Relationship Between Current Depressive Symptoms and Telomere Length in a Large, Multiethnic Sample

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ABSTRACT

Objective: Previous research has suggested that depressive symptoms may be associated with telomere length; however, findings have been mixed, and few studies have sought to generalize the results beyond samples of white individuals. The present study, conducted from August 2013 through August 2015, sought to examine the relationship between depressive symptoms and leukocyte telomere length in a large (N = 2,710), multiethnic sample (African American, white, Hispanic) and to determine if this relationship differed across ethnic/racial groups. Analyses were based on data taken from the Dallas Heart Study, a recent epidemiologic-style, population-based study of adults from Dallas County, Texas.

Methods: Depressive symptoms were measured using the Quick Inventory of Depressive Symptomatology, and leukocyte telomere length was measured using a quantitative polymerase chain reaction technique. Analyses of the relationship between depressive symptoms and telomere length were conducted using multiple linear regression models.

Results: Among the whole sample, there was no significant relationship between depressive symptoms and telomere length in either a basic ($\beta = -0.025$, $P = .190$) or an adjusted ($\beta = -0.015$, $P = .443$) model. However, among non-Hispanic white participants, depressive symptoms were significantly associated with telomere length in both basic ($\beta = -0.083$, $P = .014$) and adjusted ($\beta = -0.066$, $P = .049$) models.

Conclusions: These findings suggest that ethnic/racial identification may be a factor in the relationship between depressive symptoms and telomere length and could impact the generalizability of previous research.

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Depression is one of the leading predictors of disability, morbidity, and mortality worldwide[1] and has been implicated in a range of illnesses and diseases, including heart disease,[2] stroke,[3] dementia,[4] and type 2 diabetes.[5] However, the mechanisms by which depression exerts its systemic effects are poorly understood. From a systems-level perspective, depression has been associated with changes in several important areas, including the hypothalamic-pituitary-adrenal axis,[6] immune system,[7] and aspects of the sympathetic nervous system,[8] although less is known about how depression affects human physiology on a cellular level. Previous research has suggested that stress, and particularly the chronic stress associated with mood disorders such as major depressive disorder, may be one pathway of cellular aging,[9] with processes such as increased inflammation and oxidative stress being important mechanisms.[10] One potential marker of cellular aging and perhaps stress is telomere length.[11]

Telomeres are repetitive nucleotide sequences at the ends of chromosomes in most eukaryotic organisms. 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 serves to stabilize the telomere by preventing the telomere ends from being identified as break points, an event that would typically trigger cellular senescence, apoptosis, or several other events, which might compromise the integrity of the genetic information.[12] During cellular division, DNA polymerase is unable to completely replicate the 3′ end of the strand; consequently, the telomere shortens by a small amount at each cell division, a phenomenon known as the end replication problem.[13] As a result of this process, telomere length gradually declines over time until the telomere is critically short, at which point the T-loop can no longer hold the structure of the telomere together and cellular senescence or apoptosis is induced.[14] Shortened telomere length has been associated with a variety of disease states and pathologies, including cardiovascular disease,[15,16] pulmonary fibrosis,[17] bone marrow failure syndromes,[18] cancer,[19] type 2 diabetes,[20] dementia,[21] and mortality.[22] Shorter telomere length is also associated with early life adversity.[23,24]

Some early research suggested that depression may have a shortening effect on telomere length, potentially through an increase in cellular-level stress.[25,26] Many of the early studies in this area appeared to show a significant negative association between depression and telomere length,[10,25–27] though some did not.[28,29] More recent research, which has tended to employ larger sample sizes and more epidemiologic-style study designs, has demonstrated more mixed results, although importantly these later studies tended to rely on symptom-based measures of depression rather than clinical diagnoses. One group[30] found that depressive symptoms were negatively associated with telomere length in one younger cohort of their study, while another found that participants with a history of a major depression diagnosis had shorter telomere lengths compared to controls.[31] However, several other large epidemiologic-style studies did not report a significant association between depression and telomere length.[32–35] As a recent study[35] noted, these larger studies have

often benefited from increased power to detect significant differences due to their more robust sample sizes, but their often equivocal findings may be due to significant heterogeneity across depression measurement, course and severity of depression, and, especially, sample composition. The 2015 study by Needham et al[35]is the only study of this type to date to include an ethnically/racially diverse sample, but the authors found no direct effect of depressive disorders on telomere length, nor did this relationship vary across race/ethnicity.

