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Research paper

Depression and telomere length: A meta-analysis

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ABSTRACT

Background: Several recent studies have investigated the relationship between telomere length and depression with inconsistent results. This meta-analysis examined whether telomere length and depression are associated and explored factors that might affect this association.
Methods: Studies measuring telomere length in subjects with clinically significant unipolar depression were included. A comprehensive search strategy identified studies in PubMed, MEDLINE, PsycINFO, Global Health, The Cochrane Library, and Web of Science. A structured data abstraction form was used and studies were appraised for inclusion or exclusion using a priori conditions. Analyses were conducted using standardized mean differences in a continuous random effects model.
Results: Thirty-eight studies ($N=34,347$) met the inclusion criteria. The association between depression and telomere length was significant, with a Cohen's d effect size of -0.205 ($p<0.0001$, $I^2=42\%$). Depression severity significantly associated with telomere length ($p=0.03$). Trim and fill analysis indicated the presence of publication bias ($p=0.003$), but that the association remained highly significant after accounting for the bias. Subgroup analysis revealed depression assessment tools, telomere measurement techniques, source tissue and comorbid medical conditions significantly affected the relationship.
Limitations: Other potentially important sub-groups, including antidepressant use, have not been investigated in sufficient detail or number yet and thus were not addressed in this meta-analysis.
Conclusions: There is a negative association between depression and telomere length. Further studies are needed to clarify potential causality underlying this association and to elucidate the biology linking depression and this cellular marker of stress exposure and aging.

1. Introduction

Individuals with major depressive disorder (MDD) have excess morbidity (Young et al., 2014) and mortality (Lou et al., 2014; Young et al., 2014; Zivin et al., 2012) as compared to the general population (Lou et al., 2014). One hypothesis regarding the cause of this excess morbidity and mortality that has gained much attention involves telomere biology. Telomeres are nucleotide sequences consisting of tandem TTAGGG repeats ranging from a few to 15 kilobases in length that provide genomic stability and shorten with each cellular division (Blackburn, 2005). Telomere shortening is strongly associated with age in most somatic tissues (Aubert and Lansdorp, 2008) and is influenced by genetic and epigenetic regulation, as well as by cellular stress and inflammation (Ridout et al., 2015). Conceptualizing chronic disease as a prolonged stress exposure, several studies have reported an association between telomere length and various somatic diseases, such as heart disease (Haycock et al., 2014; Hoen et al., 2011) and diabetes (Zhao et al., 2013). It has been proposed that telomere shortening resulting from chronic stress exposure may be a mechanism of excess morbidity or mortality (Deelen et al., 2014) or a useful indicator of progression of a process of senescence that raises mortality rates by other mechanisms (Ridout et al., 2015).

Simon et al. (2006) examined the relationship between mood disorders and telomere length and found that telomeres were significantly shorter in patients with mood disorders overall ($n=44$) and also in the group of subjects with MDD ($n=15$). Since this initial study, there have been numerous efforts to replicate these findings, which have variously reported that depression has no effect or is associated with a reduction in telomere length (see Supplementary Table 1 for references). Several factors might influence these divergent findings, including differences in telomere measurement technique, depression assessment method, population of

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interest, co-existing somatic illness, gender, and age. Additionally, a majority of these studies have had small sample sizes, limiting the power to draw definitive conclusions. One meta-analysis has pointed to an association between depression and telomere length (Schutte and Malouff, 2015). However, on review of the literature 39% more subjects could be included in the present meta-analysis. Additionally, that meta-analysis did not examine how depression severity, duration, tissue source, smoking, or comorbid chronic medical conditions may moderate the association between depression and telomere length. In the present study, we aimed to expand the subjects included by doubling the databases searched and expanding the search terms to capture all relevant articles. Furthermore, we included studies examining telomere length from all tissue sources, including leukocytes, brain tissue, and saliva, and studies of subjects with comorbid medical factors. The objective of this meta-analysis was to clarify the relationship between depression and telomere length by means of a systematic examination of the literature, comparing subjects with MDD to those without, and to identify moderators of this association.

2. Methods and materials

2.1. Protocol and registration

A review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42015016812) and conceptualized in October 2013. This study was designed, executed, and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Liberati et al., 2009).

