TELOMERE LENGTH, UNCOMMON GENETIC VARIATION, AND DEPRESSION

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ABSTRACT

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Previous research attempting to better understand the genetic basis of depression has demonstrated few clear findings. The present study employed a cross-sectional design to analyze the association between leukocyte telomere length and depression in 2,710 participants from the Dallas Heart Study (DHS), as well as the potentially moderating influence of ethnicity/race, APOE allele variation, and average self-reported hours of sleep per night. Furthermore, in an exploratory exome-wide association study, we analyzed associations between a subset of 2,949 participants from the DHS with depression data available and 247,870 genetic variants. Scores from the primary measure of depression—The Quick Inventory of Depressive Symptomatology (QIDS)—showed a significant negative association with telomere length but only in the Caucasian subset of the sample. Scores from the secondary measure of depression—The DHS's "felt depressed" question—showed a significant negative association with telomere length across the whole sample, as well as in the African American subset, but not within the Caucasian or Hispanic subsets. Neither APOE allele variation nor average nightly sleep was a significant moderator of the association between depression and telomere length. No significant associations between depressions scores and specific genetic variants were found in the exome-wide

association study. These finding help clarify the relationship between depression and telomere length by highlighting the importance of ethnicity/race in the relationship between depression and telomere length. Future research involving depression and telomere length should account for ethnicity/race in their analyses, while future exome-wide association studies of depression should seek more severe and well-defined cases of depression.

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PRIOR PUBLICATIONS

Wignall, N. D., & Brown, E. S. (2014). Citicoline in addictive disorders: a review of the literature. *Am J Drug Alcohol Abuse, 40*(4), 262-268. doi: 10.3109/00952990.2014.925467

Wignall, N. D., & de Wit, H. (2011). Effects of nicotine on attention and inhibitory control in healthy nonsmokers. *Exp Clin Psychopharmacol, 19*(3), 183-191. doi: 10.1037/a0023292

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CHAPTER I

Introduction

Depression is a complex condition that contributes to significant health and economic burdens worldwide (Mathers & Loncar, 2006). While mental health clinicians and researchers have made important progress in the identification and treatment of depression in recent decades, it is still poorly understood and difficult to treat (Belmaker & Agam, 2008). Recent approaches to the identification and treatment of depression have focused on better understanding the biological basis of depression (Duman, 2014; Han & Yu, 2014; Nemeroff, 2002).

One recent line of inquiry has investigated the effect of depression on telomere length. Although telomere shortening or erosion is a natural consequence of normal cell division, depression may increase the rate of telomere erosion (Simon et al., 2006). However, the research literature on the relationship between depression and telomere length is relatively small and largely equivocal in its findings (see Tables 1 and 2 for a summary). The primary purpose of the present investigation was to help clarify this literature by examining the relationship between depression and leukocyte telomere length in a large sample and to attempt to account for several potentially moderating variables, especially ethnic/racial differences.

A second aim of this investigation was to examine more broadly the genetic basis of depression. While previous candidate gene and genome-wide association studies of depression have been largely inconclusive (Flint & Kendler, 2014), a new method of genetic analysis, exome-wide association study, was available and has not previously been used to examine genetic variations associated with depression. This newer method of analysis may provide

greater clarity on the relationship between genetic variance and the emergence of depressive symptoms as it examines uncommon sources of genetic variation, which previous methodologies have been unable to investigate.

CHAPTER II

Background and Literature Review

I. What is Depression?

While the term *depression* is commonly used to describe a range of symptoms and phenotypes all related to low mood, the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-*5*) (*Diagnostic and Statistical Manual of Mental Disorders*, 2013) demarcates several distinct depressive disorders (e.g. major depressive disorder, persistent depressive disorder/dysthymia, as well as several bipolar disorders which include depressive episodes), each of which include a similar set of symptoms, but may vary according to frequency, intensity, or other co-occurring factors (First, 2013).

Major depressive disorder is the prototypical depressive disorder and is characterized by a two-week period of persistently depressed mood and/or markedly diminished interest or pleasure in previously enjoyed activities. Additional symptoms include significant changes in appetite or weight, poor sleep quality, psychomotor retardation or agitation, fatigue, feelings of worthlessness or guilt, difficulty thinking or concentrating, and suicidal thinking (*Diagnostic and Statistical Manual of Mental Disorders*, 2013).

While major depressive disorder is typically diagnosed after a thorough clinical interview, many self-report or clinician-administered assessment measures exist to provide a more convenient means of determining the presence of depressive symptoms (Bentley, Pagalilauan, & Simpson, 2014). Along with the recent rise in interest of conceptualizing psychiatric conditions along dimensional rather than categorical lines, symptom-based measures

of depression have received renewed interest, especially as a way to determine sub-clinical or non-pathological levels of depression in persons who might simply have been labeled as not having met criteria according to a traditional clinical interview (Widiger & Samuel, 2005).

In the last several decades, depression appears to have grown rapidly into societal and cultural consciousness. The health professions have also improved considerably in their ability to recognize, diagnose and treat depressive disorders in recent years, yet depression remains a significant problem (Millan, Goodwin, Meyer-Lindenberg, & Ove Ogren, 2015). Epidemiological research suggests that the lifetime prevalence of major depression is generally between 8 and 12% worldwide; however the range is wide, with the lowest prevalence found in Japan (3%) and the highest in the United States (17%) (Andrade et al., 2003; Kessler et al., 2003). Furthermore, depression has consistently been found at double the rate in women compared to men (Kuehner, 2003; Seedat et al., 2009), is more common in conjunction with or after serious medical conditions such as stroke, Parkinson's disease, and cardiovascular disease (Alboni, Favaron, Paparella, Sciammarella, & Pedaci, 2008; Rickards, 2005), and appears to have differential effects by race/ethnicity (Riolo, Nguyen, Greden, & King, 2005).

In recent years, both clinicians and researchers have increasingly turned toward a more biological perspective on depression (Fakhoury, 2015; Maletic & Raison, 2014). The search for so-called "biomarkers" of depression has been especially emphasized, with the hope that if a biological signature for depression were available, clinicians would be better able to confidently identify its presence or absence and to treat it effectively (Jani et al., 2015; Woods, Iosifescu, & Darie, 2014). One potential biomarker for depression is telomere length.

II. What are Telomeres?

The term telomere—derived from the Greek words *telos* meaning end and *meros* meaning part—refers to the genetic material at the ends of chromosomes. The term was coined relatively independently in the 1930s by Herman J. Muller, Cyril D. Darlington, and J. B. S. Haldane (Muller, 1938) who noted that the ends of chromosomes are different than ends of other genetic material resulting from breakage since, unlike broken strands, they will not fuse with other ends. After these initial observations, Muller and Barbara McClintock were the first to describe the role telomeres play in maintaining chromosomal stability (McClintock, 1939).

Leonard Hayflick made the important discovery that cell populations have only a limited capacity for replication. Known as Hayflick's Limit or replicative senescence, this limit refers to the number of times a typical human cell population divides until individual cell division ceases (Hayflick, 1965). In the late 1960s Alexey M. Olovnikov, a Soviet graduate student, inspired by both Muller and McClintock as well as Hayflick's work, theorized that telomeres—and telomere shortening specifically—might be the mechanism responsible for Hayflick's limit (Olovnikov, 1973).

The next major milestone in the timeline of telomere study came in the late 1970s when Elizabeth Blackburn uncovered the basic structure of telomeres as small repeated sequences of DNA (Blackburn & Gall, 1978). She later went on with Jack Szostak to demonstrate how telomeres are conserved evolutionarily and contribute to the chromosome's stability over time (Szostak & Blackburn, 1982) and with her graduate student Carol Greider first described the enzyme telomerase which lengthens telomeres (Greider & Blackburn, 1985). As a result of these early discoveries into the nature of telomeres, the last twenty years have seen an enormous amount of interest in telomere biology.

An early analogue for telomere function was the concept of the mitotic clock. Research in the early 1990s bore out Olovnikov's early theorizing and demonstrated that telomeres actually shorted predictably with cellular division and replication. Furthermore, when samples were taken from older people and compared to those of younger people, the telomeres of the older people were found to be significantly and predictably shorter, leading to the concept of telomeres as a marker or proxy for biological—as opposed to chronological—age (Harley, Futcher, & Greider, 1990). Most recently, the study of telomere structure and function has been applied to specific disease states and phenotypes in the hopes of elucidating the mechanisms behind various forms of premature aging and mortality.

III. Telomere Structure and Function

Telomeres are repetitive nucleotide sequences located at the ends of chromosomes in most eukaryotic organisms (i.e. those whose cells contain a nucleus). For vertebrates, including humans, the specific sequence of the nucleotides is TTAGGG. Although telomere length varies considerably between species, in humans the length is typically between 0.5 and 15 kilo base pairs (bp). At the far end of the telomere is a single-strand portion called the telomere loop or T-Loop, which is maintained by several proteins known as the Shelterin Complex. This loop is approximately 300 bp long and serves to stabilize the telomere by preventing the telomere ends from being identified as break points, an event which would typically trigger cellular senescence, apoptosis, or several other events which might compromise the integrity of the genetic information (Bailey & Murnane, 2006; d'Adda di Fagagna et al., 2003). In addition to its protective function, telomere shortening also functions as a tumor suppressing mechanism, since it limits the proliferative potential of cells (Shay & Wright, 2005).

Additionally, telomeres have a particular attribute which makes them essential to the larger process of DNA replication. During cellular division, DNA polymerase is not able to completely replicate the 3' end of the strand so the telomere shortens by approximately 30 to 200 base pairs. This phenomenon is known as the end replication problem (Aubert & Lansdorp, 2008). As a result, telomere length gradually declines over time (approximately 20 to 40 base pairs each year in human leukocyte telomeres) until the telomere is critically short. Once this point has been reached, the T-Loop can no longer hold the structure of the telomere together and cellular senescence or apoptosis is induced (Zakian, 2012).

Interestingly, the end-replication problem is thought to only contribute to a small percentage of the overall loss in telomere length (Levy, Allsopp, Futcher, Greider, & Harley, 1992), suggesting that other factors may play a role in the degradation of telomere length (von Zglinicki, 2000, 2002). Telomere degradation is known to be associated with T-cell proliferation initiated by pro-inflammatory cytokines (Carrero et al., 2008). These same pro-inflammatory cytokines have also been implicated in the inhibition of cellular apoptosis, which prevents the most damaged cells from being removed from the population, as well as leading to a higher percentage of cells with short telomere lengths (Mangan & Wahl, 1991). Finally, increased inflammation may also trigger an increase in cortisol and related hypothalamic-pituitary-adrenal (HPA) axis factors (Silverman & Sternberg, 2012), which are thought to influence telomere length by decreasing the transcription of the telomerase catalytic element (J. Choi, Fauce, & Effros, 2008).

In addition to inflammation, oxidative stress may be associated with an increased rate of telomere length attrition. Oxidative stress is the term used to define an imbalance in a biological system between reactive oxygen species (reactive molecules that contain oxygen) and the

system's ability to remove the reactive components or repair the damage they cause (Devasagayam et al., 2004). A sustained level of oxidative stress can result in structural cellular damage as well as functional disruptions in the typical cellular signaling mechanisms (Valko et al., 2007). In addition to increasing the rate of telomere attrition, oxidative stress has been implicated in a host of disease states ranging from cancer (Halliwell, 2007) and heart attacks (Ramond et al., 2013) to autism (James et al., 2004) and chronic fatigue syndrome (Kennedy et al., 2005).

While various factors have been identified that appear to contribute causally to an increased rate of telomere length attrition, some evidence also suggests that the causality is unclear given shortened telomeres also contribute to inflammatory, HPA axis, and autonomic dysregulations (Verhoeven, Revesz, Wolkowitz, & Penninx, 2014). For example, one study showed that monocytes with shorter telomere lengths demonstrated an increase in inflammatory activity compared to those cells with longer telomere lengths (Merino et al., 2011). Others have suggested that shorter telomeres might contribute to impaired mitochondrial functioning, followed by a decrease in fatty acid oxidation and glucose utilization resulting in an increased vulnerability to the effects of oxidative stress (Fyhrquist, Saijonmaa, & Strandberg, 2013; Satoh et al., 2008). More recent work in this area by Sahin et al has shown that telomere dysfunction activates the p53 tumor suppressor protein, which in turn suppresses mitochondrial functioning via suppression of PGC-1a abd PGC-1b promoters (Sahin et al., 2011). In sum, it appears as though decreased telomere length and dysregulation within several stress systems throughout the body interact with each other such that they set the stage for impairments in healthy functioning across a range of domains (Verhoeven et al., 2014).

While telomeres tend to degrade and shorten over time, they can be extended through the action of the enzyme telomerase, which is composed of telomerase reverse transcriptase (TERT) and a telomerase RNA component (TERC). When active, telomerase adds TTAGGG repeats to the 3' ends of chromosomes. In animal studies, telomerase is found to be elevated in cancerous cells (Lu, Zhang, Liu, Songyang, & Wan, 2013), while the deletion of TERT or TERC was found to result in telomere shortening, fusion, genomic instability, and aging-related phenotypes (Blasco, Rizen, Greider, & Hanahan, 1996; Y. Liu et al., 2000). While the majority of human somatic cells do not express telomerase, even in cells where it is expressed (the most common are embryonic stem cells, male germ cells, activated lymphocytes, and certain adult stem cells) it is typically not sufficient to completely counteract the cumulative shortening of telomeres via replication and external insult (Blackburn, 1992; Cong, Wright, & Shay, 2002; Lingner, Cooper, & Cech, 1995; Shay & Wright, 2005; Wright, Piatyszek, Rainey, Byrd, & Shay, 1996). However, interesting recent work in animal models has provided evidence that by reactivating telomerase production, common symptoms of telomere degeneration such as tissue atrophy, organ failure, or stem cell depletion can be at least partially reversed (Jaskelioff et al., 2011).

