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The association between psychiatric disorders and telomere length: A Meta-analysis involving 14,827 persons

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Abstract

Objective—This study examined the relationship between leukocyte telomere length (LTL), a marker of cell aging, and psychiatric disorders in adults compared to controls using meta-analytic methods.

Methods—Data were abstracted from studies examining the relationship between LTL and adult psychiatric disorders. In addition to an overall estimate of effect size, subgroup analyses and meta-regression were performed to examine whether covariates (including psychiatric diagnoses) moderated the estimate.

Results—A significant overall effect size showing LTL shortening was found across all psychiatric disorders (Hedge's g = −0.50, p< 0.001). Subgroup analyses did not demonstrate significant differences in effect size based on individual covariates (psychiatric disorder, sex, age or assay method). The meta-regression indicated that although type of disorder and, likely, age moderate the overall effect size, the heterogeneity between studies could be explained by a model that included these variables as well as sex and assay method. Although not significantly different, post-traumatic stress disorder, anxiety disorders and depressive disorders had comparatively larger effect sizes (−1.27, −.53, and −.55), and psychotic and bipolar disorders had comparatively smaller ones (−.23 and −.26).

Conclusions—We observed a robust effect size of LTL shortening for psychiatric disorders as a whole compared to controls. The results were less straightforward regarding relative differences in the strength of this association by specific disorder. Future studies should focus on mechanisms explaining accelerated cell aging with psychiatric illness, defining directions (if any) of causality and elucidating possible differences in this association between disorders.

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Conflicts of Interest

Drs. Darrow, Lindqvist, Penninx, Delucchi, Wolkowitz and Mathews and Ms. Verhoeven and Ms. Révész report no financial relationships with commercial interests.

Keywords

telomere length; depressive disorders; anxiety disorders; psychosis; post-traumatic stress disorder; bipolar disorders

Introduction

Psychiatric disorders place a heavy psychological disease burden on patients and are associated with increased risk of serious medical conditions and early mortality. Meta-analyses show that individuals with psychiatric disorders are more likely to suffer from cardiovascular disease, stroke, dementia, diabetes, and obesity(1–4), conditions *that are generally considered aging-related as their prevalence increases steeply with age*. Although some of the increased risk may be explained by lifestyle differences, as persons with psychiatric disorders are more likely to smoke, drink alcohol, eat poorly and exercise less(5), associations between psychiatric status and medical morbidity remain significant after adjusting for these factors(2). These findings suggest that physiological mechanisms play an important role in the relationship between psychiatric disorders and physical health, leading to the hypothesis that this relationship may be mediated by accelerated cellular aging(6).

One well-studied indicator of cellular aging is telomere length (TL). Telomeres are repetitive DNA-protein complexes with repeated TTAGGG nucleotide sequences that cap the end of chromosomes and protect them from damage. TL is largely genetically determined, but also depends on developmental and environmental factors (7). Telomeres are not fully replicated during every cell division, causing mitotic cells to become progressively shorter over the lifespan if not acted upon by telomerase, the major telomere-lengthening enzyme(8). Physiological disturbances (e.g., increased inflammation and oxidative stress) thought to be important in the development of some psychiatric disorders(6, 9), may also accelerate telomere shortening(10, 11)

TL is typically measured in leukocytes (LTL). Numerous epidemiological studies have reported associations between shorter LTL and somatic conditions (e.g., cardiovascular disease(12), obesity(13), diabetes(14)). However, it is unclear whether telomere shortening is a cause of deleterious effects or a marker of cumulative exposure to cytotoxic environments(15). Stem cells with critically shortened telomeres may undergo apoptosis or genomic instability, leading to loss of reparative function(16). Also, senescent lymphocytes can hypersecrete inflammatory cytokines, promoting certain diseases and leading to further telomere shortening(15). Due to the progressive shortening of TL with age and association with diseases of aging, TL can be seen as an index of biological aging. If accelerated telomere shortening is associated with certain psychiatric disorders, it might help explain the relationship between medical morbidity and those disorders, even though causality remains in question.

Multiple studies have examined the relationship between LTL and psychiatric disorders with mixed results(17–19). This inconsistency is likely to have several causes, including differences in methodology, demographic composition of the participant groups (e.g., age, sex) and small sample sizes. Study sample sizes have ranged from nine to over 1000

participants, but many studies had small samples (n<100). Further, the age of participants ranged from 22 to 93. For example, two studies with a similar design found a LTL difference, relative to controls, for adult patients with major depressive disorder (MDD; mean age = 42)(20), but this difference was not seen in a study of late-life MDD (mean age = 71)(21). Finally, technological approaches to extracting DNA and measuring TL may also contribute to inconsistent results(22, 23).

Given the observed association between shorter LTL and psychiatric disorders in some studies, additional investigation is needed. The goal of this study was to comprehensively examine the relationship between LTL and psychiatric disorders using meta-analysis to guide future research efforts, including determining whether investigations into potential biological or causal relationships between LTL and psychiatric illness are merited. In subgroup analysis and meta-regression, we also explored whether type of psychiatric disorder (e.g., depressive, psychotic, or anxiety disorders) and between-study differences (e.g., TL assessment method, sex and participants' age) are differentially associated with shortened telomeres.

