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ORIGINAL ARTICLE

Depression, Religiosity, and Telomere Length in the Study on Stress, Spirituality, and Health (SSSH)

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Abstract
Prospective studies on the association between depression and telomere length have produced mixed results and have been largely limited to European ancestry populations. We examined the associations between depression and telomere length, and the modifying influence of religion and spirituality, in four cohorts participating in the Study on Stress, Spirituality and Health, each representing a different race/ethnic population. Relative leukocyte telomere length (RTL) was measured by a quantitative polymerase chain reaction. Our result showed that depression was not associated with RTL (percent difference: 3.0 95% CI: −3.9, 10.5; $p = 0.41$; p-heterogeneity across studies = 0.67) overall or in cohort-specific analyses. However, in cohort-specific analyses, there was some evidence of effect modification by the extent of religiosity or spirituality, religious congregation membership, and group prayer. Further research is needed to investigate prospective associations between depression and telomere length and resources of resilience including dimensions of religion and spirituality that may impact such dynamics in diverse racial/ethnic populations.

Keywords Telomere length · Depression · Religiosity · Spirituality

Depression, a leading public health issue in the USA and worldwide (GBD 2016; Park and Zarate 2019) is a severely disabling disease that has been linked to the onset of cardiovascular disease (Ford et al. 1998; Pan et al. 2011a, b), type 2 diabetes (Rotella and Mannucci 2013), cancer (Julin et al. 2015), and several other age-related conditions (Aarsland et al. 2011; Danese et al. 2009). Although the biological mechanisms underlying the association between

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depression and these chronic diseases are not fully understood, one plausible mechanism is the shortening of telomeres mediated by immune dysregulation or oxidative stress, eventually leading to accelerated biological aging (Wolkowitz et al. 2010).

Accelerated shortening of telomeres, the protective caps at the end of chromosomes (Blackburn 2001), has emerged as a powerful biomarker of cellular biological aging (Mather et al. 2011; Sanders and Newman 2013) and cumulative stress (Reichert and Stier 2017; Wolkowitz et al. 2010). Dozens of studies have demonstrated a cross-sectional relationship between depression and shorter telomere length (Lin et al. 2016; Schutte and Malouff 2015). Recent meta-analyses including up to 38 studies (16 cross-sectional, 17 case-control, and 5 prospective cohort studies) confirmed an association between depression and shorter telomere length (Cohen's $d = -0.205$, $p < 0.0001$ (Lin et al. 2016; Ridout et al. 2016; Schutte and Malouff 2015), although longitudinal study designs have produced far more mixed results.

To date, ten prospective studies have examined the relationship between depression and telomere attrition, with a follow-up period ranging from 2 to 12 years. Of the ten studies, four found a significant association between depression and shorter telomere length over time (Shalev et al. 2014; Vance et al. 2018; Verhoeven et al. 2018; Verhoeven et al. 2016), while six reported null results (Chang et al. 2018a, b; Hoen et al. 2011, 2013; Rius-Ottenheim et al. 2012; Verhoeven et al. 2019). These conflicting results could be due to methodological differences in depression assessment, study participant characteristics, use of different covariates, or duration of follow-up in the study populations. Moreover, there are several limitations to extant studies. Minority racial/ethnic communities, many of which suffer disproportionately from persistent and severe depression (Bailey et al. 2019; Gonzalez et al. 2010), have not been well represented in the prospective studies of depression and telomere length. Further, studies assessing potential mitigating influences are also lacking, such as potential sources of resilience (e.g., religiosity or spirituality (R/S)) that may attenuate telomere shortening. R/S plays an important role in many racial/ethnic communities across the USA and could be an important coping tool that improves resilience in adverse or stressful conditions (Koenig et al. 2012), thereby providing some protection to depressed individuals and mitigate the process of cellular aging. A previous study reported a buffering effect of religiosity against depression on poor physical health (Wink et al. 2005). Similarly, a prior study also observed a protective effect of religiosity on suicidal behaviors among depressed patients with a history of childhood abuse (Dervic et al. 2006).

To address these gaps in the literature, we assessed the relationship between depression and telomere length with consideration for a potential buffering effect of religion and spirituality. We did so among 2908 Black, South Asian, American Indian, and White participants in the Study on Stress, Spirituality, and Health. We hypothesized that depression would be associated with shorter telomere length, controlling for relevant confounders and that this association would be modified by measures of religiosity and spirituality (R/S).

Methods

The Study on Stress, Spirituality, and Health

The analyses presented are from a subset of participants in the Study on Stress, Spirituality, and Health (SSSH) under the auspices of the National Consortium on Psychosocial Stress, Spirituality, and Health. This Consortium, established in 2016, is designed to examine the

underlying mechanisms through which psychosocial stress contributes to chronic disease and the extent to which these associations are moderated or mediated by religious/spiritual practices or beliefs across diverse racial/ethnic communities. The Consortium includes a sample of participants from five US-based cohorts: Black Women's Health Study (BWHS) (Rosenberg et al. 1995), Mediators of Atherosclerosis in South Asians Living in America (MASALA) (Kanaya et al. 2014), Strong Heart Study (SHS), Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (Lavange et al. 2010), and Nurses' Health Study II (NHSII) (Setty et al. 2007), as well as two Brazilian prospective cohort studies (Baependi and Advento (Egan et al. 2016; Franco-de-Moraes et al. 2017) that completed the SSSH baseline Spirituality Survey and had a blood sample assayed for telomere length. Historical data on demographics, lifestyle, behavioral factors, and chronic disease endpoints for SSSH participants were provided by each cohort and merged with the SSSH baseline Spirituality Survey data to create a multi-cohort analytic file. Available biomarker and questionnaire data from each cohort were centrally collated and harmonized at the Harvard/MGH Center on Genomics, Vulnerable Populations, and Health Disparities at Massachusetts General Hospital. All studies obtained institutional approval for cohort maintenance, as well as participation in the SSSH. SSSH protocols were approved by the Partners Human Research Committee, the Institutional Review Board (IRB) of Partners HealthCare (Boston, MA).

