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Prospective association between major depressive disorder and leukocyte telomere length over two years

Mary C. Vance[a,b,*], Eric Bui[c,d], Susanne S. Hoeppner[c,d], Benjamin Kovachy[d], Jennifer Prescott[d], David Mischoulon[c,d], Zandra E. Walton[f,h], Melissa Dong[c], Mireya F. Nadal[c,d], John J. Worthington[c,d], Elizabeth A. Hoge[e], Paolo Cassano[c,d], Esther H. Orr[i], Maurizio Fava[c,d], Immaculata de Vivo[d], Kwok-Kin Wong[d,f,g], Naomi M. Simon[c,d,g]

[a] University of Michigan, United States
[b] VA Ann Arbor Healthcare System, United States
[c] Massachusetts General Hospital, United States
[d] Harvard School of Public Health, United States
[e] Georgetown University Medical Center, United States
[f] Dana Farber Cancer Institute, United States
[g] New York University Medical School, United States
[h] University of Pennsylvania, United States
[i] Brigham and Women's Hospital, United States

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ABSTRACT

Background: Reduced leukocyte telomere length (LTL) has been found to be associated with multiple common age-related diseases, including heart disease, diabetes, and cancer. A link has also been suggested between shortened LTL and major depressive disorder (MDD), suggesting that MDD may be a disease of accelerated aging. This prospective, longitudinal study examined the association between depression diagnosis at baseline and change in LTL over two years in a well-characterized sample of $N = 117$ adults with or without MDD at baseline, using rigorous entry criteria.

Methods: Participants aged 18–70 were assessed with validated instruments by trained, doctoral-level clinician raters at baseline and at two-year follow-up, and blood samples were obtained at both visits. LTL was assayed under identical methods using quantitative polymerase chain reaction (qPCR). The effect of an MDD diagnosis at baseline on change in LTL over two years was examined via hierarchical mixed models, which included potential confounders.

Results: Individuals with MDD at baseline had greater LTL shortening over two years than individuals without MDD ($p = 0.03$), even after controlling for differences in age, sex, and body mass index (BMI). In the sub-sample of individuals with MDD diagnoses at baseline, no significant associations between LTL change and symptom severity or duration were found.

Conclusion: A baseline diagnosis of MDD prospectively predicted LTL shortening over two years. Our results provide further support for MDD as a disease associated with accelerated aging in a well-characterized sample using validated, clinician-rated measures.

1. Introduction

Major depressive disorder (MDD) is associated with elevated morbidity and mortality from multiple age-related medical illnesses, including cardiovascular disease and cancer (Carney and Freedland, 2017; Cosci et al., 2015). This risk remains after controlling for potential health behavior confounders, such as smoking and exercise (Penninx et al., 1998). Investigations into biological mechanisms suggest that dysregulated stress and immune responses are present in individuals with depression (Chrousos, 1998; Pariante and Miller, 2001; Raison and Miller, 2003; Simon et al., 2006), that they may accelerate aging by causing chronic "wear and tear" in cells and tissues, and that

* Corresponding author at: University of Michigan Institute for Healthcare Policy and Innovation, National Clinician Scholars Program, 2800 Plymouth Road, Building 14, Suite G100, Ann Arbor, MI 48109-2800, United States.
E-mail address: marycv@med.umich.edu (M.C. Vance).

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they result in increased vulnerability to age-related medical disorders (Kop et al., 2010; Maes et al., 2011). Genetic predispositions to accelerated biological aging may also confer increased risk for depression (Michalek et al., 2017).

Emerging evidence supports telomere length as a marker of cellular aging. Telomeres are nucleoprotein complexes comprised of long, double-stranded TTAGGG repeats that cap the ends of chromosomal DNA. By preventing end-to-end recombination at chromosomal termini during cell division, telomeres protect DNA and thereby maintain chromosomal integrity (Blackburn, 2010). Telomeres shorten with repeated cell divisions, due to incomplete replication of the telomere ends and stress-related oxidative damage (Wolkowitz et al., 2011). Therefore, telomere shortening could reflect a stress response.

Leukocyte telomere length (LTL) has typically been measured for clinical studies, because peripheral blood is readily accessible (Price et al., 2013). LTL is an ideal marker of stress-related cellular aging, due to the sensitivity of telomeres to stress-related oxidative damage (Hovatta, 2015; Zhang et al., 2014). Multiple studies have assessed the relationship between MDD and LTL, but results from individual studies so far have been mixed (e.g., see Lindqvist et al., 2015; Schutte and Malouff, 2015 for reviews).

Four recent meta-analyses found significant associations between depression and shorter LTL. A meta-analysis by Schutte and Malouff (2015), pooling 25 cross-sectional and longitudinal studies ($N = 21{,}040$), found depression to be significantly associated with shorter telomere length ($r = -0.12$, 95% CI = −0.17 to −0.07, Cohen's d not reported). Lin et al.' meta-analysis (2016) of 16 case-control studies pooled $N = 7207$ participants and cross-sectionally compared telomere length between depressed individuals and healthy controls, revealing significantly shorter telomere length in the depressed group (Hedges' $g = -0.42$ corresponding to $r = -0.21$, 95% CI = −0.60 to −0.25). Ridout et al. (2016) pooled 38 cross-sectional, case-control, and cohort studies involving $N = 34{,}347$ subjects and found a significant association between depression and telomere length (Cohen's $d = -0.205$, 95% CI = −0.288 to −0.122). Finally, Darrow et al.'s meta-analysis (2016), which examined 27 studies utilizing various designs and pooled $N = 14{,}827$ participants, found that psychiatric disorders overall (including depressive disorders, PTSD, anxiety disorder, psychotic disorder, and bipolar disorders) were associated with significantly shorter LTL (Hedges' $g = -0.50$, 95% CI = −0.70 to −0.30). Furthermore, the subgroup effect size of depressive disorders was moderate (Hedges' $g = -0.55$, 95% CI = −0.92 to 0.18), although this result did not reach statistical significance.

