THE ASSOCIATION OF AFFECTIVE, BEHAVIORAL, AND COGNITIVE

COMPONENTS OF HOSTILITY

WITH TELOMERE LENGTH, A MARKER OF BIOLOGICAL AGING

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Variability within species in the rate of biological aging and noticeable differences in susceptibility to diseases of aging suggest ecological factors, such as trait characteristics, may contribute to individual vulnerability. In this regard, some evidence shows a relationship between hostile tendencies and risk for the most prevalent disease of aging, coronary heart disease (CHD). One plausible pathway through which hostility may increase risk for such age-related disease is through premature cellular aging. Recent evidence suggests that the length of telomeres in cells provides a biomarker of biological aging that predicts all-cause mortality and coronary disease morbidity and mortality. The present study examined associations of hostile temperaments with telomere length in a sample of African American (n = 35) and European American (n = 160) men (aged 40-70 years) at increased risk for CHD by virtue of their hypertensive status. In addition, the moderation of this association by race and age was also explored. Results showed no significant associations of hostile affects, behaviors, or cognitions, as measured by the Cook-Medley Hostility (CMH) scale and the Speilberger State Trait Anger Expression Inventory (STAXI), and telomere length. Although race did not moderate any associations between hostility and telomere length, there was a trend towards significant interactions of age with hostile cognitions (β = .87, p = .06), CMH hostile affect (β = .91, p = .057), and STAXI anger-in (β = 1.01, p = .07) in the prediction of telomere length, suggesting an

inverse association of hostility with telomere length among younger subjects (40's), which may contribute to increased risk for diseases of aging in this age group. In contrast, older subjects (60's) showed a positive association of hostility with telomere length. In addition, across the whole sample, there was a significant positive association of years of education with telomere length ($r = .15$, $p < .05$). This association was independent of a number of demographic and health covariates among European Americans, but not African Americans, suggesting that among European American males with hypertension, those with fewer years of education show greater cellular aging. In contrast, hostility may be protective among older hypertensives.

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PREFACE

1.0   INTRODUCTION

Aging, or the process of growing older, refers to the accumulation of physical, psychological, and social changes that occur over time. Physically, these changes often include declines in function, marked by a decrease in physiological capacity and in the ability of the body to maintain homeostasis (Caruso & Silliman, 2008). This biological aging is related to cellular degeneration, which increases risk for the development of diseases of aging (Miller, 2000). Prevalent degenerative diseases associated with the aging process include cardiovascular disease, diabetes, arthritis, neurodegenerative diseases (e.g. Alzheimer's disease), and cancers of the breast, prostate, colorectal, lung, gastric system, head, and neck (Weinryb, Hsieh, & Lavizzo-Mourey, 2000). Variability within species in the rate of biological aging and noticeable differences in susceptibility to diseases of aging suggest ecological factors may contribute to individual vulnerability. Amongst the potential factors that could contribute to individual vulnerability are trait characteristics.

In particular, research on trait characteristics has shown a relationship between hostile tendencies and risk for the most prevalent disease of aging, coronary heart disease (CHD). This relationship is more reliable in younger populations and when hard disease outcomes are examined, with more hostile individuals showing higher rates of CHD mortality and morbidity than their less hostile counterparts (Krantz & McCeney, 2002; Miller et al., 1996; Barefoot et al., 1989). There are a number of ways that hostility might affect CHD disease susceptibility. One

plausible explanation is through the association of hostility with lifestyle-risk factors, such as obesity, poor diet, increased prevalence of smoking and alcohol consumption, and decreased rates of physical activity (Bunde & Suls, 2006; Siegler et al., 2003; Siegler, 1994). However, taken together, these lifestyle factors do not fully account for hostility-related increases in disease risk. Another possibility is that hostility covaries with known demographic risk factors for cardiovascular disease, such as race. In this regard, a consistent body of evidence shows that African Americans endorse higher levels of hostility than European Americans (Barefoot et al., 1991; Siegler, 1994), and are at increased risk for CHD mortality (Albert et al., 2004; Rosamond et al., 2007). Finally, it is widely suggested that biological pathways also play a role, with activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal cortical axis proposed to increase risk for disease (McEwen & Seeman, 1999). Hostility has been associated with activation of these biological pathways, and thus may contribute to hostility-CHD associations (Krantz & McCeney, 2002; Pope & Smith, 1991; Suarez et al., 1998).

Recent attention has turned to the possibility that psychological risk factors, such as stress, depression, pessimism, and possibly hostility result in premature cellular aging and thus increase vulnerability to diseases of aging (Epel et al., 2004; Lung, Chen, & Shu, 2007; O'Donovan et al., 2009; Simon et al., 2006). Here, studies have examined telomere length as a biomarker of biological aging (Bekaert, De Meyer, & Oostveldt, 2005). Telomeres are the non-genetic tandem DNA repeats on the end of chromosomes that protect DNA from loss during cell division (Blackburn, 1991). The length of telomeres gradually decreases each time the cell divides until they reach a critically short length, which activates cell cycle arrest (Blackburn, 1991). Thus, the length of telomeres shortens across the lifespan (Gilley et al., 2008). Recent evidence suggests that telomere length predicts all-cause mortality and coronary disease

morbidity and mortality, with individuals who have shorter telomeres being at increased risk for CHD and mortality independently of their chronological age (Bakaysa et al., 2007; Brouilette et al., 2007; Farzaney-Far et al., 2008; Fitzpatrick et al., 2007; Jiang et al., 2007). Thus, it has been suggested that telomere length is a marker of the biological age of the organism (Gilley et al, 2008; Jiang et al., 2007; Kirkwood & Austad, 2000).

Initial evidence suggests that psychological and demographic risk factors for CHD (Krantz & McCeney, 2002), such as psychological stress, depression, pessimism, socioeconomic status, and African American race also covary inversely with telomere length (Cherkas et al., 2006; Epel et al., 2004; Damjanovic et al., 2007; Diez-Roux et al., 2009; Lung et al., 2007; O'Donovan et al., 2009; Simon et al., 2006). Thus, it is possible that hostility also co-varies with cellular aging, suggesting a biological pathway through which hostility could increase disease risk. To begin to explore this possibility, the current study examined the association of hostile temperaments with telomere length among a sample of African American and European American, mid-life men at increased risk for CHD by virtue of their hypertensive status. In addition to examining associations between hostility and telomere length across the sample, we conducted exploratory analyses to examine the possibility that race and age moderated the strength of this association.

Before turning to the details of the study, several aspects of hostility and health will be reviewed. First, the nature of hostility, along with its cognitive, affective, and behavioral components, will be considered, followed by information about its measurement and relationship to disease. Differences in the prevalence of hostility and cardiovascular disease among Blacks and Whites will then be discussed. Following this, possible mechanisms linking this psychosocial risk factor to disease will be reviewed. Next, the role of telomere length as a

marker of biological aging will be considered and its association with other psychosocial risk factors and race examined. Finally, an overview of the proposed study will be provided.

1.1   HOSTILITY, ANGER, AND AGGRESSION: HISTORICAL ANTECEDENTS AND CURRENT CONCEPTUALIZATIONS

The identification of hostility as a risk factor for disease resulted from work examining psychosocial risk for coronary disease (Friedman et al., 1968; Friedman & Rosenman, 1974; Siegman & Smith, 1994). Initial work in this area identified the Type A coronary-prone behavior pattern (TABP), a dispositional clustering of characteristics, including impatience, ambitiousness, competitiveness, hostility, aggressive behavioral tendencies, and a sense of time urgency that was proposed to increase risk for CVD (Friedman & Rosenman, 1974). A number of studies showed increased risk for heart disease among individuals exhibiting TABP after controlling for traditional risk factors (Rosenman et al., 1975; Friedman, et al., 1968; Blumenthal et al, 1978). However, not all findings were consistent (Shekelle et al., 1985; Dembroski et al., 1985; Krantz et al., 1979). Inconsistent findings led to a close examination of whether some sub-components of the syndrome conferred greater disease risk than others. In this regard, it was proposed that a predisposition toward hostility, and the tendency to experience anger and irritation, were particularly "toxic" elements of the TABP (Matthews et al., 1977). Empirical evidence provided support for hostility as an active ingredient of TAPD (Dembroski et al., 1985), and associations between hostility and risk for heart disease were identified in a number

of studies that had previously shown no association between TABP and CHD incidence[1] (Dembroski et al, 1989; Shekelle et al., 1985).

1.1.1 Defining Hostility

Buss (1961) delineated hostility from anger and aggression by defining *hostility* as negative attitudes towards others, *anger* as negative emotional responses, and *aggression* as behavioral responses directed toward another, whether verbal or physical in nature. More recent conceptualizations of *hostility* characterize it as multidimensional, encompassing affective, behavior, and cognitive (ABC) elements (Barefoot et al., 1989; Siegman, 1994; Smith, 1994). The affective component, also referred to as the experiential aspect of hostility, describes the tendency to frequently experience anger, varying from mild irritability to full blown rage, accompanied by other closely related negative emotions including: resentment, hate, disgust, and envy (Smith, 1994). The behavioral element, also referred to as the expressive element, is characterized by aggressive verbal and physical behavior towards others. Physical aggression presents with either overt behavior, such as violent acts, or with more passive aggressive behaviors (Smith, 1994). Verbally aggressive individuals may use rudeness, sarcasm, overt derogation, or insult to show aggression. They may likewise act in a competitive manner during conversations by frequently cutting others off, raising the volume of their speech, making snide comments, and using terse responses. Lastly, the cognitive elements include thoughts of

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[1] Dembroski et al. (1989) report antagonistic hostility as the strongest predictor of incident CHD, independent of traditional risk factors.

cynicism and social mistrust, with hostile individuals often harboring skepticism of others, expectations of antagonistic interactions, and a belief that people are not to be trusted and are driven by selfish motives (Smith, 1994).

These dimensions of hostile temperament often co-occur and can affect each other in a multidirectional manner. For example, emotional experiences of anger can be a consequence or a cause of the cognitive and aggressive elements. Similarly, hostile attitudes may generate angry feelings and aggressive behavior, but may also be the result of anger and overt aggressive behaviors (Buss, 1961). Thus, although clear theoretical distinctions between hostile cognitions, affect, and behaviors can be made, a great deal of overlap exists.

One frequently used measure of hostility when examining the association between hostility and health outcomes is the Cook-Medley Hostility (CMH) Scale (Cook & Medley, 1954). Barefoot and colleagues (1989) adapted the original version of this scale, by removing items that were unrelated to the affective, behavioral, and cognitive dimensions of hostility to derive a four subscale measure of hostile temperament. These subscales were based on theoretically driven item analysis and proposed to measure hostile cognitions (cynicism and hostile attributions), hostile affect, and hostile behavior (aggressive responding) (Barefoot et al., 1989). The *cynicism* subscale includes items reflecting a general worldview that others are deceitful and untrustworthy, while the *hostile attribution* subscale items tap the belief that the individual is the target of others ill will, jealously, and criticism, and that as such they are not to be trusted. Items on the *hostile affect* subscale assess the tendency to experience anger, annoyance, impatience, disappointment, and contempt under specific circumstances. Items measuring *aggressive responding* reflect a tendency to be competitive, give payback, act for selfish gain, and act in a generally rude and defensive demeanor. Although these later subscales

are labeled as tapping affective and behavioral hostility, they also contain cognitive elements, thus limiting their ability to assess unique behavioral or affective dimensions. As such, it has been suggested that the CMH scale primarily taps hostile cognitions (Costa et al., 1986; Martin et al., 2000; Miller et al., 1996).

Another measure of the affective and behavioral components of hostility that is widely used in the literature is Speilberger's Trait Anger and Anger Expression Scale (STAXI; Speilberger, 1988). In this measure, individuals report their proneness to experiencing anger (*Trait Anger*), and their typical style of anger expression, either outwardly expressive of their emotion (*Anger-Out*), actively inhibiting the expression of their anger while continuing to experience these feelings (*Anger-In*), or successfully regulating the emotional response (*Anger-Control*) (Spielberger, 1988). Trait anger can also be broken down into two elements: 1. *Anger temperament,* a general tendency to experience anger without provocation, and 2. *Anger Reactions,* a general tendency to feel anger when criticized or being mistreated (Spielberger, 1994). However, it should be noted that this affective response measure also contains items assessing behavioral and cognitive elements (Miller et al., 1996). For example, anger-out contains items that reflect a tendency to display aggressive behaviors, while anger-in also taps aspects of hostile cognitions such as brooding, cynicism, and mistrust (Miller et al., 1996).

Although the CMH scale and the STAXI have some construct overlap, there are clear differences between the dimensions of hostility they are measuring. While the CMH scale devotes much of its attention to hostile cognitions, the STAXI seeks to measure hostile affective experience and differential styles of expression. Interestingly, there is some evidence that these dimensions differentially predict CHD morbidity and mortality, as discussed below.

1.2   HOSTILITY AND CHD: MECHANISMS TO DISEASE

Although a large literature supports associations of hostile tendencies with CHD (see Siegman, 1994; Chida & Steptoe, 2009; Miller et al., 1996; Myrtek et al., 2001; Krantz & McCeney, 2002), not all findings are consistent. Debate remains regarding whether the general tendency towards hostility or its cognitive, affective, or behavioral sub-dimensions are the primary contributor to disease risk. While some findings suggest that deconstructing hostility into cognitive, affective, and behavioral components may help to shed light on the unique contribution of each to disease risk, additional research in this area is necessary (Miller et al., 1996; Lahad et al., 1997; Smith et al., 2004).