Study Populations

This analysis includes 2908 participants (443 men and 2465 women) from four SSSH cohorts with data on depression and telomere length: BWHS, MASALA, NHSII, and SHS.

BWHS is a prospective cohort study of African American women across the USA. In 1995, 59,000 African American women aged 21–69 years were enrolled through self-administered questionnaires mailed to subscribers of *Essence* magazine, members of black women's professional organizations, as well as the friends and relatives of early respondents (Rosenberg et al. 1995). Information on several components including demographics, lifestyle factors, and medical history were collected at baseline and updated biennially (Rosenberg et al. 1995). This study includes 1000 women randomly selected from among 2463 BWHS participants who completed the SSSH R/S survey in 2016–2017 and provided a blood sample between 2013 and 2017 (Lu et al. 2019). Blood samples were collected at Quest Diagnostics Patient Service Centers and processed by Quest Diagnostic regional laboratories; and frozen aliquoted samples were shipped and stored at a temperature of − 80 °C at the Boston University Core Genetics Facility (Lu et al. 2019). Leukocyte telomere assays were successfully completed for 997 women. Among 997 women, we excluded 21 participants that failed to complete core questions in the R/S survey. A total of 976 BWHS participants were included in the current analysis.

MASALA is a community-based prospective cohort of 906 South Asian men and women, aged 40–84 years that were enrolled into the study between 2010 and 2013 from two clinical field centers—University of California, San Francisco (UCSF) and Northwestern University, Chicago (Kanaya et al. 2014). To be eligible, participants were required not to have any known cardiovascular disease and not to have undergone any heart or blood vessel procedures (Kanaya et al. 2014). At their in-person baseline examination, MASALA participants completed questionnaires on sociodemographic, lifestyle and behavioral factors, and provided a fasting blood sample. Of the 906 participants, 696 provided consent for DNA extraction. Blood samples were collected by certified phlebotomists or nurses at the two clinical field

centers; aliquoted samples were processed and stored at USCF for future use (Kanaya et al. 2013). Between 2015 and 2018, participants were invited back for a follow-up examination where the SSSH R/S survey was administered. Our sample population includes 574 MASALA participants for whom historic data, R/S survey, and DNA samples were all available. We excluded participants with failed telomere assay ($N = 3$), incomplete data on the main R/S questions in the R/S survey ($N = 98$), leaving a sample of 473 MASALA participants.

NHSII is a prospective cohort study that began in 1989 when 116,671 female registered nurses from 15 US States aged 25–42 years completed and returned mailed questionnaires (Setty et al. 2007). Participants receive follow-up questionnaires biennially to update lifestyle, health, and medical history, with an average response rate greater than 90% (Setty et al. 2007). In 2016, all eligible women (those who previously provided a blood sample and completed the most recent wave of data collection) were invited to complete the R/S survey; 4268 women returned the survey. Heparin samples were collected through mailed kits between 2010 and 2013 or for a subset of women in 2015; samples were returned to the lab on ice by overnight shipping where it was processed into plasma, white blood cells, and red blood cells and frozen in the vapor phase of liquid nitrogen freezers (Huang et al. 2016; Huang et al. 2019). Leukocyte telomere assays were completed for 1131 NHSII participants. We excluded participants whose telomere assay failed to run ($N = 1$), outlier ($N = 1$), missing data on depression ($N = 10$), two with missing information on the use of antidepressants($N = 2$), and participants with missing data on the main core questions in the R/S survey ($N = 133$). A total of 984 NHSII participants were included in the current analysis.

SHS began as a population-based, longitudinal cohort of 4549 American Indians from 13 communities in three geographical areas: Arizona, North and South Dakota, and Oklahoma (North et al. 2003). The Strong Heart Family Study (SHFS), from which SSSH participants are drawn, is a component of the SHS that began in 2001–2003 (Phase IV) and consists of 3776 participants (14–93 years old) from 94 extended families ascertained from sibships in the original Strong Heart Study (North et al. 2003; Storti et al. 2009). A follow-up clinical examination for SHFS participants was conducted in 2006–2009 (phase V). This present study includes participants in phase IV or phase V who were enrolled in the SSSH and completed the R/S survey and for whom DNA samples were successfully assayed for leukocyte telomere length ($N = 731$). We excluded 111 participants with missing data on depression, 26 with missing data on anti-depressant use, and 119 participants with missing data on core questions in the R/S survey, thus including 475 SHS participants in this analysis.

Measures

Depression

Data on depressive symptoms were collected via the 20-item Center for Epidemiologic Studies Depression Scale (CES-D)(Radloff 1977) in 2005 (BWHS), 2010–2013 (MASALA), or 2001–2003 (SHS) and via the five-item Mental Health Index (MHI-5) from the Short-Form Health Survey Questionnaire (SF-36) (Ware Jr. 2000) in 2001(NHSII). The CES-D measures the severity of depressive symptoms in community settings (Radloff 1977), with high reliability and validity in detecting the presence and the severity of depressive symptoms (Van Dam and Earleywine 2011). Respondents were asked to report on the frequency of specific feelings or behaviors during the past week, with the following response options: rarely or none (less than 1 day), some or little (1–2 days), moderate (3–4 days), or most of the time (5–7 days).

Total scores ranging from 0 to 60 and a cutoff point ≥ 16 has traditionally been used to indicate the presence of severe depressive symptoms (Wise et al. 2006). The MHI-5 has also been validated and found to have high sensitivity and specificity for detecting major depression (McHorney et al. 1994; Ware Jr. 2000). Using the MHI-5 in NHSII, respondents rate the frequency of particular feelings over the past 4 weeks to questions pertaining to their mental health, including depression and anxiety, with answers ranging from all, most, a good bit, some, a little, or none of the time. Participant scores range from 5 to 30, using a standard linear transformation they were standardized to include a range from 0 to 100 with high scores indicating better mental health (McHorney et al. 1994; Ware Jr. 2000). As in several previous studies (Chang et al. 2018a; Pan et al. 2011a), we used MHI-5 score ≤ 52 to indicate the presence of severe depressive symptoms.

