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Depression, anxiety, and telomere length in young adults: Evidence from the National Health and Nutrition Examination Survey

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Abstract

Telomere length has been hypothesized to be a marker of cumulative exposure to stress, and stress is an established cause of depression and anxiety disorders. The goal of this study was to examine the relationship between depression, anxiety and telomere length, and to assess whether this relationship is moderated by race/ethnicity, gender, and/or antidepressant use. Data were from the National Health and Nutrition Examination Survey, 1999–2002. Telomere length was assessed using the quantitative polymerase chain reaction method of telomere length relative to standard reference DNA. Past year major depression (MD), generalized anxiety disorder (GAD) and panic disorder (PD), as well as depressed affect and anxious affect, were assessed using the Composite International Diagnostic Inventory (N=1,290). Multiple linear regression was used to assess the relationship between depression and anxiety disorders and telomere length. Among women, those with GAD or PD had shorter telomeres than those with no anxious affect (β: −0.07, $p<0.01$), but there was no relationship among men (β: 0.08, $p>0.05$). Among respondents currently taking an antidepressant, those with MD had shorter telomeres than those without (β: −.26, $p<.05$), but there was no association between MD and telomere length among those not using antidepressants (β: −.00, $p>.05$). Neither depressive nor anxiety disorders were directly associated with telomere length

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AUTHOR CONTRIBUTIONS

B. Needham and B. Mezuk conceptualized the study and drafted the manuscript. B. Needham conducted the data analysis. N. Bareis conducted the literature review and provided feedback on the analysis plan. J. Lin and E. Blackburn developed, executed and oversaw the laboratory portion of the study and provided criteria feedback on the manuscript draft. E. Epel provided criteria feedback on the manuscript draft.

CONFLICTS OF INTEREST:

J. Lin, E. Blackburn, and E. Epel were co-founders of Telome Health.

in young adults. There was suggestive evidence that pharmacologically-treated MD is associated with shorter telomere length, likely reflecting the more severe nature of MD that has come to clinical attention.

INTRODUCTION

Epidemiologic studies have established that depression and anxiety disorders are predictive of numerous health outcomes in later life, including risk of cardiovascular disease, [1] type 2 diabetes, [2] osteoporosis, [3] cognitive decline, [4] and mortality, particularly among those with established cardiovascular and metabolic disease. [5, 6] The mechanisms underlying these associations remain largely unspecified. However, there is a growing body of research examining the biological correlates of depression and anxiety disorders that has shown these conditions are associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis, [7, 8] sympathetic nervous system, [9] sex hormones [10, 11] and the immune system. [12] The latter is particularly relevant in light of research pointing to inflammation as a key biological mediator of morbidity and mortality in mid- and late-life, sometimes called *inflammaging.* [13] These physiologic systems are complex and interact with each other, and studies of biomarkers of these systems (e.g., circulating levels of cortisol, cytokines) are limited in their ability to index biological stress exposure organism-wide and within cells. Constructs such as allostatic load aim to capture this multi-system impact, and thus are thought to provide a more holistic approach to understanding the biological impact of depression and anxiety.[14] However these models are limited in that they still rely on circulating levels of extracellular biomarkers that are known to vary substantially over the course of the day and be influenced by various acute environmental exposures (e.g., tobacco and alcohol use, dietary intake, physical activity, acute psychological stress). [15]

In light of the inherent variability of circulating levels of hormones, and increasing evidence that allostatic load and related measures do not always reflect differences in cumulative exposure to stressors as has been hypothesized, [16] researchers have turned to other potential biomarkers that are more summative in nature. Leukocyte telomere shortness has emerged as a biomarker and causative agent of aging that may potentially mediate part of the risk of chronic diseases associated with depression and anxiety. [17] Telomeres are the protective caps at the ends of eukaryotic chromosomes. Telomeric DNA naturally shortens with mitosis (unless compensated by physiological replenishment, including the telomere-elongating enzyme telomerase), and when telomeres become critically shortened, cellular senescence is triggered.[18, 19] Throughout human lifespans telomerase action is generally insufficient to sustain telomere length and, consistent with the hypothesis that telomere shortening is a marker of functional organismal aging, a growing body of evidence suggests that shorter telomeres are associated with declining health in later life. Shorter telomeres are associated with and often predict co-morbid conditions including cardiovascular disease, [20–24] type 2 diabetes, [25–27] dementia, [28–31] cancer, [32, 33] and increased mortality, [32, 34–45] independent of chronological age.

