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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).

All analyses were performed using Comprehensive Meta-Analysis Software (Version 2.2.064 Biostat, Englewood, New Jersey) utilizing the standard meta-analysis function with a random effects model (DerSimonian and Laird, 1986). Heterogeneity of effect sizes was calculated using the I^2 statistic, which gives a measure of the percentage of variation between the studies attributable to between-study differences rather than to sampling error (Thorlund et al., 2012) (0% no observed heterogeneity, 25% low, 50% moderate and 75% high heterogeneity). A random effects model was utilized because initial analysis using a fixed effects model revealed significant heterogeneity between studies ($I^2=85\%$). Confidence intervals (CI; 95%) around the effect size and p-values for the meta-analysis and sub-group analyses were calculated. To ascertain if the results were strongly influenced by any single study, sensitivity analyses were performed utilizing the "leave-one-out" strategy (Patsopoulos et al., 2008). Publication bias was assessed by inspecting the funnel plot on primary outcome measures and quantified using Egger's regression intercept (Egger et al., 1997). Duval and Tweedie's trim and fill analysis (Duval and Tweedie, 2000), using a random effects model and looking for missing studies to the right of the mean, was used to estimate the effect size after accounting for publication bias. Random effects meta-regression models were used to examine the association between depression severity and years since MDD onset with telomere length.

2.5.1. Moderator analysis

To explore the possible reasons for heterogeneity, moderator analyses were performed. Meta-regression was used for analyzing the continuous moderators of mean age, smoking status, percent male gender in a study and to examine a combined model of significant moderators using the method of moments random-effects meta-regression model (Bornstein et al., 2009). For categorical moderators, subgroup analyses were conducted using a continuous random effects model (DerSimonian and Laird, 1986). Subgroups were assembled using the following criteria: *Comorbid chronic medical condition* – studies of patients with a chronic medical condition in addition to depression were placed in the Condition group. *Telomere measurement technique* – the majority of studies utilized the ratio of telomere repeat copy numbers to single-copy gene numbers (T/S ratio) using quantitative real-time polymerase chain reaction (qPCR) to measure telomere length ($k=30$); four studies utilized Southern blot and one study each utilized quantitative fluorescent in situ hybridization (qFISH), telomere content (TC), low-coverage whole-genome sequencing, and terminal restriction fragment lengths. Thus, we compared qPCR vs. all other techniques and also qPCR vs. Southern blot. *Source tissue* – the source tissue from which DNA was extracted for telomere measurement was noted in the methods section of the studies and grouped according to the categories of (1) leukocyte and (2) other (other included $k=5$ studies, with brain $k=3$ studies and saliva $k=2$ study). *Depression assessment* – measures of depression were grouped based on whether they utilized a clinical interview or self-report method. Measures determining clinically significant depression in the interview category included the Structured Clinical Interview for DSM-IV (SCID), Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDIS-IV), Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, and Composite International Diagnostic Interview (CIDI). Measures with thresholds to identify clinically significant depression in the self-report category included the Geriatric Depression Scale (GDS), Children's Depression Inventory, short version (CDI-s), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Center for Epidemiologic Studies Depression Scale (CES-D), Patient Health Questionnaire (PHQ-9) and the Taiwanese depression questionnaire (TDQ). Although not a questionnaire measure, we also included here a study that reported on diagnosis of depression from a clinical sample bank that was not further defined in this category because a clinical interview was not specified. A multivariate meta-regression was performed using variables found to be statistically significant moderators.

3. Results

We identified 603 studies through the literature search (Fig. 1). After duplicates were removed, abstracts of 222 articles were screened for eligibility and 168 were excluded. Five additional articles were identified after searching the study and review article references. Of the 54 full-text articles that were assessed for eligibility, 23 studies were excluded (9 authors did not reply to inquiries for non-published data, 10 contained overlapping data with other studies, 3 review articles resulting from the manual reference search, 1 study examined internalizing disorders rather than depression). Two papers contained two independent data sets as described in the methods section, leading to 38 data sets. These studies are summarized in Table 1; for 5 studies additional data were provided in correspondence with the authors (Garland et al., 2014; Ladwig et al., 2013; Phillips et al., 2013; Shalev et al., 2014; Tyrka et al. 2015).

The random effects model revealed an association between depression and telomere length, with an overall effect size, reported as Cohen's d, of -0.205 (Fig. 2; 95% CI -0.288 to -0.122, $p<0.0001$). The association between depressive symptom severity and effect size was significant ($B=-1.00$, 95% CI -1.90 to -0.0985, $p=0.030$, $I^2=68\%$). Years since onset of first episode of MDD was not significantly associated with effect size ($B=-0.020$, 95% CI -0.045 to 0.004, $p=0.11$ $I^2=68\%$).

Sensitivity analyses revealed that no one study affected the overall significance of the results. Visual inspection of the Funnel Plot (Supplemental Fig. 1, white fill) showed asymmetry about the combined effect size. Egger's regression intercept was -1.63 (95% CI -2.65 to -0.606, $t=3.23$, two-tailed $p=0.003$), suggesting the presence of publication bias. We performed Duval and Tweedie's trim and fill analysis (Duval and Tweedie, 2000) to determine how the effect size would be changed were there no publication bias. Under the random effects model, the effect size was calculated as -0.145 (95% CI -0.231 to -0.059 Supplemental Fig. 1, black fill), indicating that the effect remained highly significant after this adjustment. Heterogeneity was detected in the primary meta-analysis ($I^2=42\%$). The following analyses aimed to examine possible sources of heterogeneity through moderator analysis (Table 2).

