across cognitive outcomes in the present study indicate that the findings may be spurious. Alternatively, findings may be unique to characteristics of the HANDLS sample. For example, HANDLS is one the few epidemiologic studies to have adequate representation of Whites living in poverty. Further, the urban environment of Baltimore City, Maryland may have influenced the findings. Given these considerations, replication of the present study's cognitive and

sociodemographic patterns is needed to determine if the current findings generalize to other racial/ethnic and SES groups, individuals living in non-urban settings, and the broader population.

Should future studies replicate these results, further work is needed to examine the mechanisms linking TL attrition to declines in working memory, delayed verbal memory, and verbal fluency across different race and poverty status subgroups. The present study used sensitivity analyses to explore potential mediating effects of hsCRP and the presence of one or more cardiometabolic diseases in these associations. Although sensitivity analyses did not cause the significant effects to attenuate, it is plausible that formal methods of examining mediation would have yielded different results. Specifically, structural equation modeling is a powerful analytic technique for examining potential mediation in longitudinal analyses.

Next, future studies should seek to use more comprehensive cognitive batteries that encompass additional domains, such as visuospatial abilities, confrontation naming, and receptive language. Given the unclear patterns in literature, future investigations might also consider comparing results when using individual cognitive test outcomes versus composite variables of broader domains. This approach may help to clarify the potential importance of overlapping variance among tests of related abilities (e.g., executive functioning subdomains of working memory, verbal fluency, and cognitive flexibility).

Future work should follow participants over longer periods and further into older age. Due to increased power, adding more measurement points may elucidate additional linkages between TL change and cognitive functioning across different domains of function. In addition, ongoing longitudinal monitoring of these trends might uncover associations between TL change and the emergence of clinical brain health endpoints, such as AD and other forms of dementia.

Examining markers of dementia pathology through advanced neuroimaging techniques (e.g., beta-amyloid through positron emission tomography) is another path for future research.

Finally, future investigations should examine the role of behavioral and psychosocial factors in associations between TL attrition and decline in executive functions and memory. A growing body of literature has identified TL as a potential marker of accelerated biological aging associated with psychological stress (Epel et al., 2004; Shalev et al., 2013). Other studies have shown potentially beneficial effects of health behavior interventions, such as exercise and mindfulness meditation, for increasing TL or telomerase activity (T. L. Jacobs et al., 2011; Puterman et al., 2010; Schutte & Malouff, 2014). To this researcher's knowledge, the role of psychological stressors and/or health behaviors in relations of TL attrition and cognitive decline has not been previously examined. Increasing our understanding of how these factors influence concurrent cellular and cognitive aging would increase the public health significance of the present work.

**Implications and Public Health Significance**

As described previously, identification of potentially modifiable risk factors for cognitive decline and dementia is of critical import. The present study sought to determine whether a marker of cellular aging – TL attrition – was associated with decline across key domains of cognitive function, and whether sociodemographic patterns mapped onto racial and socioeconomic disparities in clinical and subclinical brain health endpoints that tend to disproportionately impact African Americans and/or those living in poverty. Overall, the present findings indicate a possible role of TL attrition in aspects of executive functioning and memory, although change in TL was not associated with decline in most cognitive outcomes assessed herein. In addition, sociodemographic patterns were inconsistent and not in the hypothesized

patterns across cognitive outcomes. Given these inconsistencies and the equivocal prior literature examining TL-cognition associations, it is premature to draw conclusions regarding any individual-level and public health implications of the present work. At a minimum, the present findings justify future replication studies, and possibly research on mechanisms underlying potential relations of telomere dynamics to age-related cognitive trajectories. Perhaps most importantly, the present study's sociodemographic patterns support the need for biopsychosocial approaches to telomere science, which will likely have an increasingly important role in research on aging and age-related diseases, including cognitive decline.

## Conclusions

In conclusion, the present study demonstrated that associations between TL change and age-related cognitive decline may be domain-specific and vary by race and poverty status. Specifically, findings demonstrated that greater TL attrition was associated with steeper declines in (a) working memory among Whites living in poverty and African Americans living above poverty, (b) delayed verbal memory among Whites (irrespective of poverty status), and (c) verbal fluency among all participants (irrespective of race and poverty status). Subsequent adjustment for a marker of systemic inflammation and the presence of one or more cardiometabolic diseases did not result in attenuated effects.