Several studies have examined associations between depression, anxiety and telomere length, with conflicting results (see Table 1 for a summary of findings). Here we briefly

review three prior population-based studies most relevant to our investigation. First, using data from the Netherlands Study of Depression and Anxiety (mean age: 42 years, standard deviation (SD): 13 years), Verhoeven and colleagues (2013) reported that individuals with a history of major depression (MD) had shorter telomeres relative to controls and that severity and duration of depression were inversely associated with telomere length.[46] They also reported that use of psychotropic medication was not associated with telomere length among those with MD, but were unable to examine this relationship among individuals without MD. Next, using data from the West of Scotland Twenty-07 Study (mean age: 56 years, SD: 15 years), Phillips et al. (2013) reported that depressive symptoms were inversely associated with telomere length, but only among the youngest cohort (37 years). [47] Finally, using data from the Netherlands Prevention of Renal and Vascular End-stage Disease Study (mean age: 53 years, SD: 11 years), Hoen et al. (2013) reported that anxiety, but not depression, was associated with shorter telomeres. [48]

As demonstrated above and detailed in Table 1, differences in study design (cohort vs. case-control), ascertainment of depression and anxiety (scales to indicate non-specific distress vs. psychiatric diagnoses indicated by schedules or clinical interviews), duration and severity of psychopathology (clinically-detected vs. not), and sample composition (clinical vs. general population) likely contribute to these disparate findings. Notably, no study to date has examined these relationships using a nationally-representative sampling frame with an ethnically diverse sample. As a result, it is unclear whether existing findings are generalizable to the broader population with a history of depressive and anxiety disorders, or what role antidepressant medications may play in this relationship.

The aims of this study were: (1) to provide a synthetic qualitative review of the existing research regarding the relationship of depression and anxiety disorders with telomere length; (2) to examine associations between depression and anxiety and telomere length in a diverse, nationally-representative sample of young adults; and (3) to determine whether these associations vary according to race/ethnicity, gender, and/or use of antidepressants.

METHODS

Sample and Procedures

Since 1960, the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) has conducted The National Health and Nutrition Examination Survey (NHANES) to provide estimates of the health and nutritional status of the US civilian non-institutionalized population. NHANES 1999–2002 is a cross-sectional, nationally-representative sample of 21,004 individuals aged two months and older. NHANES 1999–2002 utilized a 4 stage sampling design: 1) primary sampling units (PSUs) consisting primarily of single counties, 2) area segments within PSUs, 3) households within segment areas, and 4) persons within households. The NHANES survey consists of a face-to-face interview and a health examination in a mobile examination center (MEC). NHANES 1999–2002 oversampled low-income persons, those aged 12 – 19, persons aged ≥ 60, African Americans, and Mexican Americans in order to obtain more accurate estimates in these populations.

All NHANES 1999–2002 respondents aged 20 and over were asked to provide DNA samples. Of 10,291 eligible respondents, 7,826 (76%) both provided DNA and consented specifically to future genetic research. The psychiatric assessment (described below) was administered to a half-sample of participants aged 20 – 39. Data on telomere length and psychiatric history were available for 1,290 participants. Of these, we excluded 126 respondents whose self-reported race/ethnicity was “other” or “other Hispanic,” since a goal of this study was to examine race/ethnic differences in associations between depression and anxiety and telomere length, and these groups are too diverse for our purposes. The final analytic sample includes 1,164 respondents. This age group is appropriate for measuring the relationship between depression/anxiety and telomere length because depression onset peaks during this period, [49] and chronic medical conditions that may introduce residual confounding of this relationship are uncommon.

Human subjects approval for this study was provided by the Institutional Review Board at the CDC and all participants provided informed consent.

Telomere Length

Aliquots of purified DNA were provided by the laboratory at the Division of Health and Nutrition Examination Surveys, National Center for Health Statistics, CDC. Using standardized procedures, DNA was extracted from whole blood and stored at −80° C. Telomere length (TL) was assessed using the quantitative polymerase chain reaction (qPCR) method to measure telomere length relative to standard reference DNA (T/S ratio). This assay was performed in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, and is described in detail elsewhere. [50, 51] Each sample was assayed three times on three different days to ensure accurate measurement. The samples were assayed on duplicate wells, resulting in six data points. Sample plates were assayed in groups of three plates, and no two plates were grouped together more than once. Each assay plate contained 96 control wells. Any assay runs with eight or more invalid control wells were considered a failed run and were excluded from further analysis (>99% of runs passed this criterion).