Methods

The current study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement for meta-analyses(24).

Literature Search

The search, review of abstracts, and abstraction of data were conducted by postdoctoral research fellows (SD and DL) and graduate students (DR and JV) supervised by experts in meta-analysis, psychiatric disorders, and telomere measurement (KD, BP, OW & CM). We followed a three-stage approach to identify appropriate articles. First, in May 2014, PubMed, PsychInfo and Embase databases were searched using terms related to telomeres and psychiatric disorders (see Table 1 for full search strategy). Publication year ranged from 1974 to 2014. Second, we identified additional articles by reviewing online tables of contents for recent issues of journals known to publish relevant articles through November 2014. Third, all authors of articles included in the meta-analysis, as well as those known to be interested in similar research, were contacted to obtain unpublished data pertinent to this analysis.

Two independent raters (SD/DL or DR/JV) screened each abstract regarding the inclusion and exclusion criteria (described below). Discrepancies were resolved by a third author (OW or CM). Articles that passed the initial screening were reviewed in full (see Data Extraction) following the same method to make the final determination.

Inclusion and exclusion criteria—Articles had to describe original research, be conducted in adult humans, measure LTL, examine the relationship between LTL and a psychiatric disorder, and include a non-psychiatric control group (included both independent and matched group designs). Studies were excluded if LTL was measured post-mortem, in persons below age 18, and if blood collection for LTL measurement and diagnostic assessment occurred at separate time points (i.e., longitudinal studies in which diagnostic

status was determined in a different wave than blood collection). Studies that examined dementias or developmental disabilities were excluded, as these disorders are associated with known structural brain and other systemic abnormalities, potentially confounding the analyses. Substance use disorders were also excluded, as substances may have a direct effect on telomere length independent of any relationship between vulnerability to substance misuse and telomere length. Presence of a psychiatric disorder was defined using DSM-IV or ICD-10 criteria for a current (i.e., within the past year) Axis I disorder. In order to examine the relationship between LTL and psychiatric *disorders* rather than dimensional psychiatric *symptoms*, we excluded studies that only employed continuous measures of psychiatric symptoms rather than diagnostic criteria. We included studies in which the primary objective was not necessarily to examine the relationship between a psychiatric disorder and TL (e.g., a study examined the relationship between TL and lithium response) if one of the groups was formed based on the presence of a psychiatric diagnosis. When comorbid psychiatric symptoms and/or disorders were present, we used primary diagnoses only to categorize participants.

Data Extraction

Data were independently abstracted by two members of the research team. The coders initially agreed on 96% of the data points. Data on the following variables were collected: study design, telomere assay method, LTL (mean and SD), sample size, diagnosis, age, sex, and other covariates (e.g., body mass index) included in the original analyses.

When studies included multiple groups that met criteria for a psychiatric disorder (e.g., one group met criteria for MDD and the other for bipolar disorder (BD)), the data were abstracted separately for these groups whenever possible. In studies with multiple psychiatric case groups and only one healthy control group, the same control group was used for each case group; the data from these cases are not completely independent.

Telomere assay method—Studies were included regardless of the method used to measure LTL and the method was recorded; methods included Quantitative fluorescence in situ hybridization (FISH), Quantitative polymerase chain reaction (PCR or Q-PCR), and Southern Blot.

Leukocyte telomere length data—If LTL data were not normally distributed and the researchers used log transformations to meet the assumptions of normality, the log-transformed data were used.

Covariates—We noted how studies controlled for variables known to be related to TL (e.g., age, sex). Studies were classified as “adjusted” for covariates if they 1) employed matched group designs, 2) statistically adjusted for covariates, or 3) both. Studies were classified as “unadjusted” if they employed independent groups designs and did not statistically control for covariates. Wherever possible, we used data that were statistically adjusted for covariates determined *a priori* by the researchers (i.e., if a study included multiple sequential analyses examining additional covariates, we abstracted the adjusted data

from the analysis with the fewest covariates) to attempt to abstract data as similar as possible across studies.

Statistical Analyses

Statistical analyses were performed using RevMan version 5.3(25) and SPSS version 19. The random-effects model was employed because we hypothesized that there would be significant variations in effect sizes as a result of the diverse study designs. The means, standard deviations, and sample sizes for each group were used to calculate a standardized mean difference effect size (adjusted Hedge's *g*) for each study and the inverse variance method was used to combine the results across studies. A Hedge's *g* is interpreted as the difference between the mean LTL (independent of the units of measurement) for the two groups divided by the pooled standard deviation of the groups (e.g., −0.5 indicates the mean LTL of the psychiatric disorder group was 0.5 standard deviations smaller than the control group mean LTL). Effect sizes are described according to the following standards: 0.2 is small, 0.5 is moderate, and 0.8 is large(26). Heterogeneity was evaluated using the Higgins I^2 statistic and the Cochran's Q test(27). I^2 represents the proportion of observed variance that reflects true (rather than chance) differences in effect size. A significant Q test (i.e., $p<0.05$) indicates that observed differences in effect size are not likely due to chance alone. Thus, significant, high heterogeneity indicates that some variable(s) (i.e., between-study difference) is/are causing different effect size estimates. Additionally, the funnel plot was examined to assess for publication bias based on the assumption that studies employing smaller samples with negative results are less likely to be published(27). A significant Egger test ($p < 0.01$) indicates possible publication bias.