1.2.1   Hostility and CHD

Numerous reviews have focused on hostility as a psychological risk factor for CHD (Kuper et al., 2002; Miller et al., 1996; Myrtek, 2001; Chida & Steptoe, 2009), with some reviews concluding that there is no association (Kuper, Marmot, & Hemingway, 2002; Bunker et al., 2003), others suggesting that hostility is a risk factor only for younger populations (Miller et al., 1996; Krantz and McCeney, 2002), yet others concluding that hostility is associated with increased risk for disease (i.e. MI, mortality) (Myrtek, 2001), or that the association is present but attributable to covariates, such as lifestyle risk factors (Siegler, 1994; Chida & Steptoe, 2009). To help shed light on discrepant findings in the literature, Miller and colleagues (1996)

conducted a meta-analysis of the association of hostility with health outcomes, examining whether inconsistencies in the extent literature (1) reflect variability in the nature of measures of hostility, differentially tapping underlying dimensions of the construct (cognitive, affective, or behavioral), or (2) are a function of differences in the study populations or outcome measure. They concluded that affective and cognitive components of hostility (i.e. cynicism, mistrust, anger) were associated with CHD risk and all-cause mortality primarily in healthy populations, while expressive or behavioral dimensions of hostility (i.e. aggression, anger-out) showed the strongest association with CHD, findings that persisted after controlling for known risk factors. In regard to study design, null findings were most often observed in studies examining populations that likely had pre-clinical disease (Miller et al., 1996).

In support of these conclusions, more recent prospective evidence shows a stronger association of hostility with coronary artery calcification and risk for incident disease among younger populations. For example, findings from the European Prospective Investigation of Cancer (EPIC)-Norfolk study show no overall linear association of hostility (using a measure tapping both cognitions and behavior) with CVD risk and all-cause mortality among older adults; however, hostility did predict CVD risk and all-cause mortality in younger participants (less than 60 years old) and in those with the highest levels of hostility after adjustments for demographic characteristics and smoking status (Surtees et al., 2005). Similarly, Chang and colleagues (2002) found that in an initially healthy sample of male medical students, the tendency to get angry when under stress predicted increased incidence of premature CVD in a 45 year follow-up. Likewise, in a young adult sample, CM hostility predicted the extent of coronary artery calcification prior to the presence of clinical disease (Iribarren et al., 2000). A similar pattern of findings was observed in a large sample of initially healthy postmenopausal women from the

Women's Health Initiative. Here, cynical hostility (derived from the CMH scale) predicted incident CHD and all cause mortality; however, this association was not significant after adjustment for health and lifestyle risk factors (Tindle et al., 2009).

Further evidence supports Miller et al.'s (1996) conclusion that experiential and expressive dimensions of hostility show strong associations with risk for CHD. For example, data from the Atherosclerosis Risk in Communities (ARIC) study and the Veterans Administration Normative Aging Study show a positive linear relationship between trait anger (tapping the tendency to experience anger and act aggressively) and CHD (Kawachi et al., 1996; Williams et al., 2000). Others have demonstrated that the inhibition of anger expression, trait anger, and anger-out may contribute along with hostility to the progression of atherosclerotic disease processes in initially healthy and high risk samples (Atchison & Condon, 1993; Bleil et al., 2004; Dembroski et al., 1985, Matthews et al., 1998).

Evidence also supports stronger associations with disease risk when hostility is measured by structured interview or behavioral observations, rather than by self report. For example, among a sample of high risk men from the Multiple Risk Factor Interventions Trial, Matthews and colleagues (2004) showed that higher hostility ratings, derived from the Interpersonal Hostility Assessment interview, predicted cardiovascular mortality over a 16 year follow-up. Similarly, using a different interview to assess hostility, Davidson & Mostofsky (2010) found greater risk for incident CHD over a follow-up period (median 9.7 years) among individuals who tended to use anger to justify or intensify feelings.

In sum, although not all evidence is consistent, results of a number of large epidemiological studies suggest that cynical hostility, trait anger, anger expression, and

aggression are predictors of cardiovascular morbidity and mortality, especially in an initially young and healthy sample. Importantly, although clear theoretical distinction can be made between the various affective, behavioral, and cognitive components of hostility, limited research to date has reported on the unique contributions of each. Thus, additional research is necessary before conclusions can be drawn regarding the extent that individual components of hostility contribute to the prediction of disease (Krantz & McCeney, 2002).

Growing evidence shows that aspects of the social environment interact with hostile dispositional tendencies in the prediction of health risk. For example, high anger reactors who are situated in an environment that requires the inhibition of emotions, such as individuals who work for a verbally aggressive boss (Houston, Smith, & Cates, 1989), or who experience threatening marital interactions (Smith & Gallo, 1999), may be particularly vulnerable, possibly as a result of exposure to situations that elicit emotions and/or demand emotional restraint. Alternatively, cynically hostile individuals may interpret situations as threatening, and misinterpret social situations, contributing to the creation of a hostile environment by creating social conflict, and reducing available social support (Smith & Pope, 1990; Smith & Ruiz, 2002; Smith, Glazer, Ruiz, & Gallo, 2004). Indeed, high hostility has been found to predict greater likelihood of interpersonal conflict and termination of close relationships (Miller, Markides, Chiriboga, & Ray, 1995), and to be associated with more negative life events and less social support (Hardy & Smith, 1988; Scherwitz, Perkins, Chesney, Hughes, 1991). Thus, sociodemographic characteristics and the social environment likely interact with dispositional hostile tendencies in the prediction of health outcomes, which may be contributing to discrepant findings.

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1.2.2 Prevalence of hostility and CHD across racial/ethnic groups

Consistent evidence shows that rates of CVD morbidity and mortality in the United States are higher among African Americans than European Americans (Albert et al., 2004; Rosamond et la., 2007). Racial differences in cardiovascular risk factors, including higher rates of hypertension, diabetes, and physical inactivity among African Americans may contribute to this increased disease risk (Albert et al., 2004; Kurian & Cardarelli, 2007). However, racial disparities may also be related to socio-environmental factors, including socioeconomic standing and differential exposure to discrimination and racial injustice (Lewis et al., 2006; Lillie-Blanton & Laveist, 1996; Nazroo, 2003). Possibly as a consequence of these environmental factors, African Americans endorse higher mean rates of hostility than European Americans (Siegler, 1994; Scherwitz et la., 1991; Barefoot, 1991).

Thus, it is possible that race-related differences in hostility may contribute to the higher incidence of cardiovascular disease among African-Americans in the United States of America. Consistent with this possibility, findings from the Women's Health Initiative suggest a stronger association of cynical hostility with CHD and all-cause death in black women than in white women (Tindle et. al., 2009). Likewise, in a study of cardiovascular risk amongst Black and White young adults, a significant interaction between hostility and race in the prediction of cardiovascular risk was observed, with hostility being a stronger predictor of risk in Blacks than in Whites (Cooper & Waldstein, 2004). Recent evidence also supports a stronger association of trait anger with carotid IMT, a preclinical marker of atherosclerosis, among African-American men than European-Americans and women after controlling for other risk factors (Williams et

al., 2007). Additional research is warranted examining the possibility that race moderates the strength of the association between hostility and risk for CHD.

1.3   MECHANISMS

Although current evidence supports a positive association of hostility with disease risk, the mechanisms of this relationship are not well understood. It has been proposed that angry emotions and hostile behaviors and cognitions impact risk through both behavioral and biological mechanisms (Siegman, 1994; Smith, 1994). Behaviorally, hostility may influence health through its association with lifestyle-risk factors, such as poor diet, smoking, alcohol use, obesity, and physical inactivity, although the association of hostility with these lifestyle factors has not always been consistent (Bunde & Suls, 2006; Seigler, 1994; Seigler et al., 2003). Taken together, these environmental and lifestyle factors typically do not account for all of the variability in CHD associated with hostility (Miller et al., 1996; Smith & Ruiz, 2002). Thus, it has been suggested that hostility may also influence health through its repeated and prolonged arousal of biological systems that directly and indirectly influence biological risk factors (Rozanski, 1999).

In this regard, evidence shows that hostile cognitions, emotions, and behaviors activate the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal system (HPA axis) (Houston, 1994; Pope & Smith, 1991; Rozanski, 1999; Suarez, 1998; Cannon, 1929). Repeated or prolonged activation of the SNS promotes elevations in blood pressure, vascular

endothelial injury, inflammatory activity, and platelet coagulation responses, which likely contribute to the pathogenesis and course of CVD. Indeed, in comparison to their less hostile counterparts, hostile individuals typically show greater cardiovascular and neuroendocrine responses to stress (Davis & Matthews, 2000; Houston, 1994; Pope & Smith, 1991; Suarez, 1998; Chang et al., 2002), prolonged elevations in blood pressure after a stressor (Vella & Freidman, 2009), a lack of habituation of the cardiovascular response after repeated exposures to stress (Ernst, Francis, Enwonwu, 1990), elevated ambulatory blood pressure throughout the day (Suarez & Blumenthal, 1991; Raikkonen, Matthews, Flory, et al., 1999), and a greater likelihood of developing hypertension (Yan et al., 2003). In parallel to activation of the SNS, dysregulated HPA function alters the effectiveness of glucocorticoids to downregulate inflammatory activity, increases fat deposition, and elevates blood glucose levels (Black & Garbutt, 2002; McEwen, 2000; Rushmer, 1989; Schurmeyer & Wickings, 1999; Silverthorn, 2001). These repeated and prolonged physiologic disruptions can result in an accumulation of damage and dysfunction, as seen in greater platelet activity (Markovitz et al., 1996), greater endothelial dysfunction (Harris et al., 2003), increased pro-coagulant and pro-inflammatory states (Black & Garbutt, 2002; von Kanel & Dimsdale, 2000; von Kanel, Mills, Fainman, & Dimsdale, 2001), increased visceral fat deposition (Kuo et al., 2007), and increased oxidative damage to DNA and lipids (Epel et al., 2006; Flint, Baum, Chambers, & Jenkins, 2007; Gumuslu et al., 2002). These biological pathways are proposed to contribute to the associations of hostile characteristics with risk for CHD (Steptoe & Brydon, 2005; Krantz & McCeney, 2002; McEwen, 2000; Musselman et al., 2003).

1.4   SUMMARY

In sum, hostile negative emotions, behaviors, and cognitions may increase risk for CHD via the pathophysiological consequences of sympathoadrenal and HPA dysregulation. The magnitude of this physiologic dysregulation may be stronger among individuals disposed to heightened hostility, including disadvantaged populations, and those in socioenvironmental circumstances that contribute to physiological activation (i.e. greater inhibition of their emotions, Houston, Smith, Cates, 1989; more daily conflict, Smith & Gallo, 1999). Recent attention has focused on the possibility that psychosocial risk factors, such as stress and depression, which are associated with SNS and HPA dysregulation, may also have deleterious effects on cellular processes, impacting rates of biological aging and vulnerability to age-related diseases. In this regard, interest has focused on a proposed biomarker of biological age, telomere length. Recent findings show that psychological risk factors for CHD, including stress, depression, and pessimism are associated with shorter telomere length (Epel et al., 2004; Lung et al., 2007; O'Donovan et al., 2009; Simon et al., 2006). In the current proposal, we intend to extend this literature to include an examination of whether hostility and/or its sub-dimensions are associated with telomere length and to provide an exploratory examination of whether race or age moderate the magnitude of this association.

2.0   TELOMERES

2.1   TELOMERE BIOLOGY

Telomeres are tandem DNA repeats on the end of chromosomes that protect the rest of the DNA of chromosomes from loss during cell division (Blackburn, 1991). Every time a cell divides a piece of the DNA sequence at the end of the chromosome is lost. Thus, telomeres of somatic cells shorten with each cell division (losing approximately 20 to 200 bp), until they reach a critical length, which activates cell cycle arrest and cellular senescence (Blackburn, 1991). Without cellular arrest, the cell would continue to replicate, lose coding DNA, and become susceptible to mutations (Houben et al., 2008; Jiang et al., 2007). Thus, telomere attrition serves a protective function, reducing functionality of potentially damaging cells.

Many cells contain an enzyme, telomerase, which functions to rebuild telomeres and maintain their length (Epel, 2009; Blackburn, 2005). Telomerase is active during embryonic development in most cell lines, but its activity was thought to be dramatically reduced in adults when it appears to remain active primarily in stem cells, progenitor cells, and activated lymphocytes (Jiang et al., 2007; Collins & Mitchell, 2002; Hiyama & Hiyama, 2007). Interestingly, however, recent research suggests that this enzyme may be more active than previously thought, and may in fact, contribute to telomere rebuilding beyond early development. Indeed, recent epidemiological research shows that between 16 and 25% of adults show lengthening of peripheral blood mononuclear cell telomeres over time (Aviv et al, 2009;

Ehrlenbach et al., 2009; Epel et al., 2009; Farzaneh-Far et al., 2010), with a strong positive association between baseline telomere length and telomere attrition, such that shorter telomeres are more likely to elongate and longer telomeres show more loss over the same period of time (Aviv et al 200 ;Ehrlenbach et al., 2009; Epel et al., 2009; Farzaneh-Far et al., 2010). These findings parallel research showing increased telomerase activity in cells with shorter telomeres (Blackburn, 2000).

Accordingly, recent attention has focused on genetic and non-genetic contributions to variations in telomerase activity. For example, genetic polymorphisms have been identified in a functional promoter of hTERT (the gene encoding telomerase) that appears to be related to the expression of telomerase and the maintenance of telomere length (Matsubara, 2006). Non-genetic factors also contribute to variability in telomerase activity, including the presence of reactive oxygen species, cytokines (i.e. IL-2, IL-6, TNF-alpha), estrogen, and growth hormones (see Lin et al, 2009 for review). Future work would benefit from a more careful examination of the contribution of telomerase activity to the maintenance or elongation of telomeres over time.

