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The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis

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Abstract

This meta-analysis examined the association between the level of childhood psychosocial stressors and telomere length, an important health biomarker. The meta-analysis, including 27 samples and 16,238 participants, found a significant association of −0.08 between a higher level of childhood stressors and shorter telomere length at a mean age of 42 across studies. Moderator analyses showed a trend in the direction of effect sizes being significantly larger with shorter times between the stressors and telomere measurement. Moderator analyses showed significantly higher effect sizes for studies that used a categorical method for assessing child stressor level and for assays completed with qPCR rather than with the Southern blot method. There was no significant moderation of effect size by whether study assayed leukocytes or buccal cells, whether the study assessed child stressor level by memory-based recall versus archival records, and whether the study controlled for age, sex, or additional variables. The results, focused on childhood events, add to prior findings that perceived stress and negative emotions are associated with telomere length.

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Key words: childhood stressors, childhood trauma, meta-analysis, telomere, telomere length.

Contributions: LMH, identified articles; coded data; wrote parts of introduction, method, and results; completed Figure 1, entered references; NSS, originated idea for the meta-analysis; checked codings; wrote final version of introduction, wrote parts of discussion; JMM, supervised entire project, checked codings, wrote final version of results and discussion, submitted manuscript; ESE, contributed idea for specific focus of the meta-analysis, provided advice about coding decisions, made suggestions about improvements to the manuscript.

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Introduction

Psychosocial stressors experienced during childhood, such as maltreatment or neglect, predict an increased risk of negative health outcomes across the life span (Felitti *et al*., 1998; Shonkoff, Boyce, & McEwen, 2009; Shonkoff & Garner, 2012; Wegman & Stetler, 2009). Experiencing high levels of childhood psychosocial stressors is associated with the later development of depression, bipolar disorder, post-traumatic stress disorder, and substance abuse, as well as cardiovascular disease, gastrointestinal disorders, metabolic disorders and respiratory problems (Green *et al*., 2010; Wegman & Stetler, 2009). High levels of childhood psychosocial stressors are associated with an increased risk of premature death (Brown *et al*., 2009). Stressors experienced during early developmental windows may have epigenetic effects and enduring influences on biomarkers and nervous and immune system functioning (Shonkoff & Garner, 2012). For example, high levels of childhood stressors alter physiologic, cellular, and immune stress responses (Drury *et al*., 2014).

Telomere length may link childhood psychosocial stressors with later health developments. Telomeres are a biomarker associated with various aspects of health (Rode, Nordestgaard, & Bojesen, 2015). Telomeres are the nucleoprotein complexes at the end of chromosomes that preserve genetic information, regulate cellular replicative capacity, and prevent end-to-end fusion (Blackburn, Greider & Szostak, 2006). Telomere length erosion can occur through repeated cell division and through exposure to oxidative stress and inflammation (O'Donovan *et al*., 2011). The general trend is for telomeres to shorten with aging; however, telomere biology is dynamic (Blackburn, Epel, & Lin, 2015) and telomeres can lengthen as well as shorten over time (Epel, 2012). Short telomere length is associated with or predicts many of the common diseases of aging, such as cardiovascular disease, stroke, cancer, vascular dementia, osteoporosis, obesity and diabetes (Blackburn *et al*., 2015; Rode *et al*., 2015), and all-cause mortality (Rode *et al*, 2015).

Systematic reviews (Næss & Kirkengen, 2015; Oliveira, *et al*., 2016) of studies of stressors and telomere length suggest that greater exposure to stressors may be associated with shorter telomeres. However, the evidence is mixed, with not all studies finding a significant relationship between exposure to stressors and telomere length. Exposure to stressors, which are events, may lead to greater perceived stress, a psychological phenomenon. Meta-analyses of effect sizes of the relationship across studies of *perceived stress* and telomere length reported a significant meta-analytic association (Schutte & Malouff, 2014; Mathur *et al*., 2016). To date no meta-analysis of effect sizes of the relationship between childhood psychosocial stressors and telomere length across studies has been published. Such a meta-analytic investigation could provide an overall effect size of relationship between

childhood psychosocial stressors and telomere length across studies and examine moderating variables that may account for differences in findings across studies. The findings of such a meta-analysis might provide information regarding mechanisms of aging and disease in relation to early-life experience.

