Shortened Telomere Length in Patients with Mood Disorders:

A Meta-Analytic Study

Pao-Yen Lin, MD, PhD (paoyenilin@gmail.com) 1,2,*
Yu-Chi Huang, MD, MS (ychuang01@gmail.com) 1
Chi-Fa Hung, MD, PhD (chifa.hung@gmail.com) 1

1Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and
Chang Gung University College of Medicine, Kaohsiung, Taiwan
2Center for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung
Memorial Hospital, Kaohsiung, Taiwan

Drs. Pao-Yen Lin and Yu-Chi Huang contributed equally as first authors of this study.

*Address correspondence to:
Dr. Pao-Yen Lin, MD, PhD
Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital
123, Dapi Road, Niaosong District, Kaohsiung City 833, Taiwan
Telephone number: 886-7-7317123 ext. 8751
Fax number: 886-7-7326817
E-mail address: py1029@adm.cgmh.org.tw

Running title: Telomere in depression and bipolar disorder
ABSTRACT

**Background:** Accelerated telomere shortening is associated with stress-related cell damage and aging. Patients with mood disorders, including depression and bipolar disorder, have been shown shortened life expectancy and associated with multiple age-related systemic diseases. Previous studies have examined leukocyte telomere length (LTL) in patients with mood disorders, but showed inconsistent results.

**Methods:** We conducted meta-analyses for cross-sectional comparison of LTL between depressive patients and control subjects (15 studies involving 6875 subjects), and between patients with bipolar disorder and control subjects (6 studies involving 907 subjects). The effect size of each individual study was synthesized by using a random effect model.

**Results:** Our analysis showed telomere length is significantly shortened in subjects with depression ($p=1\times10^{-6}$). Significant heterogeneity among studies examining LTL in subjects with depression was found, and it can possibly be explained by methods used in measuring telomere length ($p=9\times10^{-6}$). No evidence of publication bias or moderating effect of age and gender distribution on synthesized results was found. In addition, analysis of LTL in bipolar disorder, although preliminary, showed a trend of shortening in patients with the disorder ($p=0.135$).

**Conclusions:** Our results support that major mood disorders, especially depression, are associated with accelerated cell aging. Future studies are required to clarify whether the
association is mediated through environmental stress, and whether effective treatment can halt the cell aging.

Keywords: bipolar disorder; depression; meta-analysis; stress; telomere
**Introduction**

Telomeres, the complexes composed of both tandem repeated guanine-rich DNA and specified protein, cap the ends of eukaryotic chromosomes. They protect DNA from damage and related consequences of genome instability when cells undergo repetitive mitotic divisions [1, 2]. The rate of telomere shortening could be decreased by the cellular enzyme telomerase, an RNA-dependent DNA polymerase [2]. The function of telomerase is to maintain telomere length by synthesizing telomeric repeat sequences to the ends of chromosomal DNA during cell replication to maintain cells in healthy status [3, 4]. Among different lymphocytes in healthy individuals, telomerase activity was suggested to be positively associated with telomere length [5, 6]. Normal human somatic cells are reported to have 5 to 15 kilobase pairs (kbp) in telomere length, which shortens in 15-20 bp per year while cell divide in average [7, 8]. Cells will be susceptible to senescence and apoptosis when telomeres length becomes critically short, between 0 to 2.8 kbp [2, 9].

Telomere length is suggested to be a valuable biomarker of aging [8, 10]. Aside from normal aging, evidence from cross-sectional studies suggests that telomere length was not only related to individual’s age-related physical illnesses, such as cardiovascular disease (CVD) [11], cancer [12], Alzheimer disease [13], and mortality [14], but was also associated with major mood disorder, including major depressive disorder (MDD) [15] and bipolar disorder (BD) [16, 17].

MDD and BD have been recognized as serious public health problems causing detrimental impact and excess medical costs [18-20]. MDD has worldwide high point and lifetime prevalence of 4.4% and nearly 16.2% respectively [20, 21]. On the contrary, BD
manifested as the other mood polarity opposite to depression [22], and was involved
2-5% of general population [23, 24]. Higher health vulnerability among mood disorders
was suggested [25]. The patients with MDD or BD not only suffered from psychological
impact, but also endured excess risks of age-related physical diseases of CVD, stroke,
diabetes, metabolic syndrome, dementia, and related mortality [17, 26-29]. Among them,
CVD was responsible for more than one third of all deaths in patients with BD and the
risk of cardiac death was increased by 68% in those with depression [16, 30]. The
association among MDD, BD, and accelerated age-related physical and functional decline
supports the concept that premature telomere length shortening over time in mood
disorders.