3.1. Study techniques as moderators of telomere length and depression

As seen in Table 2, the set of studies that utilized interview-based methods showed a larger effect of depression on telomere length ($d=-0.337$, 95% CI -0.485 to -0.188, $p<0.0001$, $I^2=34\%$) than studies measuring depression using self-report instruments ($d=-0.078$, 95% CI -0.217 to 0.008, $p=0.076$, $I^2=40\%$); the difference between these groups was significant ($p<0.0001$).

Studies measuring telomeres using either qPCR or other measurement techniques showed a significant effect of depression on telomere length (Table 2). Studies utilizing telomere measurement techniques other than qPCR showed a larger effect and no heterogeneity between studies ($d=-0.717$, 95% CI -1.14 to -0.294, $p=0.001$, $I^2=0\%$) than studies utilizing qPCR to measure telomeres ($d=-0.111$, 95% CI -0.175 to -0.046, $p=0.001$, $I^2=35\%$); the difference between these groups was significant ($p<0.0001$). When comparing the two most frequently used techniques,

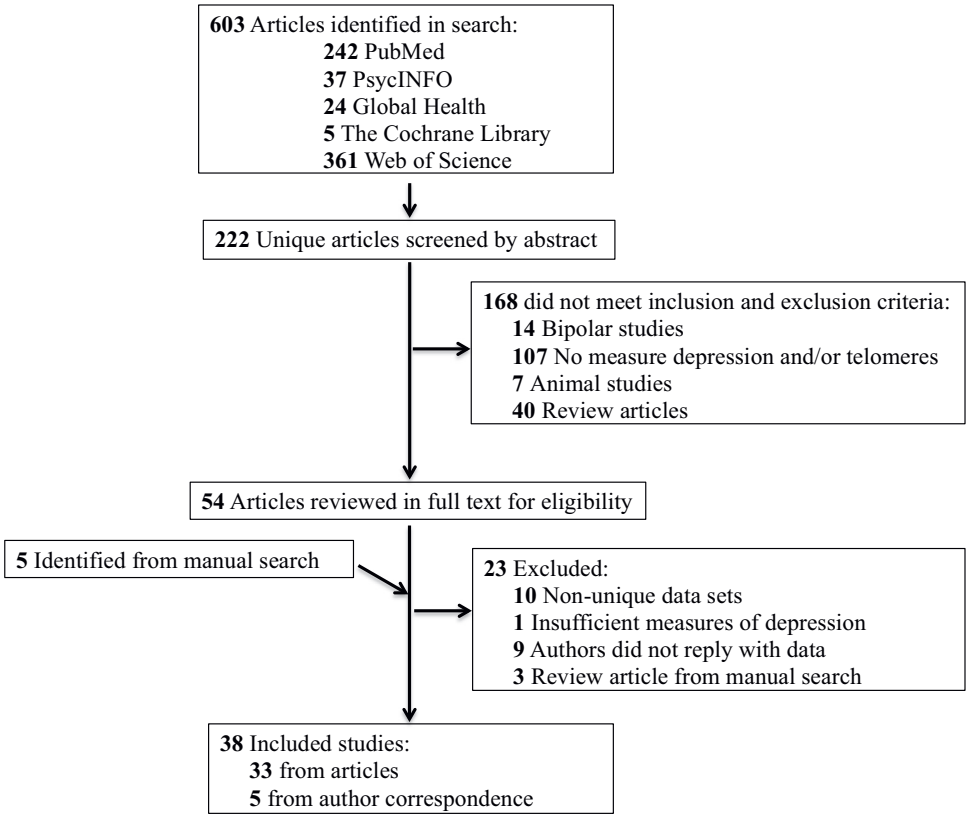

Fig. 1. PRISMA flowchart. PRISMA flow diagram for identification and inclusion of studies in the meta-analysis.

Southern blot vs. qPCR, the results were still significantly different ($p<0.0001$; $d=-0.500$ vs. -0.113 respectively).

The majority of studies ($k=33$) measured telomere length in leukocytes, and these showed a highly significant association between depression on telomere length ($d=-0.210$, 95% CI -0.297 to -0.120, $p<0.0001$, $I^2=44\%$ Table 2). When comparing differences between the leukocyte source tissue group and all other source tissues combined, there was a significant effect of source tissue between groups ($p<0.0001$), with the Other tissue group having a smaller, non-significant, effect size ($d=-0.181$, 95% CI -0.428 to 0.065, $p=0.15$, $I^2=20\%$ Table 2).