These findings raise the possibility that cellular aging may have adverse effects on aspects of executive functioning and memory that may be disproportionate among select sociodemographic subgroups. Further, these associations appear to exist above and beyond the effects of chronological age on cognitive functioning. Going forward, researchers should attempt to replicate and extend these findings in novel samples of participants from racially/ethnically and socioeconomically diverse groups living in urban and non-urban settings. Future research

should also seek to clarify potential mediating effects of inflammatory markers, including cytokines, and cardiometabolic risk factors through use of comprehensive measures and formal mediation approaches. Other potential mediators that could be examined in future research are neuroanatomical measures and markers of dementia pathology. Ultimately, clarification of biological indicators underlying associations between TL change and executive functioning and memory trajectories may pave the way for

**Table 1**

*Participant Characteristics Stratified by Self-Identified Race and Poverty Status and in the Overall Sample at Baseline and Follow-up*

(a) Baseline (Wave 1)

| Variable | AA (*n*=139) | White (*n*=127) | sig. | Above Poverty (*n*=135) | Below Poverty (*n*=131) | sig. | All (*N*=266) |
|---|---|---|---|---|---|---|---|
| African American, *n* (%) | — | — | — | 78 (57.8%) | 61 (46.6%) | nd | 139 (52.3%) |
| Below poverty, *n* (%) | 61 (43.8%) | 70 (55.1%) | nd | — | — | — | 131 (49.2%) |
| Women, *n* (%) | 68 (48.9%) | 66 (57.3%) | nd | 71 (52.6%) | 63 (48.1%) | nd | 134 (50.3%) |
| < HS/GED, *n* (%) | 40 (28.7%) | 49 (62.8%) | nd | 33 (24.4%) | 56 (42.7%) | ** | 89 (33.5%) |
| Age, *M* (*SD*) | 48.0 (9.6) | 48.1 (8.0) | nd | 47.7 (9.5) | 48.4 (8.2) | nd | 48.0 (8.9) |
| hsCRP (mg/L), *M* (*SD*) | 5.8 (16.0) | 4.5 (8.0) | nd | 4.5 (8.4) | 6.0 (6.3) | nd | 5.2 (12.9) |
| Cardiometabolic diseases, *n* (%) | 70 (50.4%) | 51 (67.0%) | nd | 60 (44.4%) | 61 (46.6 %) | nd | 121 (45.5%) |
| Telomere length (kb), *M* (*SD*) | 5.6 (0.7) | 5.7 (0.7) | nd | 5.7 (0.6) | 5.6 (0.8) | nd | 48.0 (8.9) |

(b) Follow-up (Wave 3)

| Variable | AA (*n*=157) | White (*n*=147) | sig. | Above Poverty (*n*=155) | Below Poverty (*n*=149) | sig. | All (*N*=304) |
|---|---|---|---|---|---|---|---|
| African American, *n* (%) | — | — | — | 85 (54.8%) | 72 (48.3%) | nd | 157 (51.6%) |
| Below poverty, *n* (%) | 72 (45.6%) | 77 (52.4%) | nd | — | — | — | 149 (49.0%) |
| Women, *n* (%) | 81 (51.6%) | 77 (52.4%) | nd | 81 (52.2%) | 72 (48.3%) | nd | 158 (51.9%) |
| < HS/GED, *n* (%) | 46 (29.3%) | 57 (38.8%) | nd | 38 (24.5%) | 6≥ (43.6%) | *** | 201 (33.9%) |
| Age, *M* (*SD*) | 52.5 (9.5) | 52.8 (0.5) | nd | 52.0 (9.5) | 53.3 (8.4) | nd | 52.6 (9.0) |
| hsCRP (mg/L), *M* (*SD*) | 7.1 (12.4) | 7.0 (8.7) | nd | 5.3 (8.4%) | 8.9 (7.3) | ** | 7.0 (10.8) |
| Cardiometabolic diseases, *n* (%) | 94 (59.9%) | 80 (54.4%) | nd | 81 (52.3%) | 93 (14.9%) | nd | 174 (57.2%) |
| Telomere length (kb), *M* (*SD*) | 5.6 (0.9) | 5.7 (7.6) | nd | 5.7 (0.6) | 5.6 (0.8) | nd | 5.6 (0.7) |

*Note*. AA = African American; HS/GED = High school or general education diploma; kb = kilobase pairs; hsCRP = High-sensitivity C-reactive protein; Cardiometabolic diseases = Presence of one or more cardiometabolic diseases. Independent samples *t*-tests and $\chi^2$ tests of independence were used to assess differences between race and sex groups.