The present study sought to extend the previous literature in this area by examining the relationship between depressive symptoms and telomere length in a large sample and to examine how previous results might generalize to an ethnically/racially heterogeneous sample specifically designed from the outset to examine differences within ethnic/racial groups. To the best of our knowledge, the present study is the first to investigate the relationship between depressive symptoms and telomere length in a sample with a non-white majority.

Clinical Points

- No significant relationship between telomere length and current depression symptom severity was observed in a racially/ethnically diverse sample.
- A subgroup analysis revealed a significant relationship between telomere length and depressive symptom severity in white but not in African American or Hispanic persons.

METHODS

Sample

The Dallas Heart Study (DHS)[36] is a population-based, multiethnic study of more than 6,000 adults from Dallas County, Texas. Initial data collection took place during a 2-year period from 2000 to 2002. This first collection of data is referred to as DHS-1. This was an epidemiologic sample of Dallas County residents that oversampled specifically for African Americans to examine cardiovascular disease risk factors in this population. Although, as the title suggests, the primary goal of the DHS was to examine cardiovascular risk factors, the sample was a representative sample of Dallas County and not a sample limited to persons with existing cardiovascular disease or risk factors for cardiovascular disease. Thus, a major objective of the DHS was to examine racial and ethnic differences in health and disease risk. In 2007, the study was converted from a cross-sectional to a longitudinal design. Referred to as DHS-2, this second wave of the study invited all previous DHS-1 participants to return for another evaluation, and some additional participants were enrolled in DHS-2 to make up for attrition from DHS-1. All participants signed written informed consent forms approved by The University of Texas Southwestern Medical Center Institutional Review Board.

A total of 3,408 participants had available telomere length data and constitute the population on which the present analysis was based. On the basis of this subset of the DHS sample, the study sample was further clarified according to the following criteria: only participants who identified as African American (non-Hispanic), white (non-Hispanic), or Hispanic were included. Additionally, any participant with missing data on the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)[37] 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. For analyses in which covariate data were missing, those participants with missing data were excluded from the specific analysis.

Depressive Symptoms

The QIDS-SR[37] (referred to hereafter simply as the QIDS) is a 16-item (with each item scored 0–3) patient-rated inventory for quantifying the severity of depressive symptoms over the past week in a brief but valid form.[37,38] The QIDS is based on the larger 30-item Inventory of Depressive Symptomatology (IDS)[39] and was designed to assess all 9 major symptom domains that define major depressive disorder, including 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. Scores on the QIDS are highly correlated with scores from the larger 30-item IDS Self-Report ($IDS\text{-}SR_{30}$) ($r = 0.91$) and the Hamilton Depression Rating Scale (HDRS) ($r = 0.85$).[39] Additionally, the internal consistency of the QIDS (Cronbach $\alpha = .86$) is similar to that of the HDRS.[37] More information regarding the psychometric properties of the QIDS can be found at http://www.ids-qids.org.

The scoring procedure for the QIDS results in a single final score (referred to subsequently as "QIDS score"), which is a continuous variable calculated by taking the sum of the following: the highest score among questions 1–4; question 5 score; the highest score among questions 6–9; question 10 score; question 11 score; question 12 score; question 13 score; question 14 score; and the highest score among questions 15 and 16. The QIDS score may range from 0 to 27. Interpretation guidelines for the severity of depressive symptoms as measured by the QIDS score are as follows: 1–5, no depression; 6–10, mild depression; 11–15, moderate depression; 16–20, severe depression; 21–27, very severe depression.[37,38]