Cross-sectional studies are limited by substantial variability in telomere length across individuals regardless of the presence of disease (Aviv et al., 2006; Takubo et al., 2002). Inter-individual variability reduces the power and reliability of cross-sectional studies, and it has been estimated that five times fewer subjects would be required to detect an association between depression and telomere length in a longitudinal study (Aviv et al., 2006).

To our knowledge, only six prospective longitudinal studies have assessed the relationship between MDD and LTL (Hoen et al., 2011, 2013 ; Rius-Ottenheim et al., 2012; Shalev et al., 2014; Verhoeven et al., 2016, 2017), yielding mixed results. These measured LTL using quantitative polymerase chain reaction (qPCR) and controlled for a range of potential confounds, including age, sex, antidepressant use, smoking, activity level, physical health, body mass index (BMI), adverse life events, and educational level. However, they were all secondary analyses of banked blood collected for other purposes, and as such they may not have treated samples under ideal clinical collection conditions. Additionally, some did not use doctoral-level trained interviewers to assess psychiatric diagnoses. For example, three studies (Rius-Ottenheim et al., 2012; Hoen et al., 2013; Verhoeven et al., 2017) used self-rated scales, and one study (Hoen et al., 2011) used a clinician-rated scale administered by research assistants.

Hoen et al. (2011) used data from the Heart and Soul study, assessing $N = 952$ participants at baseline and $n = 608$ at follow-up; they found MDD was associated with shorter LTL at baseline but not at 5-year follow-up. Hoen et al. (2013) used data from the Prevention of Renal and Vascular End-stage study and found that anxiety, but not depressive, disorders were associated with shorter LTL at follow-up in $N = 974$ participants. Shalev et al. (2014) found that persistence of "internalizing disorders" (MDD, generalized anxiety disorder, post-traumatic stress disorder) from ages 11–38 predicted shorter LTL at follow-up in a dose-dependent manner only among men. Rius-Ottenheim et al. (2012) found no association between LTL shortening over a 7-year period and depression symptom severity in elderly men from the Netherlands ($n = 203$) and Greece ($n = 123$). Verhoeven et al. (2016) found that, compared to controls, those with a current or remitted depressive or anxiety disorder had shorter LTL at both baseline and 6-year follow-up; however, neither baseline diagnosis nor symptom change were associated with the LTL shortening rate. Verhoeven et al. (2017) found that higher average scores of depression across a 10-year period were associated with shorter LTL, but within-subject increases in self-reported depression were not associated with LTL change. In summary, existing prospective studies did not consistently find an association between psychiatric disorders, including MDD or depressive symptoms, and telomere shortening, and those found varied in their persistence over time and population impacted. These mixed data indicate a need for additional longitudinal research.

Consideration of potential confounders such as age and sex (Aubert and Lansdorp, 2008; Gardner et al., 2014) as well as BMI (Müezzinler et al., 2014) is also important in studies of MDD and LTL. Exposure to traumatic events and early-life stress should also be assessed, as they are associated with both psychiatric disorders (Heim and Nemeroff, 2001) and telomere shortening (Price et al., 2013; Shalev et al., 2014). Of note, one study found that individuals with PTSD had shorter telomeres than controls, and childhood trauma exposure largely accounted for this finding (O'Donovan et al., 2011).

We used a prospective, longitudinal design to examine the association between a current MDD diagnosis at baseline in participants whose depression had an onset at least five years prior and relative LTL change over two years. We extensively characterized our sample at baseline and follow-up (see Simon et al., 2015 for baseline data), including for age; sex; race; ethnicity; educational level; living situation; BMI; smoking pack-years; exercise level; antidepressant use; trauma exposure during childhood and adulthood; depression symptom severity; general anxiety symptom severity; and perceived stress. Individuals with characteristics previously linked to shorter telomere length were excluded, such as severe obesity (Müezzinler et al., 2014) and severe ongoing medical illnesses (Kong et al., 2013). Psychiatric diagnosis was assessed by doctoral-level interviewers using the *Structured Clinical Interview for DSM-IV* (SCID; First et al., 2002). We hypothesized that MDD diagnosis at baseline would be independently predictive of greater LTL shortening over two years, even after taking into account a range of potential confounders.

2. Materials and methods

2.1. Participants

Adults aged 18–70 years with a primary diagnosis of MDD and healthy controls were recruited to the Center for Anxiety and Traumatic Stress Disorders at the Massachusetts General Hospital (MGH) through referral and advertisement. After initial screening by telephone, potentially eligible individuals were assessed in person by trained, experienced doctoral-level (MD or PhD) clinicians for psychiatric disorders using the SCID for *DSM-IV* (First et al., 2002). Participants meeting entry criteria completed interviewer-rated and self-report questionnaires, and also underwent phlebotomy, at both baseline and two-year follow-up. Participants provided written informed consent and were compensated $75 at baseline and $75 at follow-up for study