Studies of childhood stressor level and telomere length have differed in how long after childhood stressor exposure telomere length was assessed. Some studies (*e.g.*, Surtees *et al*., 2011) have related exposure to stressors in childhood to telomere length at various adult ages. Other studies (*e.g.*, Shalev *et al*., 2013) have related childhood psychosocial stressors to telomere length in childhood.

Studies have varied in assessment of childhood psychosocial stress. Some studies (*e.g.*, Kananen *et al*., 2010) used continuous measures of childhood trauma. Other studies compared participants in categories of amount of childhood psychosocial stressors, such as high or low exposure to stressors (*e.g.,* Tyrka *et al*., 2015)

Many studies (*e.g.*, Kananen *et al*., 2010) used measures relying on retrospective memory of participants or others, such as parents, of past events. Some studies (*e.g.,* Savolainen, 2014) used archival indicators of psychosocial stressors, such as being separated from parents during a war or being in institutional care.

Studies examining the association between childhood stressors and telomere length also varied in approach to telomere length assessment. Most studies used qPCR (*e.g.,* Chen *et al*., 2014), and two (Glass *et al*., 2010; Kielcolt-Glaser *et al*., 2011) used Southern blot. Most studies assessed telomere length in leucocytes (*e.g.*, Mason *et al*., 2015), and some assessed telomere length in buccal cells (Küffer *et al*., 2016). Some studies controlled for age, gender and other variables, while others did not. Given the wide variance in methods, it is important to examine whether these differences moderate the association between stressor level and telomere length.

Aims and hypotheses of the present study

The main aim of the present study was to use meta-analysis to determine an overall effect size of the association between childhood psychosocial stressor levels and telomere length. A further aim of this study was to examine potential moderators of this association.

The main research hypothesis of this study was that greater childhood psychosocial stress levels would be associated with shorter telomere length. We also hypothesized that because the dynamic nature of telomere biology allows telomere repair (Blackburn *et al*., 2015), the longer the time between stressor occurrence and when the telomere measurement was taken, the lower the association would be. However, it was not possible to code each study for the time between stressor exposure and telomere assay because many studies assessed stressor level over the entirety of childhood. To test the hypothesis as clearly as feasible, we determined whether the higher the mean age at time of telomere measurement in a study, the lower would be the association between level of childhood stressors and telomere length. That was the only directional moderator hypothesis.

Coding studies by type of stressor experienced was not feasible because many studies assessed the occurrence of a wide range of types of stressors and reported results as a sum of the number of childhood stressors. However, we did record the general nature of the stressors focused on in each study, as shown in Table 1. Studies used such a variety of psychosocial stressor measures that it was not feasible to examine specific measures as potential moderators.

In exploratory analyses we examined several possible moderators of effect size with no specific hypothesis about them. We chose these potential moderators because virtually every study provided needed information about them, because the variables could possibly be related to effect size, and because at least some prior meta-analyses relating to telomere length examined them (*e.g.*, Mathur *et al*., 2016; Schutte & Malouff, 2014). These moderator variables included (1) type of tissue assayed, (2) whether the level of stressors was measured as categorical or continuous, (3) what type of assay was used, (4) whether childhood stressor level was based retrospectively on memory of events or not, whether (5) age and (6) sex were controlled, (7) whether additional variables were controlled, and (8) whether telomere length was log-transformed due to non-normal distribution of data.

Literature Search

We systematically searched PsychINFO, Pubmed, EMBASE, CINAHL Complete, Cochrane Central, Research Gate, and Google Scholar to identify all articles, completed at any time, reporting on childhood psychosocial stressors and telomere length. The search concluded in August 2016. The key words of the search included telomere and at least one of the following terms: stress/stressor/stressful, childhood, psychological, abuse, neglect, early life, and social environment. We also reviewed the reference lists of retrieved articles for potentially relevant articles that we had not captured in the database search. Finally, we attempted to contact researchers who had published relevant research findings to ask whether they had any relevant unpublished research findings.