To explore possible sources of heterogeneity, we conducted subgroup analyses to compare effects sizes of studies employing different telomere assays, psychiatric disorders, and methods to adjust for covariates. Finally, meta-regression was used to identify potential moderators of the effect size (i.e., age, sex, assay method, psychiatric disorder). Sample size was used as a weight in all analyses.

Results

Systematic Review

The literature search resulted in 561 unique abstracts; eight recently published articles were also identified (see Figure 1). Forty-five articles passed initial screening and were reviewed in full. Of these, 27 articles met all inclusion criteria. These articles described studies examining the relationship between LTL and multiple psychiatric disorders (e.g., MDD, BD, panic disorder, schizophrenia, post-traumatic stress disorder [PTSD]); these disorders were collapsed into five categories (i.e., depressive disorders, bipolar disorders, anxiety disorders, psychotic disorders, and PTSD; see Table 2). Twenty-four authors responded to inquiries regarding unpublished data; three were in the process of publishing their new data and did not wish it to be included in the meta-analysis. The other 21 were not aware of unpublished data. Thus, all data included came from published articles, including one published abstract(47).

Two articles(35, 52) reported studies using both independent and matched groups. The samples from Kao and colleagues(35) did not completely overlap and the data from both studies were used. However, in Zhang and colleagues'(52) article, all of the participants in the matched sample analyses were also included in the independent group analyses; therefore, only data from the matched group analyses were included. Further, one article reported separate analyses for a bipolar group and a schizophrenia group, compared to different control groups(40); one article reported separate analyses for a depressed group and an anxiety group, compared to the same control group(42); and one article reported separate analyses for a depressed group, a bipolar group, and a bipolar plus anxiety group, all were matched and compared to the same control group(46). The data from all of these analyses were included as separate studies.

Thus, data from 32 studies (5,289 psychiatric cases and 9,538 controls) were included in the meta-analysis (Table 2). Specific data that were not included in the published articles but were necessary for the meta-analysis were obtained from authors of six articles (e.g., actual means and standard deviations of LTL when data were only reported in a figure).

Meta-Analysis

The overall meta-analysis demonstrated a significant medium effect size (g=−0.50; CI: −0.70, −0.30; p<0.001), indicating that psychiatric disorders overall were associated with shorter LTL (Figure 2). The Cochran's Q test (χ^2=603.31, df=31, p<0.001) and high I^2 (95%) suggested substantial heterogeneity across studies, indicating that differences in study design or participant characteristics, not chance, caused differences in individual study effect sizes(53). The funnel plot (Figure 3) did not show noticeable asymmetry, suggesting that there was no evidence of publication bias.

Examining heterogeneity due to methodological variables—We next sub-grouped studies by whether they adjusted for covariates and by assay method (Table 3).

The overall test between the pooled estimates for the unadjusted and adjusted studies was not significant. Thus, all studies were included in subsequent analyses. The overall test for the subgroup analyses examining different TL assay methods was also not significant, indicating that inclusion of different methods of telomere measurement did not result in different effect sizes.

Examining heterogeneity across different psychiatric disorders—Both the subgroup analysis and examination of the forest plot (Figure 2) suggested that LTL was shorter for patients than controls for all included psychiatric disorders, and the difference in effect sizes between disorders was not significant (Table 3). Sub-group effect sizes for depressive disorders, PTSD and anxiety disorders were statistically significant (i.e., confidence intervals did not cross zero; p=0.004, 0.003, & 0.05, respectively); those for psychotic and bipolar disorders were not significant. The PTSD sub-group had a large effect size (−1.27) and depressive and anxiety disorders had moderate effect sizes (−0.55 and −0.53, respectively). Psychotic disorders and bipolar disorder had comparatively smaller effect sizes (−0.23 and −0.26, respectively).

Within each diagnostic subgroup, there was also evidence of significant heterogeneity (I^2>90%, Table 3); the observed differences in effect sizes between studies in each disorder subgroup were more than expected by chance.

Meta-regression

Meta-regression was used to examine the effect of multiple potential moderators simultaneously. The predictor variables were assay method, type of psychiatric diagnosis, mean age, and proportion of female participants and effect size was the outcome variable. Both age and sex generally affect TL(54, 55), and were consistently reported across all studies, allowing us to examine their effects. The multivariate random-effects meta-regression modeling age, sex, assay method and psychiatric diagnoses resulted in a significant effect size (−0.50; CI −0.71, −0.30) that replicated the global effect size calculated by the primary meta-analysis (−0.50; CI −0.70, −0.30). Including studies examining psychosis significantly decreased the overall effect size compared to including those on depressive disorders, and studies on PTSD significantly increased the overall effect size compared to including those on depressive disorders (see Table 4). Notably, age approached significance, indicating that studies with younger subjects decreased the effect size. However, the test of residual variance for the overall model was significant (χ^2=45.66, df=23, p=0.003), indicating that the heterogeneity of effect size across studies was not adequately explained by the covariates included in the meta-regression. Thus, the observed effects of the individual predictors may be related to a variable not specified in the current model.