IV. Telomere Length and Disease

Over the past twenty years, there has been considerable interest in the relationship between telomere length and various disease states and negative environmental factors. One of the largest areas of inquiry has been cardiovascular disease. Shorter telomere length has been linked to many components of cardiovascular disease such as heart failure (van der Harst et al., 2007), atherosclerosis (Willeit et al., 2010, Brouilette et al., 2007), and aortic valve stenosis (Kurz et al., 2006). While many associations in this area have been found, interpreting them has been more

difficult. Shorter telomere length is typically associated with an increased risk for cardiovascular disease and its various facets, however some research has demonstrated that opposite could be true. One study, for instance, found that longer telomere length was associated with increased left ventricle mass, which is thought to be a marker for chronic exposure to risk factors for cardiovascular disease (Vasan et al., 2009). Another study in mice found that shorter telomere length could actually protect against atherosclerosis by limiting the degree of cellular proliferation in the accumulation of arterial plaques (Poch et al., 2004).

Cancer researchers have also become increasingly interested in the relationship between telomere length and various forms of—or risk factors for—cancer, especially given the role of telomeres in limiting cellular proliferation and maintaining chromosomal stability. Somewhat surprisingly given the significant overlap in telomere function and cancer biology, research attempting to detect relationships between telomere length and cancer risk have been mixed. Breast cancer risk, for instance, has been associated with both long and short telomere lengths (Shen et al., 2007). A recent meta-analysis, however, suggested that shorter telomere lengths were generally associated with an increased risk for cancer (H. Ma et al., 2011).

Some research suggests that type 2 diabetes is associated with shorter telomere length. One study did find an association between the two and attributed it to higher oxidative stress levels resulting from diabetes (Salpea et al., 2010). Another paper demonstrated that telomere length was shorter in patients with diabetes, but only for those with poor glycemic control (Uziel et al., 2007). Finally, research on patients with type 1 diabetes showed that while there was no telomere length difference between patients with diabetes and the control group, shorter telomere length was an independent predictor of diabetic nephropathy in the patient group (Fyhrquist et al., 2010).

The relationship between telomere length and overall mortality has been investigated in several instances. In one study, shorter telomere length was associated with a threefold increase in risk for dying of heart disease and an eight fold increase in the risk of dying from an infectious disease (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003). Two twin studies both demonstrated a significant association between shorter telomere length and overall mortality rates (Bakaysa et al., 2007; Kimura et al., 2008). However, several studies using older samples failed to find a significant link between telomere length and mortality (Bischoff et al., 2006; Houben, Giltay, Rius-Ottenheim, Hageman, & Kromhout, 2011).

Taken together, the research on telomere length and physical disease suggests there is likely a negative correlation between telomere length and various disease states. However, given the diversity in methodologies, hypotheses, and clinical contexts, drawing firm conclusions is difficult.

V. Telomere Length and Psychiatric Illness

The small literature to date on the relationship between depression and telomere length is conflicting (See Tables 1 and 2 for a summary). In an early study of telomere length and psychiatric illness, Simon et al. demonstrated an association between shorter telomere length and depression in 44 patients diagnosed with major depressive disorder and bipolar disorder compared to controls (Simon et al., 2006). Lung et al. replicated this finding in a larger sample of 253 depression patients (Lung, Chen, & Shu, 2007). Wolkowitz et al. found that shorter telomere length was associated with cumulative lifetime depression duration as well as higher levels of oxidative stress (F2-isoprostanes to vitamin C ratio) and inflammation (IL-6 concentrations) (Wolkowitz et al., 2011). In a later study, Wolkowitz et al. reported higher levels of telomerase

activity in major depressive disorder patients compared to controls and that it was also related to higher levels of depression and stress (Wolkowitz et al., 2012). Malan et al. failed to detect a significant relationship between telomere length and depression in a sample of female rape victims (Malan, Hemmings, Kidd, Martin, & Seedat, 2011). Wikgren et al. demonstrated that patients with major depressive disorder who also had low cortisol levels after a dexamethasone suppression test had shorter telomere lengths compared to controls (Wikgren, Maripuu, et al., 2012). This finding adds support to the hypothesis that effect of depression on telomere length is largely mediated by stress (i.e. chronically depressed patients are chronically stressed which leads to a state of hypocortisolism).

Shaffer et al. studied 267 patients with "probable depressive symptoms" but did not find any evidence of shorter telomere length in this group compared to healthy controls (Shaffer et al., 2012). Hoen et al. reported shorter telomere length in depressed patients, although depression was not predictive of changes in telomere length over a five-year period (Hoen et al., 2011). In contrast to the previous findings, Hartman et al. examined the relationship between telomere length and depression but did not find any effect of either the duration of the illness or treatment type (high or low antidepressant dose or electroconvulsive therapy) on telomere length (Hartmann, Boehner, Groenen, & Kalb, 2010).

In a study that included both patients with anxiety and those with depression, Hoen et al. found a significant relationship between anxiety and telomere length but not depression (Hoen et al., 2013). In a recent study by Puterman et al. of a large sample of patients with stable cardiovascular disease, a "multisystem resiliency model" (which included variables such as strong social connections, emotional regulation, and healthy sleep habits) significantly moderated the relationship between major depressive disorder and shorter telomere lengths

(Puterman et al., 2013). Verhoeven et al. analyzed data from a large national database and compared patients with both current and remitted depression to healthy controls: while both current and remitted major depressive disorder patients had significantly shorter telomere lengths, the data also indicated a "dose-response" gradient such that the most severely depressed patients showed the shortest telomere lengths (Verhoeven et al., 2013). In a cross-sectional study of 355 elderly participants from the Netherlands Study of Depression in Older Persons, Schaakxs et al. found that telomere length did not differ significantly between depressed and non-depressed participants, and that it was also not associated with the severity, age of onset, or duration of depression (Schaakxs, Verhoeven, Oude Voshaar, Comijs, & Penninx, 2014).

Szebeni et al. collected two glial cell populations (oligodendrocytes and astrocytes) from brain donors with major depressive disorder and compared telomere lengths in the two cell populations (matched with those from healthy controls). They found that telomere length in oligodendrocytes, but not astrocytes, was significantly shorter among the cells from patients with major depressive disorder, suggesting that specific cell types may be differentially resistant to the effects of oxidative stress and depression (Szebeni et al., 2014). In a similar study, Karabatsiakis et al. investigated the relationship between history of depression, current depressive symptoms, and telomere length from several specific white blood cell types associated with the adaptive immune system in 44 female participants compared with 50 age-matched controls. They found that a history of depression, regardless of the presence of current depressive symptoms, was negatively associated with telomere length, and that telomere length in CD8+ cytotoxic T cells and CD20+ B cells was especially affected by a history of depression (Karabatsiakis, Kolassa, Kolassa, Rudolph, & Dietrich, 2014).

Georgin-Lavialle et al. investigated the relationship between depression and telomere length in patients with mastocytosis. They found that while perceived stress was negatively associated with telomere length as well as more severe depression, depressive symptoms (as measured by the Beck Depression Inventory) were not independently associated with telomere length (Georgin-Lavialle et al., 2014). Liu et al. investigated telomere shortening in patients with type 2 diabetes and depression and found a significant association between depression and shortened telomere length, and that this relationship was mediated by patients' levels of oxidative stress (Z. Liu, Zhang, Yan, Wang, & Li, 2014).

Garcia-Rizo et al. investigated the effect of depression on telomere length with a focus on the potentially confounding effect of antidepressant medication use. In a sample of 15 depressed individual compared to 70 healthy controls, they found shortened telomere length in the depressed group compared to the controls independent of antidepressant use (Garcia-Rizo et al., 2013). In contrast, Needham et al. found that in 1,290 participants from the 1999-2002 National Health and Nutrition Examination Survey, those participants with diagnosed major depressive disorder were more likely to have shorter telomere lengths than those who were not, but only if they were also taking antidepressant medication (Needham et al., 2014).

Using data from the West of Scotland Twent-07 Study, Phillips et al. looked at the effect of depression on telomere length in a sample of 1,063 Scottish participants. Their results were mixed in that they found a negative association between depression and telomere length in the youngest cohort at two time points, however in the other two cohorts and across other time points, as well as in the total data examined cross-sectionally, no associations were found (Phillips et al., 2013). In a similarly sized longitudinal study, Shalev et al. investigated the effect of internalizing disorders—depression, generalized anxiety disorder, and post-traumatic stress

disorder—on telomere erosion. They used data from 1,037 participants of the Dunedin Study and found that, among men but not women, telomere erosion was accelerated among participants diagnosed with depression or generalized anxiety disorder but not post-traumatic stress disorder in between time points (Shalev et al., 2014). In contrast to this finding, Ladwig et al. found that post-traumatic stress disorder but not depression was negatively associated with telomere length in a large sample of 2,528 participants from the KORA F4 study in southern Germany (Ladwig et al., 2013).

Elvsashagen et al. used a quantitative fluorescence in situ hybridization technique and found that the proportion of short telomeres was greater in bipolar II patients compared to controls but that overall mean telomere length was not (Elvsashagen et al., 2011). Kao et al. showed significant differences in telomere length in schizophrenia patients compared to control subjects (Kao et al., 2008), a finding which was replicated by Fernandez-Egea et al. (Fernandez-Egea et al., 2009) but not by Mansour et al. (Mansour et al., 2011).

The research on telomere length and dementia suggest a possible association. Two studies demonstrated that patients diagnosed with Alzheimer's disease had significantly shorter telomere length compared to control groups without an Alzheimer's diagnosis (Honig, Schupf, Lee, Tang, & Mayeux, 2006; Thomas, NJ, & Fenech, 2008). One study of elderly Down's syndrome patients with a diagnosis of Alzheimer's disease, demonstrated shorter telomere length in the T cells of the Alzheimer's patients compared to controls (Jenkins et al., 2006). Another group showed that telomere length predicted dementia in individuals who had suffered a stroke (C. Martin-Ruiz et al., 2006). However, several studies have failed to demonstrate significant relationships between telomere length and dementia. In two related studies, neither telomere length nor change in telomere length was associated with dementia or mild cognitive impairment

over a two-year span (Zekry, Herrmann, Irminger-Finger, Graf, et al., 2010; Zekry, Herrmann, Irminger-Finger, Ortolan, et al., 2010). Another group failed to find a significant association between telomere length and dementia in a longitudinal study (C. M. Martin-Ruiz, Gussekloo, van Heemst, von Zglinicki, & Westendorp, 2005). Finally, a study comparing vascular dementia patients with Alzheimer's patients (there was no control group in the study) found that telomere length did not differ significantly between groups (Lof-Ohlin, Hagnelius, & Nilsson, 2008).

The research literature on telomere length and cognition in non-dementia patients is mixed. In a large study of 2,734 elderly patients spanning a seven-year period, shorter telomere length at baseline was associated with a greater decline in performance on the Modified Mini-Mental Status Examination (Yaffe et al., 2011). Two prospective studies from the Lothian Birth Cohorts did not find any evidence of an association between telomere length and cognition (Harris et al., 2006; Harris, Martin-Ruiz, von Zglinicki, Starr, & Deary, 2012). One study reported conflicting finding showing that shorter telomere length was associated with both good and poor performance on various cognitive tests (Mather et al., 2010). Finally, one study of female twins age 19 to 78, reported longer telomere length was significantly associated with better performance on measures of working memory and finger tapping reaction time (Valdes et al., 2010).

VI. Telomere Length and Environmental Factors

In addition to disease states, many psychosocial and environmental factors are thought to be associated with telomere length. Tobacco use, which is well known to directly increase levels of oxidative stress, has been associated with shorter telomere length in several studies (Morla et al., 2006; Nawrot et al., 2010; Valdes et al., 2005), with clinical implications suggesting that

smoking a pack of cigarettes per day for 40 years may lead to an erosion of telomere length equivalent to a loss of over seven years of life. Obesity is another lifestyle factor associated with inflammation and oxidative stress, and several studies have reported an association between obesity and increased telomere length attrition (Brouilette et al., 2008; Demissie et al., 2006; D. Ma, Zhu, Hu, Yu, & Yang, 2013). Longer telomere lengths have also been associated with higher levels of vitamin D, omega-3 fatty acids, folate, as well as vitamin A and B12 (Farzaneh-Far et al., 2010; Paul et al., 2009; Richards et al., 2007; Xu et al., 2009).