3.2. Chronic medical condition, age and gender as moderators of telomere length and depression

In the analysis of comorbid medical conditions, the comparison between groups was significant ($p<0.0001$, Table 3), with the Condition group showing a slightly larger effect size ($d=-0.252$, 95% CI -0.455 to -0.050, $p=0.015$, $I^2=27\%$) compared to the Other group ($d=-0.197$, 95% CI -0.290 to -0.123, $p<0.0001$, $I^2=45\%$). The linear relationship between study participant mean age and effect size was not significant ($B=0.005$, 95% CI -0.0002 to 0.011, $p=0.06$, $I^2=80\%$ Table 2), nor was the relationship between gender and effect size ($B=0.176$, 95% CI -0.141 to 0.493, $p=0.28$, $I^2=82\%$ Table 2) or percent of subjects that were smokers and effect size ($B=-0.073$, 95% CI -0.969 to 0.823, $p=0.87$, $I^2=69\%$ Table 2).

3.3. Multivariate meta-regression of significant moderators

The significant variables gleaned from the moderator analysis above were used as predictors in a multivariate meta-regression analysis. As demonstrated in Table 3, telomere measurement technique remained a statistically significant moderator ($p<0.001$), but source tissue, depression measurement technique and comorbid medical condition were no longer significant. A test of the model suggests that the overall effect size is related to the included variables ($Q=20.3$, $p=0.0004$) and that the proportion of between-study variance explained by the model was moderate ($R^2=0.29$).

4. Discussion

The findings presented in this meta-analysis support an association between reduced telomere length and clinically significant depression. Importantly, the severity of the depressive episode correlated significantly with telomere shortening. Using Cohen's categorization of effect sizes (Cohen, 1988), the effect on telomere length is small- to medium-sized; the effect magnitude was influenced by the variables examined in the moderator analyses. We found a significant effect of small-sized studies, suggesting publication bias towards reduced telomere length with depression. However, after trim and fill analysis, the effect size was in the same direction and the 95% CI still did not cross zero (Supplemental Fig. 1), indicating that the association of telomere length and depression remained significant after correcting for possible publication bias. These results are consistent with the previously published meta-analysis (Schutte and Malouff, 2015), which reported a significant correlation between depression and telomere length. Our results serve to further clarify the existing literature by including a comprehensive list of studies, such that the population presented here is approximately 40% larger than a recently published meta analysis, and by examining the effects of depression severity, years since MDD onset, chronic conditions, smoking, and tissue source on the relationship between depression and telomere length, which had previously not been examined.

Clinically significant depression has been linked to an increased risk of developing serious medical conditions including diabetes

Table 1
Characteristics of included studies.

Author, Year	Setting	Study design	Study *N* (depressed)	Male %	Mean age ± SD	Medical condition	Depression measurement technique	Telomere measurement technique	Tissue source	Telomere length (*p* value)	Level adjustment	NOS
Cai et al., 2015	CONVERGE study	Cross-sectional	11,670 (5,338)	0	–	–	DSM-IV	Low-coverage whole-genome sequencing	Saliva	OR = 0.85 (2.84×10^{-14})	3 principle components	7/10
Epel et al., 2013	Community recruitment	Cross-sectional	239 (–)	0	57 ± 4.4	–	PHQ	qPCR	Leukocyte	$r = -0.09$ (> 0.05)	None	7/10
Falci et al., 2013	Cases: medical oncology inpatient; Controls: community-dwelling	Cross-sectional	91 (–)	28.6	80.7 ± 2.3	26 Breast, 26 colorectal cancer	GDS	qPCR	Leukocyte	$\rho = -0.10$ (0.34)	None	6/10
Garcia-Rizo et al., 2013	Cases: psychiatric inpatient; controls: Community-dwelling	Nested case-control	57 (9)	40	28.3 ± 7.4	–	SCID	Telomere content	Leukocyte	Depressed: 87.9 ± 7.6 Control: 101.2 ± 14.3 (0.009)	None	5/9
Garland et al., 2014	Rowan Breast Cancer Center of the Abramson Cancer Center of the University of Pennsylvania	Nested case-control	140 (5)	0	54.6 ± 4.4	History of breast cancer	HADS	Terminal restriction fragment lengths	Leukocyte	Control: 6.2 ± 0.7 (0.059)	None	7/9
Georgin-Lavialle et al., 2014	French "AFIRMM protocol" study	Cross-sectional	19 (15)	21	44.5 ± 16.8	Mastocytosis	BDI	qPCR	Leukocyte	$r = -0.407$ (0.105)	Age, gender	8/10
Gotlib et al., 2014	Department of Psychiatry and Behavioral Sciences at Stanford University	Cross-sectional	97 (–)	0	12.0 ± 1.5	–	CDI	qPCR	Saliva	$r = -0.039$ (> 0.05)	None	8/10
Hartmann et al., 2014	Cases: psychiatric inpatients; Controls: community-dwelling	Case-control	74 (54)	43	49.1 ± 14.3	–	DSM-IV	Southern blot	Leukocyte	Depressed: 7.2 ± 0.61 Control: 7.55 ± 0.54 (0.007)	None	5/9
Hassett et al., 2012	Fibromyalgia Registry at the Chronic Pain & Fatigue Research Center; University of Michigan	Cross-sectional	66 (–)	0	44.6 ± 12.1	Fibromyalgia	CES-D	qPCR	Leukocyte	$r_{partial} = -0.247$, (0.048)	Age	7/10
Hoen et al., 2011	Heart and soul study	Nested case-control	952 (206)	81	66.7 ± 11.0	Coronary heart disease	CDIS-IV	qPCR	Leukocyte	Depressed: 0.86 ± 0.02 Control: 0.90 ± 0.01 (0.02)	Age, sex	7/9
Hoen et al., 2013	PREVEND study	Prospective cohort 2.2-year follow-up	1077 (97)	46	53.5 ± 11.3	–	CIDI	qPCR	Leukocyte	$B = 0.012$ (0.753)	Age, sex	7/9
Karabatsiakis et al., 2014	Recruited by newspaper announcement and public advertisements	Case-control	94 (20)	0	52.2 ± 7.7	–	Clinical evaluation	qFISH	Leukocyte	Depressed: 50.8 ± 15.1 Control: 68.4 ± 15.5 (< 0.0001)	None	7/9
Ladwig et al., 2013	Cooperative Health Research in the Region of Augsburg (KORA) F4 Study	Cross-sectional	2549 (126)	47	52.5 ± 11.0	–	PHQ-9	qPCR	Leukocyte	Depressed: 1.89 ± 0.32 Control: 1.88 ± 0.33 (0.74)	None	7/10
Lee et al., 2014	HIV-related clinical and community sites in San Francisco, CA	Cross-sectional	283 (137)	74	44.9 ± 8.4	HIV	CES-D	qPCR	Leukocyte	Depressed: 0.97 ± 0.32 Control: 0.98 ± 0.31 (> 0.05)	None	6/10