Antidepressant use was determined via self-report and/or medication inventory. In BWHS, antidepressant medication use was ascertained in 2005 by the question, "Do you take any of the following medications or vitamins at least 3 days a week?" Patients who marked yes for "Antidepressants (Prozac, Zoloft, Elavil, etc.)" were classified as using antidepressant medications. The questionnaire also included the open-ended question, "Please list all other medications or supplements that you currently take at least 3 days a week," which was used to identify additional users of antidepressant medications. In MASALA, the use of antidepressant medication was ascertained (2010–2013) by the question, "Are you taking any prescription medications, over-the-counter medications, vitamins, herbs or supplements?" For participants that responded "yes" to this question, the medication was verified and recorded by the interviewer. In SHS, participants were asked to bring their current medications to their clinical examination (2001–2003). The name, strength, and the total number of doses prescribed per day, week, or month was recorded by the interviewer. In NHSII, antidepressant medication use was ascertained in 2001 by the question "Mark if used regularly in the past 2 years:" "Prozac," "Zoloft," "Paxil," "Celexa," and "other antidepressants" (e.g., Elavil, Tofranil, Pamelor).

In secondary analyses, we cross-classified participants according to various combinations of severe depressive symptoms and use of antidepressants: (1) severe depressive symptoms or antidepressant use, (2) severe depressive symptoms and antidepressant use, (3) severe depressive symptoms without antidepressant use, and (4) antidepressant use only.

Religiosity and Spirituality Dimensions

Data on measures of religiosity and spirituality (R/S) were obtained from the baseline SSSH Spirituality Survey, which collected data across the cohorts sometime between 2016 and 2019. For this study, we considered R/S measures that captured key aspects of this multidimensional construct hypothesized to moderate the depression-telomere length relationship. R/S measures included five validated and two de novo measures. The first came from the Brief Multidimensional Measure of Religion and Spirituality (Fetzer/National Institute on Aging Working Group 1999):self-described extent of religiosity or spirituality ["To what extent do you consider yourself a religious or spiritual person?" dichotomized as "very religious" = 1 and "moderately," "slightly," or "not at all" = 0]. The second and third measures came from the Duke Religion Index (Koenig and Büssing 2010): frequency of religious services attendance, [How often do you attend religious services?" dichotomized as frequently ("several times per week" or "once a week" = 1) and not frequently ("2–3 times per month," "about once a month," "rarely" or "never") = 0]; and frequency of private prayer, ["How often do you pray by yourself?"

dichotomized as frequently ("several times a day" or "once a day" = 1) and not frequently ("more than once a week," "once a week," "several times a month," "several times a year," or "never" = 0)]. Two items were de novo, created with the input of R/S experts and the help of participant focus groups: being part of a religious congregation or community ("yes" = 1); and frequency of group prayer ["How often do you pray in a group other than at a religious service?" dichotomized identically to the item on private prayer. The final two items came from the Religious Coping Scale (Pargament et al. 2000): positive religious coping consisted of seven items in response to a question stem about facing stressful situations (e.g., "I saw my situation as part of God's plan," "I tried to make sense of the situation with God," "I worked together with God to relieve my worries"); negative religious coping was measured with six items (e.g., "I wondered what I did for God to punish me," I questioned God's love or care for me," "I wondered whether God had abandoned me")]. Responses to each of the religious coping items ranged from 1 = "not at all" to 4 = "a great deal." Scores were summed and dichotomized based on the median score (above median = 1).

Social Support

We assessed social support as another resource for resilience using the Berkman-Symes Social Networks Index (Berkman and Syme 1979) or ENRICHD Social Support Index (Berkman et al. 2000; Mitchell et al. 2003). The Berkman-Symes (BS) Social Networks Index was used in BWHS (2010), SHS (2018), and NHSII (2013). It asked, "Can you count on anyone to provide you with emotional support (talking over problems or helping you make a difficult decision?") using a 5-point response scale ("none of the time" to "all of the time"). "Some of the time," "most of the time," and "all of the time" were categorized as having social support (= 1), while "a little of the time" and "none of the time" were categorized as having no social support (= 0). In addition to the above, those answering "Yes, monthly" or "Yes, weekly" or "Yes, daily" to the question ("Is there anyone special person you know that you feel very close to; someone you feel you can share confidences and feelings with?") asked of participants in NHSII (2013) was also classified as having social support. In MASALA, three questions from the ENRICHD Social Support Index assessed whether someone provides emotional support, shows love or affection, and can be trusted. Each question used a 5-point scale ("none of the time" = 1 to "all of the time" = 5). Responses were summed and those with scores ≥ 12 were categorized as having social support (Lagisetty et al. 2016).

Covariates

We considered covariates known to be associated with depression or telomere length (Bruin et al. 2018; Valdes et al. 2005), including demographics (age, gender, employment status, educational attainment, and employment status); lifestyle factors (smoking status, Alternative Healthy Eating Index with alcohol [AHEI], and physical activity); and other health-related factors (presence of hypertension, use of antidepressants). We used the most recent available data prior to or at the time of exposure: 2001, 2003, and 2005 (in BWHS); 2010–2013 (in MASALA); 2001–2003 (in SHS); and 2001 (in NHSII). The 2009 and 2011 NHSII questionnaires provided data on physical activity and AHEI in NHSII participants respectively. Body mass index (BMI) was computed using the person's weight in kilograms divided by the square of a person's height in meters (kg/m^2). Physical activity was measured as in MET-hour/week in BWHS, MASALA, and NHSII, but as average pedometer steps/week in SHS.