Telomere Length

In the current study, DNA was taken from circulating leukocytes using an Autopure LS (Qiagen, Valencia, California). As previously described in more detail within a study with the same data,[40] a quantitative polymerase chain reaction (PCR) method was employed to determine telomere lengths, with several modifications as described in another article.[41] Telomere length was expressed as a T/S ratio—the copy number of the telomere DNA (T) to a single-copy gene (S). The measurement was standardized by expressing the

Table 1. Descriptive Statistics of Participants Included in the Primary Analysis

Variable	Whole Sample (N = 2,710)	African American (n = 1,387)	White (n = 950)	Hispanic (n = 373)
Age, mean (SD), y	49.72 (11.14)	49.06 (11.32)	52 (10.6)	46.4 (10.6)
Female, %	59	63	55	57
Ethnicity/race, %				
African American	51	…	…	…
White	35	…	…	…
Hispanic	14	…	…	…
Body mass index, mean (SD), kg/m^2	31.29 (7.43)	32.57 (8.04)	29.53 (6.51)	30.97 (6.25)
Education, mean (SD), y	12.7 (2.2)	12.7 (1.5)	13.5 (1.7)	10.8 (3.5)
Any tobacco use, %	45	44	48	39
Current antidepressant use, %	11	8	16	7
Telomere length,[a] mean (SD)	1.7955 (0.259)	1.7958 (0.2654)	1.7803 (0.2503)	1.8332 (0.2548)
QIDS score				
Mean (SD)	5.51 (3.87)	5.92 (4.10)	4.88 (3.43)	5.55 (3.83)
Range (depressive symptom severity), n				
0–5 "none"	1,623	762	638	223
6–10 "mild"	787	446	241	100
11–15 "moderate"	230	124	61	45
16–20 "severe"	108	96	7	5
21–27 "very severe"	7	4	3	0

[a]Telomere length expressed as a T/S ratio—the copy number of the telomere DNA (T) to a single-copy gene (S).
Abbreviation: QIDS = Quick Inventory of Depressive Symptomatology.
Symbol: … = not applicable.

T/S ratio relative to a cultured cell line with extremely short telomere lengths (MCF-7 cells). Regarding quality control, if the coefficient of variation for the sample was more than 14%, the measurement was repeated until a value less than 14% was obtained (mean coefficient of variation was 4.08 with a standard deviation of 3.06). The final telomere length variable (a unitless T/S ratio) was a mean of at least 2 independent measurements and was log transformed in order to approximate a normal distribution.

Covariates

Ethnicity/race was a categorical variable consisting of the 3 ethnic/racial subgroups used for this study: African American (non-Hispanic), white (non-Hispanic), and Hispanic. Education was assessed as a continuous variable consistent with participants' number of years of education. Tobacco use was a dichotomous variable indicating the presence or absence of a history of tobacco smoking. Antidepressant use was a dichotomous variable indicating the presence or absence of current use of antidepressant medication. All covariate variables were obtained via participant self-report.

Data Analysis

Linear regressions were used to test the relationship between depressive symptoms and telomere length, with QIDS score as the primary predictor variable and telomere length as the dependent variable. Initially, a basic linear regression model (model 1) was used, adjusted for age and sex. Next, a fully adjusted model (model 2) was constructed, additionally controlling for ethnicity/race, body mass index (BMI), education, tobacco use, and antidepressant use.

Pre-planned analyses of the relationship between depressive symptoms and telomere length by ethnicity/race were conducted using pairs of regression models (basic and adjusted, as described above, with the exception of ethnicity/race) within each of the 3 ethnic/racial groups: African American (models 3 and 4), white (models 5 and 6), and Hispanic (models 7 and 8). *P* values less than .05 were considered significant. All analyses were performed using SPSS Statistics Software version 22.

RESULTS

The initial sample consisted of 3,408 participants from the DHS. We excluded participants with missing data on the variables used in the analysis. The excluded participants did not differ significantly on mean QIDS scores or telomere length from those in the final sample (*P* values ranged from .132 to .782). After these participants were excluded, the sample used for primary analyses consisted of 2,710 participants.

