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Running head: BRIEF REPORT: ANXIETY AND TELOMERE LENGTH

A Meta-Analysis of the Relationship between Anxiety and Telomere Length

Abstract

Background and Objectives: Telomeres are protective caps at the ends of chromosomes, and shorter telomeres are associated with poor physical health. The present study set out to consolidate the varying effect sizes found so far in studies of anxiety and telomere length. **Design and Methods:** A meta-analytic investigation of the relationship between anxiety and telomere length used information from 17 different samples comprising a total of 19,424 participants. **Results**: The results showed a small but significant association, r = -.06, between higher anxiety and shorter telomeres. Studies comparing individuals diagnosed with an anxiety disorder with other individuals had a significant effect size, and studies that did not use this comparison threshold did not have a significant effect size. **Conclusions**: Anxiety is associated with an important biomarker related to health. Future experimental studies that examine the impact of interventions intended to reduce anxiety in conjunction with measurement of telomere length can further clarify the impact of anxiety on telomere length.

Key Words: anxiety; anxiety disorders; health; meta-analysis; telomere

A Meta-Analysis of the Relationship between Anxiety and Telomere Length

1. Introduction

Telomeres protect the ends of chromosomes. Shorter telomeres are associated with poor health (Epel, 2012), including increased risk of stroke, myocardial infarction, diabetes (D'Mello et al., 2015) and cancer (Ma et al., 2011). Shorter telomeres prospectively often predict higher mortality (e.g., Deelen et al., 2014). For that reason, some experts view telomere length as an indicator of human aging (Lindqvist et al., 2015). Recent human and animal research findings indicate that short telomeres can play a causal role in the development of disease (Blackburn, Epel, & Lin, 2015).

Telomere length is influenced by genetic predisposition (Broer et al., 2013), age and gender (Sanders & Newman, 2013), health behaviors such as smoking (Huzen et al., 2014), and psychosocial factors, including mental health (Lindqvist et al., 2015).

A number of studies have examined the association between mental health indicators and telomere length. For example, meta-analyses indicated that overall there is a relationship between depression and shorter telomere length (Ridout, Ridout, Price, Sen, & Tyrka, 2016; Schutte & Malouff, 2015). There is a small non-significant meta-analytic trend in the direction of an association between schizophrenia and shorter telomeres (Polho, De-Paula, Cardillo, Dos Santos, & Kerr, 2015). Additionally, greater perceived stress is associated with shorter telomeres (Mathur, Epel, Kind, Desai, Parks, Sandler, & Khazeni, 2016; Schutte & Malouff, 2014).

A substantial percentage of individuals suffer from high levels of anxiety. Incident rates of anxiety disorders pooled across studies indicate that the one-year prevalence rate for anxiety disorders is 11% and the lifetime prevalence rate is 17% (Somers, Goldner, Waraich, & Hsu, 2006). A number of studies have examined the relationship between anxiety and telomere length, but these findings have not been consolidated. For instance, Hoen, Rosmalen, Schoevers, Huzen, van der Harst and de Jonge (2013) used a standardized interview schedule to diagnose

anxiety disorders in a community sample of 1078 adults. Three years later the researchers collected blood from the participants and used qPCR to assess telomere length in leukocytes. The study found a significant association between anxiety level at time 1 and telomere length at time 2.

Anxiety could affect telomere maintenance by disrupting the hypothalamic-pituitary axis and immune functioning and thereby increasing oxidative stress, which in turn can damage telomeres (Verhoeven, Revesz, van Oppen, Wolkowitz, & Penninx, 2015). Consistent with this view, studies have shown that oxidative stress can damage telomeric DNA (Grahame & Schlesinger, 2012; von Zglinicki, Bürkle, & Kirkwood (2001).

The association between anxiety and telomere length, if causal, would be important to the extent that telomere length is a valid indicator of aging. Potentially, reducing anxiety could help delay aging. The first step in evaluating the effects of anxiety on telomere length is determining whether the two variables are associated.

The aim of the present study was to meta-analyze the effect sizes found in correlational studies of anxiety and telomere length. The analyses tested the prediction that anxiety would be related to shorter telomeres and examined several possible factors that might moderate the association.

2. Method

The meta-analysis inclusion criteria for studies were: (1) a comparison of telomere length for groups with and without either an anxiety disorder listed in DSM-5 or a comparison of groups of high and low anxiety levels or a correlation between anxiety level and telomere length, (2) anxiety measured at the same time as telomere length or after, and (3) sufficient statistical results to allow the calculation of an effect size suitable for meta-analysis, and (4) if a beta weight only is reported, the other variables in the regression are not closely related to anxiety. We created this final criterion because including beta weights in a meta-analysis can prove deceptive if the other variables in the regression are closely related to the target measure

Three databases, Google Scholar, PsychINFO, and Pubmed, were searched for the term telomere and one of the following terms: anxiety, post-traumatic, PTSD, panic, phobia, obsessive-compulsive, OCD. An initial search identified 87 articles; after records were screened and full-text 22 articles were assessed for eligibility. Sixteen studies providing information for 17 different samples met the inclusion criteria. Some of the studies focused on specific anxiety disorders; some examined anxiety level. Table 1 shows the included studies.