2.2   TELOMERES AND AGING

During aging, progressive telomere shortening is observed across a large majority of human cell types, including white blood cells and cells of the vascular endothelium, myocardium, kidney, liver, colon, stomach, spleen, lung, skin, and muscles (See Jiang et al., 2007 for a review). Shortening of telomeres occurs in humans at an estimated rate of 19 to 59 base pairs per year (Ehrlenbach et al., 2009; Hodes et al., 2002; Rufer et al., 1999); with an increased rate of attrition in older individuals (Huda et al., 2007). This results in an inverse

association between chronological age and telomere length (Cawthon, 2003, Fitzpatrick et al., 2007; Lung, et al., 2007; Mayer et al., 2006; Valdes et al., 2005). Accumulating evidence suggests that short telomeres are associated with a progressive decline in cellular function and increased risk for age-related diseases such as cancer and cardiovascular disease (Gilley et al, 2008; Jiang et al., 2007; Kirkwood & Austad, 2000), raising the possibility that telomere length contributes to the pathophysiology of aging and related diseases.

In the case of atherosclerosis, recent research supports a role of cellular senescence in disease pathology. For example, senescent vascular endothelial and smooth muscle cells are thought to disrupt normal cellular processes and shift the vasculature to a pro-atherogenic and pro-thrombotic phenotype, with increases in oxidative stress and inflammatory mediators (Erusalimsky, 2009; Burton, 2009) and characteristic endothelial dysfunction (Minamino et al., 2009). Interestingly, telomere length in PBMCs correlates with telomere length in vascular endothelial cells derived from aortic biopsies (r = .62; Wilson et al., 2008), suggesting that blood cell telomere length may provide a marker for telomere length in vascular tissue.

The strongest support for telomere length as a factor in human disease is the rare congenital condition called *dyskeratosis congenita* (Vulliamy et al., 2001*). Characterized by a mutation in the gene encoding telomerase, these patients have very short telomeres and suffer premature death as a consequence of accelerated cellular senescence and tissue dysfunction, similar to typical diseases of aging such as CHD (Vulliamy et al., 2001). This condition demonstrates that telomere length is critical for survival, and that premature shortening of telomeres contributes to biological aging and disease vulnerability. In sum, compelling evidence suggests that the shortening of telomeres observed in senescent cells contributes to disease vulnerability and progression (Erusalimsky, 2009; Burton, 2009).

2.3   THE BIOLOGICAL CLOCK AND MECHANISMS OF AGING

It has been suggested that telomere length acts as the "biological clock" of an organism (Bekaert et al., 2005). In this regard, within humans telomere length is relatively constant (approximately 5-15 kb), and is thought to program maximum lifespan (Blackburn, 1991; Blasco, 2005). However, evidence suggests that biological and environmental factors may result in variability in telomere attrition rates across individuals, contributing to different lifespan trajectories. Although chronological age is associated with biological age (Bekaert et al., 2007; Cawthon, 2003; Diez-Rouz et al.2009, Valdez et al., 2005), only a portion of the variability in telomere length is explained by chronological age (~4-12%). Thus, other factors are thought to contribute to individual differences in telomere shortening over time and thus to life expectancy. To date, these factors are not well understood, although recent evidence suggests that genetic and environment factors may play a role (Gilley et al., 2008).

With regards to genetic factors, numerous reports suggest some degree of heritability in telomere length, although heritability estimates vary widely, with averages between 36-67% (Bakaysa et al., 2007; Andrew et al., 2006) but some estimating as much as 96% (Huda, 2007). Interestingly, Bakaysa and colleagues (2007) report that the correlation between twins in telomere length declined with increasing age, suggesting that unshared environmental factors likely contribute to telomere length differences later in life. In support of this, a study of elderly twins reported no heritability of telomere length (Huda, 2007). Also of note, one of the major

limitations in the estimates of heritability in these samples of twins is unaccounted for shared environmental factors (i.e. in utero and early life environment) that likely contribute to shared variance.

Gender differences in telomere length have also been reported (Cawthon, 2003; Mayer et al., 2006; O'Donovan, 2009), with one author estimating telomere attrition rates of approximately 5 bp per year more rapid among males than females (Mayer et al., 2006). Globally, females outlive their male counterparts by an estimated 3.7 years, while in the United States females live approximately 5.7 years longer than males (Finch, 2007). Thus, over the lifespan, the greater cumulative loss of telomeres may predispose men to earlier onset of age-related diseases and mortality than women.

Racial differences in the association of age with telomere length have also been reported, with cross-sectional analyses showing either higher or lower telomere length in African Americans compared to European Americans (Aviv et al., 2009; Diez-Roux et la., 2009; Hunt et al., 2008; Njajou et al., 2009). Some evidence also suggests a greater age-related decline in telomere length among blacks than whites, a finding that is independent of socioeconomic factors, behavioral risk factors, and BMI (Aviv et al., 2009; Diez Roux, et al., 2009; Hunt et al., 2008). However, not all findings are consistent (Farzaneh-Far et la., 2010). Overall, these findings raise the possibility that accelerated biological aging among blacks may partially explain increased incidence of age-related morbidity and mortality amongst this racial group.

In respect to environmental factors, rate of telomere attrition appears to be influenced by a number of molecular processes known to be associated with psychosocial factors. In this regard, telomere length has been inversely associated with infection, inflammation, and oxidative stress (Bekaert et al., 2007; Gilley et al., 2008; Houben et al., 2008; von Zglinicki, 2002).

Interesting recent evidence also supports a decrease in telomerase activity and expression of hTERT in T lymphoctyes exposed to cortisol (Choi, Frauce, Effros, 2008). If psychosocial conditions predispose people to increased production of cortisol, infection, inflammation, oxidative stress, and reduced telomerase activity, then telomere attrition under such conditions may be a direct consequence of these pathophysiological mechanisms.

In the proposed study, we examine the possibility that telomere length is associated with hostility and its cognitive, affective, and behavioral components and explore the role of race and age in the magnitude of these associations. Before turning to examine the available evidence for this association, we first examine evidence that telomeres play a role in the pathophysiology of diseases of aging.

2.4   TELOMERES, MORTALITY, AND CHD RISK

A growing body of prospective and cross-sectional research shows an inverse association of telomere length with all cause and CHD morbidity and mortality among midlife and aged adult populations, while null findings have been reported in the oldest old. For example, shorter telomere length among a sample of community volunteers was shown to predict aged 60-75 years increased risk of mortality over a 15 year period among individuals aged 60-75 years, but not those over age 75 (Cawthon, 2003). Similarly, longer telomere length in a sample of 53-71 year olds predicted survival 10 years later (Ehrlenbach et al., 2009). Shorter telomere length has also been shown to predict risk for future myocardial infarctions (Fitzpatrick et al., 2007) and CHD events (Brouilette et al., 2007), and increased all-cause mortality rates among patients with

stable coronary artery disease (CAD) (Farzaneh-Far et al., 2008). Furthermore, in a recent study of Swedish monozygotic and dizygotic twins, shorter telomere length predicted increased all-cause mortality, as well as deaths from cancer and cardiovascular disease; findings that were independent of shared genetics (Bakaysa et al., 2007). Interestingly, rates of telomere attrition over a 2.5 year period may be an even stronger predictor of mortality than one time assessments (Epel et al., 2009). In a sub-sample of European Americans from the MacArthur Study of Successful Aging, researchers found that, in the male sample and independent of baseline telomere length, greater declines in telomere length over a 2.5 year period predicted greater mortality 12 years later (Epel et al., 2009).

Cross-sectional studies also show inverse associations between telomere length and CHD-related risk (See Jiang et al., 2007 for review). Indeed, shorter telomeres have been found among patients with type 2 diabetes, cardiovascular disease, coronary heart disease, and various other diseases of the vasculature when compared to more healthy controls (Jiang et al., 2007; Samani et al., 2002; Sampson et al., 2006; Serrano & Andres, 2004). Moreover, stroke patients with shorter telomeres are at increased risk for cognitive decline and dementia (Martin-Ruiz et al., 2006). Risk factors for CHD have also been associated with shorter telomere length, including greater carotid intima media thickness, higher blood glucose levels, elevated insulin, higher diastolic blood pressure, higher interleukin(IL)-6, elevated oxidative stress, hypertensive status, and greater adiposity (Bekaert et al., 2007; Farzaneh-Far et al, 2010; Fitzpatrick et al., 2007; Demissie et al., 2006; O'Donnell et al., 2008; Wu et al., 2003).

Contrary to the above, several studies of the oldest old (74 or older) find no association or a reduced association between telomere length and morbidity or mortality (Bischoff et al., 2006; Fitzpatrick et al., 2007; Martin-Ruiz et al., 2005; Cawthon et al., 2003). This may reflect

decreased variability in telomere length among the extreme elderly, a bias of survivorship, or the consequence of other factors contributing to illness in this group. Indeed, short telomere length in white blood cells itself is not a proximal cause of death (except plausibly in the case of certain immune cell cancers). Thus, it may not be an accurate predictor of risk among elderly individuals with pre-existing organ damage.

In sum, current evidence supports circulating telomere length as a prognostic risk factor for CHD and mortality, although additional prospective and experimental evidence is needed to draw firm conclusions.

2.5   CONCLUSION

In conclusion, the research to date supports an association of hostile, angry, and aggressive tendencies with risk for CHD, a relationships that is stronger among African Americans than European Americans (Cooper & Waldstein, 2004). Hostility may confer increased risk through repeated physiological arousal from daily actual and perceived threat causing autonomic and HPA system dysregulation and contributing to high blood pressure, inflammation, oxidative stress, and cellular aging. Higher levels of exposure to environmental, economic, and social inequalities, particularly amongst African Americans may result in faster rates of biological aging, contributing to racial disparities in risk for CHD. Hostility may activate biological pathways that act directly on telomerase activity, oxidative stress, and inflammatory factors, resulting in the attrition of telomeres. Given their greater propensity for hostility, African Americans may be at heightened susceptibility for hostility-related telomere attrition than European Americans. Alternatively, poorer lifestyle factors associated with

hostility may act to increased telomere attrition through alterations in telomerase function, increases in oxidative stress, increases in inflammation, and/or via some alternative mechanism. The goal of the current project is to explore the hypothesized association between hostility and telomere length in a sample of untreated hypertensive men at high risk for CHD. A secondary aim is to conduct exploratory analyses examining the possible moderating role of race and age in this hypothesized association.

3.0 AIMS AND HYPOTHESES

AIM 1: The first aim is to examine associations of hostility with telomere length, after controlling for demographic covariates. Given the associations of race, age, and SES with telomere length, initial analyses will statistically control for these factors.

Hypothesis 1: We hypothesize that hostility will be inversely associated with telomere length, after controlling for age, SES, and race.

AIM 2: Previous literature suggests that hostility may confer increased risk for CHD via lifestyle factors. Thus, a second aim of the proposed project is to examine the degree to which lifestyle factors (adiposity, smoking, blood pressure) account for the association between hostility and telomere length.

Hypothesis 2: We hypothesize that the relationship between hostility and telomere length will remain after controlling for lifestyle factors.

EXPLORATORY AIMS:

(1) Based on the literature that unique affective, behavioral, and cognitive components of hostility, measured by the CMH and STAXI, independently predict cardiovascular risk, we hypothesized that these components may uniquely be associated with telomere length. Thus, after conducting initial analyses examining associations of the hostile cognitions

and hostile affect factors with telomere length, we went on to explore whether the total CMH or the STAXI trait anger or anger expression scores, along with their subscales, predicted telomere length.

(2) The increased incidence of disease morbidity and mortality amongst blacks as compared to whites, greater hostility amongst blacks, and recent findings suggesting differential rates of telomere attrition across these two racial groups suggests that the hypothesized association between hostility and telomere length may be moderated by race. A predisposition towards hostility may have more detrimental effects on health in blacks as a consequence of socio-environmental factors eliciting more frequent daily responses to threat. Thus, we hypothesize that the association between hostility and telomere length will be moderated by race, such that blacks will show a stronger association between hostility and telomere length than whites.

(3) Given the evidence that hostility is a stronger predictor of morbidity and mortality in younger than older healthy populations, and that both hostility and telomere length vary with age, further exploration of the moderating role of age in the hypothesized association between hostility and telomere length is warranted. Here, it is hypothesized that there will be an inverse association of hostility with telomere length among younger individuals, reflecting premature biological aging, that will not be observed among older individuals.

4.0   METHODS

4.1.1   Participants

This project sampled 243 male untreated hypertensive subjects from the University of Pittsburgh Reactivity and Cardiovascular Risk Trial (REACT). REACT is a study of cardiovascular reactivity and correlates of preclinical atherosclerotic disease conducted in the mid-1990's. From this group of 243 eligible male hypertensive participants, sufficient DNA was available to measure telomere length on 208 subjects. Of these subjects, two did not have complete hostility data, and eight were excluded due to immune related conditions: chronic prostatitis (n = 1), rheumatic fever with heart complications (n = 3), and thyroid dysregulation (n = 4) (De Marzo et al., 2003; Fireman, 2003; AHA). An examination of the distribution of telomere length for outliers revealed three individuals with lengths that were more than 3 standard deviations above the mean. Thus, these individuals were also excluded, resulting in a final sample size of 195. This study included both European American (82%) and African American (18%) untreated hypertensive men, with ages ranging from 40-70 years (mean = 55.6, SD = 9.2).