Telomere Length

All telomere assays were performed in the DeVivo Laboratory at Brigham and Women's Hospital (Boston, MA). Genomic DNA was isolated from peripheral blood leukocytes using the QIAmp 96-spin blood protocol (Qiagen, Chatsworth, CA). Relative leukocyte telomere length (RTL) was measured using the quantitative polymerase chain reaction (qPCR) by laboratory personnel blinded to participants' characteristics (Crown and Crisp 1966). The qPCR was run on the Applied Biosystems QuantStudio 6 Flex Real-Time PCR. Relative telomere length is reported as the exponentiated ratio of telomere repeats copy number to a single gene copy number (T: S), as described by (Cawthon 2002), and corrected in relation to a reference sample. Quality control (QC) analyses were conducted on two different sets of pooled DNAs extracted from the same blood samples. Each QC sample was plated into several locations within each plate and across multiple plates as study samples were assayed. The combined intra-assay and inter-assay coefficients of variation (CVs) for the telomere was 8.96% for BWHS, 7.00% for MASALA, 10.32% for NHSII, and 4.68% for SHS. These CVs are within the range of those in other high-quality telomere studies (Zhao et al. 2014).

Statistical Analysis

The natural logarithm of relative telomere length (RTL) was transformed to z scores to reduce potential batch effects across the four cohorts. We selected covariates to be included in our analysis using the forward selection method $p \leq 0.20$. Our initial model adjusted for age. Model 2 included age plus employment status (except for SHS where information was not available), income, and educational attainment (except for NHSII where information was not available). We also adjusted for gender in MASALA and SHS. Model 3 included the additional covariates of BMI, AHEI, and physical activity. Model 4 controlled for the presence of hypertension, and antidepressant use. We created a missing data indicator variable for each measured covariate with missing responses. Generalized linear models with robust standard errors were used to examine the association between depression and telomere length, adjusting for potential confounders by cohorts. In the SHS, generalized estimating equations (GEE) with a working independence correlation structure were used to account for clustering by family relatedness among participants. We also assessed possible effect modification by dimensions of R/S and social support using Wald tests of the cross-product terms. Analyses were conducted separately within each cohort and a summary effect estimate was calculated using a random-effects model (DerSimonian and Laird 1986). We used random-effects models because they account for any observed heterogeneity whether or not the heterogeneity is statistically significant. To assess between cohort heterogeneity, we calculated the Q statistic, a measure of the statistical significance of heterogeneity, and the I^2 index, a measure of the extent of heterogeneity (Higgins et al. 2003). P values were two-sided, with $p < 0.05$ considered to be statistically significant. All statistical analyses were carried out using SAS version 9.4.

Results

Table 1 presents descriptive characteristics of study participants according to the presence of severe depressive symptoms. The prevalence of severe depressive symptoms was considerably higher in BWHS (35%) and SHS (31%) relative to MASALA (10%) and NHSII (9%). Across all cohorts, participants with severe depressive symptoms were more likely to be current

Table 1 Characteristics of study participants according to the presence of severe depressive symptoms

Variable	BWHS ($N = 976$) depression		MASALA ($N = 473$) depression		NHSII ($N = 984$) depression		SHS ($N = 475$) depression	
	Yes	No	Yes	No	Yes	No	Yes	No
N (%)	341 (35)	638 (65)	48 (10)	425 (90)	84 (9)	900 (91.5)	147 (31)	328 (69)
Log-RTL (mean (SD))	− 0.27 (0.7)	− 0.27 (0.7)	− 0.99 (0.7)	− 0.99(0.8)	0.52 (0.7)	0.37 (0.7)	0.12 (1.0)	0.07 (0.9)
Age at blood draw, (mean (SD))	55.9 (7.6)	56.5 (7.4)	55.9 (9.3)	55.5 (9.2)	57.3 (3.8)	57.5 (4.5)	39.7 (13.2)	39.8 (12.6)
Female, *n* (%)	341 (100)	638 (100)	21 (43.8)	168 (39.8)	84 (100)	900 (100)	118 (80.3)	195 (59.5)
Married, *n* (%)	131(38.4)	317 (49.7)	39 (81.3)	398 (93.7)	63 (75.0)	736 (82.1)	39(54.9)	67(40.9)
≥ College grad, *n* (%)	216 (63.3)	456 (71.5)	37(77.1)	391(92.0)	NA	NA	9(6.2)	41 (12.5)
Employed, *n* (%)	261(76.8)	508 (79.9)	31 (66.0)	317(74.6)	74(89.2)	808(89.9)	NA	NA
Smoking status, *n* (%)								
Never	248 (72.7)	464 (72.7)	36 (75.0)	349 (82.1)	49 (58.3)	615 (68.3)	48 (32.9)	100 (30.5)
Former	60 (17.6)	134 (21.0)	8 (16.7)	63 (14.8)	22 (26.2)	245 (27.2)	31 (21.2)	88 (26.8)
Current	33 (9.7)	40 (6.3)	4 (8.3)	13(3.1)	13 (15.5)	40 (4.4)	67 (45.9)	140 (42.7)
Body Mass Index, kg/m^2, *n* (%)								
< 25	83 (24.4)	179 (28.2)	15(31.3)	168(39.6)	44 (55.0)	456 (53.5)	15 (10.3)	49 (14.9)
25–29.9	99 (29.1)	190 (30.0)	25 (52.1)	197 (46.5)	24 (30.0)	230 (27.0)	40 (27.4)	78 (23.8)
≥ 30	158 (46.5)	265 (41.8)	8 (16.7)	59 (13.9)	12 (15.0)	167 (19.6)	91 (62.3)	201 (61.3)
Physical activity, *n* (%)[a]								
Quintile 5	27 (15.7)	74(20.3)	8(16.7)	86 (20.2)	17 20.7)	177 (19.9)	18 (13.7)	68 (22.7)
AHEI, *n* (%)[2]								
Quintile 5	47 (14.9)	138 (22.7)	5 (10.6)	88 (21.0)	10 (11.9)	177 (19.7)	16 (13.9)	64 (22.6)
Hypertension, *n* (%)	141 (41.4)	249 (39.0)	23 (47.9)	171 (40.2)	14 (16.7)	162 (18.0)	31 (21.1)	59 (18.0)
Antidepressant use, *n* (%)	89 (26.1)	61 (9.6)	7 (14.6)	8 (1.9)	25 (29.8)	115 (12.8)	21 (14.3)	25 (7.6)
Extent of religiosity, *n* (%)								
Very	134 (39.3)	311 (49.0)	6 (12.5)	77 (18.1)	27 (32.1)	374 (41.6)	40 (27.2)	101 (30.8)
Not/slightly/ moderately	207 (60.7)	324 (51.0)	42 (87.5)	348 (81.9)	57 (67.9)	526 (58.4)	107 (72.8)	227 (69.2)
Religious congregation								
Yes	222 (65.1)	433 (68.2)	20 (41.7)	130 (30.6)	38 (45.2)	582 (64.6)	61 (41.5)	134 (40.9)
No	119 (57.2)	202 (31.8)	28 (58.3)	295 (69.4)	46 (54.8)	318 (35.3)	86 (58.5)	194 (59.2)
Service attendance, %								
≥ 1/week	146 (42.8)	283 (44.6)	12 (25.0)	90 (21.2)	26 (31.0)	406 (45.1)	36 (24.5)	53 (16.2)
Private prayer (self), %								
≥ 1/day	253 (74.2)	496 (78.1)	35 (72.9)	246 (57.9)	41 (48.8)	531 (59.0)	99 (67.4)	227 (69. 2)
Group prayer, %								
≥ 1/day	19 (5.6)	60 (9.5)	1 (2.1)	18 (4.2)	2 (2.4)	56 (6.2)	17 (11.6)	26 (7.9)
Positive religious coping mean (SD)	3.1 (0.8)	3.2 (0.7)	3.0 (0.7)	2.6 (0.9)	2.6 (1.0)	2.8 (0.9)	2.9 (0.8)	2.8 (0.9)
Negative religious coping mean (SD)	1.6 (0.6)	1.4 (0.4)	1.8 (0.7)	1.4 (0.6)	1.4 (0.6)	1.2 (0.4)	2.0 (0.8)	1.7 (0.7)