* $p < .05$

** $p < .01$

*** $p < .001$

nd = nonsignificant difference ($p \geq .05$)

**Table 2**

*Bivariate Correlations among Study Variables*

| Variable | 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. | 11. | 12. | 13. | 14. | 15. | 16. | 17. | 18. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Race | 1.0 | | | | | | | | | | | | | | | | | |
| 2. Poverty Status | -.09* | 1.0 | | | | | | | | | | | | | | | | |
| 3. Sex | .02 | .02 | 1.0 | | | | | | | | | | | | | | | |
| 4. Age | -.01 | .05 | .03 | 1.0 | | | | | | | | | | | | | | |
| 5. TL change (Δkb) | -.02 | -.01 | -.00 | .04 | 1.0 | | | | | | | | | | | | | |
| 6. Baseline TL (kb) | -.05 | -.07 | .18** | -.11** | -.39** | 1.0 | | | | | | | | | | | | |
| 7. HS education | .10 | -.20** | .05 | .03 | .06 | .03 | 1.0 | | | | | | | | | | | |
| 8. hsCRP (mg/L) | .03 | .11** | -.12** | .07 | -.08* | -.12** | -.13** | 1.0 | | | | | | | | | | |
| 9. Cardiometabolic | .08 | .06 | -.03 | .37** | -.02 | -.06 | .01 | .13** | 1.0 | | | | | | | | | |
| 10. DSF | -.19** | -.08 | -.05 | -.14** | .01 | .07 | .18** | -.03 | -.06 | 1.0 | | | | | | | | |
| 11. DSB | -.18** | -.06 | -.06 | -.07 | -.00 | .08 | .22** | -.07 | -.04 | .57** | 1.0 | | | | | | | |
| 12. TMT Part A (sec) | .24** | .17** | .10* | .21** | -.03 | -.05 | -.16** | -.04 | .14** | -.34** | -.31** | 1.0 | | | | | | |
| 13. TMT Part B (sec) | .26** | .17** | .02 | .19** | -.05 | -.10* | -.26** | .16** | .17** | -.35** | -.46** | .57** | 1.0 | | | | | |
| 14. Animal Naming | -.16** | .07 | .07 | -.18** | .02 | .09* | .22** | -.06 | -.08 | .24** | .32** | -.30** | -.39** | 1.0 | | | | |
| 15. BVRT | .06 | .12** | -.11** | .29** | -.02 | -.07 | -.17** | .15** | .16** | -.24** | -.30** | .30** | .45** | -.36** | 1.0 | | | |
| 16. CVLT learning | .14** | .07 | -.17** | -.24** | .03 | -.07 | .19** | -.09* | -.07 | .18** | .25** | .29** | -.42** | .36** | -.41** | 1.0 | | |
| 17. CVLT sdfr | .23** | .03 | -.15** | -.27** | .03 | .00 | .10* | -.10* | -.06 | .20** | .32** | .29** | -.43** | .38** | -.38** | .81** | 1.0 | |
| 18. CVLT ldfr | .20** | .09 | -.12** | -.29** | .03 | -.01 | .13** | .13** | -.06 | .16** | .26** | .29** | -.39** | .36** | -.36** | .79** | .86** | 1.0 |

*Note*. Race (0: White, 1: African American); Poverty Status (0: Above, 1: Below); Sex (0: Women, 1: men); TL = Telomere length; kb = kilobase pairs; HS education = High school-or-greater education (0: ≥HS/GED, 1: <HS); hsCRP = High-sensitivity C-reactive protein; Cardiometabolic = Presence of one or more cardiometabolic diseases (0: No, 1: Yes); DSF = Digit Span Forward; DSB = Digit Span Backward; TMT = Trail Making Test; BVRT = Brief Visuospatial Memory Test (total errors); CVLT = California Verbal Learning Test-II; CVLT learning = CVLT total learning trials; CVTL sdfr = CVLT short delay free recall; CVLT ldfr = CVLT long delay free recall. The TMT Parts A and B and BVRT were log-transformed to correct for non-normally distributed residuals

* $p < .05$

** $p < .01$

**Table 3**

*Interactive Relations of TL Change, Poverty Status, Race, and Age with Change in Digit Span Backward (N = 317)*

| Variable | *b* | *se* | *p* |
|---|---|---|---|
| TL change | 0.78 | 0.38 | .039 |
| Poverty status | -0.14 | 0.32 | .666 |
| Race | -0.90 | 0.31 | .004 |
| Age | -0.00 | 0.02 | .949 |
| Sex | -0.18 | 0.23 | .419 |
| High school-or-greater education | 1.10 | 0.24 | <.001 |
| Baseline TL | 0.18 | 0.17 | .286 |
| TL Change × Poverty Status | -1.26 | 0.46 | .006 |
| TL Change × Race | -0.70 | 0.49 | .156 |
| TL Change × Age | 0.02 | 0.04 | .639 |
| Poverty Status × Race | 0.13 | 0.44 | .776 |
| Poverty Status × Age | -0.02 | 0.44 | .477 |
| Race × Age | -0.03 | 0.03 | .398 |
| TL Change × Poverty Status × Race | 1.23 | 0.67 | .069 |
| TL Change × Poverty Status × Age | 0.06 | 0.05 | .240 |
| TL Change × Race × Age | 0.05 | 0.05 | .378 |
| Poverty Status × Race × Age | 0.06 | 0.05 | .192 |
| TL Change × Poverty Status × Race × Age | -0.16 | 0.07 | .023 |