4.1.2 Procedures

Participant recruitment and screening has been reported previously (Bleil et al., 2004). In summary, participants were recruited from Pittsburgh, Pennsylvania and surrounding areas through mass mailings and advertisements in the local media. Potential participants who met initial selection criteria were then seen for two screening visits, at which time hypertensive status was confirmed by measurement of resting blood pressure (included if systolic blood pressure was between 140-180 mmHg and/or diastolic blood pressure between 90-110 mmHg). Participants in this study were excluded if they had any of the following: secondary hypertension, history of cerebrovascular accident, known coronary artery disease, current use of cardiovascular medication, diabetes, cancer, chronic renal failure, chronic hepatitis or cirrhosis, pulmonary disease requiring daily medication, alcoholism, major psychiatric disorder or current psychotropic medication, or less than eighth grade education. In addition, participants were excluded from the study if they were currently receiving or had previously received > 2 years of antihypertensive treatment, or > 1 year of treatment within last 5 years. If eligible, subjects were asked to provide overnight fasting blood samples and fill out numerous psychosocial and health questionnaires. DNA from peripheral blood mononuclear cells (PBMC) was isolated and frozen for later analysis. The study protocol was approved by the University of Pittsburgh Institutional Review Board, and informed, written consent was obtained from all participants.

4.1.3 Measures

<u>Race</u>: Participants were asked to report their race on a self-report demographics form during their initial visit.

<u>Socioeconomic Status (SES)</u>: Individual SES was determined through measurement of educational attainment (number of years spent in school) and family income (income brackets: 1=less than $10k; 2=10k-19,999; 3=20k-34,999; 4=35k-50k; 5=more than 50K).

<u>Health and lifestyle risk factors</u>: A number of health risk factors were obtained from participants, including: smoking history, BMI, waist-hip ratio, percentage body fat, and blood pressure.

History of arthritis. A total of thirty-three individuals reported a history of arthritis. Given evidence that rheumatoid arthritis is associated with shortening of telomere length (Koetz et al., 2000), presence of arthritis was included as a covariate in all analyses.

Smoking history was measured by asking participants to report whether they ever smoked (Y/N) and/or whether they currently smoked (Y/N).

Adiposity Composite. BMI and waist-hip ratio were determined through measurement of height and weight and waist-hip measurements respectively. Calculations of individual BMI were made using the following formula: BMI = Weight (kilograms)/Height (meters^2). Percent Body Fat was determined through skin fold assessments (Durnin & Rahaman, 1967). To reduce the number of related predictors in statistical models, we computed a composite score for adiposity from these three measures by summing standardized scores.

Blood pressure was taken three times after 5 minutes of sitting on two consecutive visits to the office. The second two readings from each visit were averaged to determine resting blood pressure.

Hostility

Cook-Medley Hostility (CMH) scale: Trait hostility was measured using 39-items from the Cook-Medley Hostility (CMH) Scales (Cook & Medley, 1954; Barefoot et al., 1995), which includes the following four subscales, as derived by Barefoot and colleagues (1989): cynicism, hostile attributions, hostile affect, and aggressive responding. These subscales are thought to tap cognitive, affective, and behavioral dimensions of hostility respectively (Barefoot et al., 1989), although others have proposed that the items primarily assess hostile cognitions (Costa et al., 1986) and do not reliably assess aggressive tendencies, anger expression or experience. The CMH has adequate test-rest reliability (Shekelle, Gale, Ostfeld, & Paul, 1983) and internal consistency (Cronbach's alpha = .83) (Contrada & Jussim, 1992). Scores on the CMH are positively associated with the hostility dimension of the NEO-PI and negatively correlated with the agreeableness dimensions (Barefoot et al., 1989). See Appendix A for individual items within each scale.

Speilberger Trait Anger and Anger Expression scale (STAXI). The STAXI is a 44-item scale designed to assess state and trait anger (Speilberger, 1988). The Trait Anger subscale assesses the degree to which a person typically feels anger in general, while the Anger Expression subscale assesses 3 different dimensions of angry reactions: (1) outwardly towards others (Anger-Out), (2) held in or suppressed (Anger-In), or (3) emotionally controlled responses (Anger-Control). Test-retest reliability (Jacob, 1988; Bishop 1998), internal consistency (.86 for Trait Anger; .73 - .84 for Anger Expression),

and convergent validity of the STAXI has been established (Spielberger, 1988). See Appendix B for individual items within each subscale.

Combined Hostility Measure. Given significant associations between the subscale scores from the CMH and STAXI (Table 1), we conducted a principal components factor analysis with varimax rotation of the nine hostility subscales (CMH hostile affect, hostile attributions, aggressive responding, cynicism; STAXI angry reactions, angry temperament, anger-in, anger-out, and anger-control). Individual subscale loadings can be seen in Table 2. Based on these loadings, two principal factors were identified accounting for 34.1% and 25.8% of the variance, respectively: Factor 1 representing a cognitive component (herein referred to as *Hostile Cognitions*) and Factor 2 emphasizing an affective/expressive component (herein referred to as *Hostile Anger*). Standardized scale scores were calculated based on these factor loadings. These factor loadings are similar to two of the three components of hostility identified by others (Martin, Watson, Wan, 2000), with the CM Hostility subscales, derived by Barefoot and colleagues (1995), primarily loading on a cognitive component, and the subscales of the STAXI (apart from the anger-in subscale) loading on an expressive/affective component.

Table 1. Intercorrelations Between Cook-Medley Hostility and the STAXI Scales and Subscales

Cook-Medley Hostility	1	2	3	4	5	6	7	8	9	10	11	12
1. CMH 39-item	-	72**	74**	87**	88**	32**	13	37**	.18*	16*	32**	33**
2. CM Hostile Affect	-	-	48**	57**	51**	25**	20**	25**	.21**	13	32**	34**
3. CM Aggressive Responding	-	-	-	55**	53**	33**	12	38**	.19**	23**	22**	31**
4. CM Hostile Attributions	-	-	-	-	66**	34**	15*	37**	.16*	19**	31**	33**
5. CM Cynicism	-	-	-	-	-	18*	04	23**	.10	05	24**	21**
STAXI												
6. STAXI Trait Anger	-	-	-	-	-	-	70**	80**	.51**	61**	31**	68**
7. STAXI Angry Temperament	-	-	-	-	-	-	-	22**	.47**	53**	09	52**
8. STAXI Angry Reaction	-	-	-	-	-	-	-	-	.30**	36**	35**	48**
9. STAXI Anger Control	-	-	-	-	-	-	-	-	-	.48**	.07	.82**
10. STAXI Anger Out	-	-	-	-	-	-	-	-	-	-	12	70**
11. STAXI Anger IN	-	-	-	-	-	-	-	-	-	-	-	50**
12. STAXI Anger Expression	-	-	-	-	-	-	-	-	-	-	-	-

p < .05, **p< .01

Table 2. Rotated Component Matrix

	Component	
	1	2
STAXI Angry Temperament	.031	**.804**
STAXI Angry Reaction	.470	**.489**
STAXI Anger Control	-.093	**-.773**
STAXI Anger Out	.087	**.861**
STAXI Anger In	**.574**	.046
CM Hostile Affect	**.749**	.140
CM Cynicism	**.814**	-.057
CM Hostile Attribution	**.850**	.097
CM Aggressive Responding	**.743**	.247

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization.

Telomere Length: Relative telomere length was determined from frozen DNA samples using a qualitative real time polymerase chain reaction (qRT-PCR) methodology described elsewhere (Cawthon, 2003). Results of this method correlate highly (r = .68) with the traditional southern blot methodology (Cawthon, 2002). Briefly, the final reaction mixture for assessment of the telomere repeat gene copy number contained the following: 10ul 2X Quantitect SYBR Green Mix, .05 μl 1 M DTT, .27ul 20 μM Tel-1b primer (GGTTTTTGAGGGTGAGGGTGAGG GTGAGGGTGAGGGT), .9 μl 20 μM Tel-2b primer (TCCCGACTATCCCTATCCCT ATCCCTATCCCTATCCCTA), 6.78 μl nuclease free water, and 2 μl of 12.5 ng/μl DNA sample. Samples were run in ABI 7900HT Sequence Detection System at the following cycling conditions: 95° for 5 minutes, and 40 cycles of 95° for 15 seconds then 54° for 2 minutes. The copy number for a single-copy gene, 36B4 (S), was run on a parallel plate and used for normalization of T values by the quantification of the number of diploid genomes present in each sample. The final reaction mixture for the single-copy 36B4 gene contained the following: 10ul 2X Quantitect SYBR Green Mix, .3ul 20 μM 36B4 U primer (CAGCAAGTGGGAAGGTGT AATCC), .5 μl 20 μM 36B4 D primer (CCCATTCTATCATCAACGGGTACAA), 7.2 μl nuclease free water, and 2 μl of 12.5 ng/μl DNA sample. The samples measuring 36B4 were run under the following cycling conditions: 95° for 5 minutes, and 40 cycles of 95° for 15 seconds then 58° for 1 minute 10 seconds.

Relative telomere length was determined on DNA isolate from peripheral blood mononuclear cells (PBMC), and was run in triplicate on a 96-well plate along with a reference DNA sample used to determine genome quantity within each well. Triplicate values were assessed for reliability, and mean values were calculated. A cycling thresholds (C_t) was derived for each sample. C_t values derived from this qRT-PCR methodology reflect the number of PCR

cycles required for the sample DNA to express enough product to meet the threshold of magnitude of the selected fluorescent signal.

In addition, a standard curve, which was generated by serial dilution of a 50ng/µl sample of control DNA, was included on each plate. The standard curve derived from this control sample was then used to calculate relative telomere length by plotting the C_t of the other samples against the standard curve of this control sample. Telomere length values in the present analyses represent the ratio of relative telomere (T) gene expression to single copy (S) gene expression (T/S ratio). Inter-plate and intra-plate variations were low, with coefficients of variation below 3%.

4.1.4   Statistical Analyses

All statistical analyses were performed using SPSS software (Version: 17.0). Initial descriptive statistics and distribution analyses were performed. Data was check for normality and the following variables were natural log transformed to more closely approximate a normal distribution: Telomere Length (T/S ratio), STAXI Angry temperament, and STAXI Anger-Out. Initial correlation analyses were performed to check for multicollinearity of variables.

> **Hypothesis 1:** It was hypothesized that hostility would be inversely associated with telomere length, after controlling for age, SES, race, and arthritis status. For all analyses, we used separate models to examine variability in telomere length associated with the two hostility dimensions derived from the factor analysis, hostile cognitions and hostile anger. For this purpose, we ran two linear regression analyses, with age, education, family income, race, and arthritis status entered in step 1, following by the hostility

measure in step 2 of a model predicting telomere length. Our hypothesis would be confirmed if the relationship between the hostility measure and telomere length is significant at $p < .05$, after covariates have been entered.

Hypothesis 2: We hypothesized that any relationships between hostility and telomere length would remain after controlling for lifestyle factors. To test this hypothesis, we employed linear regression analyses entering age, education, family income, race, and arthritis status in step 1, adiposity, systolic and diastolic blood pressure, and smoking history in step 2, and the two dimensions of hostility in step 3 of separate models predicting telomere length.

Exploratory Analyses 1: After conducting initial analyses examining associations of the hostile cognitions and hostile affect factors with telomere length, we went on to explore whether the total CMH or the STAXI trait anger or anger expression scores, along with their subscales, predicted telomere length. For this purpose, we ran a series of linear regression analyses similar to those used to test hypothesis 1 and 2.

Exploratory Analyses 2: We conducted exploratory analyses examining whether the relationship of hostility with telomere length was moderated by race. Here, a series of linear regression analyses was performed, testing the interaction of race and hostility in the prediction of telomere length. For these analyses, age, SES, and arthritis status were entered in step 1, race and the dispositional characteristic (centered) in step 2, and the interaction term of race and the dispositional characteristic in step 3 of the models.

Exploratory Analyses 3: Finally, we explored whether the relationship between hostility and telomere length was moderated by age. For these analyses, race, arthritis status, and SES was entered in step 1, age (centered) and the dispositional characteristic (centered) in step 2, and the interaction term of age and the dispositional characteristic in step 3 of models predicting telomere length.

4.1.5 Power Analysis

There is no existing literature that reports on the possible association between hostility and telomere length. Thus, we used prior studies examining associations of stress with telomere length to estimate sample size. Findings by Epel and colleagues (2004) show an inverse association between stress and telomere length, a finding that persists after controlling for age, BMI, vitamin use, and smoking (r = -.27). Based on this effect size of .27 (f^2 = .0786), we estimated that to detect a significant increase in R^2 with the power = .95, and 13 predictors in the model, our sample size needed to be 168 or greater (G-power; Buchner et al., 1997). Thus, we predicted that our sample size of 195 would be adequate to detect an effect of this size. Post-hoc power analyses suggested we were underpowered to detect small effects. The effects for our primary hypotheses were extremely small (R squared change of .003 or less), and post-hoc power analyses demonstrate we had very low power (1-β = .11). To increase power to .80 or greater our sample size would need to be > 2,620. Exploratory analyses testing interactions of age with hostility in the prediction of telomere length were also underpowered to reliably detect effects; however, these effect sizes were slightly larger than the primary hypotheses, although

still small (R squared change equal or less than .019). Post-hoc power analyses suggested limited

power of $1 - \beta = .48$, an effect that would require a sample size greater than 420 to achieve

power of .80.

5.0   RESULTS

5.1   PRELIMINARY ANALYSES

Descriptive statistics for all the variables are displayed in Table 3. Consistent with the hypertensive status of our sample, average blood pressure was significantly higher than age expected norms (SBP = 148.9 versus norm = 129.2; DBP = 93.1 versus norm = 75.5; O'Donnell et la., 2008). Average BMI for this sample was 28.2, which is consistent with national averages (McDowell et al., 2008) and falls within the overweight classification. In this regard, only 15% of the sample was considered normal weight, 57% were overweight, and the remaining 28% were obese. CM Hostility subscale scores and STAXI trait anger scores were similar to national samples of similarly aged groups (Barefoot, 1991; Williams et al., 2007; Williams et al., 2000).