Descriptive statistics are provided in Table 1. The mean (SD) age for the sample was 49.7 (11.1) years, and the majority of participants (59%) were women. The sample consisted of 1,387 African American (51%), 950 white (35%), and 373 Hispanic (14%) participants. The mean (SD) number of years of education was 12.7 (2.2), and the mean (SD) BMI was 31.29 (7.43) kg/m^2, while 1,199 subjects (44%) had a history of tobacco use and 297 subjects (11%) were currently prescribed an antidepressant. Descriptive statistics are also reported for ethnic/racial subgroups (see Table 1). The overall mean telomere length was 1.80 (SD = 0.26), and mean telomere length did not differ significantly among racial/ethnic groups. The mean (SD) QIDS score was 5.51 (3.87); white participants had significantly lower QIDS scores than both African American ($P < .001$) and Hispanic participants ($P = .011$), but African American and Hispanic participants did not differ significantly. Telomere length was significantly associated with both age ($r = -0.197$, $P < .001$) and sex ($r = -0.078$, $P < .001$).

Table 2. Association Between QIDS Score and Telomere Length

Sample	β	*P* Value
Whole sample		
Basic model[a]	−0.03	.19
Full model[b]	−0.02	.44
African American		
Basic model[a]	< −0.01	.94
Full model[c]	0.01	.76
White		
Basic model[a]	−0.08	.01
Full model[c]	−0.07	.049
Hispanic		
Basic model[a]	−0.01	.922
Full model[c]	< −0.01	.946

[a]Adjusted for age and sex.
[b]Adjusted for age, sex, ethnicity/race, BMI, education, tobacco use, and antidepressant use.
[c]Adjusted for age, sex, BMI, education, tobacco use, and antidepressant use.
Abbreviations: BMI = body mass index, QIDS = Quick Inventory of Depressive Symptomatology.

Results of the linear regression analyses are shown in Table 2. In a basic model controlling for age and sex in the whole sample, QIDS score was not significantly associated with telomere length (β = −0.025, *P* = .190). In a fully adjusted model that additionally controlled for race/ethnicity, BMI, education, tobacco use, and antidepressant use, the association remained nonsignificant (β = −0.015, *P* = .443). There was also a nonsignificant interaction between white race/ethnicity and QIDS score (*P* = .177). In the ethnically/racially stratified analyses, QIDS score was negatively associated with telomere length among white participants in both basic (β = −0.083, *P* = .014) and fully adjusted models (β = −0.066, *P* = .049). Although QIDS score was related to telomere length in the white sample, the effect size was modest (Cohen $f^2 = 0.059$). No significant associations were found within African American participants in either basic (β = −0.002, *P* = .942) or fully adjusted (β = −0.008, *P* = .761) models. Similarly, no significant associations were found within Hispanic participants in either basic (β = −0.005, *P* = .922) or adjusted (β = −0.004, *P* = .946) models.

DISCUSSION

The primary findings of this study are (1) that depressive symptoms were not significantly associated with telomere length in either a basic or an adjusted model within a large, multiethnic, population-based sample as a whole and (2) that within analyses stratified by ethnicity/race, depressive symptoms were negatively associated with telomere length among white participants but not among African American or Hispanic participants. To date, this is 1 of only 2 studies[33] examining the relationship between depressive symptoms and telomere length in a sample of over 2,000 participants and the first to do so in a sample with a non-white majority. Consistent with the original intent of the DHS, we conducted subgroup analyses within ethnic/racial groups. These between-group differences help to extend the current literature in terms of the generalizability of previous findings of a link between depressive symptoms and telomere length. Most prior research in this area has used largely, if not entirely, white samples. Given that both depression risk[42,43] and telomere length[44,45] have been shown to differ based on ethnic/racial identification, this lack of racial/ethnic diversity is a significant shortcoming of the literature on this topic. A recent study[35] investigated the relationship between depressive symptoms and telomere length in a multiethnic sample using data from the National Health and Nutrition Examination Survey. That study found a significant association among participants taking an antidepressant medication (which the researchers hypothesized may have been a marker for more severe depressive symptomatology), but not in the sample as a whole or within ethnic/racial subgroups. Some differences between that study and the present study are important to note. The present study had a larger sample size and thus greater power to detect relationships between depression and telomere length in ethnic/racial subgroups. Another important difference given the large effect of age on telomere length[46] is the 20-year difference in mean age of participants between the 2 studies, with the mean age of participants in the present study substantially higher.