*Note.* TL = Telomere length

**Table 4**

*Interactive Relations of TL Change, Poverty Status, Race, and Age with Change in CVLT Long-Delay Free Recall (N = 308)*

| Variable | Model 1 | **Model 2** |
|---|---|---|
| TL change | 0.68 | **0.73** |
| Poverty status | -0.34 | **-0.33** |
| Race | -1.93*** | **-1.93*****|
| Age | -0.16*** | **-0.16*****|
| Sex | -0.82* | **-0.80*** |
| High school-or-greater education | 0.92** | **0.94**** |
| Baseline TL | -0.19 | **-0.19** |
| TL Change × Poverty Status | -1.07 | **-1.18** |
| TL Change × Race | -1.15 | **-1.19** |
| TL Change × Age | 0.18** | **0.15**** |
| Poverty Status × Race | 0.58 | **0.58** |
| Poverty Status × Age | 0.03 | **0.03** |
| Race × Age | 0.05 | **0.05** |
| TL Change × Poverty Status × Race | 2.32* | **2.58*** |
| TL Change × Poverty Status × Age | -0.11 | **-0.04** |
| TL Change × Race × Age | -0.22** | **-0.15**** |
| Poverty Status × Race × Age | -0.04 | **-0.04** |
| TL Change × Poverty Status × Race × Age | 0.12 | |

*Note.* CVLT = California Verbal Learning Test-II, TL = Telomere length. Unstandardized regression coefficients (*b*) across two model iterations. Model 2 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 5**

*Interactive Relations of TL Change, Poverty Status, Race, and Age with Change in Verbal Fluency (N = 319)*

| Variable | Model 1 | Model 2 | **Model 3** |
|---|---|---|---|
| TL change | -0.18 | -0.22 | **0.00** |
| Poverty status | -0.17 | -0.17 | **-0.13** |
| Race | -2.00*** | -2.00*** | **2.01*** |
| Age | -0.16*** | -0.16** | **-0.15**** |
| Sex | 0.82 | 0.81 | **0.82** |
| High school-or-greater education | 2.57*** | 2.56*** | **2.59*** |
| Baseline TL | 0.17 | 0.16 | **0.15** |
| TL Change × Poverty Status | -0.65 | -0.59 | **-0.95** |
| TL Change × Race | 0.85 | 0.89 | **0.60** |
| TL Change × Age | 0.12 | 0.13 | **0.09*** |
| Poverty Status × Race | -0.07 | -0.07 | **-0.10** |
| Poverty Status × Age | 0.10 | 0.10 | **0.07** |
| Race × Age | 0.05 | 0.05 | **0.03** |
| TL Change × Poverty Status × Race | -0.13 | -0.27 | |
| TL Change × Poverty Status × Age | -0.05 | -0.08 | |
| TL Change × Race × Age | 0.02 | -0.01 | |
| Poverty Status × Race × Age | 0.01 | -0.05 | |
| TL Change × Poverty Status × Race × Age | -0.00 | | |

*Note.* TL = Telomere length. Unstandardized regression coefficients (*b*) across three model iterations. Model 3 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 6**

*All Mixed-Effects Regression Models for Digit Span Forward (N = 312)*

| Variable | Model 1 | Model 2 | Model 3 | **Model 4** |
|---|---|---|---|---|
| TL change | 0.15 | 0.19 | 0.25 | **0.00** |
| Poverty status | -0.14 | -0.13 | -0.15 | **-0.14** |
| Race | -0.79* | -0.79* | -0.79* | **-0.78***** |
| Age | -0.02 | -0.01 | 0.03 | **-0.03*** |
| Sex | -0.27 | -0.26 | -0.26 | **-0.26** |
| High school-or-greater education | 0.95*** | 0.96*** | 0.95*** | **-0.93***** |
| Baseline TL | 0.14 | 0.14 | 0.14 | **0.09** |
| TL Change × Poverty Status | 0.09 | 0.02 | -0.13 | |
| TL Change × Race | -0.14 | -0.17 | -0.35 | |
| TL Change × Age | -0.02 | -0.04 | 0.00 | |
| Poverty Status × Race | -0.03 | -0.03 | 0.01 | |
| Poverty Status × Age | 0.01 | 0.01 | 0.03 | |
| Race × Age | -0.04 | -0.04 | -0.02 | |
| TL Change × Poverty Status × Race | -0.77 | -0.62 | | |
| TL Change × Poverty Status × Age | -0.00 | 0.03 | | |
| TL Change × Race × Age | 0.02 | 0.05 | | |
| Poverty Status × Race × Age | 0.04 | 0.05 | | |
| TL Change × Poverty Status × Race × Age | 0.06 | | | |