The mean of the T/S values was calculated, and the largest or the smallest T/S value in the set of 3 values (whichever deviated most from the mean) was marked as a potential outlier. Then the mean of the T/S value was re-calculated without the potential outlier. If the absolute value of the log of the ratio between the recalculated mean (excluding the potential outlier) to the value of the potential outlier was greater than .4, then the value was marked as an outlier (98.7% of all samples contained no outliers). The conversion from T/S ratio to base pairs (bp) was calculated based on comparison of telomeric restriction fragment (TRF) length from Southern blot analysis and T/S ratios using DNA samples from the human diploid fibroblast cell line IMR90 at different population doublings. The formula to convert T/S ratio to bp was 3,274 + 2,413 * (T/S). DNA samples were coded and the lab was blinded to all other measurements in the study. The CDC conducted a quality control review of the TL data before linking it to the NHANES 1999–2002 public use data files for analysis.

Depression and anxiety disorders

Three modules from the World Health Organization Composite International Diagnostic Interview (CIDI), a fully-structured diagnostic interview that operationalizes the criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), [52] were administered during the MEC interview. The modules included generalized anxiety disorder (GAD), major depression (MD), and panic disorder (PD), assessed over the past 12 months. The reliability and validity of the CIDI has been extensively investigated, and this instrument has moderate concordance with clinical psychiatric interviews. [53] The modules were administered in either English or Spanish by trained lay interviewers.

We used information from the CIDI MD module to construct a dummy-coded categorical variable indicating (a) MD, (b) depressed affect, or (c) no depressive symptoms in order to assess this symptomology in a more dimensional manner. Past-year MD was determined using DSM-IV diagnostic criteria, indicating presence of dysphoria or anhedonia plus a clustering of four or more symptom groups (i.e., appetite disturbances, sleep problems, fatigue, guilt, psychomotor agitation/retardation, cognitive disturbances, and suicidal ideation) that lasted at least two weeks. Respondents who endorsed the item on dysphoria (i.e., period of feeling sad, depressed, or empty for two weeks or longer) but did not meet diagnostic criteria for MD were categorized as having depressed affect. All other respondents were categorized as having no depression, which served as the reference category for both MD and depressed affect. Similarly, we used the CIDI GAD and PD modules to construct dummy variables for (a) GAD or PD, (b) anxious affect, or (c) no anxiety symptoms. Past-year GAD was determined using DSM-IV diagnostic criteria, indicating a period of excessive anxiety or worry lasting six months or more accompanied by feelings of tension, fatigue, concentration problems, irritability, or sleeping disturbances. Past year PD was determined using DSM-IV criteria, indicated by recurrent panic attacks (i.e., short, discrete period of fear or discomfort accompanied by cardiovascular, respiratory, and cognitive symptoms) accompanied by a month or more of worry about the attacks. These two diagnoses were combined into a single variable indicating past-year GAD or PD. Respondents who endorsed a period of anxious affect (i.e., a period of a month or more in which they felt worried or tense or anxious about everyday problems such as work or family on most days) but who did not meet diagnostic criteria for GAD or PD were categorized as having anxious affect. All other respondents were categorized as having no anxiety, which served as the reference category for both the GAD/PD and anxious affect categories. Finally, we combined measures of depression and anxiety into a single dummy-coded variable: (a) MD, GAD or PD, (b) depressed or anxious affect, and (c) no depressive or anxiety symptoms, which served as the reference category for the combined measures.

Moderators

We examined three hypothesized moderators: race/ethnicity (non-Hispanic white, African American, and Mexican American), gender, and current antidepressant use. Medications were assessed by visual inspection of pill bottle(s); if the medication container(s) were not available, respondents were asked to verbally report the name(s) of the medication(s). Medications were then were classified using Lexicon Plus, a comprehensive database of all prescription medications available in the United States. [54] Current drug lists from archive

websites (i.e., www.drugs.com, Mayo Clinic) were used to identify brand and generic names for all antidepressant medications on the market at the time of data collection (1999 – 2002). Respondents who reported using one or more medications in the following classes were categorized as currently using an antidepressant: selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs or SSNRIs), tricyclic and tetracyclic antidepressants, and monoamine oxidase inhibitors (MAOIs).

Data Analysis

The first step in the analysis was to examine associations of TL with depression and anxiety symptomology. Telomere length was transformed by natural logarithm prior to regression modeling to satisfy the assumption of normality. Using a linear model, we regressed log-transformed telomere length (T/S ratio) on each of the symptom variables and demographic characteristics, including age (in years), gender (female=1; male=0), and race/ethnicity (dummy variables for African-American and Mexican American with non-Hispanic white as the reference category). Next, given prior evidence of race/ethnic and gender differences in both depression and anxiety and TL, we estimated models stratified by race/ethnicity and gender. Because only about 50% of cases of MD or anxiety disorders in the general population receive treatment,[55] the use of antidepressant medications in this sample likely indicates more severe symptomology that has come to clinical attention. Therefore, we also examined models stratified by antidepressant use as an indicator of clinical severity. After estimating stratified models, we used *z*-tests[56] to compare corresponding parameter estimates across groups according to race/ethnicity (African American versus non-Hispanic white, Mexican American versus non-Hispanic white, and African American versus Mexican American), gender (women versus men), and antidepressant use (non-users versus users). Significant *z*-tests suggest moderating effects of race/ethnicity, gender, and/or antidepressant use.