In past one decade, many clinical investigations have shown shortened telomere
length in leukocytes in patients with mood disorders [15, 31-33]. It was estimated that
telomere length shortening may represent 5-13 years accelerated aging in subjects with
MDD or BD [31, 33, 34]. But some conflicting results were also found in depression [33,
35-37] and BD [38, 39]. The discrepancy in results among these studies may be related to
difference in sample composition, psychiatric diagnosis and methods in measuring
telomere length. In addition, individual studies with small sample size may have
insufficient statistical power to detect small but significant effects. In this study, we
conduct a meta-analysis to pool relevant results from all eligible studies to analyze
leukocyte telomere length (LTL) in patients with depression and BD, and would like to
examine the overall difference in LTL between patients and controls and possible
moderating effects to account for the difference.
Methods

Literature search

To identify eligible studies, two independent reviewers (P.-Y. Lin and Y.-C. Huang) searched for studies available by January 2015 in the electronic databases of PubMed at the National Library of Medicine, Scopus, and Google Scholar. The search was performed by using the search terms (telomere) AND (depression OR bipolar disorder OR manic), without special limitation in language. The references of relevant articles and review articles in this area were searched for citations not indexed in above database. The titles and abstracts of studies obtained by this search strategy were screened by the independent reviewers to determine if they were potentially eligible for inclusion in this meta-analysis, and to exclude studies that were apparently non-eligible, such as review articles, non-human studies, and studies not mentioning telomere. In case of disagreement in eligibility, we reached agreement through consensus.

Inclusion criteria of studies in the meta-analysis

The included manuscripts passing the initial screening were examined based on the inclusion criteria used in this meta-analysis, including studies that: (1) included patients with depression or BD (no matter bipolar I or II patients), (2) used samples from leukocyte DNA, (3) measured telomere length, (4) included case-control comparison between subjects with depression or BD and control subjects, and (5) dataset were not overlapping with other studies. When dataset from two studies were overlapping, we only included the study with larger sample size between them.
Meta-analytic methods

The first outcome was to compare LTL between patients with depression and controls. The second outcome was to compare LTL between BD patients and controls. The diagnoses of depression and BD were based on criteria provided in individual studies.

For each identified study, the effect sizes (ESs) expressing the difference in telomere length between patients and controls were described as standardized mean differences (SMDs) based on Hedges’s adjusted $g$, where values greater than 0 indicated that the telomere was longer in patients. The means and standard deviations of telomere length of both patients and controls were used to derive the ES from each included study. When these data could not be available from these articles, we contacted the authors to acquire the data or we derived the ES from other statistical parameters, such as $t$ value or $p$ value. The ESs of individual studies were synthesized by the random effects model [40]. The significance of the pooled ES was determined by the $z$-test. Sensitivity analyses were performed in the analysis that resulted in significant difference to determine if any individual study was responsible for the significant result. Each study was individually removed and the significance was re-tested.

Heterogeneity was examined to determine whether the group of ESs came from a homogeneous source and assessed by Q statistics, their related $p$-value, and the $I^2$ statistic, which is the percentage of the variability in the estimate of effects that is due to heterogeneity rather than random error. Larger value of $I^2$ statistic indicates higher heterogeneity. A rejection of homogeneity suggests that there may be systemic differences existing among the included studies. In addition, we used Egger’s regression
to statistically test for evidence of the publication bias [41]. To examine whether mean age, gender distribution (percentage of females), or duration of illness of included subjects moderates the ES, we performed meta-regression by using unrestricted maximum likelihood method. In addition, we examined the pooled effect in separate groups of studies based on the methods used for measuring telomere length (southern blot, polymerase chain reaction (PCR), or fluorescent in situ hybridization (FISH)).

Statistics in meta-analyses were performed by applying Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA). Two-sided $p$ values $< 0.05$ were considered statistically significant. We reported the methods and the results of meta-analyses by following the MOOSE checklist [42].

Results

Our literature search resulted in 95 results for initial consideration in the meta-analysis. By examining their titles and abstracts, 39 studies were excluded because they were review articles (n=14), non-human studies (n=14), not measuring telomere length (n=8), or comments on other studies or case reports (n=3). When we examined the text of remaining 56 studies by inclusion criteria, 24 of them were excluded because they did not include patients with depression or BD, 4 studies were excluded because they measured brain telomere length [43-46], 5 studies were excluded because they did not provide case-control comparison of telomere length [47-51], and 3 studies were excluded because they overlapped with other studies [33, 52, 53]. Finally, 20 studies were included in the current meta-analysis [15, 25, 31, 32, 34, 36-39, 54-64], and the selection process was shown in Figure 1. The characteristics of the included studies were described in
First, we compared the LTL between patients with depression (n=3248) and controls (n=3627), extracted from 15 studies [15, 31, 32, 36, 37, 54-63]. In these studies, the study by Garcia-Rizo et al. [56] measured telomere DNA content, instead of telomere length. Telomere content was directly proportional to telomere length measured by Southern blot, so this study was included. In addition, the study by Karabatsiakis et al. [63] contained patients with depression history, with or without current depressive symptoms, so it was regarded to provide two individual comparisons. Our analysis showed a significant decrease in telomere length in the patient group (ES=-0.47, 95% CI=-0.65 to -0.28, \( p=1*10^{-6} \)) (Figure 2A). Sensitivity analysis showed that the significant difference in telomere length was not influenced by any single study. Through the funnel plot, the distribution of included studies seems to bias toward larger ES (Figure 2B), and a trend of publication bias was found by using Egger’s analysis (t=1.97, df=14, \( p=0.07 \)).