*Note.* TL = Telomere length. Unstandardized regression coefficients (*b*) across four model iterations. Model 4 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 7**

*All Mixed-Effects Regression Models for the CVLT Total Learning (N = 310)*

| Variable | Model 1 | Model 2 | Model 3 | **Model 4** |
|---|---|---|---|---|
| TL change | 0.73 | 0.64 | 0.56 | **-0.11** |
| Poverty status | -0.69 | -0.70 | -0.62 | **-0.42** |
| Race | -3.05** | -3.05** | -3.04** | **-2.79**** |
| Age | -0.39*** | -0.40*** | -0.35*** | **-0.28***** |
| Sex | -2.07** | -2.10** | -2.09** | **-2.21**** |
| High school-or-greater education | 3.31*** | 3.29*** | 2.59*** | **3.35***** |
| Baseline TL | -1.35* | -1.35* | -1.33* | **-1.26*** |
| TL Change × Poverty Status | -1.94 | -1.74 | -1.39 | |
| TL Change × Race | -0.63 | -0.57 | -0.19 | |
| TL Change × Age | 0.19 | 0.25* | 0.09 | |
| Poverty Status × Race | 0.48 | 0.47 | 0.35 | |
| Poverty Status × Age | 0.05 | 0.05 | -0.03 | |
| Race × Age | 0.22* | 0.22* | 0.14 | |
| TL Change × Poverty Status × Race | 2.24 | 1.81 | | |
| TL Change × Poverty Status × Age | -0.02 | -0.13 | | |
| TL Change × Race × Age | -0.07 | -0.18 | | |
| Poverty Status × Race × Age | -0.16 | -0.16 | | |
| TL Change × Poverty Status × Race × Age | -0.20 | | | |

*Note.* CVLT = California Verbal Learning Test-II, TL = Telomere length. Unstandardized regression coefficients (*b*) across four model iterations. Model 4 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 8**

*All Mixed-Effects Regression Models for the CVLT Short-Delay Free Recall (N = 319)*

| Variable | Model 1 | Model 2 | Model 3 | **Model 4** |
|---|---|---|---|---|
| TL change | 0.57 | 0.63 | 0.55 | **0.11** |
| Poverty status | -0.73 | -0.72 | -0.68 | **-0.38** |
| Race | -1.90*** | -0.18*** | -1.89*** | **-1.60*** ** |
| Age | -0.18* | -0.16*** | -0.16*** | **-0.12*** ** |
| Sex | -0.56 | -0.54 | 0.54 | **-0.60** |
| High school-or-greater education | 1.00** | 1.02** | 1.02*** | **1.05** ** |
| Baseline TL | -0.32 | -0.32 | -0.31 | |
| TL Change × Poverty Status | -0.93 | -1.05 | -0.83 | |
| TL Change × Race | -0.28 | -0.33 | -0.07 | |
| TL Change × Age | 0.14* | 0.10* | 0.03* | |
| Poverty Status × Race | 0.59 | 0.59 | 0.54 | |
| Poverty Status × Age | 0.05 | 0.04 | 0.01 | |
| Race × Age | 0.08 | 0.08 | 0.05 | |
| TL Change × Poverty Status × Race | 0.69 | 0.98 | | |
| TL Change × Poverty Status × Age | -0.12 | -0.05 | | |
| TL Change × Race × Age | -0.16* | -0.09 | | |
| Poverty Status × Race × Age | -0.07 | -0.07 | | |
| TL Change × Poverty Status × Race × Age | 0.13 | | | |

*Note.* CVLT = California Verbal Learning Test-II, TL = Telomere length. Unstandardized regression coefficients (*b*) across four model iterations. Model 4 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 9**

*All Mixed-Effects Regression Models for the Trail Making Test Part A (N = 319)*

| Variable | Model 1 | Model 2 | Model 3 | **Model 4** |
|---|---|---|---|---|
| TL change | -0.02 | -0.01 | -0.00 | **-0.01** |
| Poverty status | 0.10 | 0.10 | 0.10 | **0.12**** |
| Race | 0.23*** | 0.22*** | 0.23*** | **0.25***** |
| Age | 0.01* | 0.01* | 0.01* | **0.01***** |
| Sex | 0.09* | 0.09* | 0.09* | **0.09*** |
| High school-or-greater education | -0.16*** | -0.16*** | -0.16*** | **-0.16***** |
| Baseline TL | -0.01 | -0.01 | -0.01 | **-0.01** |
| TL Change × Poverty Status | 0.04 | 0.02 | -0.01 | |
| TL Change × Race | 0.03 | 0.02 | 0.00 | |
| TL Change × Age | -0.00 | -0.01 | -0.00* | |
| Poverty Status × Race | 0.04 | 0.04 | 0.04 | |
| Poverty Status × Age | -0.01 | 0.00 | 0.00 | |
| Race × Age | -0.01 | -0.01 | -0.00 | |
| TL Change × Poverty Status × Race | -0.11 | -0.06 | | |
| TL Change × Poverty Status × Age | -0.01 | 0.00 | | |
| TL Change × Race × Age | -0.00 | 0.01 | | |
| Poverty Status × Race × Age | 0.00 | 0.00 | | |
| TL Change × Poverty Status × Race × Age | 0.02 | | | |