2.2. Study eligibility criteria

Human studies of unipolar depression meeting either clinical or rating scale thresholds for MDD and controls not meeting these thresholds were included. Prospective observational and retrospective studies were considered for inclusion. Only studies utilizing validated methods of measuring clinically significant depression and defined techniques to measure and analyze telomeres were included (these are further clarified in the moderator analysis sub-section of the Section 2); all included studies used appropriate tools and thresholds for measurement of MDD. Studies of bipolar depression were excluded. In the case of reports that contained data from non-independent overlapping data sets, the report with the larger number of subjects was included.

2.3. Information sources and search strategy

A comprehensive electronic search strategy in August 2015 identified studies indexed in PubMed, PsycINFO, Global Health, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), and Web of Science; no limitations on publication dates were set. The search was performed by two of the investigators with clinical and research experience in the topic of interest (K.K.R and S.J.R.) in consultation with a librarian trained in systematic reviews; both investigators reviewed titles, abstracts, and articles, and disagreements were settled by consensus. The search strategy included terms for MDD (depression, major depressive disorder, depressive episode, mood disorder, and depress*) and telomeres (telomeres, telomerase, and telo*). The search terms were adapted for use with other bibliographic databases in combination with database-specific filters limiting the search to studies published in the English language, where these are available (Supplemental Table 2 provides the full search strings). Additionally, reference lists of primary studies included in this review and the reference lists of relevant, previously published reviews were searched. Studies were appraised for inclusion or exclusion using the a priori criteria described above.

2.4. Data extraction

Data were extracted independently (K.K.R. and S.J.R.) using the predetermined structured form. The extractors were not blinded to the study results, authors, or institutions; inter-rater reliability was high ($>95\%$). Conflicts regarding data extraction were resolved by consensus with a third reviewer (L.H.P and A.R.T.). Data extraction variables included study design, participant clinical descriptions (age, percent subjects of male gender in the study, comorbid chronic medical condition), telomere measurement method and tissue source, telomere length for depressed and comparison subjects, depression measurement method, and measures of depression severity and treatment, in addition to bibliographic information. When possible, telomere length data that were adjusted at least for age and gender were abstracted from the studies rather than the unadjusted values. At the protocol level, study risk of bias was assessed using the guidelines suggested by Cochrane Reviews (Higgins, updated March 2011) and the Agency for Healthcare Research and Quality (Quality, 2015), through the incorporation into the study selection criteria of standard objective markers such as study design and population characteristics, as described above. The Newcastle–Ottawa Scale (NOS) for cross-sectional, case-control, or cohort designs (Stang, 2010) were used to assess risk of bias within studies. All studies were reviewed by one author (K.K.R); blinded replications of these assessments were completed with good reproducibility (94%; S.J.R.). When data were unavailable in the original manuscripts, authors of individual studies were contacted for additional information. Simon et al. (2006) reported telomere length for controls, subjects with mood disorders, and for subjects meeting criteria for MDD; the data regarding telomere length in MDD subjects ($n=15$) and controls ($n=44$) were used to calculate the effect size for this meta-analysis. Karabatsiakis et al. (2014) divided telomere length results from the same subjects into groups based on tissue or cell subpopulations; the results for individual groups were converted to standardized mean differences and then pooled to a common telomere length to allow comparison to other studies (Bornstein et al., 2009). A similar approach was taken to group white matter oligodendrocytes in the study by Szebeni et al. (2014). Liu et al. (2014) presented depressed and control group data for subjects with and without diabetes separately; these were treated as separate datasets in the meta-analysis, represented as Liu et al. (2014). A similar approach was taken for the paper by Rius-Ottenheim et al. (2012), which presented data for two different regional populations.

2.5. Statistical analysis

Data were converted into standardized mean differences (SMDs) using the effect size calculator (Wilson, 2010) and reported as Cohen's d (Cohen, 1988). The SMD is the mean difference in telomere length between the depressed and non-depressed groups divided by the pooled standard deviation of the distribution of the score used in the study. This results in a unitless effect size measure that is comparable to other studies using similar measures of outcome. By convention, effect sizes of 0.2, 0.4, and 0.8 are considered small, medium and large, respectively (Cohen, 1988). If only correlations (r) or odds ratios (OR) were reported, they were converted to Cohen's d using the formulas using the equation $d=2r/(1-r^2)^{1/2}$ or $d=\mathrm{OR}(3^{1/2}/\pi)$, respectively (Bornstein et al., 2009).