All regression models incorporated the complex sampling design of NHANES (i.e., strata and PSU indicators), as well as sample weights for the genetic subsample. [57] Analyses were conducted on-site at the CDC Research Data Center in Atlanta, GA and remotely using ANDRE, the CDC's remote access system for the analysis of restricted data. All p-values refer to two-tailed tests.

RESULTS

Qualitative review of existing studies

Table 1 describes existing studies of depression and anxiety disorders with TL and/or telomere content (18 in total). All but one report [58] assessed TL in leukocytes, and all but four [59–62] used the qPCR method for assessing mean TL. Approximately 40% (7 out of 18) had a sample size of <100, and in several cases the sample was derived from a study that had been designed to assess a different research question (e.g., Heart and Soul Study, a cohort of patients discharged with coronary heart disease [63, 64]). All samples were comprised almost exclusively of non-Hispanic whites. Overall, about half of the studies reported significantly shorter TL in cases of MD or anxiety disorders versus comparison groups. The majority of studies that reported no association between MD and TL had samples that were relatively

young (less than 50 years of age). Finally, there were substantial differences in the ascertainment of MD and anxiety disorders; many relied on psychiatric clinic populations, [60–62, 65, 66] which are more severe than cases in the general population.

Present investigation

Table 2 shows the demographic characteristics of the sample from NHANES 1999 – 2002 stratified by depression and anxiety status. The sample was relatively young (mean age: 29.4 years). In the past year, 17% of the sample had MD or depressed affect; 10.1% of these individuals were currently using an antidepressant. Similarly, 19% had GAD, PD, or anxious affect in the past year; 11.8% of these were currently using an antidepressant.

Table 3 shows the results of the regression models. There was no association between depression or anxiety status and TL in the sample overall, either in the unadjusted models (results not shown) or after accounting for age, gender and race/ethnicity (Cohen's d: 0.06). In race-stratified analyses, neither depression nor anxiety was significantly associated with TL among non-Hispanic whites, African-Americans, or Mexican-Americans. In analyses stratified by gender, past-year GAD/PD was significantly associated with shorter TL among women (β: −0.07, p<0.01), but not men (β: 0.08, p>0.05); and the difference in coefficients for women and men was statistically significant (*z*: −2.27, p<.05). Compared to women with no anxiety symptoms, women with past year GAD/PD had telomeres shorter by 169 base pairs. Given the observed cross-sectional rate of telomere shortening in this study of 19 bp per year, this difference is roughly equivalent to 9 years of additional aging. Finally, in analyses stratified by antidepressant use, past-year MD was associated with shorter TL among current antidepressant users (β: −.26, p<.05), but not among non-users (β: −.00, p>.05). The difference in coefficients for antidepressant non-users and users was statistically significant (*z*: 2.18, p<.05). Compared to current antidepressant users with no depressive symptoms, current users with MD had telomeres shorter by 651 bp, which corresponds to approximately 34 additional years of aging.

In order to assess the likelihood that our study was underpowered to reject the H_a (i.e., that depression or anxiety are directly associated with shorter TL) we conducted a *post hoc* power analysis. For depression, given our sample size (n=198 and n=996 for those with vs. without a past-year history of MD or depressed affect, respectively) and setting type 1 error (α) at 0.05 (two-sided), we had 50% power to detect an effect size of 0.15, and 80% power to detect an effect size of 0.22. As a comparison, Verhoeven and colleagues reported an effect size of 0.13 in their analysis of current MD cases vs. controls, for which they had 67% power to detect. [46] Thus, while our study was marginally underpowered, the effect size we report here is also approximately half of what has been reported in previous studies.

DISCUSSION

The primary finding from this study is that depressive and anxious symptomatology, overall, have no direct relationship with TL in young adulthood. Although associations did not vary across race/ethnicity, among women (but not men) past-year GAD/PD was associated with shorter TL. There was no direct effect of antidepressant medication use on TL, but among current users of antidepressants, those with past-year MD had shorter TL than those with no

depression. To our knowledge, this is the first study to examine relationships between antidepressant medication use and depressive and anxious symptomology, as well as the first to examine variation in these relationships by race/ethnicity, in a nationally-representative sample.