Socioeconomic status has recently become the subject of study in telomere length research. A 2006 study of 1,552 female twins by Cherkas et al. found an association between lower socio-economic status and shorter telomere length (Cherkas et al., 2006). In contrast, Adams et al. did not find a significant relationship between socio-economic status and telomere length in a study composed of a homogenous birth cohort at 50 years of age (Adams et al., 2007). Batty et al. found that while there was no association between telomere length and educational attainment, unemployed men had significantly shorter telomere lengths than those who were employed (Batty et al., 2009). Woo et al. reported that higher levels of community standing were associated with shorter telomere length in men (Woo, Tang, Suen, Leung, & Wong, 2009). In two prospective cohort studies, low educational attainment was significantly associated with shorter telomere length (Steptoe et al., 2011; Surtees et al., 2012). Needham et al. reported shorter telomere length among subjects whose parents had lower educational attainment (Needham, Fernandez, Lin, Epel, & Blackburn, 2012). Finally, in a cohort of older adults, Adler et al. showed a positive association between telomere length and educational attainment, as well as interaction effects suggesting more beneficial effects of educational attainment for Blacks compared to Whites (Adler et al., 2013).

In 2004, Epel et al. found a relationship between shorter telomere length and higher levels of perceived stress, longer durations of chronic stress, and higher levels of oxidative stress (defined as a subject's F2-isoprostanes to vitamin E ration) (Epel et al., 2004). Damjanovic et al. replicated this finding while studying telomere length in Alzheimer's disease patients (Damjanovic et al., 2007). Parks et al. also found that perceived stress was associated with shorter telomere length in a sample of 647 women (Parks et al., 2009). In a similar study, Bekaert et al. reported an association between shorter telomere length and an increase in markers of inflammation and oxidative stress (Bekaert et al., 2007). Finally, Humphreys et al. reported a link between shorter telomere length and high levels of psychological stress in women who had experienced partner violence, demonstrating that duration of time spent in the abusive relationship and having children was associated with shorter telomere length (Humphreys et al., 2012).

Several studies have also linked shorter telomere length to various forms of childhood adversity and stress, including maltreatment (Tyrka et al., 2010), severe social deprivation (Drury et al., 2012), and trauma (O'Donovan et al., 2011). Shalev et al. reported that a child's exposure to two or more types of violence (e.g. domestic violence, bullying, physical maltreatment) was significantly associated with more rapid telomere erosion between the ages of five and ten (Shalev et al., 2013). Keicolt-Glaser et al. found that childhood adversity moderated the effect of later-life stress and telomere length in older caregivers (Kiecolt-Glaser et al., 2011). One study by Theall et al. reported that children living in neighborhoods which were characterized as "high disorder" (that is, chaotic and unpredictable) had shorter telomere lengths compared to children living in less disordered neighborhoods (Theall, McKasson, Mabile, Dunaway, & Drury, 2013). Finally, childhood adversities and early life stress have also been

associated with shorter telomere length, both in samples of patients with anxiety disorders and cancer as well as healthy controls (Kananen et al., 2010; Surtees et al., 2011).

In 2008, Ludlow et al. investigated the relationship between telomere length, telomerase activity, and physical activity. They found that a moderate level of physical exercise was associated with longer telomere length compared with high or low levels of physical activity (Ludlow et al., 2008). Cherkas et al. also studied the relationship between telomere length and physical activity in 2,401 healthy twins and found that the telomere lengths of the most active subjects were longer than those of age and sex controlled non-exercisers (Cherkas et al., 2008). Moderate physical activity and exercise in midlife has also been reported to moderate the relationship between increased stress and shorter telomeres (Puterman et al., 2010), as well as being associated with longer telomere lengths in old age (Savela et al., 2013). In one study ultra-marathon runners had significantly longer telomere lengths compared to controls (Denham et al., 2013). Savela et al. found that in a sample of 7,813 women, moderate to vigorous physical activity was associated with increased telomere length (Savela et al., 2013). In contrast to the above findings, Mathur et al. compared 17 marathon runners to 15 age and sex-matched sedentary controls and found no difference in telomere lengths (Mathur et al., 2013).

One of the more interesting though little studied variables in the research on telomere length is sleep. Liang et al. showed a significant relationship between telomere length and sleep duration in women under age 50 but not in those over 50 (Liang et al., 2011). Prather et al. reported that in a community-dwelling sample of healthy women, sleep duration and onset were not related to telomere length but that chronic poor sleep quality was (Prather et al., 2011). However, another study by Jackowska et al. of older adults reported that short sleep duration was associated with shorter telomeres but only in men (Jackowska et al., 2012). In a recent study of

human immunodeficiency virus infected adults, Lee et al. found that increased sleep duration was associated with longer telomere length, though self-reported sleep quality was not associated with telomere length (K. A. Lee et al., 2014).

VII. Telomere Length and APOE Genotype

One of the most widely studied genes, APOE, is responsible for the production of apolipoprotein E, a glycoprotein with a variety of functions including lipid metabolism and transport, triglyceride homeostasis, and immunomodulation (Zhang, Wu, & Wu, 2011). The gene and its allelic variations have been widely studied in a variety of pathologies and conditions including cardiovascular disease (Knopman et al., 2009), multiple sclerosis (Shi, Zhao, Vollmer, Tyry, & Kuniyoshi, 2008), and Alzheimer's disease (Kim, Basak, & Holtzman, 2009).

In part due to its modulatory influence on cytokines and therefore various inflammatory processes and cellular stress, APOE has more recently been investigated in the context of telomere length. In a study of 253 patients with major depressive disorder, Lung et al. (Lung et al., 2007) found an association between the APOE(2) allele variant and increased telomere length, suggesting that the APOE(2) allele might serve a "buffering" effect against telomere length shortening in major depressive disorder. Wikgren et al. studied 427 healthy individuals and found that carriers of the APOE(4) allele had significantly higher rates of telomere shortening compared with non-carriers (Wikgren, Karlsson, et al., 2012). The authors suggest that this finding may be due to a finding from previous research showing distinct anti-inflammatory and antioxidant properties of the three APOE isoforms (e2 > e3 > e4) (Jofre-Monseny, Minihane, & Rimbach, 2008). Jacobs et al. similarly found increased telomere attrition rates over a two-year period among female APOE(4) carriers (Jacobs et al., 2013). Zerky et al.,

however, found no association between telomere length and APOE allele variant (Zekry, Herrmann, Irminger-Finger, Graf, et al., 2010).

VIII. Genetic Variants and Depression

It is increasingly apparent that a better understanding the biological basis of depression is crucial to making progress in the treatment of depression. In the United States, major depression has a 16.9% lifetime prevalence rate and the largest impact of any disease on disability (Demyttenaere et al., 2004), to say nothing of the heavy burden it places on health care systems (2001). While both pharmacological and behavioral treatments have shown some efficacy (Cuijpers, Andersson, Donker, & van Straten, 2011; Khin, Chen, Yang, Yang, & Laughren, 2011), it is difficult to predict who will respond, in what time frame, and under what circumstances. A better understanding of the biological origins of depression—its genetic foundation in particular—would likely enable far more effective interventions and preventative measures (Doherty & Owen, 2014). But despite progress in other disease states, to date the genetic analysis of depression has yielded few successes (Cohen-Woods, Craig, & McGuffin, 2013).

A genetic basis for depression has been contemplated since the early part of the 20th century, with most family studies suggesting a greater than 2.0 odds ratio increased risk of developing major depressive disorder in first-degree relatives (Sullivan et al., 2009). Results from twin studies also support a strong genetic component in the development of major depressive disorder (Kendler, Gatz, Gardner, & Pedersen, 2006), including a recent meta-analysis of twin studies to date that calculated a combined heritability estimate for major depression of 37% (Sullivan, Neale, & Kendler, 2000). There has also been shown to be a higher prevalence rate of major depression for women, and further analyses have shown that depression

is significantly more heritable in women than in men (Weissman et al., 1996). Twin studies have also corroborated the above heritability rates, suggesting that similar environmental factors did not significantly contribute to the increased heritability (Kendler, Gardner, Neale, & Prescott, 2001; Kendler et al., 2006). Taken together, the evidence suggests that there is a clear genetic component to risk for developing depression. While family and heritability research strongly implicates genetic variation in the development and maintenance of depression, elucidating the underlying mechanics of this association has proved a difficult task.

The candidate gene approach is one common method for associating variance in genetic makeup (genotype) with specific traits or diseases (phenotype). In this approach, individual genes are selected *a priori* based on knowledge of the gene's specific function or influence in regard to the phenotype in question. The experimental group with the genetic variant in question is then compared to a control group which does not have the genetic variant and the frequency of the phenotype in question is compared between groups. A major limitation of this approach is that it requires and assumes information about a specific gene and its relationship to the phenotype in question. As a result, candidate gene approaches are often more useful in a confirmatory rather than exploratory function.

According to a recent reviews of candidate gene approaches, 200 genes have been investigated across approximately 1,500 separate studies of depression, however these studies are generally inconsistent (Bosker et al., 2011; Flint & Kendler, 2014). After reviewing meta-analyses of the 26 most promising genes, seven genes reached significance: 5HTTP/SLC6A4, DRD4, APOE, GNB3, MTHFR, HTR1A, and SLC6A3. However it is likely that these were false positives since they were not replicated in studies using a more advanced methodology (described below) (Flint & Kendler, 2014).

A second method for studying the relationship between genetic variation and specific phenotypes is the genome-wide association study (GWAS), which compares the entire genome of an experimental group with that of a control group to determine if specific DNA sequence variations (single-nucleotide polymorphisms or SNPs) vary predictably in the experimental group compared to the control group. If so, these SNPs are then said to be associated with the particular phenotype in question. Later confirmatory analyses such as the candidate gene approach may be useful subsequently in refining the analysis.

The GWAS was first successfully implemented in 2005 (R. J. Klein et al., 2005). Since that time, a huge variety of traits and disease states have been investigated (Johnson & O'Donnell, 2009). While thousands of SNPs have been identified and associated with specific disease states, the vast majority of these genetic variants have had only very limited power individually to predict specific phenotypes (Manolio, 2010). As a result, GWAS have tended to use increasingly large sample sizes in order to more reliably detect significant differences and also to investigate more specific phenotypes (Ioannidis, Thomas, & Daly, 2009).

A recent review (Flint & Kendler, 2014) summarized the nine published GWAS of major depression to date. They summarized their findings by noting:

> Nothing significant has been found and indeed many of the papers and reviews of this field make that point… Overall, we can conclude that no study has robustly identified a locus that exceeds genome-wide significance for major depression or genetically related traits.

It has been suggested that the primary cause for these negative finding is that GWAS have largely been underpowered and thus unable to detect contributory genetic variants. While GWAS are quite good at detecting common variants that have small effects, they are less useful for discovering rare variants (Wray et al., 2012), which may possess much larger relative effects.

A related methodology called exome-wide association study (EWAS) has recently increased in popularity, in part due to the high costs and inefficient nature of GWAS (Do, Kathiresan, & Abecasis, 2012). The exome is the section of the genome formed by exons, which are the protein-coding portions of the genome that remain in RNA after transcription. While relatively small in frequency (exons constitute approximately 1% of the entire genome), exons are important since mutations in the exome are far more likely to have significant phenotypic consequences than mutations in the rest of the genome. In fact, approximately 85% of the mutations which have a large effect on disease states occur in the exome (M. Choi et al., 2009). The value of the EWAS is that it is able to more powerfully and efficiently uncover rare coding variants not typically seen by GWAS (Kiezun et al., 2012). Though this methodology is relatively new, several studies have identified rare variants not detected by GWAS that contribute to a given disease state, including insulin secretion and type II diabetes (Huyghe et al., 2013), prostate cancer (Oh et al., 2015), and Alzheimer's disease (J. A. Chen et al., 2015).

CHAPTER III

Methods

I. Aims and Hypotheses

Primary Aim: *To investigate the relationship between telomere length and depression.*[1]

Hypothesis I: Depression scores will be negatively associated with telomere length. Scores on both primary and secondary measures of depression will be negatively associated with telomere length in a basic model controlling for age and gender, as well as in a full model controlling for ethnic/racial status, body mass index (BMI), education, tobacco use, and antidepressant use.

Secondary Aim I: *To investigate the relationship between telomere length and depression in the context of ethnic/racial differences.*

Hypothesis II: Depression scores will be negatively associated with telomere length across ethnic/racial subgroups. Scores on both measures of depression will be negatively associated with telomere length in both basic and full models within three ethnic/racial subgroups: African American, Caucasian, and Hispanic.

Secondary Aim II: *To investigate the relationship between telomere length and depression in the context of APOE allele variation.*

Hypothesis III: Presence of the APOE(4) allele will influence the relationship

[1] Although we cannot determine the presence of clinically diagnosed depression, for clarity and simplicity the term depression is used broadly throughout the manuscript to refer to the entire

between telomere length and depression such that for carriers of the APOE(4) allele, the negative association between telomere length and depressive will be stronger than for non-carriers of the APOE(4) allele. The APOE(2) and APOE(3) alleles will not significantly influence the association between depression and telomere length.

Secondary Aim III: *To investigate the relationship between telomere length and depression in the context of differences in self-reported sleep quantity.*

Hypothesis IV: Self-reported hours of sleep per night will influence the relationship between telomere length and depression such that the negative relationship between telomere length and depression will be stronger for subjects who report receiving fewer hours of sleep per night.

Exploratory Aim: *To identify potential genetic contributors to depression using a novel exome-wide analysis.*

Hypothesis V: Using an EWAS to examine rare coding variants, significant positive associations between specific SNPs and the primary measure of depression will be identified.