Table 1 (*continued*)

Author, Year	Setting	Study design	Study *N* (depressed)	Male %	Mean age ± SD	Medical condition	Depression measurement technique	Telomere measurement technique	Tissue source	Telomere length (*p* value)	Level adjustment	NOS
Lin et al., 2014	The University of Texas MD Anderson Cancer Center and Baylor College of Medicine	Prospective cohort 3.6 year follow-up	464 (–)	79.7	64.9 ± 11	Bladder cancer	CES-D for current depression, SCID-IV for lifetime MDD	qPCR	Leukocyte	OR; 95% CI: 0.86; 0.48–1.53 (0.609)	Age, gender, ethnicity, smoking status, cancer grade, treatments by stage and vital status	8/9
Liu et al., 2014	Division of Endocrinology, Tongji Hospital	Nested case-control	71 (17)	40	54.6 ± 8.4	Diabetes	HADS-D	qPCR	Leukocyte	Depressed: 1.70 ± 0.52 Control: 2.11 ± 0.44 (< 0.05)	None	5/9
Liu et al., 2014	Division of Endocrinology, Tongji Hospital	Nested case-control	52 (5)	30	51.3 ± 7.7	–	HADS-D	qPCR	Leukocyte	Depressed: 2.01 ± 0.16 Control: 2.32 ± 0.24 (< 0.05)	None	5/9
Lung et al., 2007	Cases: Psychiatric hospital; Controls: Community-dwelling	Case-control	664 (253)	Not reported	50.0 ± 14.4	–	SCID	Southern blot	Leukocyte	Depressed: 8.17 ± 0.61 Control: 9.13 ± 1.49 (< 0.01)	None	6/9
Needham et al., 2014	The National Health and Nutrition Examination Survey	Cross-sectional	1164 (75)	43.6	29.4 ± 5.9	–	CIDI	qPCR	Leukocyte	$\beta = -0.03$ (> 0.05)	Age, gender and race/ethnicity	8/10
Phillips et al., 2013	West of Scotland Twenty-07 Study	Prospective population-based cohort 15-year follow-up	1063 (81)	45	55.7 ± 15.1	–	HADS	qPCR	Leukocyte	Depressed: 0.77 ± 0.21 Control: 0.79 ± 0.20 (0.39)	None	6/9
Rius-Ottenheim et al., 2011	Zutphen Elderly Study (the Netherlands)	Prospective population-based cohort 7-year follow-up	122 (–)	100	86.5 ± 2.2	–	GDS-15	qPCR	Leukocyte	$\beta = -0.51$ (0.59)	Age	8/9
Rius-Ottenheim et al., 2011	Cretan Elderly Study (Greece)	Cross-sectional	102 (–)	100	85.2 ± 1.9	–	GDS-15	qPCR	Leukocyte	$\beta = -0.044$ (0.66)	Age	8/10
Savolainen et al., 2012	Helsinki Birth Cohort Study	Cross-sectional	1950 (–)	46.4	61.5 ± 2.9	–	BDI	qPCR	Leukocytes	$\beta = 0.058$; 95% CI −0.052, 0.168 (0.303)	Age, sex and stock DNA concentration	8/10
Schaakxs et al., 2014	Netherlands Study of Depression in Older Persons	Case-control	483 (355)	35	70.5 ± 7.3	–	CIDI	qPCR	Leukocyte	Depressed: 5035 ± 431 Control: 5057 ± 729 (0.59)	Age, sex, and education	8/9
Shaffer et al., 2012	Nova Scotia Health Survey 1995	Cross-sectional	2225 (269)	50	48.2 ± 18.9	–	CES-D	qPCR	Leukocyte	B = 50.2; 95% CI −22.8 to 123.1 (0.18)	Age, sex	10/10
Shalev et al., 2014	Dunedin Multidisciplinary Health and Development Study	Prospective, population-based cohort 35-year follow-up	829 (177)	51	38 ± –	–	DSM-IV	qPCR	Leukocyte	Depressed: 1.00 ± 0.31 Control: 1.06 ± 0.32 (0.026)	None	7/9
Simon et al., 2006	Cases: MGH Mood Disorder Genetics Study; Controls: Harvard Health Volunteer Specimen Bank	Case-control	59 (15)	51	50.4 ± 8.1	–	SCID	Southern blot	Leukocyte	Depressed: 6.87 ± 0.89 Control: 7.64 ± 1.10 (0.018)	None	6/9