Previous studies have often not been able to examine whether antidepressant medications have a direct association with TL, largely because in most of these prior reports cases of depressive and anxiety disorders were drawn from clinic populations while the comparison participants were screened for psychopathology. For example, in the recent publication by Verhoeven et al. (2013) only two individuals in the control group were taking an antidepressant. In our study, because of the lack of a direct association between either these conditions or these medications with TL, we interpret our findings regarding antidepressant use as indicative that severe depressive symptomology (i.e., that which has come to the attention of a physician and is being treated) is associated with shorter TL. [46] This is consistent with the recent analysis by Shalev et al. (2014) that found that recurrent depressive and anxiety disorders, as well as psychotropic medication use, were associated with shorter TL in middle adulthood; [67] however, unlike the present study, they found that the relationship between psychotropic medication use and TL was independent from depressive and anxious psychopathology.

Another important gap in the literature addressed by this paper is the lack of investigation into the relationship between depressive and anxious symptomology and TL in racially diverse samples. As shown by Table 1, previous studies have been conducted using primarily, and often exclusively, non-Hispanic white populations. Evidence suggests that both risk of psychopathology[68] and TL varies across racial/ethnic groups in the US, [69–73] and thus it is important to examine whether these relationships vary across groups. Although our results suggest that there are no race/ethnic differences in associations between MD and GAD/PD and TL, replication studies in other multi-ethnic samples are needed.

Findings from this study should be interpreted in light of study strengths and limitations. Key strengths of this report include the population-based sampling design, which mitigates the risk of selection bias (“Berkson’s bias”) that is likely present in studies that use clinic populations to ascertain cases of depressive and anxiety disorders. [74] Depressive and anxious symptomology was assessed using a structured diagnostic instrument that has good reliability.[75] Finally, the diversity of the study population allowed us to examine heterogeneity in the relationship between depression and anxiety disorders and TL across racial/ethnic groups. This study also has limitations. Because TL captures and can contribute to characteristics of biological aging, including risks for various diseases, [17] it is possible that depressive and anxious symptomology are only associated with TL in later life, when organisms are less resilient to stress, which may explain our lack of an association in this relatively young sample. However, several prior studies with age composition similar to ours [47, 66, 67] have reported significant inverse relationships. We examined TL as measured in leukocytes, not brain, and while previous studies have shown that TL is correlated across tissues, [76–78] it is possible that other tissues may have shown stronger relationships with TL. Finally, we did not have a measure of telomerase. Previous research has shown that telomerase activity is significantly elevated in those with MD compared to controls, [79] and

recent work has shown that the combination of short telomeres with high telomerase activity is indicative of greater cell stress than short telomeres alone. [80]

In conclusion, this study illustrates many issues related to sample selection and study design that may have contributed to an abundance of positive findings in the extant literature. Despite these limitations, the existing research literature, coupled with the empirical investigation presented here, indicates that severe depressive symptomatology, as indicated by being medically treated either in a clinical setting or by psychotropic medications, is associated with shorter TL even in early adulthood. However, less severe forms of psychopathology were not associated with TL.