Inclusion criteria of studies in the meta-analysis

We reviewed retrieved articles to determine whether they (1) reported an association between a level of any clear childhood psychosocial stressor and telomere length and (2) stated the sample size. We included studies that reported *r*, standardized beta, and between-groups statistics such as means and standard deviations.

Excluded articles

We excluded studies that examined the association between childhood socio-economic status (SES) and telomere length (*e.g.*, Adams *et al*., 2007; Carroll, Diez-Roux, Adler & Seeman, 2013; Cohen *et al*., 2013; Mitchell *et al*., 2014; Robertson *et al*., 2012; Needham *et al*., 2012, 2013) on the basis that SES in the studies included high as well as low status and did not focus on children in very low SES families. Thus, SES was not a pure measure of psychosocial stress level. We also excluded reports that provided the same results as a report we included in the meta-analysis: Brody, Yu, Beach & Philibert (2015) and Révész, Milaneschi, Terprstra & Penninx (2016). Three studies fit the inclusion criteria but did not provide the data needed for meta-analysis (Zhang *et al*., 2014; Robles, Carroll, Bai, Reynolds, Esquivel, & Repetti, 2016; Theall *et al*., 2013). We attempted unsuccessfully to obtain the needed information from the corresponding authors.

Coding process

Coding involved recording three types of information relating to effect size: *r* or some other statistic that indicates effect size, *N* for the key analysis, and the direction of the association between stressor level and telomere length. Coding also included entering data for each study about the possible moderators of effect size. When studies reported results for more than one measure of level of childhood stressors, we calculated the average effect size across the measures.

Two of us completed the initial coding together. Then a third

member of our research group independently coded the effect sizes and moderators. A comparison of the independent coding showed agreement on 95% of the decisions. For all disagreements regarding coding, we made final decisions by consensus.

Relevant studies identified

The literature search retrieved 2,122 potentially relevant articles. Figure 1 shows the study selection process that resulted in the 27 samples that met all inclusion criteria.

Meta-analytic methods

We report effect sizes below as *r*. When studies reported standardized beta weights with other variables included in the regression, we used the results that controlled for sex and age and as few other variables as possible. It is sensible to include age and sex controlled effect sizes because studies have found that women tend to have longer telomeres (Gardner *et al*., 2014) and that younger individuals tend to have longer telomeres (Marioni *et al*., 2016). Most of the studies did control for those variables, either statistically or by comparing high and low stressor groups that were very similar with regard to the variables.

The Comprehensive Meta-Analysis Program (Borenstein, Hedges, Higgins & Rothstein, 2014) calculated the overall weighted effect size. We used a random effects model in order to allow for between-studies variation. The Q statistic assessed effect-size homogeneity across studies. Finally, trim and fill method and fail-safe *N* assessed the impact of possibly missing studies.

Results

Table 1 shows the key characteristics of each included sample. Figure 2 shows graphically the effect size for each sample. The overall meta-analytic association between level of childhood psychosocial stressors and telomere length, with 27 samples, including 16,238 total participants, was r=-0.082 (95%CIs -0.122, -0.042), P<0.001. There was a significant level of heterogeneity among effect sizes, $Q(26)$=109, P<0.001, I^2=76, suggesting the possibility of finding moderators of effect size.

The fail-safe *N* was 338, indicating that 338 studies with 0 effect size would be needed to reduce the overall effect size to a nonsignificant level. Duval and Tweedie's trim-and-fill statistic indicated that the overall effect size was not significantly affected by the results of small N studies and that no adjustment in effect size was needed. See Figure 3 for the funnel plot of effect sizes.