In addition, significant heterogeneity existed among the studies included in this analysis (Q=106.26, df = 15, \( I^2 = 85.88\% \), \( p<1*10^{-8} \)). Next, we examined whether the heterogeneity resulted from age, gender distribution, duration of illness, or the methods used in measuring telomere length. In our meta-regression analysis, the ESs from all included studies were not significantly moderated by mean age (point estimate of slope=0.001, \( p=0.93 \)), percentage of female subjects (point estimate of slope=-0.34, \( p=0.54 \)), or duration of illness (point estimate of slope=0.01, \( p=0.82 \)). When we separated the studies by methods measuring telomere length, the studies [15, 31, 56, 58] using southern blot (ES=-0.79, 95% CI=-1.06 to -0.53, \( p<1*10^{-9} \)), using PCR [32, 36, 37, 54, 55, 57, 59-62] (ES=-0.23, 95% CI=-0.37 to -0.09, \( p=0.001 \)), and using FISH
[63](ES=-1.17, 95% CI=-1.66 to -0.68, \(p=3\times10^{-6}\)) all showed significant decrease in LTL in subjects with depression (Figure 3A). But there was a significant difference in the ESs from studies using the three different methods (Q=23.34, df =2, \(p=9\times10^{-6}\)).

Considering that telomere length can be influenced by various medical and psychiatric disorders [65-67], we also performed the analysis comparing the telomere length between patients with purely MDD (n=2710) and controls (n=1645) from 9 studies [15, 31, 32, 37, 54, 56, 58, 60, 62]. The analysis also showed a significantly decrease in telomere length in MDD patients (ES=-0.39, 95% CI=-0.65 to -0.13, \(p=0.003\)) (Figure 3B). However, significant heterogeneity still existed among the studies (Q=63.33, df = 8, \(I^2=87.37\%, \ p<1\times10^{-6}\)). Sensitivity analysis showed that the significant difference in the telomere length was not influenced by any single study. Meta-regression analysis showed the ESs from all included studies were significantly moderated by percentage of female subjects (point estimate of slope=1.80, \(p=0.03\)), but not by mean age (point estimate of slope=0.01, \(p=0.38\)). In addition, we detected no publication bias in the analysis of telomere length in MDD (t=0.64, df=7, \(p=0.54\)).

Next, we compared LTL between patients with BD (n=474) and controls (n=433), extracted from 6 studies [25, 31, 34, 38, 39, 64]. Our analysis showed a trend of shortening in LTL in BD patients, although not significant (ES=-0.30, 95% CI=-0.70 to 0.09, \(p=0.14\)) (Figure 4A), and significant heterogeneity among studies was found (Q=38.00, df=5, \(I^2=86.84\%, \ p<1\times10^{-6}\)). Sensitivity analysis showed that removal of the study by Martinsson et al. (2013)[38] would result in a finding of significant decrease of LTL in patients with BD. In addition, we detected a trend of publication bias in this analysis (t=2.50, df=4, \(p=0.07\)) (Figure 4B), where there might be a bias toward the
studies with stronger effect and larger within-study variance.

**Discussion**

The goal of the present study was to investigate the relationship of LTL shortening, the reliable marker of cellular aging (8, 65), among patients with mood disorders in comparison to healthy control groups. The major finding of our study was to confirm that the patients with depression were significantly associated with LTL shortening which reflected accelerated cellular aging. This result also supports the conclusion of one recent meta-analysis study [68]. On the contrary, no statistical significance of LTL shortening was found in BD patients in our study. However, while removing one study which specifically recruited BD patients who received lithium treatment [38], the significant LTL shortening in BD patients was also found.

Stress itself is implied to promote adaptation to achieve allostasis [69]. However, psychological stress is an important risk factor for premature aging, earlier onset of aging-related illnesses and mood disorder [70, 71]. In light of a major role in physiopathological mechanisms, higher degree or chronic psychological stress is proposed to have destructive impact on regulative mediators in adaptive systems to increase biochemical oxidative stress and inflammation level in cellular level [67]. While telomere maintenance system is disturbed, decompensated telomerase-mediated telomere elongation mechanism resulted in telomere length shortening and accelerating aging [10, 67, 70].