Table 3. Descriptive Statistics of Demographic, Socioeconomic, Health & Lifestyle Factors, Hostility, and Telomere Length.

Variable	Mean (SD) or %	n
Age	55.8(9.2)	195
Race (% white)	82%	195
Years of Education	14.8(2.8)	195
Family Income	3.8(1.3)	193
BMI	28.2(3.2)	195
% Body Fat	29.1(4.5)	195
Waist-Hip Ratio	1(.07)	194
Adiposity Composite	-.01 (2.12)	194
Systolic Blood Pressure	148.9(10.6)	195
Diastolic Blood Pressure	93.1(7.3)	195
Current Smoker	12.8%	195
Ever Smoked	64.6%	195
CMH 39-item	15.3(7.2)	195
CM Hostile Affect	2.6(1.4)	195
CM Aggressive Responding	3.3(1.8)	195
CM Hostile Attributions	4.1(2.6)	195
CM Cynicism	5.3(2.9)	195
STAXI Trait Anger	16.4(3.7)	195
STAXI Angry Temperament	5.8(1.9)	195
STAXI Angry Reaction	7.7(2.2)	195
STAXI Anger Control	23.6(5)	195
STAXI Anger Out	13.9(3.5)	195
STAXI Anger IN	15.7(3.7)	195
STAXI Anger Expression	22(8.5)	195
Telomere Length (.12-1.1)	.37(.2)	195

Next, intercorrelation analyses were conducted to assess for multicollinearity of covariates (See Table 4). Tolerance values were > .7 with the majority over .9, suggesting there were no multicollinearity concerns. Age was significantly associated with higher systolic blood pressure, lower diastolic blood pressure, and decreased likelihood of being a current smoking. African-Americans were on average younger than European Americans, and had fewer years of education, lower income, lower systolic BP, higher diastolic BP, higher rates of current smoking, and greater likelihood of ever smoking. Higher level of education was significantly associated with higher family income and less likelihood of ever smoking. Family income was also inversely associated with lifetime history of smoking. As expected, BMI was significantly associated with percentage body fat. However, waist-hip ratio showed smaller associations with BMI and no association with percentage body fat.

Table 4. Intercorrelations Between Demographic, Health & Lifestyle Variables.

Demographics

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	-	.18*	.04	.07	13	.10	11	.06	.03	41**	.45**	12	.30**
2. Race (Black)	-	-	.26**	.46**	003	.08	.10	.07	.11	.20*	14*	21**	42**
3. Education	-	-	-	52**	.12	03	10	.10	01	.11	02	.08	.23**
4. Family Income (n = 193)	-	-	-	-	.08	10	08	.08	05	.04	.01	.13	.23**

Health and Lifestyle Variables

	1	2	3	4	5	6	7	8	9	10	11	12	13
5. Arthritis Status	-	-	-	-	-	04	06	03	06	08	03	16*	.09
6. Body Mass Index	-	-	-	-	-	-	47**	17*	77**	.12	14*	.15*	.23**
7. Percent Body Fat	-	-	-	-	-	-	-	11	75**	.03	.01	.09	.28**
8. Waist-Hip Ratio (n = 194)	-	-	-	-	-	-	-	-	60**	.06	07	.06	.02
9. Adiposity Composite (n = 194)	-	-	-	-	-	-	-	-	-	.10	11	.14*	.24*
10. SBP	-	-	-	-	-	-	-	-	-	-	.003	13	.12
11. DBP	-	-	-	-	-	-	-	-	-	-	-	.04	07
12. Ever Smoked	-	-	-	-	-	-	-	-	-	-	-	-	28**
13. Current Smoker	-	-	-	-	-	-	-	-	-	-	-	-	-

5.1.1 Associations of demographic, socioeconomic, health & lifestyle factors, hostility and telomere length

Pearson product-moment and Point-biserial correlations were used to examine associations of telomere length with demographic, socioeconomic, and lifestyle factors (See Table 5). As expected, telomere length was significantly associated with age ($r = -.17$, $p < .05$) and education ($r = .15$, $p < .05$). No other significant associations of demographics or lifestyle and health factors with telomere length were observed. Next, bivariate associations of the hostility measures (the hostile cognition and anger factor scores, and the CMH and STAXI scale and subscale scores) with telomere length were conducted (See Table 6). No significant associations were observed.

Table 5. Correlations of Telomere Length With Demographic, Socioeconomic, and Health & Lifestyle Factors.

Variable	Entire Sample[a] r	European American Only (n = 160) r
Age	**-.17***	**-.17***
Race	.02	--
Education	**.15***	**.21****
Family Income, n = 193	.06	.11
BMI	-.003	-.04
% Body Fat (Log)	.006	-.03
Waist-Hip Ratio, n = 194	-.13	**-.21****
Adiposity Composite, n = 194	-.07	-.13
SBP	-.07	-.02
DBP	.12	.11
Current Smoker	-.02	-.03
Ever Smoked	-.03	-.08

*p<.05, **p <.01

[a] Sample size n = 195 unless otherwise noted

Table 6. Correlations of Telomere Length With the Cook-Medley Hostility and the Speilberger State Trait Anger Expression Scales and Subscales.

	Entire Sample (n = 195)	European American Only (n = 160)
Factor Scales	r	r
Hostile Cognitions	.032	.05
Hostile Anger	.013	.004
Cook-Medley Hostility	r	
CMH 39-item	.014	.02
CM Hostile Affect	.06	.08
CM Aggressive Responding	-.012	.01
CM Hostile Attributions	.006	.03
CM Cynicism	.007	-.02
STAXI		
STAXI Trait Anger	.047	.07
STAXI Angry Temperament	.000	-.01
STAXI Angry Reaction	.086	.12
STAXI Anger Control	.000	.02
STAXI Anger Out	.006	.00
STAXI Anger IN	.032	.05
STAXI Anger Expression	.016	.01

5.2   PRIMARY AIMS

5.2.1   Hypotheses 1 and 2: Associations of hostility with telomere length

Although we found no significant bivariate associations of telomere length with our measures of hostility, we went on to test the magnitude of these relationships with covariates in the model. To test our first hypothesis, that the hostile cognitions and hostile affect factors would be inversely associated with telomere length, independently of age, SES, race, and history of arthritis, we ran a series of linear regression analyses. Results of these analyses can be seen in Table 7. Contrary to our hypothesis, we found no significant independent associations of the hostile cognition or hostile anger factor scores with telomere length.

In the second hypothesis, we proposed that associations between hostility and telomere length would be independent of lifestyle and health factors, including smoking status, adiposity, and blood pressure. Results of these analyses can be found in Table 7. Again, results provided no support for our hypothesis, with no significant associations of hostile cognitions or hostile anger factor scores with telomere length after controlling for lifestyle and health factors. These hypotheses were also tested on the European American sample alone, excluding African Americans from the analyses. The results of these analyses can be seen in Table 8. Similar to the results testing hypotheses 1 & 2 in the full sample, these subset analyses yielded no significant findings.

Table 7. Regression Analyses of Cognitive, Affective, and Behavioral Components of Hostility Predicting Telomere Length.

Predictor	Controlling for Age, SES, Race, Arthritis Condition (n = 192)				Controlling for Age, SES, Race, Arthritis Condition, Adiposity, Blood Pressure, and Smoking History (n = 191)		
	Beta	R Squared	P value		Beta	R Squared	P value
Age	-.16		.04	Age	-.13		.15
Education	.14		.095	Education	.13		.12
Income	-.01		.92	Income	-.00		.97
Race (Black)	.02		.82	Race (Black)	.01		.91
Arthritis History	-.01		.90	Arthritis History	-.02		.81
Step 1: Covariates		.045	.12	Adiposity	-.08		.26
				SBP	.01		.89
				DBP	.08		.36
				Smoking History	-.01		.85
				Step 1: Covariates		.057	.28
Hostile Cognitions	.04	.002	.59		.03	.00	.68
Hostile Anger	-.03	.001	.64		-.03	.001	.73
CMH Scale 39-item	.02	.00	.80		.01	.00	.88
CM Hostile Affect	.03	.001	.65		.03	.001	.72
CM Hostile Attributions	.002	.00	.98		-.01	.00	.90
CM Aggressive Responding	-.02	.00	.80		-.02	.00	.77
CM Cynicism	.04	.002	.58		.04	.00	.62
STAXI Trait Anger	.004	.000	.96		.01	.00	.94
STAXI Angry Temperament	-.04	.001	.60		-.04	.00	.62
Angry Reaction	.05	.003	.47		.05	.00	.49
Anger Control	.02	.000	.81		.00	.00	.96
Anger Out	-.02	.000	.81		-.01	.00	.88
Anger In	.05	.003	.47		.05	.00	.50
Anger Expression	-.002	.000	.98		.01	.00	.93

Table 8. Regression Analyses of Cognitive, Affective, and Behavioral Components of Hostility Predicting Telomere Length in European Americans (Excluding African American Subjects)

Predictor	Controlling for Age, SES, Arthritis Condition (n = 157)			Predictor	Controlling for Age, SES, Arthritis Condition, Adiposity, Blood Pressure, and Smoking History (n =156)		
	Beta	**R Squared**	**P value**		**Beta**	**R Squared**	**P value**
Age	-.15		.08	Age	-.17		.08
Education	.18		.04*	Education	.19		.04*
Income	-.01		.95	Income	-.01		.93
Arthritis History	.04		.63	Arthritis History	.04		.60
Step 1: Covariates		.057	.06	Adiposity	-.15		.07
				SBP	.11		.22
				DBP	.04		.64
				Smoking History	-.09		.29
				Step 1: Covariates		.096	.055
Hostile Cognitions	.09	.007	.27		.09	.007	.28
Hostile Anger	-.05	.002	.54		-.03	.001	.76
CMH Scale 39-item	.05	.003	.52		.06	.003	.49
CM Hostile Affect	.06	.003	.46		.07	.005	.37
CM Hostile Attributions	.04	.002	.61		.03	.001	.73
CM Aggressive Responding	.03	.001	.71		.04	.001	.66
CM Cynicism	.05	.002	.59		.06	.003	.50
STAXI Trait Anger	.03	.001	.71		.04	.001	.66
STAXI Angry Temperament	-.05	.002	.57		-.04	.002	.59
Angry Reaction	.09	.009	.24		.09	.008	.24
Anger Control	.04	.002	.58		.01	.000	.91
Anger Out	-.04	.002	.62		-.01	.000	.93
Anger In	.10	.009	.22		.09	.008	.26
Anger Expression	-.01	.00	.92		.02	.000	.80

5.3 EXPLORATORY ANALYSES

5.3.1 Association of subscale measures with telomere length

We went on to examine any association of the full scale hostility measures (CMH and STAXI) or their subscales with telomere length to determine whether specific elements of anger expression and/or hostile dispositions were related to telomere length, but again found no significant associations (See Table 7).

5.3.2 Race as a moderator

Although there were no overall differences in telomere length between African-Americans and European-Americans, there were differences in levels of hostility, with African-Americans scoring significantly higher on the hostile cognitions factor score ($t(193) = 3.54$, $p = .001$), CMH total hostility ($t(193) = 4.69$, $p < .001$), CMH hostile attributions subscale ($t(193) = 4.51$, $p < .001$), CMH aggressive responding ($t(193) = -2.28$, $p < .05$, and CMH cynicism ($t(193) = 5.71$, $p < .001$) than European-Americans (See Table 9). Given these racial differences, we next conducted exploratory analyses to examine whether race moderated the association of hostility with telomere length. For this purpose, we ran a series of linear regression analyses entering age, SES, and history of arthritis in step one, race and the respective hostility measure (centered) in step two, and the interaction term in step three. There were no significant interactions of race and hostility in the prediction of telomere length (See Table 10).

Table 9. Mean Hostility Score By Race.

	Blacks (n = 35)	Whites (n = 160)	
Cook-Medley Hostility	**Mean (SD)**	**Mean (SD)**	**P value of difference**
Hostile Cognitions	**.53(.91)**	**-.11(.99)**	**.001**
Hostile Anger	-.04(.95)	.00(1.03)	.83
CMH 39-item	**20.236.1)**	**14.2(7)**	**.000**
CM Hostile Affect	2.8(1.4)	2.5(1.4)	.26
CM Aggressive Responding	**3.9(1.6)**	**3.1(1.8)**	**.02**
CM Hostile Attributions	**5.8(2.4)**	**3.8(2.4)**	**.000**
CM Cynicism	**7.7(2.4)**	**4.8(2.8)**	**.000**
STAXI			
STAXI Trait Anger	16.7(3.6)	16.3(3.7)	.59
STAXI Angry Temperament	5.8(2.2)	5.8(1.8)	.84
STAXI Angry Reaction	8(1.8)	7.6(2.3)	.37
STAXI Anger Control	22.5(4.3)	23.8(5.2)	.15
STAXI Anger Out	13.5(2.9)	13.95(3.5)	.79
STAXI Anger IN	15.1(3.3)	15.8(3.8)	.29
STAXI Anger Expression	22.2(7.1)	21.8(8.8)	.83

Table 10. Regression Analyses Testing the Interaction of Race With Cognitive, Affective, and Behavioral Components of Hostility Predicting Telomere Length.