One study (Malan, Hemmings, Kidd, Martin, & Seedar (2011), examined whether short telomere length soon after a woman was raped was associated with a diagnosis of post-traumatic stress disorder months later. The study, with 64 participants, found a significant association. Because the study measured telomere length before measuring PTSD, we excluded it from the meta-analysis. The researchers suggested that the significant findings raise the possibility that short telomeres make a person vulnerable to developing PTSD. That could be, although it is also possible that a third variable, such as unhealthful genes, leads to both short telomeres and developing PTSD after a trauma.

For each study we recorded effect size data, such as a correlation, along with sample size, and direction of the correlation. For evaluation of potential moderators, we recorded for each study: gender of the sample, mean age of the sample, type of anxiety disorder, whether age and gender were statistically controlled, type of cell used for telomere assays, whether the design was longitudinal, and whether telomere length was log transformed due to non-normality, which relates to the distribution of telomere length in the sample. o.

In order to evaluate overall study quality as a moderator, we created a quality index by assigning one point for each of the following five factors: (1) used a diagnostic interview schedule to assess anxiety; (2) controlled statistically for sex or used only one sex; (3) controlled statistically for age; (4) stated in report that assay was done blind to anxiety level; (5) longitudinal research design. Scores on the index could vary from 0 to 5, with higher scores

indicating higher quality. For purposes of analysis, we categorized studies as higher (index > 3) or lower (index 3 or below).

3. Results

The search produced analyses for 17 different samples (reported in 16 articles) with a total of 19,424 participants. The samples studied included mostly a range of individuals in the community (Hoen et al., 2013; Ladwig et al., 2013). Other samples were drawn from specific groups such as soldiers (Boks et al., 2015; Zhang et al., 2014), war veterans (Jergović et al., 2014); women with fibromyalgia (Hassett et al., 2012), or HIV positive individuals (Lee et al., 2014).

Table 1 shows the contributions of each analysis to the meta-analysis, along with information describing each study. Figure 1 shows a forest plot of the effect sizes.

Insert Table 1 about here

Insert Figure 1 about here

The meta-analytic association between anxiety level and telomere length was r = -.06 (95% CIs -.08, -.03), p < .001, indicating higher levels of anxiety were associated with shorter telomeres. Duval and Tweedie's trim and fill bias analysis suggested that two studies were missing, leading to an adjusted effect size of r = -.05 (95% CIs -.08, -.02). The classic fail-safe N was 148, meaning that 148 studies with 0 effect size would be needed to make the meta-analytic result non-significant.

Table 2 shows the results for categorical moderator variables; only one showed a significant effect: Samples with both men and women had a significantly higher effect size than studies with only men or only women. There was a nonsignificant trend in the direction of higher effect sizes for comparisons of clinical and non-clinical groups versus correlations of anxiety and telomere length. Method of moments meta-regression showed that the association between mean age of the sample and telomere length was less than .001, p = .40.

Insert Table 2 about here

4. Discussion

The meta-analytic results show a small but significant association, r = -.06 (adjusted r = -.05), between higher anxiety and shorter telomeres, across 17 different samples and a total of 19,424 participants. The importance of finding a significant relationship between anxiety and telomere length lies in (1) the connection anxiety experienced over a long period of time and greater mortality (Khan, Faucett, Morrison, & Brown, 2013), and (2) the relationship between shorter telomeres and greater mortality (Deelen et al., 2014). Anxiety could lead to shorter telomeres, which in turn could lead to a shorter life.

The -.05 magnitude of the adjusted meta-analytic effect size is similar to the -.06 effect size found in a meta-analysis of the association between perceived stress and telomere length (Mathur et al., 2016). The similarity may be due to anxiety and perceived stress measures assessing overlapping characteristics, such as feeling nervous (Cohen, Karmarck, and Mermelstein, 1983). The results of Mathur et al. (2016) relating to stress suggested that effect sizes may be larger when comparisons are based on group comparisons; similarly, in the present meta-analysis studies comparing individuals who had a diagnosed anxiety disorder with other individuals had a significant effect size, and studies that did not compare clinical and non-clinical groups did not have a significant effect size.