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has been shown to play as a valuable mediator of regulating biological response to stress and the vulnerability to relapse in the underlying pathology of mood disorder [72-74]. Inadequate
glucocorticoid-mediated regulation and neuroendocrine dys-regulation of relevant stress,
such as inflammation and enhanced activation of immune system or sympathetic nervous
system, were observed in mood disorders [73]. Although individuals may be temporarily
adaptive in activating mediators while responding to chronic stress, they tend to be
susceptible for long-term biological damages [72]. The phenomenon of higher baseline
and peak corticotrophin (ACTH) concentrations in BD patients even during remission
episode and elevated cortisol level in MDD patients supports the systemic alternation to
chronic exposure to stress [69, 74].

Higher perceived psychological stress and chronic stress are not only associated
with accelerating aging of telomere length shortening, but also responsible for the
psychopathology of mood disorder [71, 75]. Several integrative review articles were
published to discuss relationship between psychological stress and depression and
telomere length [67, 76-80]. Accelerated telomere length shortening may be induced by
increasing oxidative stress that damaged telomeric DNA and related cell turnover in
individuals with mood disorder [81, 82]. The complex mechanisms of HPA axis,
brain-derived neurotrophic factor, oxidative or inflammatory stress, excitotoxicity,
neurosteroids, LTL and telomerase are suggested to link MDD to biochemical mediators
related to cell dysfunction or damage [76]. With the above pathogenic processes, a
depression model was highlighted to suggest that depression as not only a mental illness
but a whole body disease [76], which also reflects the elevated allostatic load and wear
and tear on the body and brain [69]. However, the exhaustive process which links TL
shortening in peripherally cellular level to the perturbation of neurotransmitters or
structure change in the brain among individuals with mood disorder is still unclear [60,
Bipolar I disorder (BD-I) and Bipolar II disorder (BD-II) were two main domains of BD with lifetime prevalence rate 1.0% and 1.1%, respectively [23]. The load of short telomeres and LTL shortening were suggested to be strongly associated with a high number of depressive episodes rather than duration of illness in BD patients [34, 38]. The depressive episode-related stress model for accelerated telomere shortening and aging was hence hypothesized to explain the association of systemic stress or toxicity and cellular aging in mood disorder [76]. One composite measure conducted three peripheral dimensions assessment, including neurotrophins, oxidative stress markers and inflammatory markers, to design the systemic toxicity index in order to separate acute mood state from control group. The result revealed that systemic toxicity or stress was elevated in depressive episodes, but not during euthymic episode in BD [34, 83]. As a result, accumulative numbers of mood episodes in BD had endangered tendency toward accelerated aging relate to loss of life expectancy following with increasing systemic toxicity in patients with BD [83]. However, lack of detailed information of different mood status in BD patients in ordinary researches limits analysis in the association of mood state and LTL shortening. Further study should investigate the different impact on LTL shortening between acute depressive-episode stress and chronically accumulated stress in BD groups.

Previous studies examining the telomere length shorting in individuals with comorbidity of MDD and physical diseases show inconsistent findings [55, 57]. These findings may indicate that physical or age-related diseases may further complicate and confound the study results. In our study, significant LTL shortening was analyzed while
comparing the MDD patients with or without physical illness to the healthy controls. However, methods for assessing depression, severity of depression, follow-up duration, healthy controls selection and varied sample size may all contribute to heterogeneity among selected studies in this analysis.

Furthermore, significant difference in the ESs by using different methods for determining telomere length is analyzed. The reliable method to detect telomeric DNA and measure telomere length was critical to provide accurate information for telomere biology [84]. Although various methods used in assessing telomere length, namely quantitative fluorescence in situ hybridization (qFISH), Southern blot and qPCR, showed significant telomere shortening in subjects with depression, significantly larger effect were observed in studies using qFISH and Southern blot than those using qPCR. The qFISH arrays uses directly fluorescently labeled (CCCTAA)$_3$ peptide nucleic acid (PNA) probes to be highly affinity to DNA oligonucleotide probes [84]. qFISH image analysis software was then used to capture and measure the fluorescent intensity signal which correlates to telomere length, and thus high resolution method to detect telomere length at specific chromosome ends could be available [84, 85]. The Southern blot measures both the canonical (strictly TTAGGG repeats) and noncanonical components of telomeres to determine the length of terminal restriction fragment (TRF) to present telomere length [86, 87]. The method of quantitative PCR (qPCR)-based method only measures the canonical component of telomeres to quantify telomere signals length (T) in a DNA sample, relative to a single copy gene signal (S) and express in T/S ratios for average telomere length [88, 89]. Both Southern blot and the qPCR showed good reliability in measuring telomere length [87], but the inter-assay coefficient of variation
(CV), presented for the measurement error, was reported to be lower in the method of Southern blots [87, 88]. Our meta-analysis showed a larger effect from the studies using Southern blot, supporting that qFISH arrays and Southern blot, although are more laborious and time-consuming technically [90], had higher measurement reliability than qPCR.