The mean age at telomere measurement in the studies was 42 years. The only directional hypothesis regarding potential moderators of effect size, that the younger the participants at measurement of telomere length, the higher the effect size, showed a trend towards significance, slope estimate =0.002 (95%CIs 0.000, 0.004),

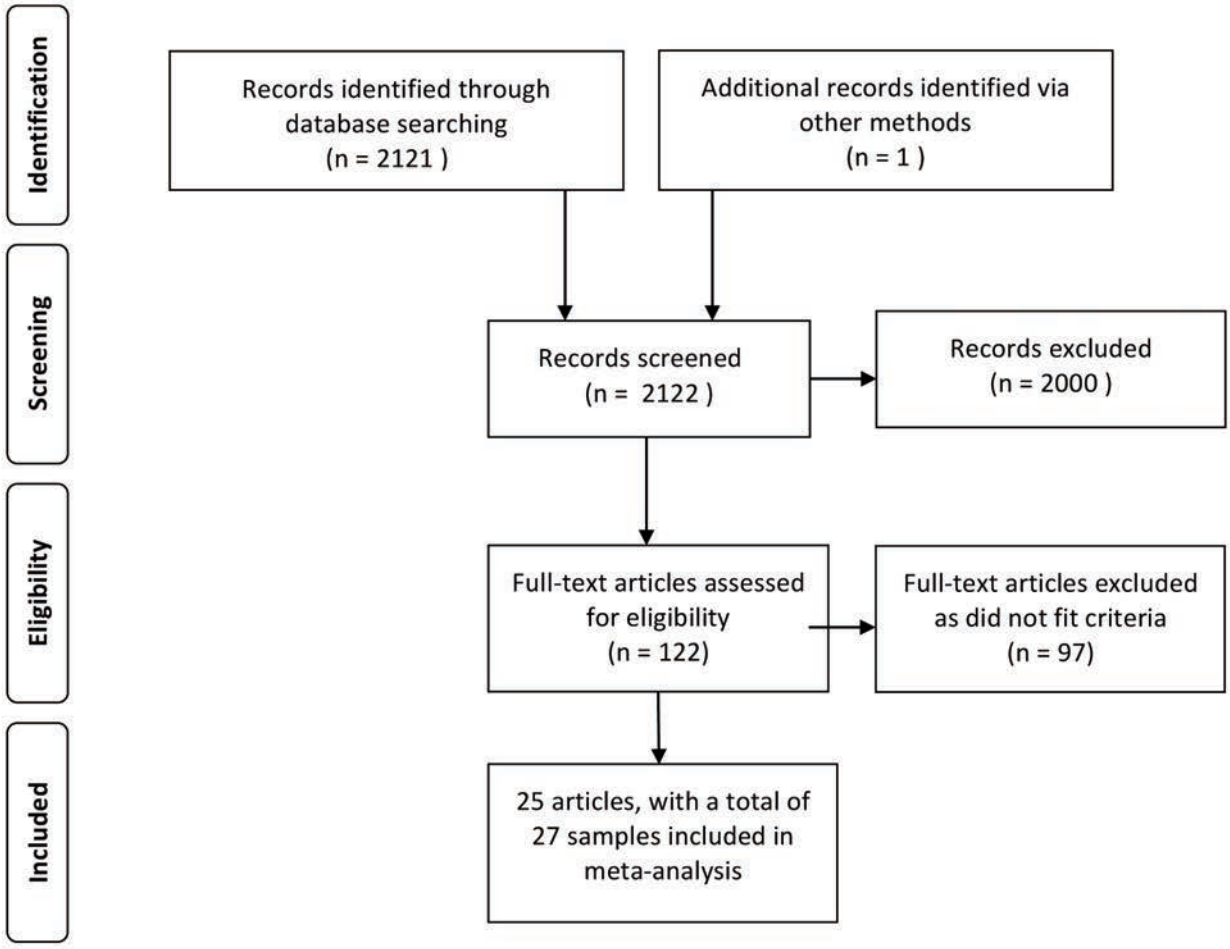

Figure 1. Flowchart of article selection.

Table 1. Descriptive data, including effect size, for studies in the meta-analysis.