Another related characteristic, depression, has also been found to be associated with shorter telomeres (Ridout et al., 2016; Schutte & Malouff, 2015). The effect sizes for the relationship between depression and telomere length found in the meta analyses reported by Ridout et al.(2016) and Schutte & Malouff (2015) were somewhat larger than the effect size for the relationship between anxiety and telomere length, but roughly comparable. It could be that various types of negative emotions and related characteristics share common biological and psychological components (Barlow, Allen, & Choate, 2004).

Study variables possibly related to study quality were not significant moderators of effect size either individually or collectively in an index of study quality. These variables included

whether the study controlled in some way for age and sex, whether the report stated that the telomere assay was done blind to anxiety level, and whether the study was longitudinal.

The meaning is unclear of the finding that the mixed-sex samples showed significantly higher correlations than single-sex samples. With 10 moderator analyses completed, the result could be due to chance. Some other moderator results showed substantial but nonsignificant effects. For instance, studies that used an interview measure of anxiety had over twice the meta-analytic effect size of studies with self-report measures.

The meta-analytic findings regarding anxiety and telomere length provide a preliminary assessment of results in this area. The correlational findings of the meta-analyzed studies do not allow inferences regarding causality; there may be residual confounding by third variables. Experimental studies that examine the impact of interventions intended to reduce anxiety on telomere length are needed to provide better information regarding the causal relationship between anxiety and telomere length. Future research might also address the moderating effect of duration of anxiety and use of anti-anxiety medication on the association between anxiety and telomere length. Explicit mention of blinding procedures would aid interpretation of results. The use of diagnostic interviews, evaluation of the reliability of telomere-length assays, and controlling for sex and age would help make future studies methodologically sound.

The research methods used by the studies varied. The best method for such research in the future involves careful assessment of anxiety, with diagnostic interview schedules when possible; controlling for age and sex or using participants of one age or sex only; evaluating and reporting reliability data for the assay of telomere length; keeping assay staff blind to anxiety level of participants and stating this blinding in the research report; and using a longitudinal design, with anxiety measurement prior to assessment of telomere length. Only the study of Hoen et al. (2013) had all these attributes.

5. Conclusions

In conjunction with research on other mental health problems, such as depression, and telomere length, the present findings regarding anxiety and telomere length suggest a role for psychological factors in relation to telomere functioning. Individuals diagnosed with an anxiety disorder may be at particular risk of telomere shortening. Future studies that explore the telomere-related biological effects of anxiety could help clarify the nature of the association between anxiety and telomere length. Experimental studies that examine the impact of interventions intended to reduce anxiety in conjunction with measurement of telomere length might clarify the impact of anxiety reduction on telomere length.

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Table 1: *Studies Included in Meta-Analysis*

Authors	Sample description	*N*	Sample sex	Sample mean age	Type of anxi-ety	Type of anxiety measure	Compari-son of diagnosed group and normals	Sex statistic-ally controlled	Age statistic-ally controlled	Telomere assay reported as blinded[3]	Telomere length log transformed	Longitud-inal study	Study quality score[7]	Correlation of anxiety level and telomere length
Boks et al. 2014	Soldiers in war zone	96	Men	27	PTSD	Self-report	No	No	No	No	No	Yes[4]	1	.241
Hassett et al 2012[1]	Fibromyalgia patients, controls	66	Women	45	Other	Self-report	No	Single sex	Yes	No	No	No	2	.005
Hoen et al 2013	Community	974	Mixed	53	Other	Interview	Yes	Yes	Yes	Yes	Yes	Yes[5]	5	-.080
Jergovic et al 2014	War veterans	45	Men	46	PTSD	Interview	Yes	Single sex	No	No	No	No	2	-.300
Kananen et al 2010	Anxiety disorder, control	939	Mixed	50	Other	Interview	Yes	Yes	Yes	No	Yes	No	3	-.080
Ladwig et al 2013	Community	2738	Mixed	56	PTSD	Self-report	Yes	No	Yes	No	No	No	3	-.047
Lee et al 2014	HIV positive	275	Mixed	45	Other	Self-report	No	No	No	No	No	No	0	.005
Lima et al 2015	Bipolar disorder patients	80	Mixed	39	Mixed	Interview	Yes	No	No	No	No	No	1	-.087
Needham et al 2014	Community	1164	Mixed	29	Other	Interview	Yes	Yes	Yes	Yes	Yes	No	4	-.020
O'Donovan et al 2011	PTSD, control	88	Mixed	30	PTSD	Interview	Yes	No	Yes	No	No	No	2	-.229
Okereke et al 2012	Community	5283	Women	59	Other	Self-report	No	Single sex	Yes	Yes	Yes	No	4	-.024
Shalev et al 2014 men	Community	313	Men	38	Mixed	Interview	Yes	Single sex	No	Yes	No	Yes[6]	5	-.083
Shalev et al 2014 women	Community	266	Women	38	Mixed	Interview	Yes	Single sex	No	Yes	No	Yes[6]	4	-..032
Surtees et al 2011	Community	1441	Women	62[7]	GAD	Self-report	Yes	Single sex	Yes	No	No	No	3	-.020
Tyrka et al 2015	Community	141	Mixed	31	Other	Both	Mixed	Yes	Yes	No	Yes	No	3	-.307
Verhoeven et al 2015	Community	1865	Mixed	41	Other	Self-report	Yes	Yes	Yes	No	No	No	4	-.069
Zhang et al 2014[2]	Soldiers in war zone	650	Mixed	29	PTSD	Self-report	Yes	No	Yes	No	No	No	2	-.101