[a] *AHEI* Alternative Healthy Eating Index, *NA* not available

Value is MET hours per week in NHSII, BWHS, and MASALA, and steps per week in SHS

smokers. Also, participants with severe depressive symptoms were more likely to be obese and less likely to be physically active (except in NHSII). With regard to religiosity and spirituality, participants with severe depressive symptoms were more likely to describe themselves as not or slightly or moderately spiritual compared to those without severe depressive symptoms: BWHS (60.7% vs. 51.0%), MASALA (87.5% vs. 81.9%), NHSII (67.9% vs. 58.4%), and SHS (72.8% vs. 69.2%) respectively. Concerning participants belonging to a religious community or congregation, the results were mixed. In MASALA and SHS cohorts, individuals with severe depressive symptoms were more likely to belong to a religious community or congregation versus those without severe depressive symptoms (MASALA, 41.7% vs. 30.6% and SHS, 41.5% vs. 40.9%). In BWHS and NHSII, however, individuals with severe depressive symptoms were less likely to belong to a religious community or congregation. Participants with severe depressive symptoms were also more likely to use negative coping strategies across all cohorts: [BWHS 1.6 (0.6) vs. 1.4 (0.4), MASALA 1.8 (0.7) vs. 1.4 (0.6), NHSII 1.4 (0.6) vs. 1.2 (0.4), and SHS 2.0 (0.8) vs. 1.7 (0.7)].

Table 2 presents the multivariable-adjusted percent difference in the log-RTL z-scores. Overall, there were no significant differences in the log-RTL z-scores between participants with severe depressive symptoms versus those without in any single cohort or our pooled analyses: model 1 [3.2% (−3.9, 10.5) $p = 0.37$; p-heterogeneity = 0.53], model 2 [2.0% (−4.9, 9.4); $p = 0.63$; p-heterogeneity = 0.46], model 3 [1.0 (−5.8, 8.3); $p = 0.76$; p-heterogeneity = 0.67], and model 4 [3.0% (−3.9, 10.5); $p = 0.41$; p-heterogeneity = 0.67]. Additionally, our secondary analyses using alternative definitions of depression, either including antidepressant use or cross-classifying antidepressant use and depressive symptoms, resulted in similar null results (Supplemental Tables 1 and 2). However, we observed some heterogeneity between studies with the use of antidepressant medication that was not observed in our main analyses (Supplemental Table 2).

Table 3 shows results on severe depressive symptoms stratified by social support, the extent of religiosity, positive religious coping, and negative religious coping and their interactions in the SSSH cohorts and pooled analysis. We observed no statistically significant interactions with social support (p-INT = 0.32), extent of religiosity (p-INT = 0.54), religious congregation membership (p-INT = 0.54), religious service attendance (p-INT = 0.44), group prayer (p-INT = 0.97), private prayer (p-INT = 0.22), positive religious coping (p-INT = 0.37), and negative religious coping (p-INT = 0.12) in our pooled analysis, and there was heterogeneity between studies. However, in specific cohorts, when we stratified by R/S, we observed some significant associations. In MASALA, among participants who described themselves as very religious or spiritual, the difference in log-RTL z-scores between participants with severe depressive symptoms and those without severe depressive symptoms was 214.1 (49.1, 562.0), p-INT = 0.18. Among participants in SHS that belong to a religious congregation or membership, severe depressive symptoms were associated with shorter telomere length: −25.6, (−39.5, −8.5) p-INT = 0.29. Similarly, among participants in SHS that were involved in frequent group (public) prayer, severe depressive symptoms were associated with shorter telomere length: −56.8 (−76.0, −22.3) p-INT = 0.32. However, among NHSII participants that were involved in frequent group (public prayer), the difference in log-RTL z-scores between participants with severe depressive symptoms and those without severe depressive symptoms was 88.2 (9.6, 223.0) p-INT = 0.29.