II. Study Sample Overview

The Dallas Heart Study (DHS) (Victor et al., 2004) is a population-based, multiethnic study of over 6,000 adults from Dallas County. It was designed to include 50% African American and 50% non-African American participants. Initial data collection took place over a two-year period

from 2000-2002. This first collection of data is referred to as DHS-1. In 2007, the study was converted from a cross-sectional design to a longitudinal one. Referred to as DHS-2, this second wave of the study invited all previous DHS-1 participants to return for repeat evaluation. 3,408 participants had available telomere length data and comprise the population on which the present analysis is based.

This subset included 1,678 African American participants (50.7%), 1,077 Non-Hispanic Caucasian participants (32.5%), 465 Hispanic participants (14%), 69 participants classified as "other" (2.1%), and 23 participants classified as "unknown" (0.7%). There were 1,960 females (59.2%) and 1,352 males (40.8%). The mean age of participants was 50 years.

Based on the above subset of the DHS sample, the study sample was further clarified according to the following criteria: Only participants who identified as African American, Caucasian, or Hispanic were included. Additionally, any participant with missing data on the primary measure of depression was excluded. On the basis of these criteria, the final sample used for primary analysis for the study consisted of a total of 2,710 participants.

III. Telomere Length

There are several commonly used methods to measure telomere length. Terminal Restriction Fragment (TRF) length analysis—generally considered the gold standard—uses a specific variant of the Southern blotting technique to analyze telomere DNA. The end result is a mean telomere length for a given cell population. While highly regarded, TRF is not without its shortcomings: it has difficulty detecting very short telomeres and requires a relatively substantial quantity of DNA. TRF is also considered one of the more technically difficult methods for measuring telomere length (Aubert, Hills, & Lansdorp, 2012).

Several other techniques are based on polymerase chain reaction (PCR), a method that involves increasing the number of copies of a region of DNA. Because this method focuses on a specific genetic region, it is possible to achieve an accurate estimate of telomere length with a smaller quantity of DNA. Single telomere length analysis measures the length of a single chromosome end. Monochrome multiplex PCR and quantitative PCR both determine a ratio of the telomere and a standard single gene copy. While these methods of telomere length based on PCR require relatively few cells, the variability within and between samples is high (Bojesen, 2013).

Fluorescent in situ hybridization (FISH) is an alternative technique that uses either flow cytometry (flow FISH) or digital microscopy (quantitative FISH) to determine the average telomere length. Advantages of the FISH techniques are that they tend to be highly accurate in their measurements and also capable of detecting relatively subtle changes in telomere length. However, both FISH techniques also require fresh cell samples and can also be technically challenging and time consuming (Canela, Vera, Klatt, & Blasco, 2007).

In the current study, DNA was taken from circulating leukocytes using an Autopure LS (Qiagen, Valencia, CA). As previously described (Diaz de Leon et al., 2010), a quantitative PCR method was employed to determine telomere lengths, with several modifications as described in another paper (Kozlitina & Garcia, 2012). Telomere length is expressed as a ratio of the copy number of telomere DNA to single-copy gene (T/S). Additionally, a "relative T/S" represents the ratio of the T/S for the experimental sample to the T/S for a specific cultured cell line with very short telomeres (MCF7). Finally, the mean relative T/S is the average of at least two independent measurements.

IV. Depression

The Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 2003) is a 16-item inventory for quantifying the severity of depressive symptoms in a brief but valid form. In the present study, the self-report version was used. It is based on the larger 30-item Inventory of Depressive Symptomatology (IDS) (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). The QIDS was designed to assess all of the major symptom domains defined in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorder* – 4th edition (DSM-IV) (*Diagnostic and Statistical Manual of Mental Disorders*, 2000) used to diagnose major depressive episodes. These symptom domains include: sad mood, concentration difficulties, self-criticism, suicidal ideation, lack of interest, energy/fatigue, sleep disturbance (including initial, middle or late insomnia, and hypersomnia), changes in appetite or weight, and psychomotor agitation or retardation. Each item is scored on a severity scale from 0 through 3.

The scoring procedure for the QIDS results in a single final score (referred to subsequently as "QIDS score"), which is calculated by taking the sum of the following:

The highest score among questions 1-4

Question 5

The highest score among questions 6-9

Question 10

Question 11

Question 12

Question 13

Question 14

The highest score among questions 15-16

The QIDS score may range from 0 to 27. Interpretation guidelines for the severity of depressive symptoms are as follows: 1-5, none; 6-10, mild; 11-15, moderate; 16-20, severe; 21-27, very severe (Rush et al., 2003; Trivedi et al., 2004). The QIDS has been shown to be a valid measure of depressive symptomatology: In a study of 596 adult outpatients, Rush et al. found that the QIDS had high correlations with the IDS ($r = .96$) as well as the Hamilton Rating Scale for Depression, including the 17, 21, and 24 item versions ($r = .81$, $r = .82$, $r = .84$, respectively) (Trivedi et al., 2004). The QIDS score was used as the primary measure of depression.

In addition to the QIDS, the DHS also gave participants a questionnaire that asked them several questions related to the participants' mood. One of these (referred to subsequently as the "felt depressed score") pertained to low mood and was included as an additional measure of depression. The questions were prefaced with the following text:

> *These questions are about how you feel and how things have been going with you during the past four weeks. For each question please give the one answer that comes closest to the way you have been feeling.*
>
> *How much of the time during the past four weeks have you felt downhearted and depressed?*

Responses were given on a 5-point scale ranging from "All of the time" to "None of the time." Responses were reverse scored on a scale ranging from 0 (*none of the time*) to 4 (*all of the time*). The felt depressed score was used as the secondary measure of depression.

V. APOE

Three variables were computed based on the presence of each of the three APOE allele isoforms: e2, e3, and e4. Any participant who was either homozygous or heterozygous for the e2 allele was dummy coded as a 1 on the APOE(2) variable; all other participants were coded as a 0. The same procedure was used to compute APOE(3) and APOE(4) variables dependent on the presence of the e3 and e4 alleles, respectively.

VI. Sleep

The DHS health questionnaire asked participants to enumerate the hours of sleep they achieved on a regular basis. The question was as follows:

> *How many hours of sleep do you usually get in:*
>
> - *A workday (school) night?*
> - *A weekend or non-work night?*

Data from both of these questions was combined to produce an "average nightly sleep hours" variable.

VII. Exome-Wide Association Study

All analyses for the exome-wide association study were performed using data from 4,625 participants in the DHS (Victor et al, 2004). The sample is a probability-based population sample of Dallas County. Participants were ascertained from census tracts, with oversampling of tracts

with a high proportion of African Americans to ensure equal representation of African Americans and Caucasians.

Genomic DNA extracted from circulating leukocytes from all participants was genotyped with an Illumina Infinium HumanExome BeadChip (Illumina, San Diego, CA, USA). The BeadChip interrogates 247,870 markers, including functional exonic variants (>90%), disease-associated tag markers from recently published GWAS, and ancestry-informative markers. Genotypes were called using Illumina GenomeStudio software. Quality-control filters were applied to samples and variants prior to the analysis. Participants were excluded under the following conditions: a call rate less than 99% (n = 25) or duplicate discordance (n = 1). Variants were excluded if the call rate was less than 99% (n = 1,795) or the genotype frequencies deviated from Hardy-Weinberg equilibrium in African Americans with $p < 0.0001$ (n = 221). Finally, after removing variants that were monomorphic (n = 75,970) or had a single carrier (n = 29,167) and participants without QIDS data, a total of 140,717 variants and 2,949 individuals were available for analysis.

VIII. Statistical Analyses for Aims and Hypotheses

Primary Aim: *To investigate the relationship between telomere length and depression.*

Hypothesis I: Depression scores will be negatively associated with telomere length. Scores on both primary and secondary measures of depression will be negatively associated with telomere length in a basic model controlling for age and gender, as well as in a full model controlling for ethnic/racial status, BMI, education, tobacco use, and antidepressant use.

Statistical Analysis: Multiple linear regression was used to measure the dependent variable of telomere length with either QIDS score or felt depressed score as the primary independent variable. In basic models, age and gender were included as covariates and in full models ethnicity/race, BMI, education, tobacco use, and antidepressant use were added as covariates. Gender, tobacco use, and antidepressant use were treated as dichotomous variables.

Secondary Aim I: *To investigate the relationship between telomere length and depression in the context of ethnic/racial differences.*

Hypothesis II: Depression scores will be negatively associated with telomere length across ethnic/racial subgroups. Scores on both measures of depression will be negatively associated with telomere length in both basic and full models within three ethnic/racial subgroups: African American, Caucasian, and Hispanic.

Statistical Analysis: Multiple linear regression was used to measure the dependent variable of telomere length with either QIDS score or felt depressed score as the primary independent variable within each ethnic/racial group. Model structures and covariates were identical to those of the primary aim.

Secondary Aim II: *To investigate the relationship between telomere length and depression in the context of APOE allele variation.*

Hypothesis III: Presence of the APOE(4) allele will influence the relationship between telomere length and depression such that for carriers of the APOE(4) allele, the negative association between telomere length and depression will be stronger than for

non-carriers of the APOE(4) allele. The APOE(2) and APOE(3) alleles will not significantly influence the association between depression and telomere length.

Statistical Analysis: Multiple linear regression was used to measure the dependent variable of telomere length with either QIDS score or felt depressed score along with APOE(2, 3, or 4) as the primary independent variables. Gender and age were included as covariates. Finally, an interaction term between APOE status and QIDS score was also included.

Secondary Aim III: *To investigate the relationship between telomere length and depression in the context of differences in self-reported sleep quantity.*

Hypothesis IV: Self-reported hours of sleep per night will influence the relationship between telomere length and depression such that the negative relationship between telomere length and depression will be stronger for subjects who report receiving fewer hours of sleep per night.

Statistical Analysis: Multiple linear regression was used to measure the dependent variable of telomere length with either QIDS score or felt depressed score along with average hours of nightly sleep as the primary independent variables. Gender and age were included as covariates. An interaction term between QIDS score and average hours of nightly sleep was also included in the model.

Exploratory Aim: *To identify potential genetic contributors to depression using a novel exome-wide analysis.*

Hypothesis V: *Using an EWAS to examine rare coding variants, significant positive associations between specific SNPs and the primary measure of depression will be identified.*

Statistical Analysis: Each variant was tested for association with QIDS score using a linear regression model including age, gender, BMI, and four principal components of ancestry as covariates. Additive effects of variants were tested by coding the genotypes 0, 1, and 2. A square root transformation was applied to QIDS scores prior to analysis to achieve approximate normality of the residuals. Exome-wide significance for the number of tests performed was set at 3.6×10^{-7}.

CHAPTER IV

Results

I. Descriptive Statistics

The initial sample consisted of 3,408 participants from the Dallas Heart Study. We excluded 104 participants whose ethnicity/race was described as "unknown" (n = 35) or "other" (n = 69). As a group, these participants did not differ significantly from the rest of the sample on telomere length ($t = 0.781$, $p = .440$). We also excluded any participants with missing data from either of the primary variables of interest—the QIDS (n = 568) or telomere length (n = 96). The group of participants excluded for missing QIDS data did not differ significantly from the rest of the sample on telomere length ($t = 1.50$, $p = .132$). The total sample for primary analyses consisted of 2,710 participants.

Descriptive statistics for the whole sample are provided in Table 3. The mean age for the sample was 49.7 years (*SD* = 11.1) and the majority of participants were women (59%). The sample consisted of 1,387 African Americans (51%), 950 Caucasians (35%), and 373 Hispanics (14%). The mean years of education was 12.7 (*SD* = 2.2). The mean BMI was 31.29 (SD = 7.43), while 1,199 subjects (45%) had a history of tobacco use and 11% were currently prescribed an antidepressant. The mean telomere length was 1.80 (SD = 0.30). The mean QIDS score was 5.51 (*SD* = 3.87). The mean felt depressed score was 0.86 (*SD* = 1.02). The mean average hours of sleep per night was 6.8 (SD = 1.4). Regarding APOE genotype, 261 subjects (15%) were carriers of the e2 allele, 1,602 (93%) were carriers of the e3 allele, and 550 (32%) were carriers of the e4 allele. Descriptive statistics are also reported for ethnic/racial subgroups in Tables 4 through 6,

including the results of chi-square or F-tests tests for significant differences in descriptive statistics between ethnic/racial subgroups.

II. Results for Aims and Hypotheses

Primary Aim: *To investigate the relationship between leukocyte telomere length and depression.*

Hypothesis I: *Depression will be negatively associated with telomere length.*

Results for the analysis of the association between QIDS score and telomere length in a basic model is provided in Table 7, while results for the analysis of the association between QIDS score and telomere length in a fully adjusted model are provided in Table 8. The QIDS was not significantly associated with telomere length in either the basic or fully adjusted model. The data, therefore, did not support the hypothesis that depression would be negatively associated with telomere length.

Results for the analysis of the association between felt depressed score and telomere length in a basic model are provided in Table 9, while results for the analysis of the association between felt depressed score and telomere length in a fully adjusted model is provided in Table 10. The felt depressed score was significantly associated with telomere length in both the basic and fully adjusted model. These data, therefore, provide some support for the hypothesis that depression would be negatively associated with telomere length.