Given that this study is the first to demonstrate ethnic/racial differences in the relationship between depressive symptoms and telomere length, little prior work is available to suggest possible mechanisms. One potential factor is cultural attitudes toward mental illness, specifically depression. Differences have been documented[47,48] in the experience and reporting of depressive symptoms across ethnic/racial groups. In a study of African American and white older adults, Gallo et al[47] found that African American participants were less likely than white participants to endorse symptoms related to sadness. Jagers et al[48] found increased rates of depression in white compared to African American individuals; however, a wider range of moderating variables, including marital status, employment status, and age, influenced African Americans' reporting of symptoms. Thus, cultural differences in the experience and reporting of depressive symptoms may have been a factor in the ethnic/racial differences found in the relationship between depressive symptoms and telomere length.

The present study had several important strengths. The large sample size provided increased ability to detect small but significant differences compared to previous studies. The DHS also provided data that allowed us to control for many important potentially confounding variables, including ethnicity/race, which has been surprisingly absent from this literature. In studies showing significant associations between depressive symptoms and telomere length, the effect sizes tend to be small; thus, controlling for other variables is important. The present study was able to include a wide range of variables in its analysis models. In regard to ethnic/racial effects specifically, the results of the present study contribute to the existing literature by suggesting that the link between depressive symptoms and telomere length may not generalize beyond populations of primarily white descent.

The present study also had several important limitations. While a valid measure of depressive symptomatology,[39] the QIDS asks for information pertaining to only the previous 7 days. As a result, we have no information regarding the chronicity or intensity of participants' depressive symptoms, which has been shown to be an important factor in the effects of depressive symptoms on telomere length.[10] Although the QIDS questions are based on *DSM* criteria for major depressive disorder, the instrument assesses only depressive symptom severity and does not diagnose depressive disorders, which may have been a limiting factor given that studies in the literature based on depressive disorder diagnosis (rather than symptomatology) tend to more consistently show a relationship with telomere length. Furthermore, the frequency of clinically significant depressive symptom severity was modest in the sample (Table 1), which may have limited our statistical power. Because race/ethnicity was limited to 3 categories (or "Other," which was excluded) and ascertained by self-report, it is possible that some persons of mixed race may be incorrectly categorized. While QIDS score was related to telomere length in the white sample in a predetermined subgroup analysis, the effect size was small. There was also a nonsignificant interaction between white race/ethnicity and QIDS score in the combined sample, suggesting these findings ought to be interpreted with caution. While telomeres obtained from leukocytes are generally thought to be comparable to those from other sites throughout the body,[49,50] it is possible that telomeres obtained from other organs or tissues may have resulted in different outcomes. Although the study controlled for factors such as age and sex, less well characterized factors that may influence the relationship between depressive symptoms and telomere length may have been excluded. Finally, the present study included no data on telomerase activity, which has been shown to be associated with major depression[51] and is also an important factor in telomere length more generally.[52]

In summary, the present study provides evidence that there may be ethnic/racial differences in the relationship between depressive symptoms and telomere length; notably, that the relationship may not generalize to non-white populations. Although the study found no significant effect across the whole sample, limitations related to the measurement of the chronicity of depressive symptoms, as well as an absence of information related to telomerase activity, may in part be responsible for this lack of significant effect. In line with previous work in this area, the present study suggests that the relationship between depressive symptoms and telomere length is highly complex and multiply influenced. Consequently, future studies in this area should attempt to utilize as broad and diverse a study population as possible to better account for this complexity and confirm these epidemiologic findings in clinical patient samples.

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