Discussion

This study examined the relationship between cellular aging as indicated by LTL and a wide range of psychiatric disorders, including 14,827 participants. The global meta-analysis effect size was significant (−0.50), indicating, as hypothesized, that shortened LTL is seen across many psychiatric disorders, despite the high level of heterogeneity between individual studies. The meta-regression confirmed the global effect size estimate, and indicated that the heterogeneity was not adequately explained by simultaneous consideration of differences between studies in method, assay, age, gender, and psychiatric disorder. Of these, perhaps the most interesting to examine further is psychiatric diagnosis.

We found significant effect sizes for depressive disorders, PTSD and anxiety disorders. Overall, there was no significant difference in the effect size estimates between the different disorder subgroups. However, the number of studies was small for some of the disorders, thus an additional study could clearly change the outcome of sub-group analyses. Therefore, further studies are needed to clarify whether meaningful differences in LTL by diagnosis exist. The results of the meta-regression provide some support for further study of potential differences in effect size between psychiatric disorders. The effect size was moderated by different disorders, although additional sources of heterogeneity of effect size may be identified that change this relationship.

In addition to the value derived from identifying differences *between* disorders, finding evidence of telomere shortening *across* disorders is interesting in the current context of

psychiatric research. Given the high prevalence of comorbidity between psychiatric disorders(56), heterogeneity within disorders, and the lack of robust biological underpinnings for current diagnostic constructs, psychiatric research is moving away from disorder-based constructs and increasingly trying to elucidate trans-diagnostic mechanisms(57). There is now emerging evidence to suggest that several currently defined psychiatric disorders share a common underlying genetic etiology(58). Thus, individual categorical psychiatric diagnoses are unlikely to be either necessary or sufficient for LTL shortening to be observed.

Although this meta-analysis focused on psychiatric diagnoses, there is a growing literature suggesting that chronic psychological stress and histories of repeated childhood adverse experiences (even in the absence of a formal psychiatric diagnosis) may be related to shortened LTL(17, 59). Given the relationship between chronic psychological stress and/or childhood adversity and psychiatric illness(60, 61), future research should examine whether these experiences mediate the relationship between psychiatric diagnosis and LTL observed in our data. Future studies could test this hypothesis, perhaps by measuring history, chronicity, and severity of childhood adversity, as well as perceived psychological stress, and LTL in individuals across a variety of psychiatric diagnoses. Potential biological mechanisms of telomere shortening, which may be seen across psychiatric diagnoses, include excessive immune cell mitosis (as may be seen in repeated clonal expansion of leukocytes), increased oxidative stress and inflammation, decreased brain growth factors, and imbalances in metabolic factors, the hypothalamus-pituitary-adrenal axis, and autonomic nervous system functioning(62–65).

Strengths and Limitations

Strengths of this meta-analysis are the large total sample (N=14,827) and the comparison of LTL across multiple disorders. We were able to explore and control for possible causes of heterogeneity using meta-regression, allowing a more accurate determination of the relationship of LTL and psychiatric disorder. However, we cannot rule out the influence of comorbid psychiatric or medical disorders on the effect sizes. Most of the samples included here involved participants with comorbid symptoms or diagnoses (e.g., anxiety and depression), with medical illnesses or taking a variety of medications. In addition, we were not able to examine the effects of other potential moderators, including substance use, exercise, body mass index, age of onset or the duration and severity of the psychiatric disorders since these variables were not reported consistently across studies. The results of the meta-regression suggest that while age and diagnosis contribute, covariates other than age, sex, assay method and diagnosis also contribute substantially. Furthermore, the covariates that were adjusted for within the primary studies differed (e.g., some primary studies adjusted for BMI while others did not). Thus we cannot rule out other moderators of the relationship between TL and psychiatric disorders.

Importantly, the cross-sectional nature of the studies reviewed here limited our ability to draw causal conclusions regarding the association between telomere shortening and psychiatric disorders. While most authors suggest that telomere shortening is a consequence of prolonged physiological dysregulation, another possibility is that short telomeres antedate

the development of psychiatric disorders. Of note, a recent meta-analysis in almost 20,000 subjects estimated the heritability of LTL at 70%(7). Another recent study found that girls at high genetic risk for MDD (by virtue of having mothers with MDD) had short salivary TL before any occurrence of depressive episodes(66). Longitudinal studies with measures of TL and psychiatric disorder status at multiple time points are needed to elucidate the causal relation. Importantly, the present data in no way substantiate or refute a causal relationship between telomere shortness and medical illness or mortality in individuals with psychiatric illnesses. Further clarity regarding the relationship between telomere length and medical illness and mortality is also needed(67). Finally, new publications in this area continue to be published, and the results of this meta-analysis should only be interpreted on the basis of data available through November 2014.