Secondary Aim I: *To investigate the relationship between telomere length and depression in the context of ethnic/racial differences.*

Hypothesis II: *Depression will be negatively associated with telomere length across ethnic/racial subgroups.*

Results for the analysis among African American participants of the association between QIDS score and telomere length in a basic model are provided in Table 11, while results for the analysis among African American participants of the association between QIDS score and telomere length in a fully adjusted model are provided in Table 12. The QIDS was not significantly associated with telomere length in either the basic or fully adjusted model. The data, therefore, did not support the hypothesis that depression would be negatively associated with telomere length specifically among African American participants.

Results for the analysis among African American participants of the association between felt depressed score and telomere length in a basic model are provided in Table 13, while results for the analysis among African American participants of the association between felt depressed score and telomere length in a fully adjusted model is provided in Table 14. The felt depressed score was significantly associated with telomere length in both the basic and fully adjusted models. These data, therefore, provide support for the hypothesis that depression would be negatively associated with telomere length specifically among African American participants.

Results for the analysis among Caucasian participants of the association between QIDS score and telomere length in a basic model are provided in Table 15, while results for the analysis among Caucasian participants of the association between QIDS score and telomere length in a fully adjusted model is provided in Table 16. The QIDS was significantly associated with telomere length in both the basic and fully adjusted model. The data, therefore, support the hypothesis that depression would be negatively associated with telomere length specifically among Caucasian participants.

Results for the analysis among Caucasian participants of the association between felt depressed score and telomere length in a basic model are provided in Table 17, while results for the analysis among Caucasian participants of the association between felt depressed score and telomere length in a fully adjusted model is provided in Table 18. The felt depressed score was not significantly associated with telomere length in either the basic or fully adjusted model. These data, therefore, qualify the hypothesis that depression would be negatively associated with telomere length specifically among Caucasian participants as one but not both measures of depression was negatively associated with telomere length.

Results for the analysis among Hispanic participants of the association between QIDS score and telomere length in a basic model are provided in Table 19, while results for the analysis among Hispanic participants of the association between QIDS score and telomere length in a fully adjusted model is provided in Table 20. The QIDS was not significantly associated with telomere length in either the basic or fully adjusted model. The data, therefore, did not support the hypothesis that depression would be negatively associated with telomere length specifically among Hispanic participants.

Results for the analysis among Hispanic participants of the association between felt depressed score and telomere length in a basic model are provided in Table 21, while results for the analysis among Hispanic participants of the association between felt depressed score and telomere length in a fully adjusted model is provided in Table 22. The felt depressed score was not significantly associated with telomere length in either the basic or fully adjusted model. These data, therefore, do not support the hypothesis that depression would be negatively associated with telomere length specifically among Hispanic participants.

Secondary Aim II: *To investigate the relationship between telomere length and depression in the context of APOE allele variation.*

Hypothesis III: *Presence of the APOE(4) allele will influence the negative relationship between telomere length and depression such that for carriers of the APOE(4) allele, the relationship between leukocyte telomere length and depression will be stronger than for non-carriers of the APOE(4) allele. The APOE(2) and APOE(3) alleles will not have significant moderating effects of the relationship between depression and telomere length.*

Results for the analysis of the association between telomere length and QIDS score in the context of APOE(4) allele variation are provided in Table 29. While age and gender were both significant predictors of telomere length, QIDS score, APOE(4) carrier status, and the QIDS-by-APOE(4) interaction were not. Results for the analysis of the association between telomere length and felt depressed score in the context of APOE(4) allele variation are provided in Table 30. Similarly, while age and gender were both significant predictors of telomere length, felt depressed score, APOE(4) carrier status, and the felt depressed-by-APOE(4) interaction were not. These results do not support the hypothesis that the presence of the APOE(4) allele will influence the negative relationship between telomere length and depression.

Results for the analysis of the association between telomere length and QIDS score in the context of APOE(2) allele variation are provided in Table 25. While age and gender were both significant predictors of telomere length, QIDS score, APOE(2) carrier status, and the QIDS-by-APOE(2) interaction were not. Results for the analysis of the association between telomere length and felt depressed score in the context of APOE(2) allele variation are provided in Table 26. Age, gender, and felt depressed score were all significant predictors of telomere length,

however APOE(2) carrier status, and the felt depressed-by-APOE(2) interaction were not. These results support the hypothesis that the presence of the APOE(2) allele would not influence the negative relationship between telomere length and depression.

Results for the analysis of the association between telomere length and QIDS score in the context of APOE(3) allele variation are provided in Table 27. While age and gender were both significant predictors of telomere length, QIDS score, APOE(3) carrier status, and the QIDS-by-APOE(3) interaction were not. Results for the analysis of the association between telomere length and felt depressed score in the context of APOE(3) allele variation are provided in Table 28. Age, gender, felt depressed score, APOE(3) carrier status, and the felt depressed-by-APOE(3) interaction were all significant predictors of telomere length. These results do not support the hypothesis that the presence of the APOE(3) allele would not influence the negative relationship between telomere length and depression.

Secondary Aim III: *To investigate the relationship between telomere length and depression in the context of differences in self-reported sleep quantity.*

Hypothesis IV: *Self-reported hours of sleep per night will influence the negative relationship between telomere length and depression such that the relationship between telomere length and depression will be stronger for subjects who report receiving fewer hours of sleep per night.*

Results for the analysis of the association between telomere length and QIDS score in the context of sleep quantity are provided in Table 23. While age and gender were both significant predictors of telomere length, QIDS score, sleep quantity, and the QIDS-by-sleep interaction were not. Results for the analysis of the association between telomere length and felt depressed score in the

context of sleep quantity are provided in Table 24. Similarly, while age and gender were both significant predictors of telomere length, felt depressed score, sleep quantity, and the felt depressed-by-sleep interaction were not. These results do not support the hypothesis that sleep quantity will influence the negative relationship between telomere length and depression.

Exploratory Aim: *To identify potential genetic contributors to depression using a novel exome-wide analysis.*

Hypothesis V: *Using an EWAS to examine rare coding variants, significant positive associations between specific SNPs and QIDS score will be identified.*

In the primary analysis, none of the associations between the sequence variants and QIDS scores reached exome-wide significance (i.e. none were significant after correcting for multiple testing). All variants with a p-value less than 1.0E-04 (n=60) were then examined to determine if they matched loci that had previously been associated with depression. However, none of the top hits appear to have been previously implicated in depression. Finally we collated the top variants from the published GWAS meta-analyses ($P < 1x10^{-7}$ in at least one analysis) with our association data. A total of 811 SNPs in our dataset that were located within 1 Mb of the top literature SNP were examined. Of these, 50 had a nominal association ($p < 0.05$) with QIDS score. The three leading variants from a recent meta-analysis of GWAS in depression (Flint and Kendler, 2014) were not associated with QIDS score. In general, these results do not support the hypothesis that significant positive associations between specific SNPs and QIDS score will be identified.

CHAPTER V

Discussion

I. Depression-Telomere Length Association Analysis

The primary finding of the present study was that QIDS score was not significantly associated with telomere length in either a basic or fully adjusted model comprised of the whole sample. This finding is consistent with much of the recent literature on the relationship between depression and telomere length, especially the larger cross-sectional studies most similar to the present study, which have generally not found an association between depression and telomere length. Among the case control studies, five showed a significant association between depression and telomere length, three did not find a significant relationship, and four had mixed findings (see Table 1). Among cross sectional studies, one showed a significant association, while six did not show a significant relationship and two had mixed findings (see Table 2).

While the QIDS score was not significantly associated with telomere length in the whole sample, the felt depressed score was. As this measure is unique to the present study, it is difficult to interpret in light of the previous literature. Still, that different measures of depression were differentially associated with telomere length in the present study is consistent with the literature as a whole given the variety of depression measures used and the correspondingly varied results. Two important factors may help to explain these generally discrepant findings: methodological factors in the measurement of depression and ethnic/racial factors in the experience and reporting of depression.

Methodological Factors in the Measurement of Depression

One of the most challenging aspects in the study of the relationship between depression and telomere length is the definition and measurement of depression. Many of the early studies in the area used clinician administered clinical interviews to determine the presence or absence of a diagnosis of clinical depression. This has traditionally been considered the gold standard approach. However, as the trend in study design moved away from case-controlled study designs and toward more cross-sectional, epidemiological-style designs (which often include thousands, rather than tens or hundreds, of participants), administering full clinical interviews to each participant became less feasible. As a result, many of the newer and larger studies have used briefer depression checklists or questionnaires designed to identify the presence of depressive symptoms and consequently approximate a full diagnosis.

Interestingly, this shift away from the traditional clinical interview toward symptom-based measures coincided with a similar shift in the thinking of many clinical researchers regarding how best to conceptualize depression. Increasingly depression is being considered as a cluster of often only tangentially related symptoms rather than a single, monolithic structure (Goldberg, 2011). As evidenced by recent changes in the DSM-5, this shift parallels a larger shift in thinking about mental health disorders from a categorical to a dimensional approach (D. N. Klein, 2008). Rather than trying to fit the many often discrepant symptoms of depression into a single category, the trend has been to embrace the heterogeneous nature of depression (Major Depressive Disorder Working Group of the Psychiatric et al., 2013).

These two types of measures—clinical interview or symptom-based scale—provide different strengths and weaknesses. While a trained and experienced clinician using a clinical interview may have the most likelihood of diagnosing true depression, they are more vulnerable

to bias in less experienced administrators, are costly and time-intensive, and also result in a dichotomous yes-no outcome variable, which provides researchers with less power to detect significant differences. Symptom-based assessments address these concerns in that the subjects are the ones reporting their own symptoms (which may decrease at least some forms of bias), the measures are more expedient and cost effective, and they also result in continuous outcome variables which increase power in a research setting. However, they may suffer from a lack of specificity. Thus, someone with a sleep disorder and mild to moderate stressors in their life could easily elevate a symptom-based measure without true depression being the cause.

Given these methodological differences, our discrepant results (as well as those of the literature as a whole) may be at least partly the result of different assessment tools measuring different constructs. One interpretation is that neither QIDS score nor felt depressed score are sensitive to depression, and instead, that the felt depressed question was significant because it was registering some alternative construct also related to telomere length. One such possibility is perceived stress, which has been shown to be negatively associated with telomere length (Georgin-Lavialle et al., 2014; Parks et al., 2009) and is even thought to be a mediating factor in the relationship between depression and telomere length (Gotlib et al., 2014). Although highly speculative, the felt depressed item—perhaps because of its more casual appearance relative to the QIDS—might have been more sensitive to a general sense of chronic distress than the QIDS.

Ethnic/racial Factors in Depression

Another possible explanation for the present study's discrepant results may be related to its ethnic/racial composition. Despite the commonly held view that risk for psychiatric disorders is increased in ethic/racial minority groups in the United States due to social adversity

(Dohrenwend, 2000), research to date has generally not supported that conclusion. Several community studies have found that, despite higher rates of social and economic adversity (Clark, Anderson, Clark, & Williams, 1999; Turner & Lloyd, 2004), members of ethnic/racial minority groups do not show elevated rates of psychiatric disorders (Kessler et al., 1994).

More recent research in this area has, in fact, shown decreased rates of depression in ethnic/racial minorities compared with Caucasians, (Breslau, Kendler, Su, Gaxiola-Aguilar, and Kessler (2005), potentially as a result of so-called buffering effects from factors such as ethnic identification (Mossakowski, 2003) or increased religious affiliation (Ellison, Boardman, Williams, & Jackson, 2001; B. Lee & Newberg, 2005). However there is some evidence that while incidence of depression is lower among African Americans, the duration of illness is substantially longer, leading to the conceptualization of depression as a chronic rather than episodic disorder among African Americans (Jackson & Stewart, 2003). These finding should be interpreted with caution given that ethnic/racial minorities are typically underserved and understudied in the context of mental health generally (Sohail, Bailey, & Richie, 2014).

Although rates of psychiatric disorders—and depression in particular—may not be elevated in ethnic/racial minorities, some research suggests that there may be differences in the reporting of depressive symptoms. In a study of African American and Caucasian older adults, Gallo et al. (1998) found that African American participants were less likely than Caucasian participants to endorse symptoms related to sadness. Jaggers et al (2007) found increased rates of depression in Caucasians compared to African Americans, however a wider range of moderating variables including marital status, employment status, and age influenced African Americans' reporting of symptoms. A recent review (Bagayogo, Interian, & Escobar, 2013) summarized the

literature in this area by emphasizing the importance of ethnic/racial differences in somatic symptom expression in depression specifically:

> Racial/ethnic variations in somatic symptoms in the context of depression are common, and seem to be related to depression severity. Sociocultural factors, particularly stigma, may influence the unique emphasis placed on somatic symptoms within depression, and may account for some racial/ethnic differences in somatic symptom reporting.

Given that Caucasians and African Americans may differ in their experience and reporting of depressive symptoms, it is possible that the QIDS and the felt depressed question may be differentially sensitive to these ethnic/racial differences. For example, given research suggesting African Americans are less likely to endorse depressive symptoms related to sadness explicitly (as it is presented in the QIDS), perhaps the more casual or familiar phrasing of the felt depressed made it more sensitive in this case. Consequently, because African Americans made up the majority of the sample, only the measure sensitive to African Americans' experience of depression would be strong enough to have an effect in the whole sample.

II. Depression-Telomere Length Association Analysis by Ethnicity/Race

QIDS score was significantly negatively associated with telomere length in both basic and fully adjusted models among Caucasians but not African Americans or Hispanics. Furthermore, felt depressed score was significantly associated with shorter telomere length in both basic and adjusted models in African Americans but not Caucasians or Hispanics.