Simon et al., 2015	Research Programs at MGH	Case-control	332 (166)	46	41.3 ± 13.7	–	SCID	Southern blot	Leukocyte	Depressed: 9.1 ± 2.5 Control: 8.9 ± 3 (0.65)	Education, exercise, smoking, htn, CIRS score, alcohol/drug disorder, ICG, TEQ, ETISR, and PSS	8/9
Surtees et al., 2011	EPIC-Norfolk	Cross-sectional	4012 (267)	0	62(40–81)[a]	–	HLEQ	qPCR	Leukocyte	$\beta = -0.004$; 95% CI −0.052, 0.044	Age, SF-36, social class, obesity, cigarette smoking, preexisting disease, and self-reported health	7/10
Szebeni et al., 2014	Brains obtained from Medical Examiner's Office of Cuyahoga Country	Case-control	28 (14)	93	50.9 ± 17.3	–	DSM-IV	End-point PCR	Astrocytes, oligodendro-cytes from Frontal white matter (Brodmann area 10) and temporal (uncinate fasciculus).	$UF_{astrocyte}$ $F=0.578$, (0.46) $BA10_{astrocyte}$ $F=0.354$; (0.56); $UF_{oligodendrocyte}$ $F=25.6$, (<0.0005); $BA10_{oligodendrocyte}$ $F=9.02$, (0.007)	None	6/9
Teyssier et al., 2011	Stanley Medical Research Institute	Case-control	24 (13)	Not reported	Not reported	–	MDD diagnosis in databank	qPCR	Occipital cortex	0.79 ± 0.001 for depressed and controls (>0.05)	None	4/9
Teyssier et al., 2012	Cases: Psychiatric inpatients; Controls: Hospital staff	Case-control	33 (17)	0	38.6 ± 5.2	–	SCID and MINI	qPCR	Leukocyte	Depressed: 13.42 ± 0.32 Control: 13.6 ± 0.30 (>0.05)	None	6/9
Tyrka et al., 2015	Community-recruitment of depressed and control subjects	Cross-sectional	290 (13)	39	31.0 ± 10.7	–	SCID	qPCR	Leukocyte	Depressed: 3398.9 ± 4108.5 Control: 6593.6 ± 4059.3 (<0.01)	Age, sex, SES, education, and BMI	9/10
Verhoeven et al., 2014	Netherlands Study of Depression and Anxiety	Cross-sectional	1605 (1095)	35	40.6 ± 13.1	–	CIDI	qPCR	Leukocyte	Depressed: 1.11 ± 0.30 Control: 1.15 ± 0.31 (0.003)	Age, sex, and education	9/10
Wikgren et al., 2012	Cases: Psychiatric inpatients; Controls: Betula Study	Case-control	542 (91)	48	59.1 ± 11.9	–	DSM-IV	qPCR	Leukocyte	Depressed: 5261 ± 334 Control: 5538 ± 743 (0.001)	Age, gender	8/9
Wolkowitz et al., 2011	Case: Psychiatric outpatients; Controls: Community dwelling	Case-control	35 (18)	66	36.7 ± 11.2	–	SCID	qPCR	Leukocyte	Depressed: 5101 ± 425 Control: 5141 ± 282 (0.66)	Age, gender	8/9
Yen et al., 2012	Household neighborhood sample	Cross-sectional	298 (–)	59.4	69.2 ± 2.7	–	TDQ	qPCR	Leukocyte	$\beta = 0.140$; 95% CI −0.004 to 0.015 (0.235)	Sociodemo-graphics plus mental state factors	7/10
Zhang et al., 2010	Stanley Medical Research Institute	Case-control	63 (15)	67	45.4 ± 9.1	–	MDD diagnosis in databank	qPCR	Gray matter cerebellum	Depressed: 0.97 ± 0.25, Control: 1.077 ± 0.251 (>0.1)	Disease status, age, and gender	6/9

(–) indicates value in study not specified. NOS = Newcastle–Ottawa Scale; qPCR = quantitative real-time polymerase chain reaction; SCID = Structured Clinical Interview for DSM-IV; CDIS-IV = Computerized National Institute of Mental Health Diagnostic Interview Schedule; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV; CIDI = Composite International Diagnostic Interview; GDS = Geriatric Depression Scale; CDI-s = Children's Depression Inventory, short version; BDI = Beck Depression Inventory; HADS = Hospital Anxiety and Depression Scale; HLEQ = Health and Life Experiences Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; PHQ-9 = Patient Health Questionnaire; TDQ = Taiwanese depression questionnaire; MDD = major depressive disorder; BA10 = Brodmann area 10; UF = uncinate fasciculus; Htn = hypertension, CIRS = Cumulative Illness Rating Scale; ICG = Inventory of Complicated Grief; TEQ = Traumatic Events Questionnaire; ETISR = Early Trauma Inventory Self-Report; PSS = perceived stress; SF-36 = Short form-36 physical component summary; SES = socio-economic status; BMI = body mass index; OR = odds ratio; B = unstandardized regression coefficient; β = standardized regression coefficient; r = correlation coefficient; ρ = Spearman's rank correlation coefficient; F = F statistic; CI = 95% confidence interval; OR = odds ratio.