Conclusions

This meta-analysis shows that LTL shortening is found across various psychiatric disorders, and also raises the possibility that specific types of psychiatric disorders may be differentially associated with shorter LTL. Future research should focus on identifying possible common mechanisms of telomere shortening *across* disorders, and on elucidating potential differences in telomere shortening *between* psychiatric disorders.

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Acronyms used

TL	telomere length
LTL	leukocyte telomere length
MDD	major depressive disorder
PTSD	post-traumatic stress disorder
BD	bipolar disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ICD-10	International Classification of Diseases, 10th edition

FISH	Quantitative fluorescence in situ hybridization
PCR or Q-PCR	Quantitative polymerase chain reaction
df	degrees of freedom
BMI	body mass index
SMD	standard mean difference
SE	standard error

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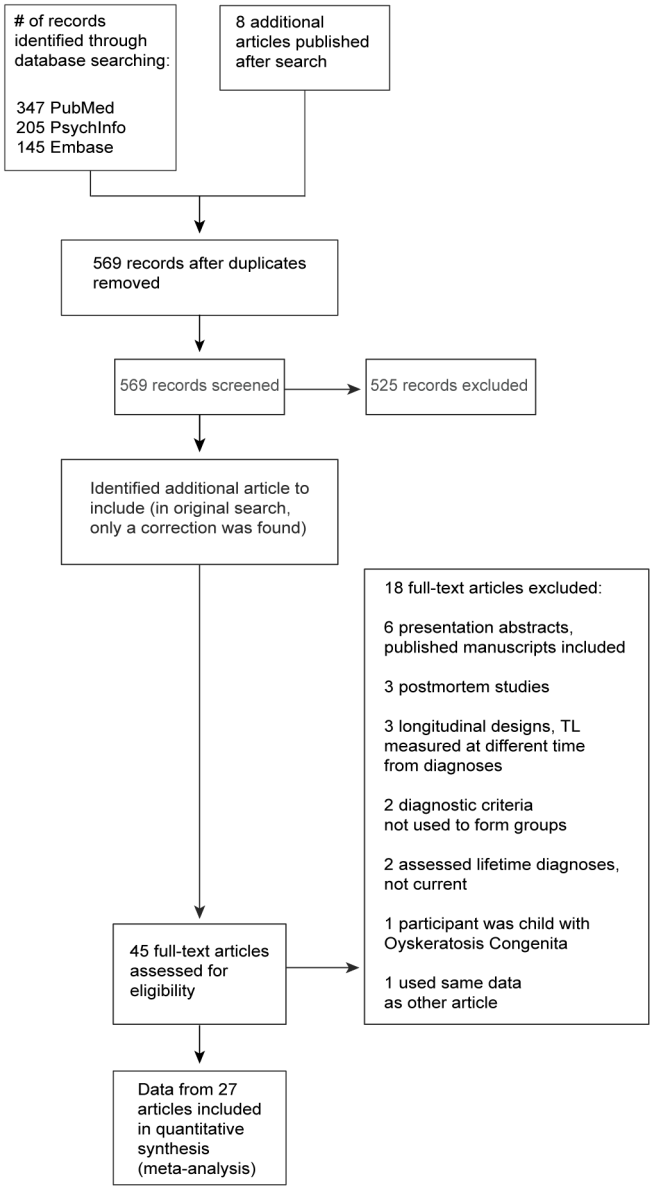