That neither QIDS score nor felt depressed score was associated with telomere length in Hispanic participants may be explained by the relatively small sample size.[2] However, the differential relationship between the two depression measures and telomere length between African Americans and Caucasians is puzzling. As described above, there are documented differences in the experience and reporting of depression across ethnic/racial groups. Given that the QIDS has not been validated in specifically African American populations, it is possible that there may be some form of bias in this measure of depression when used with an African American population, and that a more culturally sensitive measure may have shown an effect.

Ethnic/racial differences in telomere length may also play a role in the discrepant findings. African Americans and Caucasians did not differ significantly in telomere length, however Hispanics had significantly longer telomeres than either African Americans or Caucasians. Although it is possible that this is the result of the Hispanic participants in this sample being significantly younger than African Americans and Caucasians.

A small literature on ethnic/racial differences in telomere length suggests that Caucasians have shorter average telomere lengths than African Americans (W. Chen et al., 2009; Hunt et al., 2008). While Caucasian and African American infants have been shown to have equivalent telomere lengths (Okuda et al., 2002), by young adulthood, African Americans already display longer average telomere length than Caucasians, a finding that has been partly attributed to fewer replications of hematopoietic stem cells and progenitor cells in African Americans compared to Caucasians (Hunt et al., 2008). Interestingly, it has been suggested that this longer adult telomere length might explain the previous finding that African Americans are more likely to experience increased telomere erosion (Cherkas et al., 2006) as they present a larger target for free radical

[2] The number of Hispanic participants in the fully adjusted QIDS and felt depressed models were 369 and 366, respectively

accumulation (Hunt et al., 2008). In contrast to these finding, however, another study by Diez Roux et al. (2009), found that African Americans and Hispanics had shorter average telomere lengths than Caucasians, which they attributed in part to increased exposure to environmental stressors likely to result in increased inflammation and oxidative stress on a cellular level. No research to date has directly investigated telomere length among Hispanic populations. While findings in this area are mixed, it is clear that ethnic/racial differences likely play a role in the relationship between depression and telomere length.

Importantly, the results of the present study do not corroborate those from the only other study [Needham et al. (2012)] to specifically investigate ethnic/racial effects on the depression-telomere length relationship, which found no significant ethnic/racial effects. The discrepancy in results may be due to the fact that the present study had two-and-a-half times the sample size and therefore may have had the advantage of increased relative power to detect significant differences. Additionally, the specific ethnic/racial composition of the two studies was different, which may have influenced the results given the documented differences in conceptualization and reporting of depressive symptoms between ethnic/racial groups.

III. Effect of APOE Genotype Variation on Depression-Telomere Length Association Analysis

Neither the APOE(4) allele nor the APOE(2) allele variant demonstrated a significant association with telomere length in basic models of the whole sample using both QIDS score and felt depressed score as measures of depression. Similarly, in neither of these cases was the interaction between APOE allele variant and depression associated with telomere length.

As is conventional in the literature, APOE genotype data was reported as percentage of the sample who were carriers of a given allele variant. Across the sample, 15% were APOE(2) carriers, 93% were APOE(3) carriers, and 32% were APOE(4) carriers. These ratios are consistent with previous literature on the relative prevalence of the APOE allele variants across the population (Wikgren, Karlsson, et al., 2012). When stratified by race/ethnicity, African Americans had 18% APOE(2) carriers, 89% APOE(3) carriers, and 37% APOE(4) carriers. Caucasians had 15% APOE(2) carriers, 95% APOE(3) carriers, and 26% APOE(4) carriers. Hispanics had 4% APOE(2) carriers, 98% APOE(3) carriers, and 27% APOE(4) carriers. African Americans had a higher percentage of APOE(2) carriers than Hispanics, a lower percentage of APOE(3) carriers than either Caucasians or Hispanics, and a higher percentage of APOE(4) carriers than either Caucasians or Hispanics. Caucasians also had a higher percentage of APOE(2) carriers than Hispanics. These differences in relative ratios of APOE allele variations are generally consistent with previous research showing a higher ratio of the APOE(2) and APOE(4) variants in African and Oceanic populations, while higher rates of the APOE(3) variant are found in European, Indian, and Asian populations (Singh, Singh, & Mastana, 2006).

A robust literature exists demonstrating an increased risk for various cognitive difficulties such as Alzheimer's disease for carriers of the APOE(4) allele (See Bennett et al., (2015) for a review). Recent research has also suggested that the APOE(4) allele variant is a risk factor for increased telomere length erosion (Jacobs et al., 2013; Takata et al., 2012). Furthermore, some preliminary evidence exists suggesting that APOE allele variation may influence the relationship between depression and telomere length (Lung et al., 2007).

Surprisingly, both APOE(3) carrier status and the interaction between APOE(3) carrier status and felt depressed score were significantly associated with shorter telomere length,

suggesting that the association between felt depressed score and telomere length is stronger in participants who are carriers of the APOE(3) allele. These results are difficult to integrate into the small literature on APOE, depression, and telomere length, however, given that the APOE(3) allele is not thought to be a risk factor for any of the conditions mentioned above.

We had hypothesized that APOE(4) carriers might show an even larger depression-telomere length effect than would otherwise be expected. That APOE(3) carrier status and not APOE(4) was associated in one model with decreased telomere length is difficult to interpret given a lack of any previous literature documenting APOE(3) effects in either depression or telomere length. It is important to note, however, that not all participants had APOE genotype data, and of those that did, only a small number were APOE(4) carriers (n = 550) relative to APOE(3) carriers (n = 1,602). As a result, there may not have been sufficient power to detect significant differences in the depression-telomere length relationship based on APOE(4) carrier status. Finally, it is also possible that the results are simply spurious, especially since the effect was only seen in the model using the felt depressed score and not in the model using the QIDS score.

IV. Effect of Sleep on Depression-Telomere Length Association Analysis

Although sleep quantity and quality are heavily implicated in many psychiatric disorders (Sutton, 2014), including depression (Luca, Luca, & Calandra, 2013), the impact of sleep on the depression-telomere length relationship has been relatively unexplored. In the present study, mean hours of self-reported nightly sleep was not associated with telomere length in models of the whole sample using both QIDS score and felt depressed score as measures of depression as originally hypothesized. There was also no significant interaction between either QIDS score or

felt depressed score with telomere length. Finally, the interactions between QIDS and sleep as well as felt depressed and sleep were not significantly associated with telomere length. Interestingly, in a basic model of the full sample, the felt depressed variable was associated with telomere length; however in the model in which average hours of sleep and the sleep-by-felt depressed interaction were included, this association was no longer significant. Given that neither sleep nor the sleep-by-felt depressed interaction were significant, this effect may be due to the loss of power associated with the decreased sample size of the model which resulted from adding sleep as a variable (2,020 out of the total 2,710 participants had available sleep data). In aggregate, these results suggest that self-reported hours of nightly sleep is not a significant moderating variable in the relationship between depression and telomere length.

These findings are at odds with previous literature demonstrating an association between both sleep quantity and sleep quality and telomere length (Cribbet et al., 2014; Garland et al., 2014). One reason for the discrepant results may be the specific aspects of sleep measured. Most of the positive findings in this literature have associated poor sleep quality with shortened telomere length, but the present study only measured sleep quantity. Another potential rationale for these findings comes from a recent study (Prather et al., 2014), which suggested that the type of cell from which the telomere length is measured is influential in the association with sleep. They also found that perceived stress moderated this relationship such that participants high in perceived stress showed a stronger relationship between sleep quality and shorter telomere length, but the effect did not remain when perceived stress was low. To the best of our knowledge, however, no previous literature has investigated the role of sleep specifically on the relationship between depression and telomere length.

V. Study Design Analysis

Study design is an important factor in the interpretation of the findings from the present study. There are two predominant types of study design in the depression-telomere length literature. Much of the early work employed case-control designs in which a typically small number of depressed test cases were matched with non-depressed controls and their telomere lengths were compared. While several of these studies had numbers of cases in the hundreds, many had fewer than 50. See Table 1 for a comparison of case-controlled studies of depression and telomere length.

Because many of the early findings in this area were contradictory—with some studies demonstrating a depression-telomere length association and others no association—later studies tended to employ larger cross-sectional designs. By using data from epidemiological research in which both depression and telomere length data was available, larger sample sizes afforded greater power to detect small but significant differences. The majority of these studies had sample sizes close to 1,000 participants, while several had over two thousand. See Table 2 for a comparison of cross-sectional studies of depression and telomere length.

Several of these previous studies were similar to the present study both in terms of study design (cross-sectional), aims, as well as variables controlled for. Most recently, Needham et al. (Needham et al., 2014) investigated a sample of 1,290 young adult participants in the U.S. 56% of participants were female and 5% had current antidepressant use, while the sample consisted of 50% Caucasians, 20% African Americans, and 30% Hispanics. Years of education, BMI, and Tobacco use were not reported. Aside from the present study, this was the only study in the literature to specifically investigate the relationship between depression and telomere length in the context of racial/ethic differences, which was possible because of their stratified sample

(although Caucasians were still a clear majority). Importantly, the mean age was also quite low compared to other similar studies (mean age = 29.4). Given the significant influence of age on telomere length, this makes their finding difficult to interpret relative to previous research in which the mean age is generally much closer to that of the present study. While this study did not report a significant depression-telomere length association across their whole sample, they did find that there was a negative association between depression and telomere length among participants currently taking an antidepressant. Antidepressant medication use, they argued, was indicative of more severe psychopathology, which ought to have more of a shortening effect on telomere length.

Ladwig et al. (2013) used a sample of 2,528 participants of European decent with a mean age of 54.5 years. Their sample was 58% female, had a mean BMI of 27.7, 20% were current tobacco users, and 60% were classified as having "low education" attainment. Antidepressant use was not reported. This study was very similar to the present study with the exception of their ethnically/racially homogenous sample, which was composed of entirely white Europeans. They found that PTSD but not anxiety or depression was associated with decreased telomere length. Interestingly, they suggested that these differential effects may be the result of PTSD involving a larger amount of stress specifically compared to other internalizing disorders. Given that stress is thought to mediate the pathway between psychiatric disorder and telomere erosion, this finding may explain why depression specifically has shown more inconsistent results compared to PTSD.

Three other cross-sectional investigations were similar to the present study (Phillips et al., 2013; Shaffer et al., 2012; Verhoeven et al., 2013). Their respective descriptive statistics were as follows: mean age was 55.7, 42, and 48.2 years; percent female participants was 45%, 65%, and

50%. Years of education was only reported by Verhoeven et al. (12.4); Shaffer et al. reported a mean BMI of 27, while Verhoeven et al. reported approximately 47% of participants had a BMI resulting in a designation as either overweight or obese. All three studies were comprised of participants exclusively of white European decent. Phillips et al. and Shaffer et al. reported 10% and 89% current antidepressant use, respectively, as well as 21% and 12% current tobacco use. All three studies had large sample sizes and controlled for a relatively large number of important variables. It is interesting, then, that they reported such differing results. Shaffer et al. found that depression was not associated with telomere length, while Verhoeven et al. found that it was and Phillips et al. found that it was, but only in a subset of the sample stratified by age.

In sum, while it is possible that the largely negative consensus of recent studies in the area is indicative of no association between depression and telomere length, it may be that the high level of variability across the particulars of study designs obscures the relatively modest effect of depression on telomere length. This may explain why earlier case-control studies of depression and telomere length reported a larger proportion of positive findings—the particular features of the case-controlled design resulted in more homogenous samples and they tended to use similar measures of depression and thus allowed for more confidence that they were measuring the same construct.

VI. Exome-Wide Association Study Analysis

Results from previous research attempting to better understand the genetic underpinnings of depression using candidate gene approaches and genome-wide association studies have been largely negative. While many studies of candidate genes have been undertaken, and some significant findings reported, few of these findings have been proved to be reproducible. A recent

meta-analysis of these studies found seven significant candidate genes, though the mean effect size was small (Flint & Kendler, 2014). Interestingly, all the most likely sequence variants revealed by the candidate gene studies were common, including the seven that reached significance in the meta-analysis.

Genome-wide association studies typically investigate common variants in the genome. Given that all of the most promising candidate gene results were common variants, they should be detectable by GWAS with sufficient power. However, none of these genes surfaced in any of the genome-wide association studies, suggesting either that they were false positives or that the genome-wide association studies were underpowered. The largest of these studies (Major Depressive Disorder Working Group, 2013) had 9,240 cases and 9,519 controls in the discovery phase, which resulted in approximately 90% power to detect alleles with a frequency greater than 5%, yet none were found. While one study (Kohli et al., 2011) found a variant that reached genome-wide significance, none of the other studies replicated the finding, suggesting it was likely a false positive.

One interpretation of the above findings is that there are actually no loci with large genetic effects on the expression of depression, and that instead, genetic risk for the disorder is conferred by multiple loci with smaller effects in combination. An alternative, but not incompatible, hypothesis is that no robust findings have been uncovered due to the restriction of analysis to common variants rather than rare ones. It may be that a portion of the genetic effect on depression is due to variants which, although rare, have large effects.