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Table 1

Extant studies of depression, anxiety and telomere length: 2006 – 2013

First Author, Year	Study Design	Sample Source	Study Population	Measure of Psych Disor	Telomere Measure, Tissue Source	Major Findings
Simon, 2006[59]	Case-control	Cases from MGH Mood Disorder Genetics Study; Controls from Harvard Healthy Volunteer Specimen Bank	**Combined Case Group:** n=44, Mean age=51.1 (SD=7.7) 48% Female (MD w/o Anxiety; BP w/ Anxiety; BP w/o Anxiety) **Controls:** n=44, Mean age=50.5 (SD=8.4) 43% Female	SCID-IV	mTL Southern Blot Leukocytes	Psychiatric disorder associated with shorter TL
Zhang, 2010[58]	Case-control	SMRI brain tissue samples	**Psychiatric Cases:** n=106, Mean age=44 (SD=10.4), 39% Female (SZ; BP; MD) **Controls:** n=48, Mean age=45.2 (SD=9.1) 31% Female	Medical Records	mTL Q-PCR Cerebellar Gray Matter	No association between psychiatric disorder and TL
Hartmann, 2010[60]	Case-control	Psychiatric Inpatients Community-dwelling controls	**MD:** n=54, Mean age=49.1 (SD=14.1) 61% Female (Total Antidepressant Dose (TAD)<=1; TAD>1; ECT) **Controls:** n=20 Mean age=49.1 (SD=15.2) 45% Female	HAM-D TAD TAD+ECT	mTL Southern Blot Leukocytes	MD associated with shorter TL vs. controls
Wolkowitz, 2011[81]	Case-Control,	Psychiatric outpatients Community-dwelling controls	**MD:** n=18 Mean age=36.8 (SD=11.0) 67% Female **Controls:** n=17 Mean age=36.6 (SD=11.8) 65% Female	SCID HDRS	mTL PCR Leukocytes	Lifetime MD, but not current MD, associated with shorter TL
Hoen, 2011[63]	Nested case-control	Heart and Soul Study	**MD:** n=206, Mean age=61.7 (SD=10.8) 31% Female HADS Mean=8.90 (SD=4.09) **Controls:** n=746, Mean age=68.1 (SD=10.6) 15% Female HADS Mean=4.45 (SD=3.30)	CDIS-IV PHQ-9 HADS	mTL PCR Leukocytes	MD associated with shorter TL vs. controls Association not significant when adjusting for Anxiety
Elvsåshagen, 2011[62]	Case-control	Psychiatric outpatients; Community-dwelling controls	**BP-II:** n=28, Mean age=34.8 (SD=7.7) 68% Female **Controls:** n=28, Mean age=34.8 (SD=9.2) 68% Female	MINI NEQ MADRS YMRS	mTL Q-FISH Leukocytes	No association between BPII and TL. BPII had greater concentration of short telomeres vs. controls.
Rius-Ottenheim, 2012[82]	Two samples: Cross-sectional and prospective cohort 7-year follow-up	Zutphen Elderly Study & Cretan Elderly Study	**Zutphen 1993:** n=203, Mean age =77.6, 100% Male **Zutphen 2000***: n=144, Mean age =84.1, 100% Male **Crete 2000:** n=123, Mean age =84.1, 100% Male *N=75 Zutphen 2000 Cohort also in 1993 Cohort	GDS-15 Zung SDS	mTL Q-PCR Leukocytes	No association between MD and TL

First Author, Year	Study Design	Sample Source	Study Population	Measure of Psych Disor	Telomere Measure, Tissue Source	Major Findings
Wikgren, 2012[61]	Case-control	Psychiatric Inpatients, Controls from Betula study	**MD:** n=91, Mean age=60.4 (SD=13.1) 60% Female **Controls**: n=451, Mean age=58.9 (SD=11.6) 50% Female PSQ Median=47 (IQR 40–58)	Medical Records BDI BAI CES-D PSQ	mTL Unspecified method Leukocytes	MD associated with shorter TL vs. controls. Higher PSQ correlated with shorter TL among controls
Teyssier, 2012[65]	Case-control	Psychiatric inpatients, Hospital staff controls	**MD:** n=17, Age Mean=39.5 (SD=5.2) 100% Female **Controls:** n=16, Age Mean=37.6 (SD=5.2) 100% Female	SCID MINI HAM-D HAM-A Medical Records	mTL rQ-PCR Leukocytes	No association between MD and TL
Shaffer, 2012[83]	Cross sectional	Nova Scotia Health Survey 1995	**Probable MD** (CESD≥16): n=269 **Elevated MD** (CESD≥10): n=613 **Total** N=2,225 Mean age=48.2 (SD=18.9) 50% Female	CES-D	mTL PCR Leukocytes	No association between MD and TL
Okereke, 2012[84]	Nested case-control	Nurses' Health Study (NHS)	**CCI 0 or 1:** n=1,782 Mean age=59.3 (SD=6.5) **CCI 2:** n=1,024 Mean age=59.1 (SD=6.6) **CCI 3:** n=816 Mean age=59.1 (SD=6.6) **CCI 4 or 5:** n=1,022 Mean age=59.4 (SD=6.5) **CCI ≥6;** n=599 Mean age=59.4 (SD=6.5) **Total** N=5,243 100% Female	Crown-Crisp Index (CCI)	mean Relative Telomere Length (RTL) Q-PCR Leukocytes	Higher phobic anxiety associated with lower mean RTL
Garcia-Rizo, 2013[66]	Case-control	Psychiatric inpatient; Population based controls	**MD:** n=15 Mean age=30.7 (SD=10.0) 40% Female **Controls:** n=70 Mean age=27.8 (SD=6.8) 38% Female	SCID DALI	mTC Leukocytes	MD associated with lower mTC vs. controls
Hoen, 2013[48]	Prospective cohort 2-year follow-up	Prevention of Renal and Vascular End-stage Disease (PREVEND) Study	**MD:** n=97 Mean age=51.3 (SD=10.7) 64% Female **No MD:** n=980 Mean age=53.7 (SD=11.3) 53% Female **Anx**: n=108, Mean age=52.2 (SD=9.5), 63% Female **No Anx:** n=970, Mean age: 53.6 (11.5), 53% Female	CIDI	mTL qPCR Leukocytes	No association between MD and TL Anx associated with shorter TL
Ladwig, 2013[85]	Cross-sectional	Cooperative Health Research in the Region of Augsburg (KORA) F4 study. General Population	**No PTSD:** n=2,687, Mean age= 56.5 (SD=13.4), 50% Female, MD PHQ-9=3.9%, MD DEEX=18.4% **Partial PTSD:** n=262, Mean age= 52.5 (SD=10.6), 62% Female, MD PHQ-9=13%, MD DEEX=55% **Full PTSD:** n=51, Mean age= 54.5 (SD=11.8), 63% Female, MD PHQ-9=5.9%, MD DEEX=56.9%	PHQ-9 DEEX PDS IES	mTL PCR Leukocytes	No association between MD and TL Full PTSD shorter TL vs. no PTSD