Figure 1.
Selection of Studies

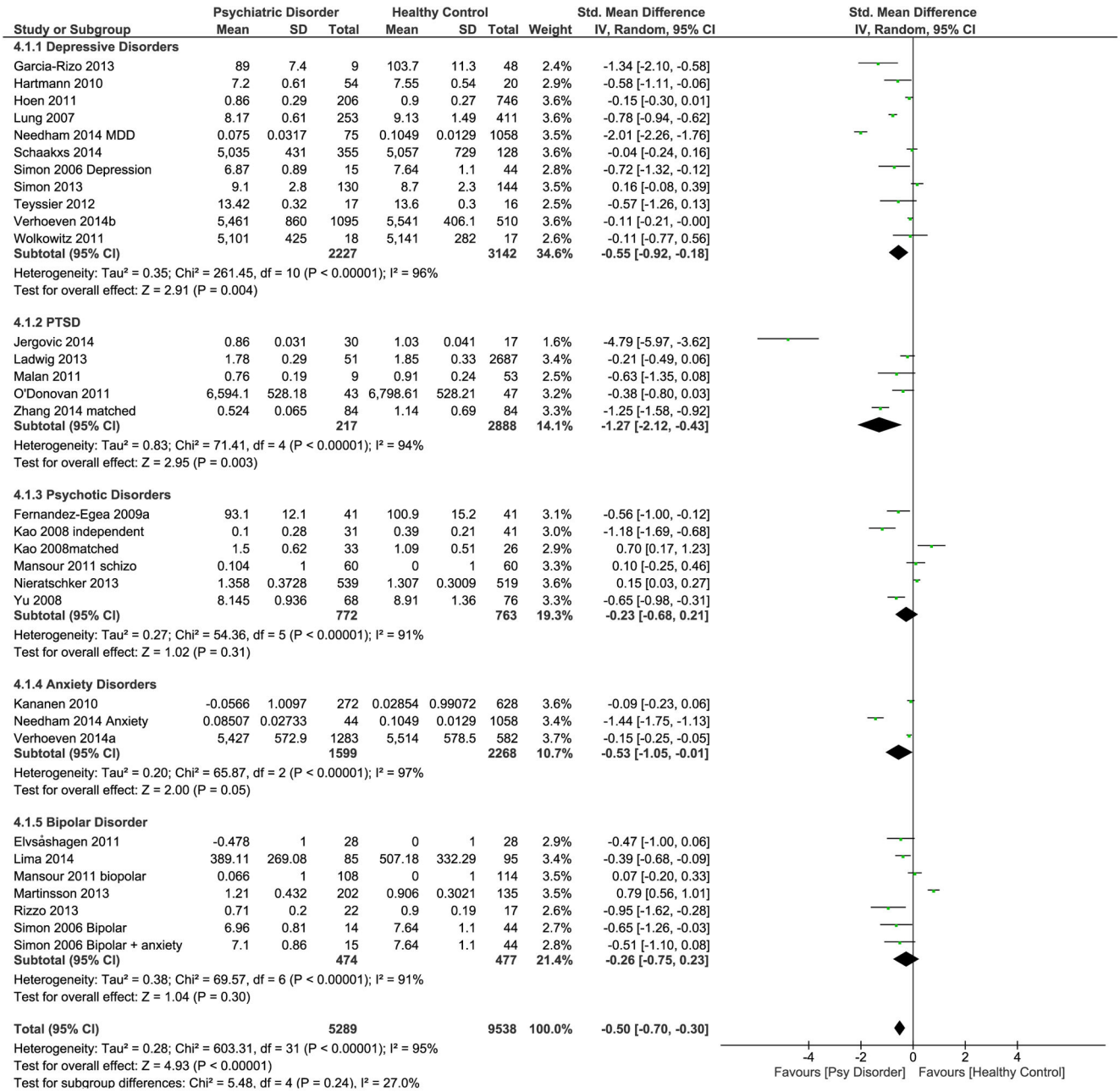

Figure 2.

Differences in effect sizes of studies examining different psychiatric disorders.