Table 2 Depression and log-transformed relative leukocyte telomere length

Cohorts	Depression	*N*	Model 1		Model 2		Model 3		Model 4	
			% Difference (95% CI)	*P* value	% Difference (95% CI)	*P* value	% Difference (95% CI)	*P* value	% Difference (95% CI)	*P* value
BWHS	No	635	Ref		Ref		Ref		Ref	
	Yes	341	−0.6 (−9.2, 8.2)	0.89	0.0 (−8.7, 9.6)	0.99	−0.1 (−8.8, 9.5)	0.99	1.9 (−7.0, 11.6)	0.69
MASALA	No	425	Ref		Ref		Ref		Ref	
	Yes	48	2.4 (−15.0, 23.6)	0.80	0.8 (−16.8, 22.1)	0.94	−0.7 (−18.0, 20.2)	0.94	3.7 (−14.7, 26.0)	0.71
NHSII	No	900	Ref		Ref		Ref		Ref	
	Yes	84	13.5 (−2.5, 32.3)	0.10	12.9 (−3.2, 31.8)	0.12	9.5 (−6.0, 27.5)	0.64	10.7 (−5.2, 29.2)	0.20
SHS	No	328	Ref		Ref		Ref		Ref	
	Yes	147	4.8 (−12.4, 25.2)	0.61	−6.6 (−23.5, 14.0)	0.50	−5.2 (−22.3, 15.7)	0.60	−5.3 (−22.8, 16.1)	0.60
Pooled	No	2288	Ref		Ref		Ref		Ref	
	Yes	620	3.2 (−3.9, 10.5)	0.37	2.0 (−4.9, 9.4)	0.63	1.0 (−5.8, 8.3)	0.76	3.0 (−3.9, 10.5)	0.41
P-het			0.53		0.46		0.67		0.67	

BWHS: model 1: adjusted for age; model 2: model 1 plus employment status, income, and educational attainment; model 3: model 2 plus BMI, alternative healthy eating index with alcohol, and physical activity; model 4: model 3 plus the presence of hypertension and use of antidepressants

MASALA: model 1: adjusted for age; model 2: gender, employment status, income, and educational attainment; model 3: model 2 plus BMI, alternative health eating index, and physical activity; model 4: model 3 plus the presence of hypertension and use of antidepressants

NHSII: model 1 adjusted for age; model 2: model 1 plus employment status, and income; model 3: model 2 plus BMI, alternative health eating index, and physical activity; model 4: model 3 plus the presence of hypertension and use of antidepressants

SHS: model 1: adjusted for age; model 2: model 1 plus gender, income, and educational attainment; model 3: model 2 plus BMI, alternative healthy eating index, and physical activity; model 4: model 3 plus the presence of hypertension, and use of antidepressants

P-het: *p* value for heterogeneity between studies

Table 3 Depression and log-transformed relative telomere length stratified by social support, religion, and spiritual dimensions

		Emotional support					Extent of Religion/Spirituality	
		No		Yes			Not, Slightly or Moderately Religious or Spiritual	
Cohort	Depression	*N*	% Difference (95% CI)	N	% Difference (95% CI)	P-INT	*N*	% Difference (95% CI)
BWHS	No	37	Ref	596	Ref	0.85	324	Ref
	Yes	48	− 9.9 (− 34.9, 24.7)	292	1.5 (− 7.8, 11.7)		207	− 1.1 (− 12.4, 11.7)
MASALA	No	25	Ref	400	Ref	0.33	348	Ref
	Yes	21	− 8.9 (18.8, − 35.0)	27	11.2 (− 11.2, 39.2)		42	− 2.2 (− 21.3, 21.5)
NSHSII	No	87	Ref	813	Ref	0.20	526	Ref
	Yes	19	15.7 (− 15.1, 57.6)	65	13.0 (− 5.5, 35.1)		57	8.2 (− 9.9, 30.0)
SHS	No	40	Ref	288	Ref	0.46	227	Ref
	Yes	38	47.3 (− 18.0, 164.5)	109	− 11.6 (− 28.9, 9.9)		107	− 4.4 (− 23.2, 19.0)
Pooled	No	189	Ref	2097	Ref	0.32	1425	Ref
	Yes	126	3.0 (− 4.9, 23.4)	593	3.0 (− 5.8, 11.6)		413	0.0 (− 7.7, 9.4)
		Religious service attendance					Private Prayer	
		Not frequent		Frequent (≥ 1/week)			Not Frequent	Frequent (≥ 1/day)
Cohort	Depression	*N*	% Difference (95% CI)	*N*	% Difference (95% CI)	P-INT	*N*	% Difference (95% CI)	*N*
BWHS	No	352	Ref	283	Ref	0.93	139	Ref	496
	Yes	195	0.6 (− 11.2, 14.0)	146	4.7 (− 8.1, 19.3)		88	6.6 (− 9.5, 25.6)	253
MASALA	No	335	Ref	90	Ref	0.56	179	Ref	246
	Yes	36	− 1.1 (20.7, 23.3)	12	49.8 (− 7.3, 142.2)		13	8.5 (− 23.8, 54.5)	35
NSHSII	No	494	Ref	406	Ref	0.95	369	Ref	531
	Yes	58	13.3 (− 5.4, 35.6)	26	15.9 (− 15.7, 59.2)		43	13.0 (− 7.6, 38.2)	41
SHS	No	275	Ref	53	Ref	0.20	101	Ref	227
	Yes	111	− 11.3 (− 26.3, 6.7)	36	12.5 (− 27.8, 75.2)		48	7.5 (− 20.6, 45.4)	99
Pooled	No	1456	Ref	832	Ref	0.44	788	Ref	1500
	Yes	400	5.1 (− 3.0, 13.9)	220	9.4 (− 3.0, 22.1)		192	8.3 (− 3.0, 22.1)	428
		Positive religious coping							
		At or below the median				Above median			
Cohort		Depression	*N*	% Difference (95% CI)		*N*	% Difference (95% CI)		P-INT
BWHS		No	360	Ref		266	Ref		0.50
		Yes	191	2.1 (− 10.2, 16.2)		141	− 1.2 (− 13.5, 12.9)		
MASALA		No	197	Ref		172	Ref		0.33