*Note.* TL = Telomere length. Trail Making Test Part A was log-transformed to correct for non-normally distributed residuals. Unstandardized regression coefficients (*b*) across four model iterations. Model 4 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 10**

*All Mixed-Effects Regression Models for the Trail Making Test Part B (N = 319)*

| Variable | Model 1 | Model 2 | Model 3 | **Model 4** |
|---|---|---|---|---|
| TL change | -0.05 | -0.06 | 0.02 | **-0.01** |
| Poverty status | 0.13 | 0.13 | 0.12 | **-0.38***** |
| Race | 0.35*** | 0.36*** | 0.36*** | **0.15*** |
| Age | 0.01* | 0.01* | 0.01 | **0.01***** |
| Sex | 0.04 | 0.04 | 0.04 | **0.04** |
| High school-or-greater education | -0.36*** | -0.36*** | -0.37*** | **-0.36***** |
| Baseline TL | -0.03 | -0.03 | -0.03 | **-0.03** |
| TL Change × Poverty Status | 0.12 | 0.13 | 0.01 | |
| TL Change × Race | 0.07 | 0.07 | -0.05 | |
| TL Change × Age | -0.01 | -0.01 | -0.00* | |
| Poverty Status × Race | 0.05 | 0.04 | 0.05 | |
| Poverty Status × Age | -0.00 | -0.00 | 0.01 | |
| Race × Age | -0.00 | -0.00 | 0.00 | |
| TL Change × Poverty Status × Race | -0.24 | -0.24 | | |
| TL Change × Poverty Status × Age | 0.00 | 0.00 | | |
| TL Change × Race × Age | 0.01 | 0.01 | | |
| Poverty Status × Race × Age | 0.01 | 0.01 | | |
| TL Change × Poverty Status × Race × Age | -0.01 | | | |

*Note.* TL = Telomere length. Trail Making Test Part B was log-transformed to correct for non-normally distributed residuals. Unstandardized regression coefficients (*b*) across four model iterations. Model 4 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 11**

*All Mixed-Effects Regression Models for the BVRT (N = 318)*

| Variable | Model 1 | Model 2 | Model 3 | **Model 4** |
|---|---|---|---|---|
| TL change | -0.21 | -0.20 | -0.08 | **-0.04** |
| Poverty status | 0.22* | 0.22* | 0.22* | **0.13** |
| Race | 0.22* | 0.21* | 0.21* | **0.13** |
| Age | 0.04*** | 0.04*** | 0.03*** | **0.03*** ** |
| Sex | -0.20** | -0.19** | -0.19** | **-2.45*** ** |
| High school-or-greater education | -0.25** | -0.25** | -0.26** | **0.00** |
| Baseline TL | 0.01 | 0.01 | 0.01 | |
| TL Change × Poverty Status | 0.30 | 0.27 | 0.11 | |
| TL Change × Race | 0.18 | 0.16 | -0.04 | |
| TL Change × Age | 0.01 | -0.00 | -0.00 | |
| Poverty Status × Race | -0.17 | -0.17 | -0.15 | |
| Poverty Status × Age | -0.02 | -0.02 | -0.00 | |
| Race × Age | -0.02 | -0.02 | -0.01 | |
| TL Change × Poverty Status × Race | -0.40 | -0.35 | | |
| TL Change × Poverty Status × Age | -0.01 | 0.00 | | |
| TL Change × Race × Age | -0.01 | -0.00 | | |
| Poverty Status × Race × Age | 0.02 | 0.02 | | |
| TL Change × Poverty Status × Race × Age | 0.02 | | | |

*Note.* BVRT = Brief Visuospatial Memory Test, TL = Telomere length. The BVRT was log-transformed to correct for non-normally distributed residuals. Unstandardized regression coefficients (*b*) across four model iterations. Model 4 (shown in **bold** above) was retained as the final regression model