[a] median (range).

Study name	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cai et al, 2015	-0.090	0.078	0.006	-0.243	0.063	-1.148	0.251
Epel et al, 2013	-0.181	0.130	0.017	-0.437	0.075	-1.388	0.165
Falci et al, 2013	-0.201	0.210	0.044	-0.612	0.210	-0.958	0.338
Garcia-Rizo et al, 2013	-1.359	0.385	0.148	-2.113	-0.605	-3.533	0.000
Garland et al, 2014	-0.794	0.458	0.210	-1.692	0.104	-1.733	0.083
Georgin-Lavialle et al, 2014	-0.891	0.481	0.231	-1.833	0.051	-1.854	0.064
Gotib et al, 2014	-0.078	0.202	0.041	-0.475	0.319	-0.385	0.700
Hartmann et al, 2014	-0.591	0.266	0.071	-1.113	-0.069	-2.218	0.027
Hassett et al, 2012	-0.510	0.255	0.065	-1.010	-0.010	-2.000	0.045
Hoen et al, 2011	-0.145	0.077	0.006	-0.297	0.007	-1.872	0.061
Hoen et al, 2013	0.035	0.105	0.011	-0.171	0.241	0.334	0.739
Karabatsiakis et al, 2014	-1.157	0.282	0.080	-1.710	-0.604	-4.101	0.000
Ladwig et al, 2013	0.030	0.089	0.008	-0.145	0.205	0.335	0.737
Lee et al, 2014	-0.032	0.118	0.014	-0.264	0.200	-0.270	0.787
Lin et al, 2014	0.083	0.161	0.026	-0.233	0.399	0.515	0.607
Liu et al, 2014a	-0.892	0.288	0.083	-1.457	-0.327	-3.096	0.002
Liu et al, 2014b	-1.329	0.453	0.205	-2.216	-0.442	-2.935	0.003
Lung et al, 2007	-0.779	0.084	0.007	-0.943	-0.615	-9.311	0.000
Needham et al, 2014	-0.122	0.118	0.014	-0.354	0.110	-1.031	0.302
Phillips et al, 2013	-0.100	0.114	0.013	-0.323	0.123	-0.877	0.380
Rius-Ottenheim et al, 2011 Zutphen	-0.102	0.126	0.016	-0.350	0.146	-0.806	0.420
Rius-Ottenheim et al, 2011 Crete	-0.088	0.141	0.020	-0.365	0.189	-0.622	0.534
Savolainen et al, 2012	-0.116	0.032	0.001	-0.178	-0.054	-3.668	0.000
Schaakxs et al, 2014	-0.042	0.105	0.011	-0.248	0.164	-0.400	0.689
Shaffer et al, 2012	0.082	0.063	0.004	-0.042	0.206	1.297	0.195
Shalev et al, 2014	-0.201	0.084	0.007	-0.365	-0.037	-2.402	0.016
Simon et al, 2006	-0.732	0.307	0.094	-1.333	-0.131	-2.388	0.017
Simon et al, 2015	0.072	0.110	0.012	-0.143	0.288	0.658	0.510
Surtees et al, 2011	-0.008	0.028	0.001	-0.063	0.047	-0.283	0.777
Szebeni et al, 2014	-1.381	0.587	0.345	-2.532	-0.230	-2.351	0.019
Teyssier et al, 2011	0.000	0.410	0.168	-0.803	0.803	0.000	1.000
Teyssier et al, 2012	-0.580	0.355	0.126	-1.276	0.116	-1.634	0.102
Tyrka et al, 2015	-0.780	0.286	0.082	-1.341	-0.219	-2.724	0.006
Verhoeven et al, 2014	-0.132	0.055	0.003	-0.239	-0.025	-2.410	0.016
Wikgren et al, 2012	-0.400	0.114	0.013	-0.623	-0.177	-3.508	0.000
Wolkowitz et al, 2011	-0.110	0.339	0.115	-0.775	0.555	-0.324	0.746
Yen et al, 2012	0.283	0.084	0.007	0.119	0.447	3.382	0.001
Zhang et al, 2011	-0.427	0.298	0.089	-1.012	0.158	-1.431	0.152
	-0.205	0.042	0.002	-0.288	-0.122	-4.843	0.000