Our meta-analysis has some limitations. First, the finding of this meta-analysis suggested the cross-sectional correlation between LTL shortening and mood disorder patients, but cannot explain possible causal relation. Further prospective researches are warranted to investigate underlying LTL-regulating mechanism and the possible stress-mediating effect which predisposes depressed or BD patients on LTL shortening. Second, this meta-analysis selected studies which investigated LTL in relation to categorical diagnoses rather than dimensional diagnoses. Therefore, the results may not be applied to the generalized population. Third, several biological or healthy-related behavioral and psychological factors which associated with LTL shortening were not well controlled, including ethnicity [15, 88], heritability [91], smoking [92], alcohol [93], obesity [94], exercise [95] or childhood maltreatment [96] in original studies.

**Conclusions**

Our study showed accelerated telomere length shortening was found in patients with mood disorders, especially depression, thus suggesting an important role of biomarker of LTL in these disorders. With these results, future studies are required to clarify whether the association is mediated through psychological stress or cytotoxic processes, and whether effective treatments can halt accelerated cell aging.
List of abbreviations

BD, bipolar disorder;
CVD, cardiovascular disease;
ES, effect size;
FISH, fluorescent in situ hybridization;
HPA, Hypothalamic-pituitary-adrenal;
LTL, leukocyte telomere length;
MDD, major depressive disorder;
PCR, polymerase chain reaction;
qFISH, quantitative fluorescence in situ hybridization;
qPCR, quantitative polymerase chain reaction;
SMD, standardized mean difference.

Completing interests

The authors declare no biomedical financial interests or potential conflicts of interest.

Authors’ contributions

Dr. Lin and Dr. Huang performed literature search and organization, and completed the first draft. Dr. Lin conducted statistical analysis and prepared figures. Dr. Hung helped with data interpretation and critical revision of the manuscript. Dr. Lin and Dr. Huang contributed equally as the first authors to this study.

Acknowledgements
Authors thank Kaohsiung Chang Gung Memorial Hospital (CMRPG8D1191) for supporting our study. The funding agent had no role in the study design, in the collection, analysis and interpretation of data, in the report writing, and in the decision to submit the article for publication.

References


53. Puterman E, Epel ES, Lin J, Blackburn EH, Gross JJ, Whooley MA, Cohen BE: Multisystem resiliency moderates the major depression-telomere length association: findings from the Heart and Soul Study. *Brain Behav Immun* 2013,


83. Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, Pasquali MA, Quevedo J, Gama CS, Post R: A systemic toxicity index developed to assess peripheral changes in mood episodes. *Mol Psychiatry* 2010,


Figure legends

Figure 1. Flowchart describing the process of study selection. *The study by Simon et al. (2006) provided both depression vs. control and bipolar vs. control comparison.

Figure 2. (A) Forest plot showing effective sizes (Hedges’s $g$) and 95% confident intervals (CIs) from individual studies and pooled results comparing telomere length between subjects with depression and controls. (B) Funnel plot examining publication bias in studies comparing telomere length between subjects with depression and controls.

Figure 3. (A) Forest plot showing effective sizes (Hedges’s $g$) and 95% CIs from individual studies and pooled results of studies using different methods (polymerase chain reaction (PCR) vs. southern blot vs. fluorescent in situ hybridization (FISH)) measuring telomere length. (B) Forest plots showing effective sizes (Hedges’s $g$) and 95% confident intervals (CIs) from individual studies and pooled results comparing telomere length between subjects with major depressive disorder (MDD) and controls.