Predictor	Controlling for Age, SES, & Arthritis Status		
	Beta	**R Squared Change**	**P value**
Hostile Cognition X Race	-.098	.006	.28
Hostile Anger X Race	.048	.002	.55
CMH Scale 39-item X Race	.014	.002	.59
CM Hostile Affect X Race	-.095	.002	.57
CM Hostile Attributions X Race	-.163	.004	.40
CM Aggressive Responding X Race	-.192	.005	.33
CM Cynicism X Race	.10	.001	.70
STAXI Trait Anger X Race	-.218	.002	.53
STAXI Angry Temperament X Race	.139	.001	.726
Angry Reaction X Race	-.453	.01	.16
Anger Control X Race	-.408	.006	.29
Anger Out X Race	.855	.005	.34
Anger In X Race	-.414	.007	.23
Anger Expression X Race	.119	.001	.61

5.3.3 Age as a moderator

Our initial bivariate analyses revealed an inverse association of age with telomere length. In light of existing evidence that hostility also varies by age (Barefoot et al., 1995), we next explored whether age moderated associations between hostility and telomere length. As expected, bivariate correlational analyses revealed inverse associations of age with the hostile cognitions factor ($r = -.12$, $p = .09$), the hostile anger factor ($r = -.16$, $p = .03$), CM total hostility

(r = -.15, p = .03), hostile affect (r = -.19, p = .007), aggressive responding (r = -.16, p = .03), STAXI trait anger (r = -.16, p = .03), STAXI angry temperament (r = -.15, p = .04), and STAXI anger out (r = -.15, p = .04) (See Figures 1a-1h). Accordingly, for each measure of hostility we ran a linear regression analysis entering race, SES, and history of arthritis in step one, followed by age (centered) and the respective hostility measure (centered) in step two, and the interaction of age with hostility in step three (See Table 11). These exploratory analyses revealed a trend towards significance for the interaction of age with the hostile cognition factor score, F(1,185) =3.47, p = .06, CM hostile affect, F(1,185) = 3.68, p = .057, and anger in, F(1,185) = 3.29, p = .07, in the prediction of telomere length. In each case, there was an inverse association of the hostility measure with telomere length in the younger participants. In contrast, among older participants the association between hostility and telomere length was positive (See Figures 2a, 2b, 2c). Given that the effect sizes for these interaction terms are small, adequate power to detect significance would be improved by a larger sample size. The current sample size had low power of .44 and .48, making it difficult to reliably detect the significance of such small effects. No other significant interactions of hostility with age in the prediction of telomere length were identified.

Table 11. Regression Analyses Testing The Interaction of Age With Cognitive, Affective, and Behavioral Components of Hostility Predicting Telomere Length

Predictor	Model Controlling for Race, SES, & Arthritis Status		
	Beta	**R Squared Change**	**P value**
Hostile Cognition X Age	**.87**	**.018**	**.06**
Hostile Anger X Age	.03	.000	.93
CMH Scale 39-item X Age	.77	.013	.106
CM Hostile Affect X Age	**.91**	**.019**	**.057**
CM Hostile Attributions X Age	.69	.011	.148
CM Aggressive Responding X Age	.41	.004	.395
CM Cynicism X Age	.56	.008	.21
STAXI Trait Anger X Age	.37	.003	.44
STAXI Angry Temperament X Age	.07	.000	.91
Angry Reaction X Age	.56	.007	.24
Anger Control X Age	.56	.000	.91
Anger Out X Age	.66	.003	.45
Anger In X Age	**1.01**	**.017**	**.07**
Anger Expression X Age	.43	.005	.34

Figure 1a-1h. Mean Hostility Scale and Subscale Scores by Age Category

Figure 1a. Mean CM Hostility 39-item Score By Age Category

Figure 1b. Mean Aggressive Responding Score By Age Category

Figure 1c. Mean Hostile Affect Score By Age Category

Figure 1d. Mean Anger Out Score By Age Category

Figure 1e. Mean Trait Anger Score By Age Category
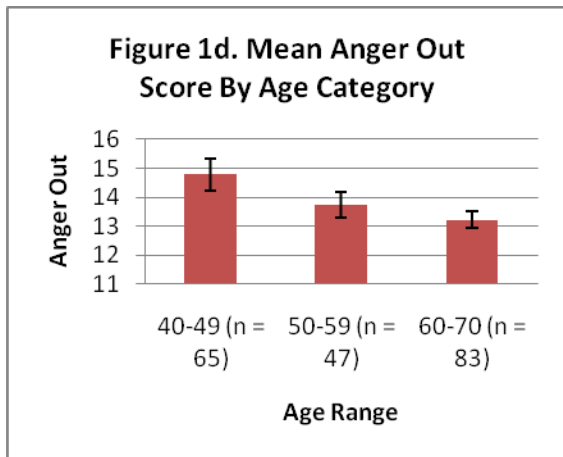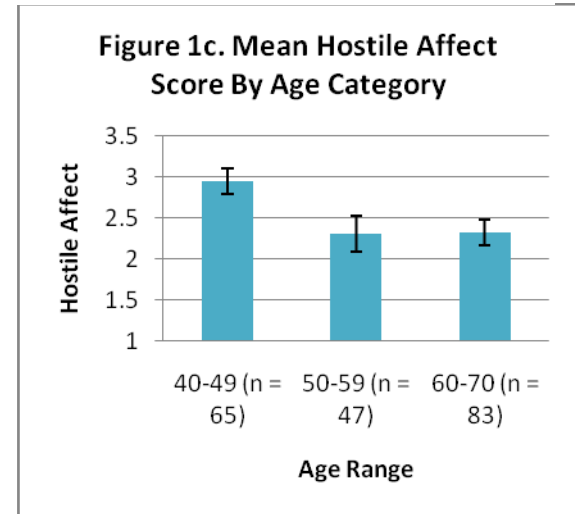

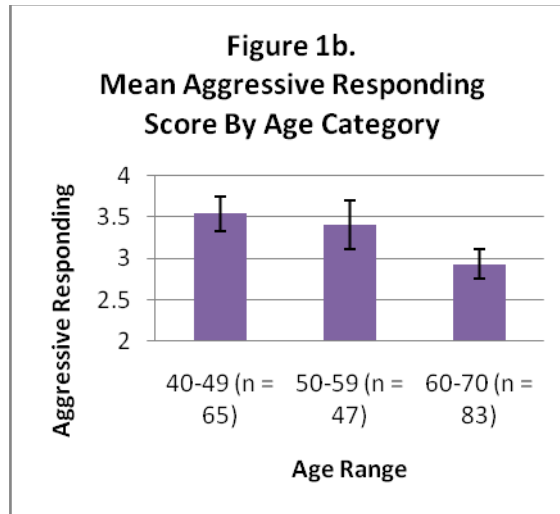Figure 1f. Mean Angry Temperament Score By Age Category
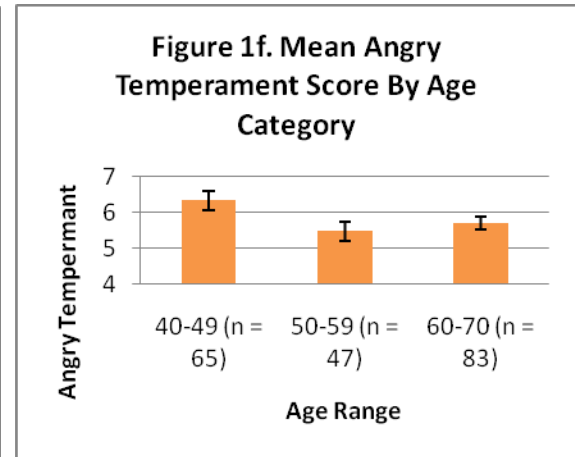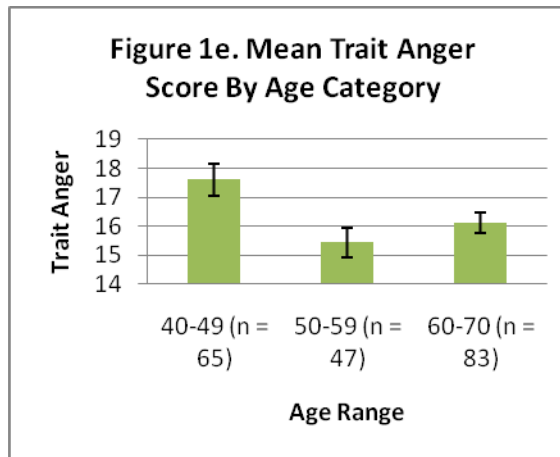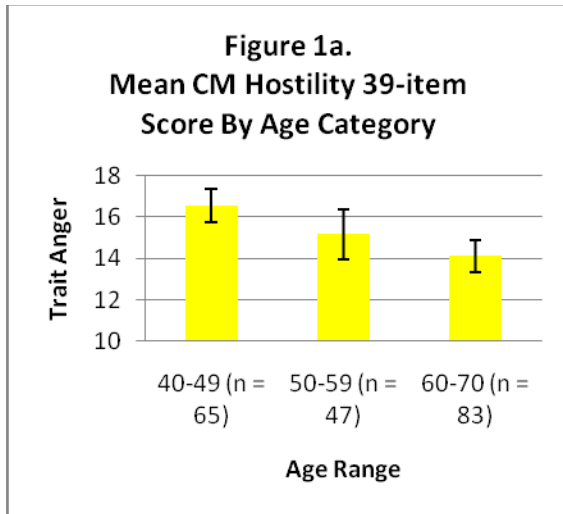
Figure 1g. Mean Hostile Cognitions Factor Score By Age Category
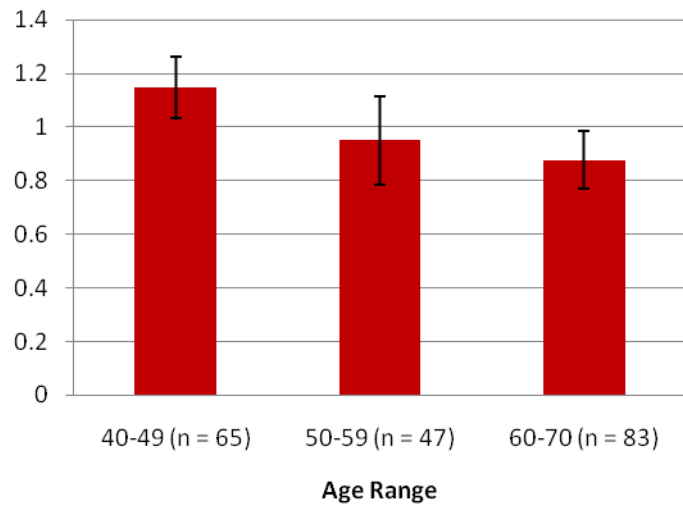
Figure 1h. Mean Hostile Anger Factor Score By Age Category
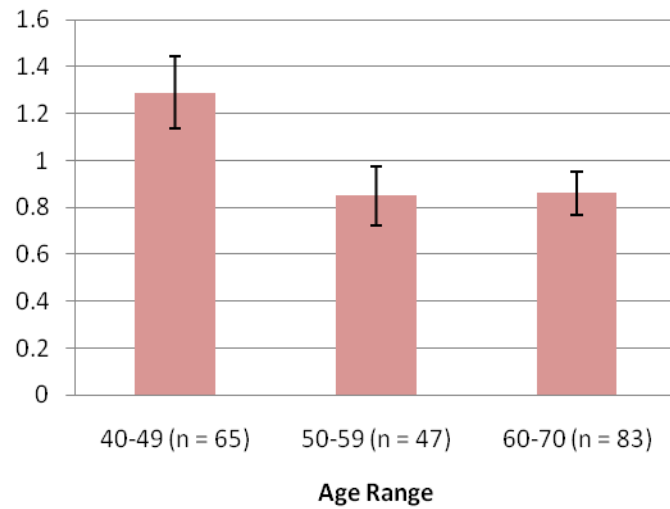
Note: Mean Hostile Cognitions and Hostile Anger scores were computed for graphical presentation as mean +1.

Figure 2a. Interaction of Hostile Cognitions and Age In the Prediction of Telomere Length
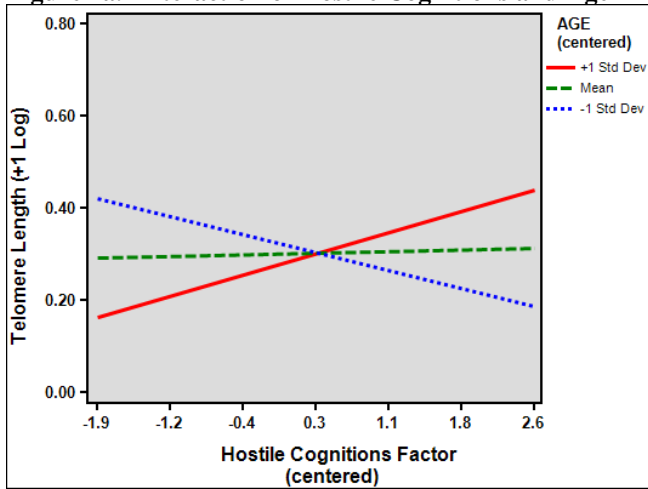
Figure 2b. Interaction of Hostile Affect and Age in the Prediction of Telomere Length
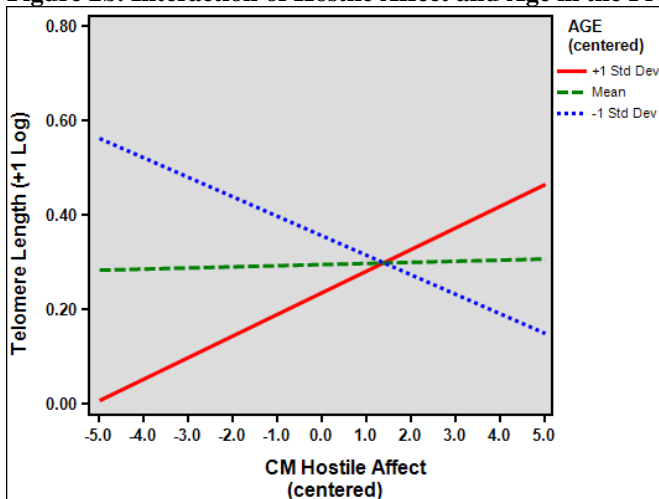
Figure 2c. Interaction of Anger In and Age in the Prediction of Telomere Length
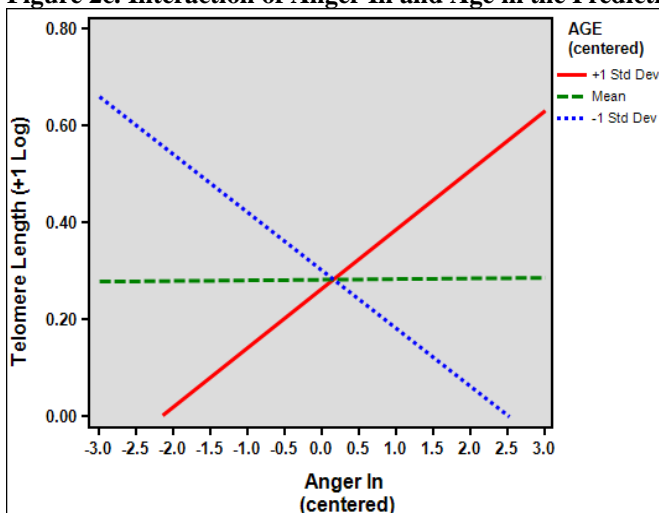
5.3.4 Association of socioeconomic factors with telomere length

The initial bivariate analyses revealed an interesting positive association of years of education with telomere length (r = .15, p < .05) (See Figure 3). However, this associations was no longer significant with age, race, history of arthritis, adiposity smoking history, and blood pressure in the model (β = .13, F(1, 187) = 3.14, p < .08). We went on to examine these associations in only the European-American participants, excluding African Americans from the model. Here a significant positive association between years of education and telomere length was observed with age, health and lifestyle factors in the model (β = .18, p < .03). These findings highlight the importance of considering race when examining associations between socioeconomic status and biological aging.