Table 3 (continued)

	Emotional support				Extent of Religion/Spirituality	
	No		Yes		Not, Slightly or Moderately Religious or Spiritual	
	Yes	15	19.6 (−11.5, 61.5)	29	11.2 (−14.7, 45.1)	
NSHSII	No	420	Ref	360	Ref	0.55
	Yes	39	25.4 (−1.3, 59.2)	31	8.0 (−16.2, 39.3)	
SHS	No	177	Ref	125	Ref	0.49
	Yes	71	4.2 (−18.9, 33.7)	58	−16.1 (−37.2, 12.1)	
Pooled	No	1154	Ref	923	Ref	0.37
	Yes	316	8.3 (−2.0, 18.5)	259	0.0 (−9.5, 10.5)	

	Extent of Religion/Spirituality			Religious congregation membership				
	Very Religious or Spiritual			No		Yes		
Cohort	*N*	% Difference (95% CI)	P-INT	*N*	% Difference (95% CI)	*N*	% Difference (95% CI)	P-INT
BWHS	311	Ref	0.37	202	Ref	433	Ref	0.95
	134	7.5 (−7.0, 24.3)		119	2.8 (−12.8, 21.1)	222	3.1 (−7.4,14.9)	
MASALA	77	Ref	0.18	295	Ref	130	Ref	0.75
	6	214.1 (49.1, 562.0)		28	3.7 (−19.6, 33.8)	20	12.9 (−18.8, 56.8)	
NSHSII	374	Ref	0.89	318	Ref	582	Ref	0.54
	27	11.9 (−17.2, 51.1)		46	11.7 (−8.9, 37.0)	38	20.3 (−6.1, 54.0)	
SHS	101	Ref	0.84	194	Ref	134	Ref	0.29
	40	5.1 (−22.5, 42.6)		86	7.3 (−16.6, 37.9)	61	−25.6 (−39.5, −8.5)	
Pooled	863	Ref	0.54	1009	Ref	1279	Ref	0.54
	207	18.5 (−6.8, 50.7)		279	6.2 (−4.9, 17.4)	341	0.0 (−18.1, 20.9)	
	Private Prayer Frequent (≥1/day)			Group Prayer Not Frequent		Frequent (≥1/day)		
Cohort	% Difference (95% CI)		P-INT	*N*	% Difference (95% CI)	*N*	% Difference (95% CI)	P-INT
BWHS	Ref		0.10	575	Ref	60	Ref	0.55
	−1.1 (−11.1,10.1)			322	2.1 (−7.2, 12.2)	19	18.6 (−4.2, 46.7)	
MASALA	Ref		0.78	407	Ref	18	Ref	0.07
	5.7 (−17.6, 35.6)			47	6.5 (−12.6, 29.9)	1	Negligible	

Table 3 (continued)

	Extent of Religion/Spirituality		Religious congregation membership				
	Very Religious or Spiritual		No		Yes		
NSHSII	Ref	0.71	844	Ref	56	Ref	0.00
	8.5 (− 15.0, 38.6)		82	9.1 (− 6.9, 27.7)	2	88.2 (9.6, 223.0)	
SHS	Ref	0.68	302	Ref	26	Ref	0.32
	− 6.6 (− 24.5, 15.5)		130	− 3.8 (− 23.3, 20.7)	17	− 56.8, (− 76.0, − 22.3)	
Pooled	Ref	0.22	2128	Ref	160	Ref	0.97
	0.0 (− 8.6, 8.3)		581	3.0 (− 3.9, 11.6)	39	1.0 (− 48.3, 97.4)	
	Negative religious coping						
	At or below the median		Above median				
Cohort	*N*	% Difference (95% CI)	*N*	% Difference (95% CI)		P-INT	
BWHS	339	Ref	287	Ref		0.21	
	122	7.3 (− 7.0, 23.9)	210	− 6.9 (− 17.7, 5.4)			
MASALA	206	Ref	163	Ref		0.30	
	10	32.9 (− 8.8, 93.9)	34	− 7.8 (− 28.3, 1.7)			
NSHSII	451	Ref	329	Ref		0.75	
	34	26.3 (− 4.0, 66.1)	36	10.5 (− 10.9, 37.1)			
SHS	184	Ref	118	Ref		0.37	
	57	0.2 (− 19.1, 24.2)	72	− 14.5 (− 38.2, 18.2)			
Pooled	1180	Ref	897	Ref		0.12	
	223	9.4 (− 1.0, 22.1)	352	− 4.9 (− 13.1, 5.1)			

BWHS: adjusted for age, employment status, income, educational attainment, BMI, alternative healthy eating index with alcohol physical activity, the presence of hypertension, and use of antidepressants

MASALA: adjusted for age; gender, employment status, income, and educational attainment; BMI, alternative health eating index, and physical activity, presence of hypertension, and use of antidepressants

NHSII: adjusted for age, employment status, income, BMI, alternative health eating index, physical activity, the presence of hypertension, and use of antidepressants

SHS: adjusted for age, gender, income, and educational attainment, BMI, alternative healthy eating index, physical activity, the presence of hypertension, and use of antidepressants

Pooled estimates were assessed through a random effect meta-analysis

P-int: P-interaction

Discussion

Our racially and ethnically diverse study population did not observe an association between severe depressive symptoms and relative leukocyte telomere length in pooled analyses. However, we observed some significant differences in telomere length limited to specific cohorts when stratified by the extent of religiosity, group prayer, and religious congregation membership. In SHS, the presence of severe depressive symptoms was associated with shorter telomere length among those belonging to a religious community or engaging in group prayer. In MASALA and NHSII, severe depressive symptoms were associated with longer telomere length among the very religious/spiritual and those engaging in frequent prayer, respectively. Other aspects of R/S, as well as social support, did not appear to be important effect modifiers of the depression-RTL relationship.