Figure 4. (A) Forest plot showing effective sizes (Hedges’s $g$) and 95% confident intervals (CIs) from individual studies and pooled results comparing telomere length between subjects with bipolar disorder and controls. (B) Funnel plot examining publication bias in studies comparing telomere length between subjects with bipolar disorder and controls.
Table 1. Summary of characteristics of included studies in current meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Patients, N</th>
<th>Controls, N</th>
<th>Diagnosis of psychiatric disorders</th>
<th>Mean age, years</th>
<th>Proportion of females</th>
<th>Sampling source</th>
<th>Methods used in measuring telomere length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon et al. 2006</td>
<td>USA</td>
<td>15 MDD subjects</td>
<td>44 healthy controls</td>
<td>MDD (DSM-IV)</td>
<td>MDD, 50.3</td>
<td>MDD, 53.3%</td>
<td>Leukocytes</td>
<td>Southern blot</td>
</tr>
<tr>
<td>Lung et al. 2007</td>
<td>Taiwan</td>
<td>253 MDD subjects</td>
<td>411 community controls</td>
<td>MDD (DSM-III-R)</td>
<td>MDD, 44.5</td>
<td>MDD, 64.0%</td>
<td>Peripheral blood</td>
<td>Southern blot</td>
</tr>
<tr>
<td>Hartmann et al. 2010</td>
<td>Germany</td>
<td>54 MDD subjects</td>
<td>20 healthy controls</td>
<td>MDD (DSM-IV)</td>
<td>MDD, 49.1</td>
<td>MDD, 61.1%</td>
<td>Leukocytes</td>
<td>Southern blot</td>
</tr>
<tr>
<td>Hoen et al. 2011</td>
<td>USA</td>
<td>206 CHD subjects with current depression</td>
<td>746 CHD subjects without current depression</td>
<td>MDD (DSM-IV)</td>
<td>MDD, 61.7</td>
<td>MDD, 30.6%</td>
<td>Leukocytes</td>
<td>PCR</td>
</tr>
<tr>
<td>Teyssier et al. 2012</td>
<td>France</td>
<td>17 MDD subjects</td>
<td>16 healthy controls</td>
<td>MDD (DSM-IV-TR and MINI)</td>
<td>MDD, 39.5</td>
<td>MDD, 100%</td>
<td>Leukocytes</td>
<td>PCR</td>
</tr>
<tr>
<td>Wikgren et al. 2012</td>
<td>Sweden</td>
<td>91 MDD subjects</td>
<td>451 community controls</td>
<td>MDD (DSM-IV)</td>
<td>MDD, 60.4</td>
<td>MDD, 60.4%</td>
<td>Leukocytes</td>
<td>PCR</td>
</tr>
<tr>
<td>Garcia-Rizo et al. 2013</td>
<td>Spain</td>
<td>9 MDD subjects</td>
<td>48 healthy controls</td>
<td>MDD (DSM)</td>
<td>MDD, 30.7</td>
<td>MDD, 40.0%</td>
<td>Leukocytes</td>
<td>Southern blot*</td>
</tr>
<tr>
<td>Georgin-Lavialle et al. 2014</td>
<td>France</td>
<td>8 subjects with mastocytosis have moderate-severe depression</td>
<td>7 subjects with mastocytosis have mild depression</td>
<td>BDI-II ≥ 19 indicating moderate-severe depression</td>
<td>NA</td>
<td>NA</td>
<td>PBMCs</td>
<td>PCR</td>
</tr>
<tr>
<td>Karabatsiakis et Germany</td>
<td>Patients with lifetime</td>
<td>50 healthy controls</td>
<td>Unipolar disorder</td>
<td>With current</td>
<td>With current</td>
<td>CD4+, CD8+, FISH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Sample Description</td>
<td>Materials</td>
<td>Controls</td>
<td>Results</td>
<td>Other Assays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
<td>--------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-----------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al. 2014</td>
<td>China</td>
<td>17 T2D patients with depression; 6 non-T2D subjects with depression</td>
<td>54 T2D patients without depression; 46 non-T2D subjects without depression</td>
<td></td>
<td>Depression, 54.8 Controls, 53.2</td>
<td></td>
<td>Leukocytes PCR</td>
<td></td>
</tr>
<tr>
<td>Verhoeven et al. 2014</td>
<td>Netherlands</td>
<td>802 remitted MDD; 1095 current MDD</td>
<td>510 controls</td>
<td>MDD (DSM-IV) Remitted MDD, 43.5 Current MDD, 40.7 Controls, 40.5</td>
<td>Depression, 70.6 Controls, 70.1</td>
<td></td>
<td>Leukocytes PCR</td>
<td></td>
</tr>
<tr>
<td>Schaakxs et al. 2015</td>
<td>Netherlands</td>
<td>355 subjects with current late life depression</td>
<td>128 never-depressed controls</td>
<td>MDD or dysthymia (DSM-IV) Depression, 70.6 Controls, 70.1</td>
<td>Depression, 66.2% Controls, 61.7%</td>
<td></td>
<td>Leukocytes PCR</td>
<td></td>
</tr>
<tr>
<td>Needham et al. 2015</td>
<td>USA</td>
<td>198 subjects with MDD or depressed affect only</td>
<td>966 subjects without depressive symptoms</td>
<td>MDD or depressed affect only (CIDI based on DSM-IV) Depression, 30.3 Controls, 29.2</td>
<td>Depression, 58.6% Controls, 56.0%</td>
<td>Peripheral blood PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrka et al. (in press)</td>
<td>USA</td>
<td>59 subjects with lifetime depressive disorder (including 48 subjects with lifetime MDD)</td>
<td>113 subjects without psychiatric disorders or childhood adversity</td>
<td>MDD or depressive disorder (DSM-IV) NA NA</td>
<td>NA</td>
<td>Leukocytes PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolkowitz et al. 2015</td>
<td>USA</td>
<td>19 MDD subjects</td>
<td>17 healthy controls</td>
<td>MDD (DSM-IV-TR) MDD, 37.5 Controls, 37.9</td>
<td>MDD, 63% Controls, 59%</td>
<td></td>
<td>Leukocytes PCR</td>
<td></td>
</tr>
<tr>
<td><strong>Bipolar disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simon et al. 2006</td>
<td>USA</td>
<td>29 BD subjects (no specified mood status)</td>
<td>44 healthy controls</td>
<td>BD (DSM-IV) BD, 51.6 Controls, 50.5</td>
<td>BD, 44.8% Controls, 43.2%</td>
<td>Leukocytes Southern blot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvsashagen et al. 2011</td>
<td>Norway</td>
<td>28 BD-II subjects (euthymic or depressed)</td>
<td>28 healthy controls</td>
<td>BD-II (DSM-IV) BD-II, 34.8 Controls, 34.8</td>
<td>BD-II, 67.9% Controls, 67.9%</td>
<td>PBMCs FISH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