Figure 3. Scatterplot of Association Between Years of Education and Age-Adjusted Telomere Length
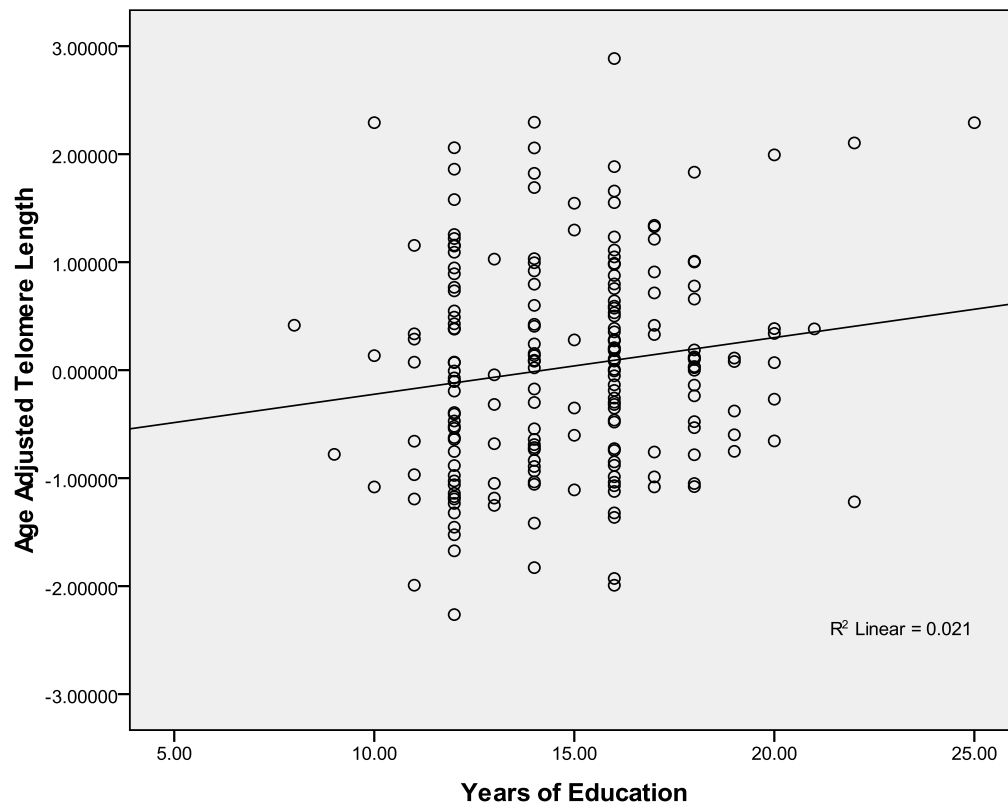
6.0   DISCUSSION

Relatively consistent evidence suggests that individuals who tend to experience anger and reports hostile cognitions are at increased risk for incident heart disease and mortality (Barefoot et al., 1989; Miller et al., 1996). One mechanism through which this increase in risk might occur is through the pathophysiological consequences of sympathoadrenal and HPA dysregulation, which may have deleterious effects on cellular processes and contribute to premature biological aging. Recent evidence demonstrates associations between other psychological risk factors for CHD and the length of telomeres in cells, a purported marker of biological age that predicts cardiovascular morbidity and mortality (Damjanovic et al., 2007; Epel et al., 2004; Lung et al. 2006; Parks et al., 2009; Bakaysa et al., 2007; Cawthon et al., 2003; Epel et al., 2009; Farzaneh-Far et al., 2008). In the current study, we sought to extend this literature by exploring the possible association of hostile dispositions with telomere length. Specifically, we examined whether individual differences in the affective, behavioral, and cognitive dimensions of hostility were related to telomere length among a sample of untreated hypertensive men at high risk for cardiovascular disease. Based on the existing literature, we predicted that factor derived dimensions of hostility, known to confer risk for cardiovascular disease, would be associated with shorter telomere length.

6.1   RELEVANCE OF FINDINGS

6.1.1   Primary hypotheses

Contrary to our hypothesis, however, we found no significant associations of hostile cognitions or hostile anger with telomere length. Further exploration of the total scores and subscale scores from the CMH and STAXI yielded similar null findings, suggesting that hostility, and its cognitive, affective, and behavioral components, are not associated with telomere length in this study. To the best of our knowledge, no previous studies have examined the association of hostility with this marker of cellular aging; however, there is growing evidence that other psychological factors that confer health risk covary inversely with telomere length. Notably, shorter telomeres have been associated with higher psychological stress (Damjanovic et al., 2007; Epel et al., 2004; Parks et al., 2009), major depressive disorder (Lung et al., 2007), a history of childhood maltreatment (Tyrka et al., 2009), and higher dispositional pessimism (O'Donovan et al., 2009), independently of demographic and health factors. Of these studies, pessimism has the most similarities to hostility, as it also represents a stable dispositional tendency to expect worse outcomes. Pessimism is thought to reflect negative general expectations for the future, while hostile cognitions include expectations of negative/hostile intentions from and interactions with others. Although similar, clearly the emphasis on social versus global expectations makes these two dispositional tendencies distinct, and comparisons between the two are limited.

The reasons that our findings are discrepant from the extant literature remain unclear. However, it is possible that sample characteristics played a role. To date, the majority of studies showing an association of psychosocial risk factors with telomere length sample relatively

healthy populations without preclinical indicators of underlying disease. In contrast, the current study recruited a sample of untreated, hypertensive men. It is likely that our sample of high risk individuals with hypertension have pre-clinical cardiovascular disease, resulting in less variability of telomere length than seen in studies of more healthy populations. Furthermore, it is possible that biological/pathological factors obscure the more subtle influences of psychosocial factors on telomere length that are seen among lower risk samples. In this regard, evidence shows stronger associations of hostility with incident CHD risk among young, initially healthy samples who are followed for many years (e.g., Surtees et al., 2005; Chang et al., 2002) than among older samples (over 60 years old) with more pre-clinical disease (e.g., Surtees et al., 2005). Thus, it is possible that there is a stronger effect of hostility on telomere length among healthier samples with no evidence of preclinical disease.

6.1.2   Race as a moderator of the association of hostility with telomere length

When compared with European Americans, African-Americans are at elevated risk for cardiovascular disease (Albert et al., 2004; Rosamond et la., 2007), show a greater decline in telomere attrition with age (Aviv et al., 2009; Diez-Roux et al., 2009; Hunt et al., 2008), and exhibit stronger positive associations between hostility and cardiovascular risk (Cooper & Waldstein, 2004; Tindle et al., 2009; Williams et al., 2007)[2]. For this reason, we examined the possibility that race moderated the association of hostility with telomere length. However, we found no evidence for differences in telomere length between European and African Americans,

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[2] Tindle and collegues (2009) report risk of CHD mortality of OR 2.02 for blacks vs. 1.18 for white; Williams et al., (2007) reports association between hostility and IMT remains significant in black men only after controlling for sociodemographic, lifestyle, and biological risk parameters. Hostility associated with triglycerides, insulin, blood pressure, and cardiac index in blacks suggesting greater cardiovascular risk compared to whites (Cooper & Waldstein, 2004)

or evidence that race moderated the association of hostility with telomere length among our sample of untreated hypertensive men. Because our sample only included 35 African Americans, we also examined associations of hostility with telomere length among only the European American participants. Again, no significant associations were observed. These findings should be interpreted with caution, however, as our power to detect small effect sizes was limited. Thus, further studies are warranted to examine whether associations of hostility with telomere length are moderated by race.

6.1.3   Age as a moderator of the association of hostility with telomere length

Consistent with evidence showing shortening of telomeres with age across both healthy and diseased populations (r values range from -.07 to -.47; Aviv et al., 2009; Bakaysa et al., 2007; Bentos et al., 2004; Cawthon et al., 2003; Demissie et al., 2006; Diez-Roux et al., 2009; Epel et al., 2004; Farzaneh-Far et al., 2010; Huda et al., 2007), we found an inverse correlation of age with telomere length (r = -.17, p < .05). This provides further evidence for telomere length as a marker of biological aging.

Growing evidence suggests that age moderates associations of hostility with cardiovascular morbidity and mortality, with younger and likely healthier samples showing stronger associations of hostility with cardiovascular risk than older samples (Miller et al., 1996). This raises the possibility that dispositional characteristics like hostility may show closer associations with biological aging in younger, rather than older samples. In support of this possibility, our findings show a trend for an inverse association of hostile cognitions, CMH hostile affect, and STAXI anger-in with telomere length, but only among younger participants.

Analyses of the slope when age is 46.6 years (1 standard deviation below the mean) shows this inverse relationship; however, the slope when age is 65 (1 standard deviation above the mean of age) appears reversed, showing a positive association of these dimensions of hostility with telomere length in the older age range (see Figure 2). This provides initial evidence that hostility is associated with shorter telomere lengths in younger individuals, who are less susceptible to the impact of pathophysiologic processes that accompany age.

It is possible that that the nature of psychosocial risk varies by age. Growing evidence suggests that mid-life hostility may predict poorer future health outcomes. In contrast, other psychosocial factors may play a greater role in predicting risk among the elderly. For example, recent evidence shows that psychological stress is more strongly associated with shorter telomere length among a female sample aged between 55 and 74 years ($n = 289$) compared to those aged between 35-54 ($n = 358$) (Parks et al., 2009). This psychosocial factor is episodic by nature and may have a different impact on telomere attrition than the influence of more consistent factors, such as dispositional characteristics. Indeed, attrition rates may be more pronounced with episodic distress in older samples, as this population is at greater risk for inflammatory activity (Chung et al., 2009), particularly when under distress (Kiecolt-Glaser, 2002; McDade et al., 2006). Given this, reasons for a positive association of hostility and telomere length among older participants in the present sample remain unclear.

Biological mechanisms may contribute to different associations of hostility with telomere length in younger and older samples. In this regard, evidence shows a positive association of baseline telomere length with the magnitude of change in telomere length, suggesting longer telomeres have more rapid attrition rates than shorter telomeres (Epel et al., 2009; Aviv et al., 2009; Farzaneh-Far et al., 2010). A number of factors have been proposed that

may account for this association, including a bias for telomerase to selectively act on the shortest telomeres, an upregulation of telomerase in cells with critically short telomeres, and the death of cells with very short telomeres (Epel et al., 2009; Aviv et al., 2009). Thus, the population of cells from peripheral blood with shorter telomeres may generally show less attrition over time as a consequence of these cellular processes. This tendency to prevent loss, maintain, or even elongate telomeres in cells with shorter telomeres may potentially mask the contribution of hostility to telomere attrition in later years.

6.1.4   Socioeconomic status and telomere length

A substantial body of research shows a graded relationship between socioeconomic status (SES) and cardiovascular and age-related disease risk, with individuals of lower SES experiencing higher rates of morbidity and all-cause mortality than their more advantaged counterparts (Adler et al., 1994; Adler & Ostrove, 1999). In this regard, our findings revealed an inverse association of number of years of education with age-adjusted telomere length (See Figure 3). However, this association did not withstand adjustment for race, arthritis history, adiposity blood pressure, and smoking history in the full sample. Secondary analyses, examining only the subset of European Americans showed a more significant positive association of years of education with telomere length that was independent of age, health and lifestyle covariates, raising the possibility that lower levels of education are associated with premature cellular aging in this racial group. These findings are consistent with the findings of others (Cherkas et al., 2006; Diez-Rouz et al., 2009; Parks et al., 2009, but not Adams et al., 2006; Epel et al., 2009), which generally find modest inverse associations of educational markers of SES with telomere

length. For example, in a sample of British female twins, Cherkas and colleagues (2006) found a positive association of occupational status with telomere length after controlling for age, smoking history, physical activity, and BMI. Further exploration of differences between dizygotic twins discordant for occupational status revealed significantly shorter telomere length of twins employed in blue-collar jobs than their respective twins employed in white-collar jobs, a finding that controls for the contribution of genetics (Cherkas et al., 2006). In contrast, Adams et al. found no significant associations between numerous socioeconomic indicators and telomere length among a sample of 50 year olds; however, this may reflect limited variation in telomere length given the age constraint. In sum the majority of studies, including our own, demonstrate an inverse association of education and employment markers of SES with telomere length. In contrast, there is no evidence for an association of family income with telomere length in our findings or the findings of others (Adams et al., 2006; Cherkas et al., 2006; Diez-Rouz et al., 2009).