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 12**

*Regression Coefficients for the Digit Span Backward Model Adjusted for High-Sensitivity C-Reactive Protein and the Presence of One or More Cardiometabolic Diseases (N = 317)*

| Variable | Previous Model | +hsCRP | +Cardiometabolic |
|---|---|---|---|
| TL change | 0.78* | 0.78* | 0.79* |
| Poverty status | -0.14 | -0.10 | -0.09 |
| Race | -0.90** | -0.87** | -0.87** |
| Age | -0.00 | -0.00 | -0.00 |
| Sex | -0.18 | -0.17 | -0.18 |
| High school-or-greater education | 1.10*** | 0.11*** | 0.19*** |
| Baseline TL | 0.18 | 0.18 | 1.11 |
| TL Change × Poverty Status | -1.26** | -1.26** | -1.25** |
| TL Change × Race | -0.70 | -0.70 | -0.69 |
| TL Change × Age | 0.02 | -0.18 | 0.02 |
| Poverty Status × Race | 0.13 | 0.07 | 0.07 |
| Poverty Status × Age | -0.02 | -0.03 | -0.03 |
| Race × Age | -0.03 | -0.03 | -0.03 |
| TL Change × Poverty Status × Race | 1.23 | 1.25 | 1.23 |
| TL Change × Poverty Status × Age | 0.06 | 0.06 | 0.06 |
| TL Change × Race × Age | 0.05 | 0.05 | 0.05 |
| Poverty Status × Race × Age | 0.06 | 0.07 | 0.07 |
| TL Change × Poverty Status × Race × Age | -0.16* | -0.16* | -0.16* |
| hsCRP | | 0.00 | 0.00 |
| Cardiometabolic | | | -0.06 |

*Note.* TL = Telomere length; hsCRP = High-sensitivity C-reactive protein; Cardiometabolic = Presence of one or more cardiometabolic diseases. Unstandardized regression coefficients (*b*) from the previous final model (see Table 3) and with additional adjustment for sensitivity variables.

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 13**

*Regression Coefficients for the CVLT Long Delay Free Recall Model Adjusted for High-Sensitivity C-Reactive Protein and the Presence of One or More Cardiometabolic Diseases (N = 308)*

| Variable | Previous Model | +hsCRP | +Cardiometabolic |
|---|---|---|---|
| TL change | 0.73 | 0.69 | 0.75 |
| Poverty status | -0.33 | -0.28 | -0.28 |
| Race | -1.93*** | -1.89*** | -1.91*** |
| Age | -0.16*** | -0.17*** | -0.18*** |
| Sex | -0.80* | -0.85** | -0.83** |
| High school-or-greater education | 0.94** | 0.87* | 0.86* |
| Baseline TL | -0.19 | -0.26 | -0.25 |
| TL Change × Poverty Status | -1.18 | -1.19 | -1.26 |
| TL Change × Race | -1.19 | -1.19 | -1.28 |
| TL Change × Age | 0.15** | -0.14** | -0.15** |
| Poverty Status × Race | 0.58 | 0.58 | 0.53 |
| Poverty Status × Age | 0.03 | 0.04 | 0.03 |
| Race × Age | 0.05 | 0.06 | 0.06 |
| TL Change × Poverty Status × Race | 2.58* | 2.47* | 2.67** |
| TL Change × Poverty Status × Age | -0.04 | -0.05 | -0.04 |
| TL Change × Race × Age | -0.15** | -0.16** | -0.16** |
| Poverty Status × Race × Age | -0.04 | -0.05 | -0.04 |
| hsCRP | | -0.03* | -0.03** |
| Cardiometabolic | | | 0.68* |

*Note.* TL = Telomere length; hsCRP = High-sensitivity C-reactive protein; Cardiometabolic = Presence of one or more cardiometabolic diseases. Unstandardized regression coefficients (*b*) from the previous final model (see Table 4) and with additional adjustment for sensitivity variables.

* $p < .05$

** $p < .01$

*** $p < .001$

**Table 14**

*Regression Coefficients for the Verbal Fluency Model Adjusted for High-Sensitivity C-Reactive Protein and the Presence of One or More Cardiometabolic Diseases (N = 308)*

| Variable | Previous Model | +hsCRP | +Cardiometabolic |
|---|---|---|---|
| TL change | 0.00 | 0.00 | -0.01 |
| Poverty status | -0.13 | -0.13 | -0.14 |
| Race | 2.01** | -2.02** | -2.03** |
| Age | -0.15** | -1.50** | -0.16** |
| Sex | 0.82 | -0.84 | 0.85 |
| High school-or-greater education | 2.59*** | 2.60*** | 2.59*** |
| Baseline TL | 0.15 | -0.16 | 0.16 |
| TL Change × Poverty Status | -0.95 | -0.93 | -0.93 |
| TL Change × Race | 0.60 | -0.62 | 0.64 |
| TL Change × Age | 0.09* | -0.09* | 0.94* |
| Poverty Status × Race | -0.10 | -1.11 | -0.14 |
| Poverty Status × Age | 0.07 | 0.07 | 0.07 |
| Race × Age | 0.03 | 0.03 | 0.03 |
| hsCRP | | 0.01 | 0.01 |
| Cardiometabolic | | | 0.37 |

*Note.* TL = Telomere length; hsCRP = High-sensitivity C-reactive protein; Cardiometabolic = Presence of one or more cardiometabolic diseases. Unstandardized regression coefficients (*b*) from the previous final model (see Table 5) and with additional adjustment for sensitivity variables.