Author	Childhood psychosocial stressor/s	No.	Mean age at telomere collection	Memory-based retrospective assessment of stressor	TL cell type	TL assay type	Categorical stressor	Age controlled	Sex controlled	Other variables controlled for	Log transformed	*r*
Asok *et al.* (2013)	Neglect, family violence etc	89	4.9	No	Buccal mucosa	PCR	Yes	No	Yes	Yes	No	-0.22*
Beach *et al.* (2014)	Life stress	183	21.8	Yes	Leukocyte	PCR	No	No	No	No	No	-0.04
Bersani *et al.* (2016)	Abuse, general trauma	76	34.6	Yes	Leukocyte	PCR	No	Yes	All same sex	Yes	No	-0.43**
Chen *et al.* Depressed (2014)	Abuse, neglect etc	20	35.9	Yes	Leukocyte	PCR	No	Yes	Yes	No	No	-0.13
Chen *et al.* (2014) Controls	Abuse, neglect etc	20	35.9	Yes	Leukocyte	PCR	No	Yes	Yes	No	No	-0.61*
Drury *et al.* (2012)	In institutional care	100	8.4	No	Buccal mucosa	PCR	No	Yes	Yes	Yes	No	-0.05
Drury *et al.* (2014)	Adverse events	80	10.2	Yes	Buccal mucosa	PCR	Yes	Yes	Yes	Yes	No	-0.28*
Glass *et al.* (2010)	Physical abuse, sexual abuse	1090	47.8	Yes	Leukocyte Southern blot		Yes	No	No	No	No	.002
Jodczyk *et al.* (2014)	Interparent violence, physical abuse etc	677	29.0	Yes	Leukocyte	PCR	No	All same age	Yes	Yes	No	-0.01
Kananen *et al.* (2010)	Parental substance abuse/ mental illness etc	974	49.8	Yes	Leukocyte	PCR	No	Yes	Yes	No	Yes	-0.09*
Kiecolt-Glaser *et al.* (2011)	Abuse, neglect etc	132	65.9	Yes	Leukocyte Southern blot		Yes	Yes	Yes	Yes	No	-0.06
Kuffer *et al.* (2016) Controls	Abuse, neglect	58	71.9	Yes	Buccal mucosa	PCR	No	Yes	Yes	No	No	0.21
Kuffer *et al.* (2016) Indentured	Abuse, neglect	62	76.2	Yes	Buccal mucosa	PCR	No	Yes	Yes	No	No	0.12
Levandowski *et al.* (2016)[a]	Childhood adversity	87	28.6	Yes	Blood	PCR	Yes	No	All same sex	No	No	-0.41**
Mason *et al.* (2015)[b]	Physical abuse, sexual abuse	1130	45.5	Yes	Leukocyte	PCR	No	Yes	All same sex	No	Yes	-0.01
O'Donovan *et al.* (2011)	Physical abuse, physical neglect etc	41	30.2	Yes	Leukocyte	PCR	No	Yes	No	No	No	-0.42*
Osler *et al.* (2016)	Parental illness/ loss, separated from home etc	324	57.0	Yes	Leukocyte	PCR	No	All same age	All same sex	No	No	-0.02
Savolainen *et al.* (2014)	Absent parent	1486	61.5	No	Leukocyte	PCR	Yes	Yes	Yes	Yes	Yes	-0.05

Continue on next page.

P=0.068, two-tailed. The association would be significant at P=0.034 with a one-tailed test. The other moderator analyses were all categorical comparisons. Table 2 shows the results. Two variables showed significant moderation of effect size: Studies that compared groups, *e.g.*, being abused or not, showed higher associations between level of childhood stressor and telomere length than studies that treated stressor level as a continuous variable. Also, studies that used qPCR had higher effect sizes than studies that used Southern Blot. If we apply a Bonferroni correction to control for alpha inflation in the analyses of the eight categorical variables, these findings would not meet the adjusted P standard of 0.05/8 or 0.006.

Table 1. Continued from previous page.