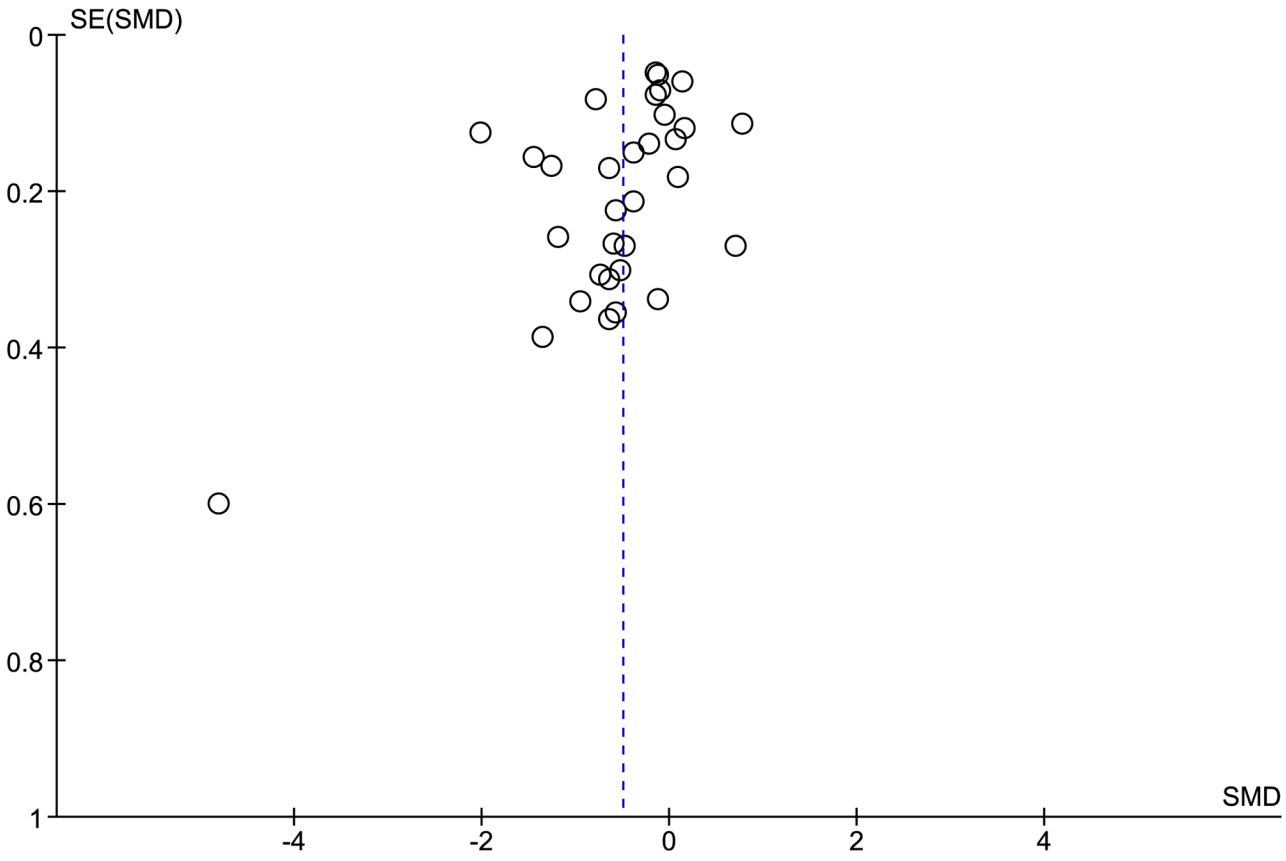

Figure 3.
Funnel Plot to examine publication bias.
Note: SMD=standard mean difference (Hedge's *g*); SE=standard error of standard mean difference. Egger test: −1.02, CI −3.89, 1.84, p=0.47

Table 1

Search strategy

	Search terms	Abstracts found
PubMed	(Telomere[MeSH Terms]) AND mental disorders[MeSH Terms]	341
	(Telomere shortening[MeSH Terms]) AND mental disorders[MeSH Terms]	21 (15 duplicates)
	(Telomere shortening[MeSH Terms]) AND mood disorders[MeSH Terms]	3 (all duplicates)
PsycInfo	su(mental disorders) AND ti(telomere) OR ab(telomere)[1]	205
subtotal		507 (45 duplicates)
Embase	Used following: “map to preferred term in Emtree” and “limit to terms indexed as major focus”	
	‘telomere’/exp AND ‘mental disease’/exp	140
	‘mental disease’/exp AND ‘telomere shortening’/exp	15
Total		565 (97 duplicates)

[1] automatically includes plural form

Table 2

Study Characteristics

	First author & year	Psychiatric Disorder Subgroup	Psychiatric Diagnoses included	Study Design	Variables used for Matching	Assay	Covariates used in analyses	Adjusted ?	Mean Age	% Female	N Psychiatric Group	N Control Group	log transformed?
1	Elvashagen 2011(27)	Bipolar	Bipolar type II	Matched	sex, age, education	FISH	-	yes	34.80	68.0	28	28	no
2	Fernandez-Egea 2009(28)	Psychosis	schizophrenzia, schizophrenifor m disorder, brief psychotic disorder, delusional disorder& psychosis NOS	Matched	BMI, age, gender, smoking habits	FISH	-	yes	28.70	31.7	41	41	no
3	Garcia-Rizo 2013(29)	Depression	MDD	Matched	age, gender, BMI, cortisol, catchment area, and smoking	FISH	-	yes	28.19	38.1	9	48	no
4	Hartmann 2010(30)	Depression	MDD	Matched	age	Southern blot	-	yes	49.10	56.8	54	20	no
5	Hoen 2011(31)	Depression	MDD	Independent	-	PCR (or Q-PCR)	age, sex	yes	66.72	18.5	206	746	no
6	Jergovic 2014(32)	PTSD	PTSD	Matched	age	PCR (or Q-PR)	-	yes	46.37	0.0	30	17	no
7	Kananen 2010(33)	Anxiety	GAD, panic disorder, social phobia, agoraphobia and phobia NOS	Matched	sex, age, university hospital district	PCR (or Q-PCR)	stress, age, gender, “various covariates “	yes	49.81	63.0	272	628	yes
8	Kao 2008(34)	Psychosis	schizophrenia	Independent	-	PCR (or Q-PCR)	age, sex	yes	31.41	27.8	31	41	yes
9	Kao 2008(34)	Psychosis	schizophrenia	Matched	age	PCR (or Q-PCR)	-	yes	34.90	0.0	33	26	no
10	Ladwig 2013(35)	PTSD	PTSD	Independent	-	PCR (or Q-PCR)	age	no	56.46	50.7	51	2687	no
11	Lima 2014(36)	Bipolar	Bipolar type I and type II	Matched	Age, sex, education	PCR (or Q-PCR)	-	Yes	30.86	30.9	85	95	no
12	Lung 2007(37)	Depression	MDD	Independent	-	Southern blot	-	no	45.00	59.5	253	411	no
13	Malan 2011(38)	PTSD	PTSD	Independent	-	PCR (or Q-PCR)	age	yes	22.65	100.0	9	53	yes
14	Mansour 2011(39)	Bipolar	Bipolar type I	Matched	age, area of residence	PCR (or Q-PCR)	age, sex	yes	26.21	46.9	108	114	no
15	Mansour 2011(39)	Psychosis	Schizophrenia & schizoaffective disorder	Matched	age, area of residence	PCR (or Q-PCR)	age, sex	yes	27.59	35.0	60	60	no
16	Martinsson 2013(40)	Bipolar	Bipolar type I, type II, & NOS	Matched	age, sex	PCR (or Q-PCR)	age, sex	yes	53.48	56.4	202	135	no
17	Needham 2014(41)	Anxiety	GAD & panic disorder	Independent	-	PCR (or Q-PR)	age, sex, race	yes	29.37	56.4	44	1058	yes
18	Needham 2014(41)	Depression	MDD	Independent	-	PCR (or Q-PR)	age, sex, race	yes	29.35	56.5	75	1058	yes
19	Nieratschker 2013(42)	Psychosis	schizophrenia	Independent	-	PCR (or Q-PCR)	age, batch, sex	yes	37.98	46.5	539	519	no
20	O’Donovan 2011(43)	PTSD	PTSD	Independent	-	PCR (or Q-PCR)	age	yes	30.43	51.1	43	47	no
21	Rizzo 2013(44)	Bipolar	Bipolar type I	Matched	age, sex	PCR (or Q-PCR)	age, BMI	yes	42.38	100.0	22	17	no