Multiple studies have examined the cross-sectional relationship between depression and telomere length and found inverse associations, including a previous SHS study (Lin et al. 2016; Ridout et al. 2016; Schutte and Malouff 2015; Zhao et al. 2016). Our study did not observe this, despite using a common laboratory to conduct the assays and carefully harmonizing data on depressive symptoms. This lack of association in part may be due to the different time periods in our study between assessment of severe depressive symptoms and collection of blood samples for RTL measurement, although we did not observe study-specific associations for MASALA, which had more concurrent measures. This is consistent with the more mixed associations observed in studies that examined prospective changes in RTL after depression assessment with 2 to 11 years of follow-up (Chang et al. 2018a, b; Hoen et al. 2011; Hoen et al. 2013; Rius-Ottenheim et al. 2012; Shalev et al. 2014; Vance et al. 2018; Verhoeven et al. 2019; Verhoeven et al. 2018; Verhoeven et al. 2016). Most studies did not observe a relationship. One reason for differences across studies is that depressive symptoms can wax and wane over time—it is possible that associations may be restricted to those with chronic depression, which could vary across study populations. Further, the trigger for the depression (e.g., early life abuse, serious health condition, etc.) may be associated with RTL as opposed to depression per se, which could vary across populations. Also, it may be that shorter telomere length is associated with the onset of depression (Chang et al. 2018c), but not the other way around, which is supported by consistency in cross-sectional—but not in prospective—studies. Additional research evaluating these is warranted.

The conflicting findings could also be explained by differences in study populations and the method of depression assessment. Our study included healthy, middle-aged population-based study participants, while other prospective studies finding significant results have included relatively young participants (Shalev et al. 2014; Verhoeven et al. 2018). Also, we ascertained depression using the MHI-5 and CES-D scales, two widely used screening instruments for clinical depression (Radloff 1977; Ware Jr. 2000). To our knowledge, three prospective studies have used the MHI-5 or CES-D instruments to ascertain the presence of depression with null (Chang et al. 2018a, b) and marginally significant findings (Verhoeven et al. 2018). Of the four known prospective studies to have found an association between depression and telomere length, three observed significantly shorter telomere length after following participants with a diagnosis of major depression/major depressive disorder assessed by the *Diagnostic and Statistical Manual of Mental Disorders*, *Third Edition*, *Revised* (*DSM-III-R*) or *Fourth Edition* (*DSM-IV*) (Shalev et al. 2014; Vance et al. 2018; Verhoeven et al. 2016). Thus, it is possible that the relationship between depression and telomere length may be sensitive to the method used to define depression or depression severity. We were unable to delineate between chronic,

remitted, or recurrent major depressive disorder, which may explain our non-significant findings in the main results.

We found no evidence of effect modification of the depression-telomere length association by R/S and social support in our pooled analysis. However, in cohort-specific analyses, there was some evidence of effect modification by the extent of religiosity or spirituality, religious congregation membership, and group prayer. The observed significant differences when we stratified by R/S in cohort-specific analyses may have been due to chance since findings were not consistent across studies, and we did not observe an overall association between severe depressive symptoms and RTL in our study populations. This study is the first we are aware of to have considered several measures of religiosity and spirituality in the association between depression and telomere length. Future studies are needed to evaluate these interactions, particularly in populations for whom depression is associated with RTL. From a biological perspective, it has been hypothesized that R/S practices enhance optimal immune functioning and reduce cellular damage during stressful or adverse conditions (Hill et al. 2016; Koenig et al. 2012).

The strengths of this study include our diverse racial/ethnic study participants, adjustments for several confounders, and a relatively long follow-up period of community-dwelling participants in our prospective analyses. This study is also the first known study to investigate the dynamics between depression and telomere length by multiple dimensions of religiosity and spirituality. However, several limitations should also be noted. Although RTL assays were performed in the same laboratory for all participating cohorts, samples were run at different times, increasing the likelihood of batch effects. To deal with this, we computed z-scores of log-RTL in our cohort-specific and meta-analyses. While we utilized a prospective design in three cohorts, our findings from MASALA participants are based on cross-sectional data. Additionally, RTL was based on the one-time measurement and not repeated measures. Further, there are differences in cohort data collection, measurement, and time points of exposures and measurements. We also observed statistical heterogeneity across the cohorts, which we attempted to minimize through thoughtful harmonization. Finally, although selected participants were from racial/ethnic diverse populations across the USA, our findings may not be generalizable to all segments of those populations. For example, SHS participants were mainly from the Dakotas and do not represent all American Indians; South Asians in the MASALA study are recruited predominantly from the San Francisco and Chicago areas and represent a disproportionately higher SES group of South Asians.

In conclusion, we observed no association between depression and telomere length across four distinct racial/ethnic populations in the USA. Further research is needed to investigate the relationship between depression and especially in diverse/racial-ethnic populations, and the resources of resiliency including dimensions of religiosity and spirituality that may impact the dynamics between depression, telomere length, and risk of future disease.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

Ethics Approval All studies obtained institutional approval for cohort maintenance, as well as participation in the SSSH. SSSH protocols were approved by the Partners Human Research Committee, the Institutional Review Board (IRB) of Partners HealthCare (Boston, MA).

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