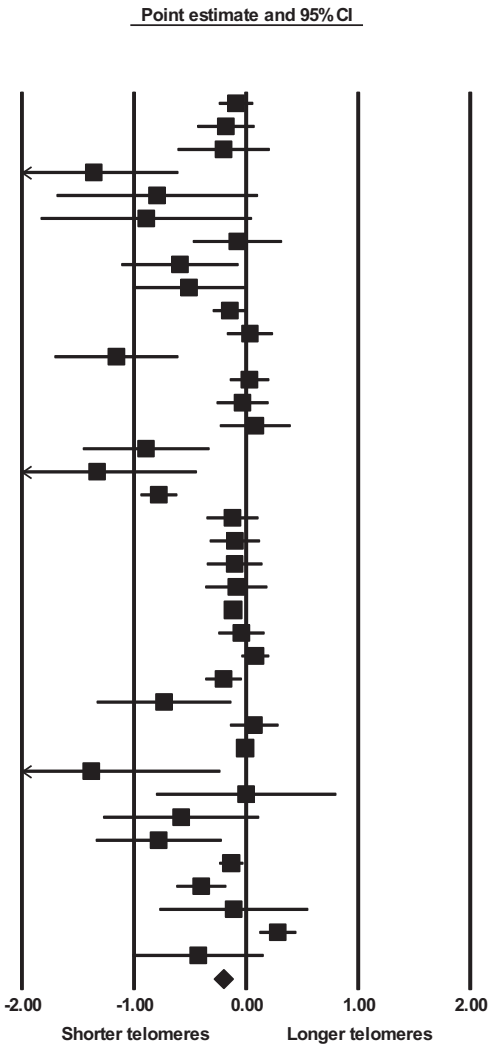

Fig. 2. Results of meta-analysis using all studies. Forest plot of point estimate effect sizes reported as Cohen's *d* (*x*-axis) evaluating depression and telomere length using the random effects model. Points represent weighted effect size, lines represent 95% confidence intervals (CI). Triangle indicates overall effect size and 95% CI.

mellitus (Musselman et al., 2003) and cardiovascular disease (Musselman et al., 1998), along with earlier mortality (Evans et al., 2005), independent of socio-demographic risk factors (Gump et al., 2005) or comorbidities (Evans et al., 2005). Telomere length has been equated to a cellular clock; affecting how quickly cells reach senescence (Ridout et al., 2015), and telomere shortening has been associated with a number of serious medical conditions (Ridout et al., 2015). It may be that telomere shortening is a potential mechanism by which MDD may contribute to an increased risk of morbidity and mortality (Wolkowitz et al., 2010). That the effect of depression on telomere length was not solely accounted for by moderators known to significantly affect telomere length (age, gender, smoking and comorbid chronic medical conditions) indicates that other influences might be responsible for this association.

The causal nature of this association is not known; future studies will be needed to further investigate the mechanism by which depression is associated with shortened telomeres (Price et al., 2013; Ridout et al., 2015). Telomere shortening is known to result from repeated mitotic divisions and exposure to a variety of cellular stress mechanisms (Blackburn et al., 2006). It has been speculated that MDD directly activates or is associated with increased cellular stress and replication, resulting in accelerated telomere shortening (Wolkowitz et al., 2010). Recent evidence also highlights the importance of genetic variation in telomerase, a regulator of telomere length and has been associated with depression (Wei et al., 2015). The results of this study suggest that there is a relationship between depression and biological measures of stress and aging, underscoring the importance of future studies exploring the mechanisms relating depression and telomere length.

We observed a negative association between telomere length and depression severity, but we did not find a significant association with years since first depressive episode. We were not able to examine the cumulative effect of depression on telomere length in terms of total number of episodes and length, severity, treatment, or treatment response of each episode because too few studies reported on these characteristics. It is possible that a severe current episode may be reflective of a more severe course of depressive illness. Future studies examining the total number and severity of prior depressive episodes would help elucidate this relationship.

To identify possible sources of heterogeneity between studies, the effects of study measurement techniques of depression and telomere length, source tissue, age, gender, and comorbid chronic medical conditions were examined as potential moderators. Both depression and telomere measurement techniques were significant moderators of the relationship between depression and telomere length, with studies utilizing interview-based and telomere measurement techniques other than qPCR demonstrating a

Table 2
Moderator analyses.

Parameter	*k* (*n*)	*d*	95% CI	I^2 (%)	*p*-Value
Depression measurement technique					**< 0.0001**
Interview-based	18 (19,988)	−0.337	−0.485 to −0.188	34	< 0.0001
Self-report	20 (14,359)	−0.078	−0.217 to 0.008	40	0.076
Telomere measurement technique					**< 0.0001**
Other method than qPCR	7 (1420)	−0.717	−1.14 to −0.294	0	0.001
qPCR	31 (32,927)	−0.111	−0.175 to −0.046	35	0.001
Source tissue					**< 0.0001**
Leukocytes	33 (22,465)	−0.210	−0.297 to −0.120	44	< 0.0001
Other	5 (11,882)	−0.181	−0.428 to 0.065	20	0.15
Chronic comorbid medical condition					**< 0.0001**
Condition	8 (2086)	−0.252	−0.455 to −0.050	27	0.015
Other	30 (32,261)	−0.197	−0.290 to −0.123	45	< 0.0001
Age	37 (22,677)	*B*=0.005	−0.0002 to 0.011	80	0.06
Gender	37 (34,323)	*B*=0.176	−0.141 to 0.493	82	0.28
Smokers in study (%)	19 (12,838)	*B*=−0.073	10.969 to 0.823	69	0.87