By scanning the exome rather than the genome, we tested the hypothesis that rare variants contribute to the expression of depression. However, in our analysis no variant reached exome-wide significance. This finding is consistent with the current consensus in the literature

that there are no common variants with significant effects on depression (Cohen-Woods et al., 2013), and suggests that there may not be any rare variants with large effects either.

Although there were no significant hits in our primary analysis, we examined the variants with the smallest p-values more closely to determine if the genes they were located in had been associated with depression previously in the literature. While several genes had been associated with psychiatric conditions such as schizophrenia (SLCO5A1, SNTG2) (Van Den Bossche et al., 2013), physical aggression (NFAT5) (Provencal et al., 2013), intellectual disability (SNTG2) (Bulayeva et al., 2015), and suicidality (KIAA1244, SNTG2) (Perlis, Ruderfer, Hamilton, & Ernst, 2012; Schosser et al., 2012), none of the top hits appear to have been previously implicated with depression. The two studies investigating suicidality were particularly interesting given the close overlap between suicidality and depression. However, in both of these studies the findings failed to replicate, suggesting they may have been false positives.

In addition to examining the top hits from this analysis, top variants from the previous literature that were available on the exome chip were also investigated. All SNPs located within 1 Mb of the top SNPs found in the literature were examined, but none reached exome-wide significance, including the three leadings variants from a recent meta-analysis of GWAS in depression (rs7296288, rs11579964, rs7647854) (Flint & Kendler, 2014). The lack of consistency across studies again suggests that there is no single strong genetic effect on depression.

One reason our study may have failed to replicate findings from previous attempts is the unique ethnic/racial composition of our sample. Most of the GWAS of depression today have included participants of primarily white European descent, while the DHS includes a far more

heterogeneous sample. Indeed, there was considerable heterogeneity among the top hits in our results when stratified by ethnicity/race.

Another possibility for the discordant results of the present findings compared to previous studies is the ill-defined nature of the depressive phenotype and the different approaches to quantifying it across studies. Many of the GWAS of depression to date have used either a clinical interview as the means determining the presence and severity of depression or a different screening tool. Given that there is significant variety in both the phenotype in question as well as the methodology used to measure it, it is perhaps not surprising that the results are discrepant. Finally, though we had access to an analysis of both rare and common variants and a large enough sample to have sufficient power to detect differences among common variants, it is possible that our power to detect uncommon variants was not sufficient.

VII. Strengths

A major strength of the present study is its large sample size and subsequently increased power to detect significant differences among important variables even after stratifying the sample. The large number of variables that were possible to control for is also a major advantage as much of the previous literature in the area has suffered from limited or inconsistent controlling variables. This is only the second study to specifically investigate ethnic/racial differences in the depression-telomere length association, and it does so with more than twice the number of participants and a non-Caucasian majority. Having two measures of depressive symptoms was advantageous in that it highlighted the importance of awareness for the multifaceted nature of the depressive phenotype. Finally, the present study was the first to employ a novel exome-wide

analysis of depressive symptoms, which allowed the important work of investigating the association between depressive symptoms and uncommon genetic variants.

VIII. Limitations and Future Directions

The design of this study was cross-sectional and as a result cannot make causal attributions about the relationship between depression and telomere length. Future studies with more prospective designs will further clarify the causality of the relationship between depression and telomere length. Furthermore, though the ethnic/racial composition of the present study was largely a strength, the proportion of Hispanics was relatively small and may have been a confounding factor in several of the analyses that were based on ethic/racial stratification.

The use of self-report measures for depression may also be considered a limitation for several reasons that could likely have been ameliorated with clinician-administered assessment. First, many participants were not able to be included in the present analyses because they were missing some or all of their data. Second, interpretation of some sections of the assessments may have been confusing for participants. However there is research demonstrating that people may be more honest and accurate in their assessment of themselves in a self-report setting rather than in the presence of a clinician (Baird, Le, & Lucas, 2006). As a result, future studies ought to include multiple measures of depression, with at least one in each category in order to control for variance in this respect.

Another limitation of the present study is the use of the QIDS as it has not previously been used in the study of telomere length and depression, and direct comparisons are, therefore, not possible. There were also relatively few participants with very high QIDS scores. Given the importance of extreme phenotypes in any genetic analysis, future research in this area ought to

attempt to find a population with a larger proportion of severely depressed participants. Finally, because the QIDS only measures the presence and severity of depressive symptoms over the past week, information on the duration of depressive symptoms was unavailable. Given that there is prior research demonstrating the impact of duration in addition to severity of depression on telomere length, future research ought to account for this important variable.

The consensus in the literature seems to be that the relationship between depression and shortened telomere lengths is mediated by stress. However, the present study was not able to account for this variable. Obtaining markers of stress—on physiological, psychological, and social levels—would help future studies to clarify the purported pathway between depression and shortened telomeres.

The measurement of telomere length in the present study was obtained from circulating leukocytes. While previous research has demonstrated correlations in telomere length across tissue types (Daniali et al., 2013; Lukens, Van Deerlin, Clark, Xie, & Johnson, 2009), it is possible that telomere length may have been more or less closely associated with depression in different tissue types. Finally, the present study did not have a measure of telomerase. Given that there is a growing understanding of the importance of the role of telomerase functioning in telomere length and erosion (Wolkowitz et al., 2012; Zalli et al., 2014), future research in this area ought to account for this important variable and perhaps better elucidate the relationship between depression, stress, and telomerase.

IX. Clinical Implications

While the present study was not clinically focused, several important implications can be drawn from the results. The present study showed that ethnic/racial differences in the association

between depression and telomere length were variable depending on the type of depression measurement used. This suggests the importance of using culturally sensitive and valid measures in the study of depression, as cultural differences in the conceptualization and reporting of depression may not be accurately captured by measures validated in a single ethnic/racial group.

The finding from the current study that depression is associated with decreased telomere length also highlights the wide-ranging effects that even sub-clinical levels of depression can have on individuals. In addition to the negative phenomenological experiences that are so often associated with depression (e.g. low mood, sadness, apathy), this study adds to a growing body of work exposing the deleterious effects of depression on all aspects of the person, including the body. Increasingly, depression is being implicated in worse health outcomes as diverse as heart disease (Khawaja, Westermeyer, Gajwani, & Feinstein, 2009), cancer (Pinquart & Duberstein, 2010), and diabetes (Egede & Dismuke, 2012). If depression also increases the rate of telomere degradation, increased aging itself may be considered one of the many harmful consequences of depression. As a result, the need for better identification and treatment of depression should likely be considered even greater than previously thought.

Finally, some early speculative work has shown that by increasing telomerase production, it may be possible to extend previously foreshortened telomeres (Effros, 2009; Giardini, Segatto, da Silva, Nunes, & Cano, 2014; Liew, Holman, & Kulkarni, 2009). If such procedures continue to develop positively, clinicians' views may need to widen considerably to account for these newer methods for the treatment of depressive symptoms.

X. Conclusion

The primary finding from this study is that depression as measured by the QIDS is not significantly associated with telomere length in a large, multi-ethnic sample after controlling for important relevant variables. However, a secondary and un-validated measure of depression was associated with shorter telomere length, even after full adjustment for potentially confounding variables. Furthermore, after analyzing the relationship between depressive symptoms and telomere length with the sample stratified by ethnicity/race, significant differential effects were found: QIDS score was associated with shorter telomere length in Caucasians but not African Americans or Hispanics, while the felt depressed variable was associated with shorter telomere length in African Americans but not in Caucasians or Hispanics. Finally, two potentially important but largely unexplored moderating variables, sleep and APOE allele variation, did not appear to have a significant effect on the relationship between depression and telomere length.

The present study is the largest to date examining the relationship between depression and telomere length. It is also one of the most comprehensive given its sample diversity and wide range of potentially confounding variables available to control for. Although the primary findings of this study are not unequivocal on the question of the relationship between depressive symptoms and telomere length, they do provide helpful clarification for future investigations, particularly regarding the importance of accounting for ethnic/racial differences in study design, measurement, and interpretation.

CHAPTER VI

Tables

(beginning on the following page)

Table 1

Prior Depression-Telomere Length Research, Case-control Designs

Author(s)	N	Age	% female	Education, years	BMI	Ethnicity/Race	% AD	% CTU	Depression measure	Main findings	Control variables	Sig.
Simon et al, 2006	44/44	51	45	n/a	n/a	93% Caucasian	n/a	37	SCID	Mood disorders associated with shorter TL	Age, gender, tobacco use	±
Lung et al, 2007	253/411	45/45	64/57	n/a	n/a	100% Asian	n/a	n/a	SCID	Depression associated with shorter TL	Age, gender	+
Hartmann et al, 2010	54/20	49	61	n/a	n/a	100% Caucasian	n/a	16	HAM-D	Depression associated with shorter TL	Age, gender, tobacco use, duration and severity of illness	+
Elvsashagen et al, 2011	28/28	35/35	68/68	82/93 % high school graduate	25/23	100% Caucasian	n/a	17.5	MINI, MADRS	TL associated with Bipolar-II diagnosis	Age, gender, education, BMI, tobacco use, exercise, illness duration	±
Puterman et al, 2013	205/743	62/68	30/15	n/a	29/28	n/a	51/89	72/82	CDIS	Resiliency buffers association between Depression and TL	Age, gender, education, BMI, exercise, AD use, adverse life events	±
Malan et al, 2011	64	22	100	92% high school graduate	n/a	20% African American, 80% "mixed"	n/a	n/a	MINI	Depression not associated with TL	Age, gender, "resilience"	-
Wolkowitz et al, 2011	18/17	37/37	67/65	15/16	26/25	72% Caucasian, 17% African American, 6% Asian, 5% Other	0	17/18	SCID	Lifetime, not current Depression associated w/ shorter TL	Age, gender, BMI	±
Teyssier et al, 2012	17/16	40/38	100	n/a	23/24	100% Caucasian	n/a	24/0	SCID, MINI, HAM-D	Depression not associated with TL	Age, BMI, alcohol, tobacco use, physical activity, Depression duration	-
Wikgren et al, 2012	91/451	60/59	60/50	n/a	27/26	100% Caucasian	89/0	15/11	BDI, CES-D	Depression associated with shorter TL	Age, gender	+
Garcia-Rizo et al, 2013	9/48	31/28	40/38	n/a	23/24	100% Caucasian	0	n/a	SCID, CIDI	Depression associated with shorter TL	Age, gender, BMI, cortisol levels	+
Schaakxs et al, 2014	355/128	71/70	66/62	10/13	n/a	100% Caucasian	77/0	n/a	SCID	Depression not associated with TL	Age, gender, education, tobacco use, alcohol, exercise, BMI, chronic disease	-
Karabatsiakis et al, 2014	44/50	53/51	100	15/14	n/a	100% Caucasian	43/0	n/a	BDI	Depression associated with shorter TL	Age, education, age at first Depression episode, # depressive episodes, AD use, hypertension	+

Abbreviations: x/x = cases/controls; % AD = percent antidepressant use; % CTU = percent current tobacco use; SCID = Structured Clinical Interview for DSM Disorders; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery—Asberg Depression Rating Scale; MINI = Mini-international Neuropsychiatric Interview; CDIS = Computerized Diagnostic Interview Schedule; BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; TL = telomere length; Sig. = statistically significant depression-telomere length relationship: + = clear significant relationship; - = clear non-significant relationship; ± = questionable relationship.

Table 2

Prior Depression-Telomere Length Research, Cross-sectional Designs

Author(s)	N	Age	% female	Education, years	BMI	Ethnicity/Race	% AD	% CTU	Depression measure	Main findings	Control variables	Sig.
Hoen et al, 2011	952	65	23	88% high school graduate	29	60% Caucasian	n/a	n/a	CDIS, PHQ	Depression associated with shorter TL	Age, gender, education, BMI, exercise, AD use, adverse life events	±
Shaffer et al, 2012	2,225	48	50	n/a	27	100% Caucasian	89	12	CES-D	Depression not associated with TL	Age, gender, BMI, cardiovascular disease	-
Hoen et al, 2013	974	53	64	n/a	27	100% Caucasian	n/a	n/a	CIDI	Depression not associated with TL	Age, gender, education, BMI, exercise, AD use, adverse life events	-
Verhoeven et al, 2013	2,407	42	65	12	47%	100% Caucasian	n/a	n/a	CIDI, IDS	Depression associated with shorter TL	Age, gender, education, BMI, tobacco use, alcohol, exercise	+
Phillips et al, 2013	1,063	56	45	n/a	n/a	100% Caucasian	10	21	HADS	Depression associated with shorter TL among youngest age group	Age, gender, social class, tobacco use, AD use	±
Ladwig et al, 2013	2,528	55	58	60% “low education”	28	100% Caucasian	n/a	20	PHQ	Depression not associated with TL	Age, gender, BMI	-
Shalev et al, 2014	827	42	48	n/a	n/a	100% Caucasian	n/a	n/a	DISC, DIS	Depression not associated with TL	Childhood maltreatment, tobacco use, substance dependence, psychiatric medication, medical illness, adult SES	-
Georgin-Lavialle et al, 2014	19	45	79	n/a	n/a	100% Caucasian	n/a	n/a	BDI	Depression not associated with TL	Age, gender	-
Needham et al, 2014	1,290	29	56	n/a	n/a	50% Caucasian, 20% African American, 30% Hispanic	5	n/a	CIDI	Depression not associated with TL	Age, gender, race/ethnicity, AD use	-

Abbreviations: x/x = cases/controls; % AD = percent antidepressant use; % CTU = percent current tobacco use; PHQ = Patient Health Questionnaire; CIDI = Composite International Diagnostic Interview; IDS = Inventory of Depressive Symptomatology; HADS = Hospital Anxiety and Depression Questionnaire; CDIS = Computerized Diagnostic Interview Schedule; BDI = Beck Depression Inventory; DISC = Depression Intensity Scale Circles; DIS = Diagnostic Interview for Depression; CES-D = Center for Epidemiological Studies Depression Scale; TL = telomere length; Sig. = statistically significant depression-telomere length relationship: + = clear significant relationship; - = clear non-significant relationship; ± = questionable relationship.