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First Author, Year	Study Design	Sample Source	Study Population	Measure of Psych Disor	Telomere Measure, Tissue Source	Major Findings
Phillips, 2013[47]	Prospective population-based cohort 15-year follow up	West of Scotland Twenty-07 Study	**Youngest (37yr):** n=337, Mean age=36.6 (SD=0.67), 53% Female **Middle (57yr):** n=441, Mean age=57.1 (SD=1.11), 55% Female **Older (76yr):** n=285, Mean age=76.1 (SD=0.84), 55% Female **Overall:** n=1,063, Mean age=55.7, (SD=15.1), 55% Female	HADS	mTL qPCR Leukocytes	MD was associated with shorter TL among youngest age group only
Puterman, 2013[64]	Nested case-control	Heart and Soul Study	**MD:** n=205, Age Mean=61.7, (SD=10.8), 30% Female **No MD:** n=743, Age Mean=68.2, (SD=10.5), 15% Female	CDIS-IV	mTL PCR Leukocytes	Resiliency buffers the association between MD and TL
Verhoeven, 2013[46]	Cross-Sectional	Netherlands Study of Depression and Anxiety (NESDA)	**Current MD:** n=1,095 Mean age =40.7 (SD=12.1) 57% Female Co-morbid Anxiety=66% **Remitted MD**: n=802, Mean age =43.5 (SD=12.5), 70% Female Co-morbid Anxiety=37% **Controls:** n=510, Mean age=40.5, (SD=14.9), 60% Female	CIDI IDS	mTL qPCR Leukocytes	Both current and remitted MD associated with shorter TL vs. controls Current MD w/Co-morbid Anxiety borderline significantly associated with shorter TL
Georgin-Lavialle, 2014[86]	Cross-Sectional	Clinical cohort of Mastocytosis patients	N=19, Mean age=45 (Range=19–78), 79% Female **PSS score≥40:** n=9, Mean=48.33, (SD=5.65) **PSS score<40:** n =10, Mean=34 (SD = 2.64)	BDI-II PSS	mTL RT-qPCR Leukocytes	No association between MD and TL Shorter TL correlated with higher levels of perceived stress.
Shalev, 2014[67]	Prospective, population-based cohort 35 year follow-up	Dunedin Multidisciplinary Health and Development Study	**History of at least one internalizing disorder** (GAD; MD; PTSD): n=455, Age=38, 58% Female **Controls:** n=372, Age=38, 39% Female	DISC DIS-IV	mTL qPCR Leukocytes	Persistence of internalizing disorders (number of waves met criteria) associated with shorter TL in men but not women at 2012 follow-up Internalizing disorders associated with greater loss of TL over 8 year period (ages 26 and 38 years) among men but not women