To date, mechanisms linking educational/employment gradients to health risk remain unclear. However, a number of contributing factors have been considered. For example, social position and education can determine access to and/or utilization of health care resources as well as contribute to an individual's physical environment, including exposure to residential and occupational pollutants and toxins. SES may also influence disease susceptibility through its association with lifestyle-risk factors, such as access to and consumption of nutritious foods, prevalence of smoking, and rates of physical activity (Adler & Ostrove, 1999; Kaplan & Keil, 1993; McEwen & Seeman, 1999; Gallo & Matthews, 2003). As these environmental and behavioral factors are also thought to contribute to biological aging, it is possible that the association between SES and telomere length is the consequence of these factors (Adams et al.,

2004). However, taken together these environmental and lifestyle factors do not fully account for SES-related disease risk (Adler & Ostrove, 1999), or SES-related variability in telomere length (Cherkas et la., 2006). Thus, attention has turned to the possibility that psychosocial antecedents of biological factors may contribute to these associations. In this regard, it is proposed that psychosocial factors (e.g. stress, anger) result in activation of efferent biological mechanisms that contribute to increased risk for disease. For example, the limited access to social resources and greater likelihood of experiencing threats to personal safety or financial security that accompany lower SES are thought to contribute to negative emotional tendencies (e.g. anxiety, stress, depressed affect, and hostility) that result in activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal cortical axis (Schurmeyer & Wickings, 1999; Musselman, Evans, & Nemeroff, 1998; Pope & Smith, 1991). The dysregulation of these systems contributes to increases in inflammation and oxidative stress, that, in turn, result in telomere erosion and premature aging (Bekaert et al., 2007; Gilley et al., 2008; Houben et al., 2008; von Zglinicki, 2002). Thus, lower socioeconomic conditions may result in increased wear to biological systems, not only as a consequence of poor health behaviors and environmental exposures (Adams et al., 2004) but also through psychosocial mechanisms, resulting in a "weathering" of physiological systems, as proposed by Geronimus (1992). This weathering may be observed as earlier reproductive aging, risk for age-related disease (e.g. hypertension, CVD), and mortality (Geronimus, 1992). It is likely that more rapid attrition of telomeres, reflecting premature cellular aging, contributes to these effects, providing one pathway through which social inequalities confer risk for early morbidity and mortality.

6.1.5 Association of lifestyle and health variables with telomere length

6.1.5.1 Adiposity

Another individual difference factor that predicts increased health risk is adiposity. Greater adiposity has been linked with elevations in disease risk (Rosamond et al., 2007). Indeed, obesity is accepted to be an inflammatory condition associated with heightened levels of systemic proinflammatory cytokines (Wellen & Hotamisligil, 2003). Evidence for an association of measures of adiposity, including BMI, waist-hip ratio, and percent body fat, with telomere length is inconsistent. Some studies show an inverse association of these measures with telomere length, with stronger associations observed among females (Cassidy et al., 2010; Cherkas et al., 2006; Epel et al., 2009; Farzaneh-Far et al., 2010; Hunt et la., 2008). In contrast, other studies, including our own, find no significant associations (Bekaert et al., 2007; Jeanclos et al., 2000; Farzaneh-Far et al., 2010; Shen et al., 2007). It is possible that discrepant findings reflect gender differences in the influence of adiposity on telomere length. There are gender differences in rates of obesity, with high rates among women, possibly as a consequence of the influence of hormones on fat distribution and storage (Lovejoy, 1996). There are also gender differences in the reliability of measures of adiposity. For example, BMI is not an ideal indicator of body fat among men who have significant muscle mass. These factors may contribute to gender differences in the association between body fat and telomere length. It is also likely that fluctuations in weight over time contribute to rates of cellular aging, raising questions about the value of one time measurements (Moreno-Navarrete et al., 2010). Further research is warranted examining life-course trajectories of body fat composition as a predictor of telomere attrition in both genders.

6.1.5.2 Smoking

As an established risk factor for cardiovascular disease, cancer, and all cause mortality, smoking is widely accepted to contribute to premature aging and mortality (Thun et al., 1997; American Heart Association, American Cancer Society). Thus, it is suggested that smoking results in premature cellular aging and shorter telomere lengths. Some existing evidence supports this association, with shorter telomere lengths observed among smokers compared to non-smokers, and inverse associations of telomere length with number of packs smoked and years of smoking (Aviv et al, 2009; Cherkas et al., 2006; Diez-Roux et al., 2009; O'Donnell et al., 2008; Valdes et al., 2005). However, not all findings are consistent. Similar to the findings of others (Bekaert et al., 2007; Ehrlenbach et al., 2009; Farzaneh-Far et al., 2008; Bakaysa et al., 2007), we observed no significant association of history of smoking or current smoking status with telomere length in the current study. Reasons for inconsistent findings remain unclear. It is possible that the effect of smoking on telomere length is more pronounced with increasing age, as is the case with the association of smoking with mortality (Thun et al., 1997). In support of this possibility, several studies that find an association between smoking and telomere length sampled older adults or included a wide range of ages (Diez-Roux et la., 2009; O'Donnell et al., 2008). Thus, it is possible that our sample age range (mean = 55.6, SD = 9.2) may have limited our ability to detect this effect. Alternatively, more accurate assessments of smoking history may yield stronger associations. For example, Diez-Roux and colleagues (2009) found an inverse association of years of smoking with telomere length. Future research should consider the intensity and duration of smoking, along with the age distribution of the sample, when interpreting the impact this health behavior has on premature biological aging.

6.1.5.3 Blood pressure

Hypertension is a known risk factor for cardiovascular diseases and is proposed to contribute to premature aging of the vasculature (Rosamond et al., 2007; Jeanclos et al., 2000; Taddei et al., 1997). Although a number of studies have shown shorter telomere lengths among hypertensive than normotensive subjects (Huda et al., 2007; Serrano & Andres, 2004), there is no evidence for a linear association between systolic blood pressure and telomere length (Bekaert et al.2007; Epel et al., 2009; Farzaneh-Far et al., 2010), and limited evidence for an association with diastolic blood pressure (Jeanclos et al., 2000). Thus, it is not surprising that we did not see an association of blood pressure with telomere length in the current sample of untreated hypertensive men. It remains possible that the telomere lengths observed in our sample are on average lower than similar individuals who are not hypertensive.

6.2 LIMITATIONS

Although our findings do not support an association between hostile tendencies and telomere length, a number of limitations in the current project prevent us from making definitive conclusions and suggest that further research is reasonable. The current study focuses on telomere length among a sample of men with untreated hypertension. The use of a high risk sample limits the external validity of findings and suggests a need to use caution in interpreting results. Untreated hypertension is an established risk factor for cardiovascular disease morbidity (Rosamond et al., 2007) that has been associated with shorter telomere lengths (Huda et al., 2007; Serrano & Andres, 2004). The overwhelming influence of biological factors on telomere

length in our sample of individuals with preclinical cardiovascular disease may have obscured the more subtle influences of psychosocial factors, such as dispositional hostility.

Another limitation of the present analyses is our method of assessing hostility. Although, factor analyses of the STAXI and the CMH scales provides reasonable construct reliability, a number of limitations of these self-report measure raise questions about validity (Miller et al., 1995; Smith, Glazer, Ruiz, Gallo, 2004). It is possible that the use of structured interviews may provide a more reliable and valid assessment of individual differences in dispositional hostility. It also remains unclear whether the measure of hostility used in the current study provides a reliable indicator of stable, dispositional differences over the life course. As this dispositional tendency is proposed to contribute to premature aging through years of accumulated wear of physiological systems, only a tendency that persists over time would noticeably influence this outcome. Although there is evidence that trait measures of hostility and anger persist over short periods of time (i.e. a few years; Barefoot, 1983; Shekelle et al., 1983; Speilberger, 198; Bishop & Quah, 1998; Jacobs, Latham & Brown, 1988), the test-retest reliability of these dimensions over decades is less certain (coefficient of r = .39 when measurement spans 22-years; Siegler et al., 1990). In this regard, and consistent with the present findings, there is evidence that hostile tendencies change over the life course, with higher CM hostility scores among young adults, slightly lower levels in middle age, and a trend toward increasing levels in the elderly (Barefoot, 1991). Both life circumstances (i.e. social relationships, social roles, responsibilities, expectations, etc.) and perhaps biological factors (i.e. hormones) could contribute to variations in hostility across the lifecourse. Further evidence that these are not stable dispositional characteristics comes from intervention studies, which show that hostile tendencies can be changed (Bennett et al., 1991; Deffenbacher, 1992). In sum, our single assessment of hostility

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and anger expression is limited, and does not accurately capture stable dispositions over the course of life, dispositions that are likely to impact cellular processes over long periods, including aging.

Another limitation of the present analyses concerns the methods employed to assess telomere length. Although internal reliability of the qRT-PCR methodology was confirmed by our lab, the assay is only semi-quantitative, as it does not give an absolute telomere length value, and fails to provide information about telomere lengths within individual cell populations or single chromosomes (Koppelstaetter et al., 2009). Cawthon (2003) reported high correlations between the qRT-PCR methodology and the more established Telomere Restriction Fragment (TRF) analyses employing Southern Blotting techniques (R squared = .68). Although this permits adequate resolution for most empirically derived hypotheses, there may still be enough noise to limit our ability to detect small effects (Koppelstaetter et al., 2009). The use of a relative methodology also prevents the clear comparison of effects across studies. Advantages of the qRT-PCR methods are its high throughput and ability to determine telomeric length with low levels of DNA (Koppelstaetter et al., 2009).

It is unlikely that the current methods contribute to our failure to find more significant effects. Indeed, the inverse association of chronic stress with telomere length has been reported using both the qRT-PCR methods (Epel et al., 2004) and the TRF analysis (Damjanovic et al., 2007; Parks et la., 2009),[3] suggesting that variations in these methods do not contribute to differences in findings. Our examination of telomere length from the DNA of peripheral blood mononuclear cells (PBMC) is also consistent with the methods of others who have found significant effects (Damjanovic et la., 2007; Parks et al., 2009). It has been suggested that the

[3] Parks and colleagues reported associations of stress with shorter telomere length in subjects over 55 years, but not in the younger cohort.

association of psychosocial factors with telomere length may reflect alterations in the ratios of different populations of white blood cells in peripheral circulation. Although there is compelling evidence that psychosocial factors do impact the cellular composition of blood, a recent study shows that caregivers tend to have shorter telomeres in T cells and monocytes than matched controls (Damjanovic et al., 2007). Thus, stress-related changes in the cellular composition of peripheral blood does not fully account for differences in telomere length. However, it is known that telomere lengths differ across white blood cell subtypes, which could contribute to assessments of cellular age and should be controlled in future work.

Finally, the external validity of the current study is compromised by the all male sample. Given that there are gender differences in the expression of hostility (Davidson & Hall, 1995), the length of telomere (Hunt et al., 2008; Epel et al., 2009), and the association of hostility with cardiovascular risk (Tindle et al., 2009), we cannot rule out the possibility of a gender difference. Future work should pursue these questions further with adequate power to detect interactions of race, gender, and hostility in the prediction of telomere length.

6.3   CONCLUSIONS

In conclusion, current models of hostility and disease risk support the hypothesis that dispositional hostility increases the rate of aging, which should be reflected by shorter telomeres, and contribute to increased risk for age-related disease. Contrary to this hypothesis, we did not find an association of hostility, or its affective, behavioral, or cognitive dimensions, with telomere length in our cross-sectional sample of untreated hypertensive men. It is possible that

sample characteristics may have limited our ability to detect effects, and future research should consider gender, along with health status, when examining these potential associations.

We did find some evidence that age may moderate the association of hostility with telomere length, with a tendency for hostile cognitions, internalized anger and hostile affect to be associated with shorter telomere length among younger, but not older men in the sample. If anything, older men in the sample showed the opposite effect, with longer telomeres among those reporting more hostility. These findings should be considered preliminary and only interpreted with caution given our limited power to detect effects and the possibility that they are spurious. However, if replicated in the future, these associations may contribute to explaining the stronger association of hostility with incident CHD observed among younger samples.

Finally, our findings show a positive association of educational attainment with telomere length, an association that was independent of age, health and lifestyle factors amongst the European American subjects. These findings contribute to a growing literature suggesting that lower socioeconomic status may influence disease risk through accelerated biological aging (Cherkas et al., 2006; Diez-Roux et la., 2009; Parks et al., 2009). Although this theory has long standing roots in the social disparities literature (Geronimus, 1992), until recently limited research has documented associations of socioeconomic disadvantage with a biomarker of aging. Thus, these findings contribute to a growing field of inquiry examining the biological pathways through which social disadvantage influences disease risk.

Future research should pursue these questions in a prospective analysis with multiple assessments of relevant predictors (i.e. psychosocial risk factors, physical activity, smoking history, socioeconomic indicators, adiposity, etc.) and changes in telomere length over time. Similarly, it is recommended that future analyses consider sampling healthy populations with a

sufficient age distribution to have adequate power to detect the interactive effects of race and gender in the association of psychosocial and socioeconomic risk with telomere length.

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