Note. Effect sizes for multiple measures of anxiety reported in Lima et al., Shalev et al. (men), Shalev et al. (women), and Tyrka et al. were averaged for calculation of the sample effect size used in the meta-analysis. [1] We used trait anxiety. [2] We used results for all participants, with age control. [3] Report states that telomere assay was done blind to anxiety level. [4]Association of six-month change in PTSD with six-month change in telomere length. [5]Association of anxiety disorder with telomere length two years later; an analysis adjusting for measurement of telomere length conducted four years prior to measurement of anxiety showed a smaller but similar effect size. [6] Association of anxiety disorder with 12-year change in telomere length. [7] We used midpoint of age range as the mean. [7] Score calculated by assigning one point for each of the following study

characteristics: Comparison of diagnosed group and normal group; sex controlled statistically or by using one sex only; age statistically controlled; telomere assay reported as blinded; longitudinal study design.

Table 2

Categorical m*oderator results*

Moderator	*k (samples)*	*r (effect size)*	Lower 95% CI	Upper 95% CI	*p (for subcategory)*	Q^1	*p (for Q)*	i^2
Sex, $Q(2) = 6.6$, $p = .04$								
Men	3	-.037	-.295	.227	.78	11.6	<.01	83
Women	4	-.022	-.042	-.003	.07	0.1	.99	0
Mixed	10	-.073	-.106	-.040	<.001	17.5	.04	48
Type of anxiety, $Q(1) = 0.2$, $p = .69$								
PTSD only	5	-.071	-.174	.033	.18	15.8	<.01	75
Other/mixed	12	-.049	-.076	-.023	<.001	20.5	.04	46
Type of anxiety measure[3], $Q(1) = 3.5$, $p = .06$								
Self-report	8	-.036	-.064	-.008	.01	14.9	.04	53
Diagnostic interview	9	-.090	-.139	-.041	<.001	15.1	.06	47
Comparison of diagnosed anxiety group with normal group[4], $Q(1) = 2.9$, $p = .06$								
No	4	.027	-.067	.120	.57	6.9	.08	56
Yes	13	-.067	-.095	-.039	<.001	23.6	.02	49
Sex statistically controlled, $Q(2) = 4.2$, $p = .12$								

No	5	-.037	-.159	.086	.55	13.7	.01	71
Yes	6	-.070	-.108	-.032	<.001	12.6	.03	60
All one sex	6	-.025	-.045	-.006	.01	5.0	.41	58
Age statistically controlled, $Q(1) = 0.3$, $p = .58$								
No	6	-.029	-.129	.072	.58	12.2	.03	59
Yes	11	-.058	-.085	-.031	<.001	25.0	.01	60
Telomere assay reported as blinded $Q(1) = 1.9$, $p = .16$								
No	12	-.067	-.109	-.024	.01	32.8	.01	66
Yes	5	-.033	-.055	-.011	.01	3.6	.47	0
Telomere length log transformed, $Q(1) = 0.3$, $p = .56$								
No	12	-.050	-.085	-.015	.01	21.7	.03	49
Yes	5	-.069	-.122	-.016	.01	15.8	.01	75
Longitudinal, $Q(1) = 0.5$, $p = .49$								
No	13	-.057	-.085	-.028	<.001	27.7	.01	57
Yes	4	-.020	-.119	.079	.69	9.4	.02	68
Study quality index, ($Q(1) = 0.91$, $p = .34$								

Score above 3	6	-.042	-.064	-.020	<.001	5.5	.36	9
Score 3 or below	11	-.068	-.118	-.018	.01	32	,.001	69

Note. When studies reported more than one effect sizes for a sample, we used the average. [1] For homogeneity Q, $df = k - 1$. [2] Percentage of variance due to sample heterogeneity [3] For this analysis, we used the interview analysis and not the self-report analysis of Tyrka et al. (2015). [4] For this analysis, we used from Tyrka et al. only the comparison of diagnosed and not diagnosed.

Figure 1. Study effect sizes in order of magnitude.