The effects of all categorical variables were determined using the continuous random effects model in subgroup analyses. The effects of age and percent male gender, which were imputed as a continuous variable, were analyzed using the method of moments random-effects meta-regression model, resulting in a meta-regression coefficient (*B*). Highlighted *p*-values represent significant moderator effects on the relationship between depression and telomere length. MDD=major depressive disorder; *k*=number of studies within subgroup; *n*=number of subjects represented from all studies *k*; *d*=effect size reported as Cohen's *d* for subgroup; CI=confidence interval; I^2=test of heterogeneity within the subgroup, with 0% no observed heterogeneity, 25% low, 50% moderate and 75% high heterogeneity.

larger association of depression with telomere length as shown by the effect size. A previous meta-analysis did not detect an effect of depression assessment method on the relationship between depression and telomere length (Schutte and Malouff, 2015). Compared to this previous meta-analysis, this analysis has a larger sample size, which might have facilitated our ability to detect the effect of depression measurement technique on telomere length. There is evidence that interview-based measures of depression are better able to detect outcomes in depression treatment (Cuijpers et al., 2010) and that clinicians may have higher severity thresholds than the self-report scales in these studies (Carter et al., 2010). Whether they used interview or self-report methods to detect clinically significant depression, most studies in this meta-analysis provided information regarding depression severity in their populations as well. There was no difference in severity between the studies using interview based or self-report methods in this meta-analysis (p=0.10876). Both interview-based and telomere measurement techniques other than qPCR are more technically cumbersome and time consuming than other approaches. It is important to note that while techniques other than qPCR yielded a larger effect size, qPCR was associated with significant effects, indicating that it is an acceptable alterative. However, this was not the case for depression measurement technique: only studies utilizing interview assessments of depression had a significant association, suggesting that this may be an important consideration for future studies.

The effect of depression on telomere length was robust in the group of studies that examined DNA from leukocytes. We did find a difference between subgroups related to source tissue, although only a few studies examined brain tissue or saliva and there was variability in telomere length in these other tissues. It is possible that the finding that only leukocyte-derived data exhibit a significant association with telomere length reflects differences in preponderance of post-mitotic mass of the source tissue. We were unable to examine subgroups of leukocyte types in this meta-analysis due to a limited number of studies reporting these data, although subtypes of leukocytes have been shown to significantly differ in subjects with depression compared to controls (Karabatsiakis et al., 2014).

Decreased telomere length has been associated with a number of chronic medical conditions (Price et al., 2013; Ridout et al., 2015); we found a significant difference between studies examining populations with and without a specific chronic medical condition, with studies examining telomere length in subjects with both depression and a comorbid chronic medical condition showing a larger effect size. However, as shown in Table 3, the effect sizes of each group would still place them in the same small to medium effect size category; any statistically significant differences noted should be evaluated cautiously, as their clinical and biological importance is unclear. While the existence of a negative association between telomere length and increasing age (Muezzinler et al., 2013), smoking (Verde et al., 2015) and effects of gender (Gardner et al., 2014) are well-established, these results show that these characteristics alone do not explain the relationship between depression and telomere length.

Limitations of this meta-analysis follow from study design differences as well as differences in baseline characteristics of study participants. The inclusion of a number of studies with small sample sizes likely contributed to the observed variation in effect size, and reduced the ability to detect differences between subgroups. The relatively small number of studies in some of the moderator categories reduced our ability to detect differences based on these categories. Many publications are based on secondary analyses from studies originally designed for other purposes, and used banked blood specimens to determine telomere length, which could affect their findings due to storage or extraction technique, inadequate power or study design (Nussey et al., 2014), and consequently the results of this meta-analysis.

5. Conclusions

This analysis shows that the association of depression with telomere shortening is robust and identifies factors that affect this

Table 3
Multivariate Meta-Regression.

Covariate	B	Standard error	95% confidence interval	*Z*-value	2-sided *p*-value
Depression measurement technique	−0.098	0.082	−0.260 to 0.063	−1.19	0.23
Telomere measurement technique	−0.438	0.122	−0.677 to −0.199	−3.59	< 0.001
Source tissue	0.075	0.137	−0.194 to 0.343	0.54	0.59
Chronic comorbid medical condition	−0.135	0.105	−0.341 to 0.072	−1.28	0.20

Test of model: Q=20.3, df=4, p=0.0004; R^2 analog for model=0.29 (proportion of total between-study variance explained by model).

association. Reduced telomere length in depression could be a mechanism by which depression contributes to increased morbidity and mortality risk; suggesting the need for future studies examining the effects of treating depression on telomere length. It is unclear at what point in the course of depression telomere length is affected, how the course of depression affects telomere length, and whether some individuals are more susceptible to telomere shortening with depression than others. Future research should help to elucidate these issues. Our results can help guide investigators by providing evidence regarding the optimal design and measurement of future studies in this area, which would include interview-based measures of depression. Newer prospective studies will determine whether telomere length and dynamics will serve merely as an additional biomarker of general health or as a primary target to evaluate severity of depression and treatment efficacy.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.11.052.

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