* $p < .05$

** $p < .01$

*** $p < .001$

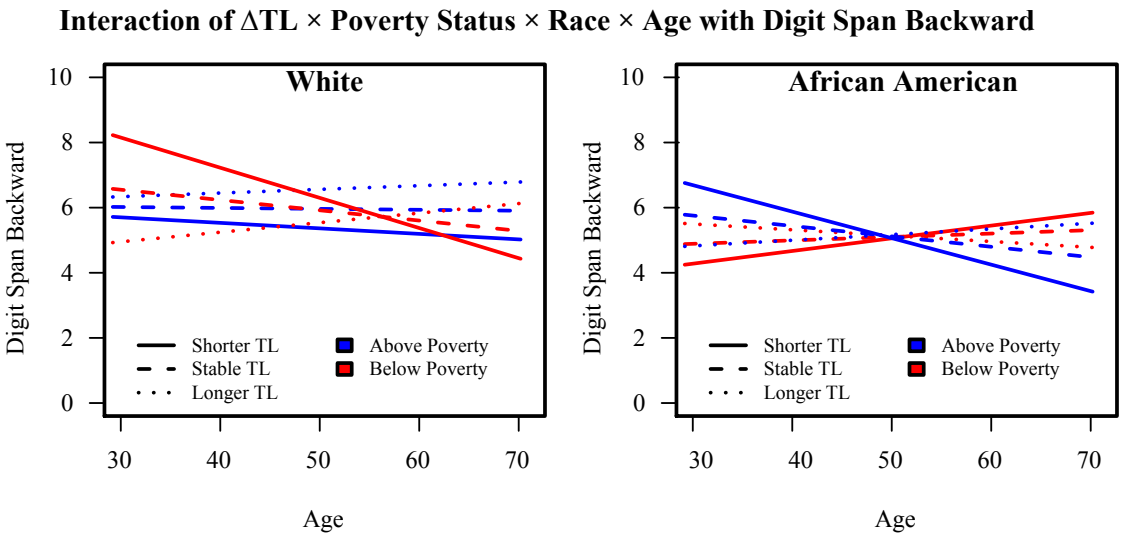


**Figure 1.** Significant four-way interaction of Telomere Length Change × Poverty Status × Race × Age with change in Digit Span Backward performance.

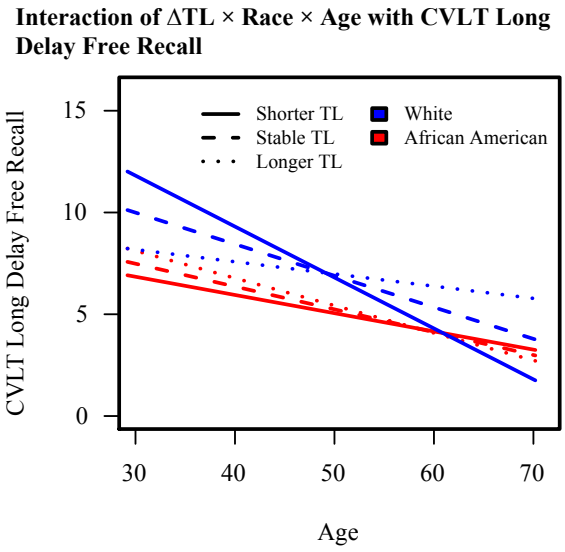


**Figure 2.** Significant three-way interaction of Telomere Length Change × Race × Age with change in CVLT long delay free recall performance.

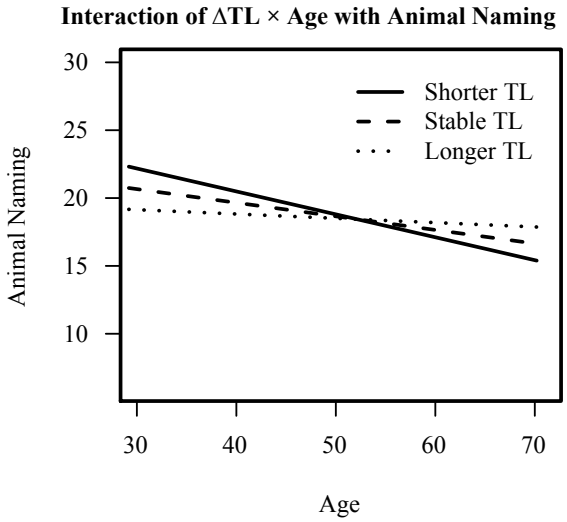


**Figure 3.** Significant three-way interaction of Telomere Length Change × Age with change in Animal Naming

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