Anx: Anxiety disorder (Generalized Anxiety Disorder, social phobia, or agoraphobia); BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BDI-II: Beck Depression Inventory revised; bp: Base Pairs; CDIS-IV: Computerized National Institute of Mental Health Diagnostic Interview Schedule; CES-D: Center for Epidemiologic Studies Depression; CIDI: Composite International Diagnostic Interview; DALI: Dartmouth Assessment of Lifestyle Inventory; ECT: Electroconvulsive Therapy; CCI: Crown-Crisp Index of Phobic Anxiety; GDS-15: Geriatric Depression Scale; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton severity anxiety; HAM-D: Hamilton Depression score; HDRS: Hamilton Depression Rating Scale; HVS: Healthy Volunteer Specimen Bank at Harvard Medical School – Partners Healthcare Center for Genetics and Genomics; IDS: Inventory of Depressive Symptoms; IQR: Interquartile Range; mTC: Mean telomere content; mTL: Mean telomere length; MADRS: Montgomery–Asberg Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview; NEQ: Stanley Foundation Network Entry Questionnaire; PBMC: Peripheral blood mononuclear cells; PCR: Monochrome Multiplex Polymerase Chain Reaction; PHQ-9: Patient Health Questionnaire; PSS: Perceived Stress Scale; PSQ: Perceived Stress Questionnaire; QPCR: Quantitative polymerase chain reaction; Q-FISH: Quantitative fluorescence in situ hybridization of PBMC; rQ-PCR: Real-time quantitative polymerase chain reaction method; SCID: Structured Clinical Interview for

DSM-IV-TR; SMRI: Stanley Medical Research Institute; TAD: Total Antidepressant Dose; sum of all antidepressants taken by one patient; YMRS: Young Mania Rating Scale; Zung SDS: Dutch translation of the Zung self-rating depression scale

Table 2

Participant characteristics stratified by depression and anxiety status

		Depression		Anxiety	
	Overall	**No depression**	**MD or depressed affect**	**No anxiety**	**GAD/PD or anxious affect**
Age (M, SD)	29.4, 5.9	29.2, 5.9	30.3, 5.8	29.3, 5.8	30.0, 6.0
Female (N, %)	657, 56.4%	541, 56.0%	116, 58.6%	539, 56.6%	118, 55.7%
Race/ethnicity (N, %)					
Non-Hispanic white	586, 50.3%	485, 50.2%	101, 51.0%	485, 51.0%	101, 47.6%
African American	227, 19.5%	188, 19.5%	39, 19.7%	184, 19.3%	43, 20.3%
Mexican American	351, 30.2%	293, 30.3%	58, 29.3%	283, 29.7%	68, 32.1%
Depression status (N, %)					
Depressed affect only	123, 10.6%	--	123, 62.1%	72, 7.6%	51, 24.1%
MD	75, 6.4%	--	75, 37.9%	25, 2.6%	50, 23.6%
Anxiety status (N, %)					
Anxious affect only	168, 14.4%	93, 9.6%	75, 37.9%	--	168, 79.3%
GAD	24, 2.1%	5, 0.5%	19, 9.6%	--	24, 11.3%
PD	27, 2.3%	13, 1.4%	14, 7.1%	--	28, 13.2%
Antidepressant use (N, %)	52, 4.5%	32, 3.3%	20, 10.1%	27, 2.8%	25, 11.8%
Telomere length (T/S ratio)	1.14, .4	1.14, .4	1.12, .2	1.14, .4	1.12, .2
N	1,164	966	198	952	212

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Table 3

Association between depression and anxiety status and log-transformed telomere length (T/S ratio)

	Full Sample	Non-Hispanic White	African American	Mexican American	Female	Male	No Antidepressants	Antidepressants
	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)
Depression								
No depression	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Depressed affect	−.01 (.02)	−.04 (.03)	.03 (.03)	.06 (.04)	−.01 (.03)	−.02 (.04)	−.01 (.02)	−.02 (.09)
MD	−.03 (.03)	−.03 (.03)	−.07 (.07)	.00 (.04)	−.05 (.05)	.00 (.05)	−.00 (.02)	**−.26 (.12)***
R^2	.05	.06	.02	.03	.06	.05	.05	.24
Anxiety								
No anxiety	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Anxious affect	−.01 (.02)	−.03 (.03)	.02 (.03)	.01 (.02)	−.05 (.04)	.01 (.02)	−.02 (.02)	.04 (.09)
GAD or PD	−.02 (.03)	−.04 (.04)	.01 (.05)	.13 (.07)	**− .07 (.02)****	.08 (.06)	−.02 (.04)	.00 (.09)
R^2	.05	.06	.01	.03	.07	.05	.05	.08
Depression or Anxiety								
No depression or anxiety	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Depressed or anxious affect	−.01 (.02)	−.03 (.03)	.03 (.03)	.05 (.03)	−.03 (.03)	.01 (.03)	−.01 (.02)	−.01 (.08)
MD, GAD, or PD	−.02 (.02)	−.03 (.03)	−.04 (.05)	.06 (.03)	−.05 (.03)	.03 (.04)	−.01 (.02)	−.03 (.10)
R^2	.05	.06	.02	.03	.06	.05	.05	.11
Total N	1164	586	227	350	657	506	1112	52

Note: All models include controls for age, gender, and race/ethnicity.

* p<.05;

** p<.01