27
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sample Information</th>
<th>Controls Information</th>
<th>Mood Status</th>
<th>Method</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mansour et al. 2011</td>
<td>Egypt</td>
<td>108 BD-1 subjects (no specified mood status)</td>
<td>114 controls</td>
<td>BD-I (DSM-IV)</td>
<td>BD-1, 24.9</td>
<td>BD-I, 50.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls</td>
<td>27.5</td>
<td>Controls, 43.9%</td>
</tr>
<tr>
<td>Martinsson et al. 2013</td>
<td>Sweden</td>
<td>202 BD subjects (no specified mood status)</td>
<td>135 healthy controls</td>
<td>BD (DSM-IV)</td>
<td>BD, 50.0</td>
<td>BD, 57.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls, NA</td>
<td>NA</td>
<td>Controls, NA</td>
</tr>
<tr>
<td>Rizzo et al. 2013</td>
<td>Brazil</td>
<td>22 BD-1 subjects (euthymic)</td>
<td>17 healthy controls</td>
<td>BD-I (DSM-IV)</td>
<td>BD-I, 44.6</td>
<td>BD-I, 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls, 39.5</td>
<td>95</td>
<td>Controls, 100%</td>
</tr>
<tr>
<td>Lima 2014</td>
<td>Brazil</td>
<td>85 BD subjects (predominantly moderately depressed)</td>
<td>95 healthy controls</td>
<td>BD-I and BD-II</td>
<td>BD, 39.5</td>
<td>BD, 24.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Controls, 38.3</td>
<td>38.3</td>
<td>Controls, 36.5%</td>
</tr>
</tbody>
</table>

* For measuring telomere content.

Abbreviations: BD, bipolar disorder; BD-I, bipolar I disorder; BD-II, bipolar II disorder; BDI, Beck Depression Inventory; CHD, coronary heart disease; CIDI, Composite International Diagnostic Interview; DSM, diagnostic and statistical manual of mental disorders; FISH, fluorescence in situ hybridization; HADS-D, Depression Subscale of Hospital Anxiety and Depression Scale; MDD, major depressive disorder; MINI, Mini-International Neuropsychiatric Interview; NA, not available; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; T2D, type 2 diabetes.
Literature search
Pubmed, Scopus, and Google Scholar
Search terms: telomere AND (depression OR bipolar disorder OR manic)
Limits: First date available to January 2015

Identified studies (n=95)

Studies screened for eligibility (n=56)

Manuscripts examined for inclusion criteria

Studies excluded (n=39)
- Review articles (n=14)
- Non-human studies (n=14)
- Not measuring telomere length (n=8)
- Comments on other articles or case reports (n=3)

Studies included (n=20)

Studies excluded (n=36)
- Not including patients with depression or bipolar disorder (n=24)
- Measuring telomere length in brain (n=4)
- Not case-control comparison (n=4)
- Overlapping with other study (n=3)
- Not providing sufficient data (n=1)