Table 3

Descriptive Statistics of the Whole Sample

Variable	Mean (SD)	% (N)	N
Age, years	49.72 (11.14)		2710
Gender			
Female		59 (1608)	
Male		41 (1102)	
Race/Ethnicity			
African American		51 (1387)	
Caucasian		35 (950)	
Hispanic		14 (373)	
Body mass index	31.29 (7.43)		2710
Education, years	12.7 (2.2)		2701
Tobacco use, any		45 (1199)	
Antidepressant use, current		11 (297)	
Telomere length	1.7955 (0.259)		2710
QIDS score	5.51 (3.87)		2710
Felt depressed score	0.86 (1.02)		2683
Sleep, hours per night	6.8 (1.4)		2020
APOE genotype			
e2 carrier		15 (261)	
e3 carrier		93 (1602)	
e4 carrier		32 (550)	

Table 4

Descriptive Statistics: African Americans

Variable	Mean (SD)	% (N)	N	*p*, vs Caucasians	*p*, vs Hispanics
Age, years	49.06 (11.32)		1387	<.001	<.001
Gender					
Female		63 (877)		<.001	.065
Male		37 (510)			
Body mass index	32.57 (8.04)		1387	<.001	.001
Education, years	12.7 (1.5)		1383	<.001	<.001
Tobacco use, any		44 (610)		.281	.128
Antidepressant use, current		8 (116)		<.001	.628
Telomere length	1.7958 (.2654)		1387	.324	.036
QIDS score	5.92 (4.10)		1387	<.001	.232
Felt depressed score	.92 (1.07)		1371	.004	.373
Sleep, hours per night	6.5 (1.5)		1086	<.001	<.001
APOE genotype					
e2 carrier		18 (155)		.175	<.001
e3 carrier		89 (762)		<.001	<.001
e4 carrier		37 (318)		<.001	.005

Note: p values from χ^2 test or *F* test for association between ethnic/racial groups.

Table 5

Descriptive Statistics: Caucasians

Variable	Mean (SD)	% (N)	N	*p*, vs African Americans	*p*, vs Hispanics
Age, years	52 (10.6)		950	<.001	<.001
Gender					
Female		55 (519)		<.001	.742
Male		45 (431)			
Body mass index	29.53 (6.51)		950	<.001	.004
Education, years	13.5 (1.7)		945	<.001	<.001
Tobacco use, any		48 (446)		.281	.011
Antidepressant use, current		16 (156)		<.001	<.001
Telomere length	1.7803 (.2503)		950	.324	.002
QIDS score	4.88 (3.43)		950	<.001	.011
Felt depressed score	.79 (.95)		944	.004	.641
Sleep, hours per night	7.1 (1.3)		641	<.001	.780
APOE genotype			645		
e2 carrier		15 (96)	645	.175	<.001
e3 carrier		95 (612)	645	<.001	.294
e4 carrier		26 (170)	645	<.001	.997

Note: p values from χ^2 test or *F* test for association between ethnic/racial groups.

Table 6

Descriptive Statistics: Hispanics

Variable	Mean (SD)	% (N)	N	*p*, vs African Americans	*p*, vs Caucasians
Age, years	46.4 (10.6)		373	<.001	<.001
Gender					
Female		57 (212)		.065	.742
Male		43 (161)			
Body mass index	30.97 (6.25)		373	.001	.004
Education, years	10.8 (3.5)		373	<.001	<.001
Tobacco use, any		39 (143)		.128	.011
Antidepressant use, current		7 (25)		.628	<.001
Telomere length	1.8332 (.2548)		373	.036	.002
QIDS adjusted total score	5.55 (3.83)		373	.232	.011
Felt depressed score	.84 (1.01)		368	.373	.641
Sleep, hours per night	7.0 (1.3)		293	<.001	.780
APOE genotype			233		
e2 carrier		4 (10)	233	<.001	<.001
e3 carrier		98 (228)	233	<.001	.294
e4 carrier		27 (62)	233	.005	.997

Note: p values from χ^2 test or *F* test for association between ethnic/racial groups.

Table 7

QIDS-Telomere Length Regression Analysis, Whole Sample, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				2710	42.789	3, 2706	<.001	.044
Age, years	-0.198	-10.518	<.001					
Gender	0.081	4.252	<.001					
QIDS	-0.025	-1.312	.190					

Table 8

QIDS-Telomere Length Regression Analysis, Whole Sample, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				2674	17.198	9, 2664	<.001	.052
Age, years	-.192	-9.897	<.001					
Gender	0.07	3.584	<.001					
QIDS	-.015	-.768	.443					
African American	.011	.516	.606					
Hispanic	.066	2.876	.004					
BMI	.043	2.212	.027					
Education, years	.066	3.111	.002					
Tobacco use	-.028	-1.435	.151					
Antidepressant use	.014	.732	.464					

Table 9

Felt Depressed-Telomere Length Regression Analysis, Whole Sample, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				2683	46.291	3, 2679	<.001	.048
Age, years	-.202	-10.713	<.001					
Gender	.084	4.404	<.001					
Felt depressed	-.069	-3.596	<.001					

Table 10

Felt Depressed-Telomere Length Regression Analysis, Whole Sample, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				2655	18.081	9, 2645	<.001	.055
Age, years	-.197	-10.117	<.001					
Gender	.074	3.801	<.001					
Felt depressed	-.059	-3.018	.003					
African American	.010	.446	.655					
Hispanic	.065	2.827	.005					
BMI	.037	1.898	.058					
Education, years	.060	2.862	.004					
Tobacco use	-.026	-1.310	.193					
Antidepressant use	.021	1.063	.288					

Table 11

QIDS-Telomere Length Regression Analysis, African Americans, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1387	21.233	3, 1383	<.001	.042
Age, years	-.185	-7.037	<.001					
Gender	.098	3.692	<.001					
QIDS	-.002	-.075	.942					

Table 12

QIDS-Telomere Length Regression Analysis, African Americans, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1372	11.942	7, 1364	<.001	.053
Age, years	-.179	-6.629	<.001					
Gender	.072	2.642	.008					
QIDS	.008	.305	.761					
BMI	.070	2.583	.011					
Education, years	.073	2.698	.007					
Tobacco use	-.042	-1.505	.133					
Antidepressant use	.013	.652	.514					

Table 13

Felt Depressed-Telomere Length Regression Analysis, African Americans, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1371	24.966	3, 1367	<.001	.050
Age, years	-.193	-7.296	<.001					
Gender	.102	3.872	<.001					
Felt depressed	-.096	-3.605	<.001					

Table 14

Felt Depressed-Telomere Length Regression Analysis, African Americans, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1360	12.869	7, 1352	<.001	.058
Age, years	-.189	-6.973	<.001					
Gender	.080	2.934	.003					
Felt depressed	-.081	-2.976	.003					
BMI	.063	2.299	.022					
Education, years	.058	2.139	.033					
Tobacco use	-.035	-1.241	.215					
Antidepressant use	.028	1.044	.297					

Table 15

QIDS-Telomere Length Regression Analysis, Caucasians, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				950	20.841	3, 946	<.001	.059
Age, years	-.238	-7.537	<.001					
Gender	.065	2.020	.044					
QIDS	-.083	-2.473	.014					

Table 16

QIDS-Telomere Length Regression Analysis, Caucasians, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				933	10.788	7, 925	<.001	.068
Age, years	-.245	-7.693	<.001					
Gender	.060	1.830	.068					
QIDS	-.066	-1.967	.049					
BMI	-.030	-.938	.348					
Education, years	.091	2.721	.007					
Tobacco use	-.002	-.049	.961					
Antidepressant use	.041	1.246	.213					

Table 17

Felt Depressed-Telomere Length Regression Analysis, Caucasians, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				944	18.663	3, 940	<.001	.053
Age, years	-.233	-7.330	<.001					
Gender	.052	1.621	.105					
Felt depressed	-.014	-.431	.666					

Table 18

Felt Depressed-Telomere Length Regression Analysis, Caucasians, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				929	10.232	7, 921	<.001	.065
Age, years	-.239	-7.519	<.001					
Gender	.049	1.502	.133					
Felt depressed	-.001	-.032	.974					
BMI	-.036	-1.137	.256					
Education, years	.099	2.961	.003					
Tobacco use	-.009	-.265	.791					
Antidepressant use	.030	.903	.367					

Table 19

QIDS-Telomere Length Regression Analysis, Hispanics, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				373	1.993	3, 369	.115	.008
Age, years	-.103	-2.004	.046					
Gender	.075	1.411	.159					
QIDS	-.005	-.098	.922					

Table 20

QIDS-Telomere Length Regression Analysis, Hispanics, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				369	1.278	7, 361	.260	.005
Age, years	-.111	-2.075	.039					
Gender	.074	1.338	.182					
QIDS	-.004	-.068	.946					
BMI	.073	1.383	.167					
Education, years	.031	.574	.566					
Tobacco use	.018	.328	.743					
Antidepressant use	-.053	-.948	.344					

Table 21

Felt Depressed-Telomere Length Regression Analysis, Hispanics, Basic Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				368	2.911	3, 364	.035	.015
Age, years	-.112	-2.162	.031					
Gender	.093	1.740	.083					
Felt depressed	-.087	-1.494	.136					

Table 22

Felt Depressed-Telomere Length Regression Analysis, Hispanics, Fully Adjusted Model

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				366	1.610	7, 358	.131	.012
Age, years	-.118	-2.202	.028					
Gender	.095	1.718	.087					
Felt depressed	-.077	-1.389	.166					
BMI	.071	1.34	.181					
Education, years	.026	.484	.629					
Tobacco use	.023	.433	.665					
Antidepressant use	-.035	-.648	.517					

Table 23

QIDS-Telomere Length-Sleep Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				2020	22.970	5, 2014	<.001	.052
Age, years	-.214	-9.854	<.001					
Gender	.086	3.902	<.001					
QIDS	-.100	-1.052	.293					
Sleep, hrs/night	-.063	-1.566	.117					
QIDS x sleep interaction	.085	.897	.370					

Table 24

Felt Depressed-Telomere Length-Sleep Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				2005	24.632	5, 1999	<.001	.056
Age, years	-.217	-9.997	<.001					
Gender	.090	4.111	<.001					
Felt depressed	-.117	-1.236	.216					
Sleep, hrs/night	-.049	-1.633	.103					
Felt depressed x sleep interaction	.056	.527	.598					

Table 25

QIDS-Telomere Length-APOE(2) Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1730	18.448	5, 1724	<.001	.048
Age, years	-.203	-8.633	<.001					
Gender	.093	3.886	<.001					
QIDS	-.003	-.117	.907					
APOE(2) carrier	.038	.913	.361					
APOE(2) x QIDS interaction	-.057	-1.346	.179					

Table 26

Felt Depressed-Telomere Length-APOE(2) Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1712	.052	5, 1706	<.001	.052
Age, years	-.208	-8.825	<.001					
Gender	.095	4.017	<.001					
Felt depressed	-.055	-2.125	.034					
APOE(2) carrier	.013	.431	.666					
APOE(2) x felt depressed interaction	-.032	-.982	.326					

Table 27

QIDS-Telomere Length-APOE(3) Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1730	18.501	5, 1724	<.001	.048
Age, years	-.203	-8.632	<.001					
Gender	.091	3.802	<.001					
QIDS	-.060	-.743	.457					
APOE(3) carrier	-.051	-1.238	.216					
APOE(3) x QIDS interaction	.048	.553	.580					

Table 28

Felt Depressed-Telomere Length-APOE(3) Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1712	20.779	5, 1706	<.001	.055
Age, years	-.208	-8.822	<.001					
Gender	.094	3.968	<.001					
Felt depressed	-.246	-2.763	.006					
APOE(3) carrier	-.080	-2.494	.013					
APOE(3) x felt depressed interaction	.192	2.106	.035					

Table 29

QIDS-Telomere Length-APOE(4) Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1730	18.317	5, 1724	<.001	.048
Age, years	-.202	-8.61	<.001					
Gender	.092	3.82	<.001					
QIDS	-.013	-.435	.663					
APOE(4) carrier	.034	.836	.403					
APOE(4) x QIDS interaction	-.014	-.237	.813					

Table 30

Felt Depressed-Telomere Length-APOE(4) Regression: Whole Sample

Variable	*B*	*t*	*p*	*N*	*F*	*df*	*p*	Adj. R^2
Overall model				1712	.053	5, 1706	<.001	.053
Age, years	-.207	-8.783	<.001					
Gender	.094	3.957	<.001					
Felt depressed	-.043	-1.496	.135					
APOE(4) carrier	.057	1.856	.064					
APOE(4) x felt depressed interaction	-.048	-1.383	.167					

CHAPTER VII

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