	First author & year	Psychiatric Disorder Subgroup	Psychiatric Diagnoses included	Study Design	Variables used for Matching	Assay	Covariates used in analyses	Adjusted ?	Mean Age	% Female	N Psychiatric Group	N Control Group	log transformed?
22	Schaakxs 2014(20)	Depression	MDD, dysthymia, & minor depression	Independent	-	PCR (or Q-PR)	age, sex, years of education	yes	70.47	65.0	355	128	no
23	Simon 2006(45)	Bipolar w/o anxiety	Bipolar disorder w/o comorbid anxiety disorder	Matched	age	Southern blot	age, sex	yes	50.74	43.1	14	44	no
24	Simon 2006(45)	Bipolar w/anxiety	Bipolar disorder w/comorbid anxiety disorder	Matched	age	Southern blot	age, sex	yes	50.78	44.1	15	44	no
25	Simon 2006(45)	Depression	MDD	Matched	age	Southern blot	age, sex	yes	50.45	45.8	15	44	no
26	Simon 2013(46)	Depression	MDD	Matched	age, sex	Southern blot	age, sex	yes	42.45	64.7	130	144	yes
27	Teyssier 2012(47)	Depression	MDD	Matched	age, BMI, physical activity, alcohol consumption	PCR (or Q-PCR)	-	yes	38.58	100.0	17	16	no
28	Verhoeven 2014a(48)	Anxiety	GAD, panic disorder, social phobia & agoraphobia	Independent	-	PCR (or Q-PR)	age, gender, education	yes	41.42	65.6	1283	582	no
29	Verhoeven 2014b(19)	Depression	MDD	Independent	-	PCR (or Q-PCR)	age, sex, education	yes	40.64	65.1	1095	510	no
30	Wolkowitz 2011(49)	Depression	MDD	Matched	age, sex, ethnicity	PCR (or Q-PCR)	age, sex	yes	36.70	66.0	18	17	yes
31	Yu 2008(50)	Psychosis	schizophrenia	Matched	age	Southern blot	age, sex	yes	38.08	75.0	68	76	no
32	Zhang 2014(51)	PTSD	PTSD	Matched	age, gender	PCR (or Q-PCR)	-	yes	27.60	9.0	84	84	no

Table 3

Results of subgroup analyses

	# of studies in each subgroup	Hedges *g* Effect size (CI)	I^2	Test of subgroup differences	
				Chi-squared (df)	p
Adjusted analyses					
Adjusted for covariates	30	−0.50 (−0.71, −0.29)	95%	0.00 (1)	0.98
Did not adjust for covariates	2	−0.51 (−1.06, 0.05)	92%		
TL assay					
FISH	3	−0.71 (−1.15, −0.27)	47%	0.91 (2)	0.63
PCR or Q-PCR	22	−0.46 (−0.71, −0.22)	96%		
Southern Blot	7	−0.52 (−0.87, −0.16)	86%		
Psychiatric disorder					
Depressive disorders	11	−0.55 (−0.92, 0.18)	96%	5.48 (4)	0.24
PTSD	5	−1.27 (−2.12, −0.43)	94%		
Psychotic disorders	6	−0.23 (−0.68, 0.21)	91%		
Anxiety disorders	3	−0.53 (−1.05, −0.01)	97%		
Bipolar disorders	7	−0.26 (−0.75, 0.23)	91%		

Note: I^2 is the proportion of observed variance that reflects real differences in the effect size for each subgroup.

Table 4

Meta-regression: Age, sex, psychiatric diagnosis, and assay method as moderators of effect size

	B	SE	df	t	p
Mean age	0.02	0.01	22	1.88	0.07
% female	0.01	0.01	22	1.59	0.13
Anxiety[1]	−0.18	0.30	22	−0.61	0.55
Bipolar[1]	0.26	0.23	22	1.20	0.24
Psychosis[1]	0.58	0.24	22	2.38	0.03
PTSD[1]	−0.54	0.26	22	−2.11	0.05
Southern Blot[2]	−0.10	0.35	22	−0.46	0.65
FISH[2]	−0.12	0.28	22	−0.44	0.67

[1]Reference group is Depression

[2]Reference group is PCR