Depression vs. controls (n=15)
Bipolar disorder vs. controls (n=6)
Figure 3

A

<table>
<thead>
<tr>
<th>Group by methods</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Hedges's g and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hedges's g</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Upper limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p-Value</td>
</tr>
<tr>
<td>FISH</td>
<td>Karabatsiakis 2014-with current depression</td>
<td>-1.132 -1.761 -0.503 -3.528 0.0004</td>
<td></td>
</tr>
<tr>
<td>FISH</td>
<td>Karabatsiakis 2014-without current depression</td>
<td>-1.202 -1.808 -0.596 -3.866 0.0001</td>
<td></td>
</tr>
<tr>
<td>FISH-pooled</td>
<td>Hoen 2011</td>
<td>-0.145 -0.299 0.010 -1.839 0.0659</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Teyssier 2012</td>
<td>0.146 -0.521 0.813 0.430 0.6675</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Wikgren 2012</td>
<td>-0.400 -0.626 -0.174 3.465 0.0005</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Georgin-Lavialle 2014</td>
<td>-0.501 -1.473 0.470 -1.012 0.3116</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Liu 2014</td>
<td>-0.114 -1.585 -0.642 -4.630 0.0000</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Verhoeven 2014</td>
<td>-0.155 -0.253 -0.057 -3.111 0.0019</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Schaakxs 2015</td>
<td>-0.050 -0.252 0.152 0.486 0.6269</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Needham 2015</td>
<td>-0.053 -0.206 0.099 0.666 0.4927</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Verhoeven 2015</td>
<td>-0.114 -1.585 -0.642 -4.630 0.0000</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>Wolkowitz 2015</td>
<td>-0.050 -0.252 0.152 0.486 0.6269</td>
<td></td>
</tr>
<tr>
<td>PCR-pooled</td>
<td>Simon 2006</td>
<td>-0.722 -1.315 -0.129 -2.387 0.0170</td>
<td></td>
</tr>
<tr>
<td>PCR-pooled</td>
<td>Lung 2007</td>
<td>-0.779 -0.941 0.617 9.423 0.0000</td>
<td></td>
</tr>
<tr>
<td>PCR-pooled</td>
<td>Hartmann 2010</td>
<td>-0.585 -1.101 0.068 -2.219 0.0265</td>
<td></td>
</tr>
<tr>
<td>PCR-pooled</td>
<td>Garcia-Rizo 2013</td>
<td>-1.340 -2.084 -0.596 -3.530 0.0004</td>
<td></td>
</tr>
<tr>
<td>southern blot</td>
<td>Simon 2006</td>
<td>-0.722 -1.315 -0.129 -2.387 0.0170</td>
<td></td>
</tr>
<tr>
<td>southern blot</td>
<td>Lung 2007</td>
<td>-0.779 -0.941 0.617 9.423 0.0000</td>
<td></td>
</tr>
<tr>
<td>southern blot</td>
<td>Hartmann 2010</td>
<td>-0.585 -1.101 0.068 -2.219 0.0265</td>
<td></td>
</tr>
<tr>
<td>southern blot</td>
<td>Garcia-Rizo 2013</td>
<td>-1.340 -2.084 -0.596 -3.530 0.0004</td>
<td></td>
</tr>
<tr>
<td>southern blot-pooled</td>
<td>Simon 2006</td>
<td>-0.722 -1.315 -0.129 -2.387 0.0170</td>
<td></td>
</tr>
<tr>
<td>southern blot-pooled</td>
<td>Lung 2007</td>
<td>-0.779 -0.941 0.617 9.423 0.0000</td>
<td></td>
</tr>
<tr>
<td>southern blot-pooled</td>
<td>Hartmann 2010</td>
<td>-0.585 -1.101 0.068 -2.219 0.0265</td>
<td></td>
</tr>
<tr>
<td>southern blot-pooled</td>
<td>Garcia-Rizo 2013</td>
<td>-1.340 -2.084 -0.596 -3.530 0.0004</td>
<td></td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Hedges's g and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon 2006</td>
<td>-0.722 -1.315 -0.129 -2.387 0.0170</td>
<td></td>
</tr>
<tr>
<td>Lung 2007</td>
<td>-0.779 -0.941 0.617 9.423 0.0000</td>
<td></td>
</tr>
<tr>
<td>Hartmann 2010</td>
<td>-0.585 -1.101 0.068 -2.219 0.0265</td>
<td></td>
</tr>
<tr>
<td>Teyssier 2012</td>
<td>0.146 -0.521 0.813 0.430 0.6675</td>
<td></td>
</tr>
<tr>
<td>Wikgren 2012</td>
<td>-0.400 -0.626 -0.174 3.465 0.0005</td>
<td></td>
</tr>
<tr>
<td>Garcia-Rizo 2013</td>
<td>-1.340 -2.084 -0.596 -3.530 0.0004</td>
<td></td>
</tr>
<tr>
<td>Verhoeven 2014</td>
<td>-0.155 -0.253 -0.057 -3.111 0.0019</td>
<td></td>
</tr>
<tr>
<td>Schaakxs 2015</td>
<td>-0.050 -0.252 0.152 0.486 0.6269</td>
<td></td>
</tr>
<tr>
<td>Wolkowitz 2015</td>
<td>0.207 -0.434 0.849 0.633 0.5266</td>
<td></td>
</tr>
<tr>
<td>Wolkowitz 2015</td>
<td>-0.387 -0.645 -0.130 -2.948 0.0032</td>
<td></td>
</tr>
<tr>
<td>Study name</td>
<td>Hedges's g</td>
<td>Lower limit</td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Simon 2006</td>
<td>-0.600</td>
<td>-1.074</td>
</tr>
<tr>
<td>Elvashagen 2011</td>
<td>-0.379</td>
<td>-0.901</td>
</tr>
<tr>
<td>Mansour 2011</td>
<td>-0.050</td>
<td>-0.312</td>
</tr>
<tr>
<td>Martinsson 2013</td>
<td>0.390</td>
<td>0.171</td>
</tr>
<tr>
<td>Rizzo 2013</td>
<td>-0.951</td>
<td>-1.606</td>
</tr>
<tr>
<td>Lima 2014</td>
<td>-0.496</td>
<td>-0.791</td>
</tr>
</tbody>
</table>

![Figure 4](image-url)