Author	Childhood psychosocial stressor/s	No.	Mean age at telomere collection	Memory-based retrospective assessment of stressor	TL cell type	TL assay type	Categorical stressor	Age controlled	Sex controlled	Other variables controlled for	Log transformed	*r*
Schaakxs *et al* . (2015)	Adverse events, trauma	496	70.6	Yes	Leukocyte	PCR	Yes for adverse events; No for trauma	Yes	Yes	Yes	No-	0.32**
Shalev *et al*. (2013)	Family violence, physical abuse etc	236	10.0	No	Buccal mucosa	PCR	Yes	All same age	Yes	Yes	No	-0.05
Surtees *et al*. (2011)	Emotional abuse, physical abuse etc	4441	62.0	Yes	Leukocyte	PCR	No	Yes	All same sex	No	No	-0.01
Tyrka *et al*. (2010)	Physical neglect, emotional neglect	31	26.9	Yes	Leukocyte	PCR	Yes	No	No	No	No	-0.31
Tyrka *et al*. (2015)	Parental loss, separation from family	179	31.0	Yes	Leukocyte	PCR	Yes	No	No	No	No	-0.09
van Ockenburg *et al* . (2015)[c]	Parental loss, parental separation etc	445	55.5	Yes	Leukocyte	PCR	No	Yes	Yes	Yes	Yes	-0.00
Verhoeven *et al* . (2015)[d]	Emotional neglect, emotional abuse etc	2936	41.8	Yes	Leukocyte	PCR	Yes for parental loss etc; No for neglect etc	Yes	Yes	Yes	No	-0.02
Zalli *et al*. (2014)	Parental loss /separation, household substance use etc	434	63.2	Yes	Leukocyte	PCR	Yes	Yes	Yes	Yes	No	-0.01

[a]Effect size based on both abused and neglected. [b]Effect size based on age-adjusted results. [c]Used sociodemographic adjustment results. [d]Used sociodemographic adjustment results for emotional neglect, emotional abuse, physical abuse, sexual abuse. *P<0.05, **P<0.001.

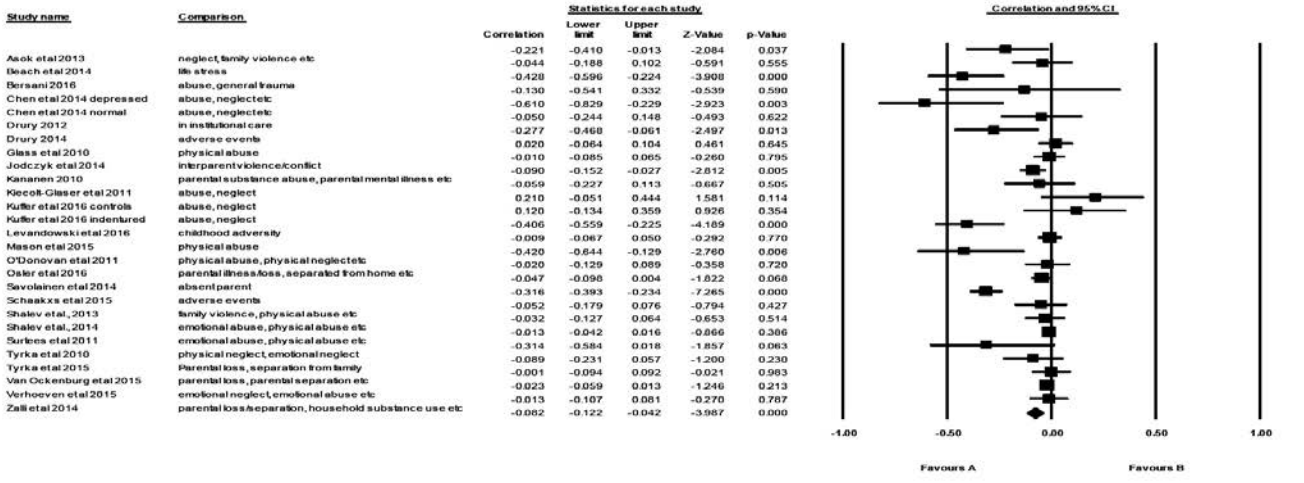

Figure 2. Graphical representation of effect size for each sample.

Discussion and Conclusions

The meta-analysis found a small but significant association (-0.08) between level of childhood psychosocial stressors and telomere length, across 27 samples that included 16,238 participants. The association was significant regardless of whether stressor level was based on recall or more objective documentation, and regardless of whether the cells assayed for telomere length were leukocytes or buccal. Childhood stressors can have a long-term impact on telomere length, as indicated by the significant association between exposure to childhood stressors and telomere length at a mean age of 42 years for participants included in the present meta-analysis.

The results provide a possible mediational explanation for the finding that psychosocial stressors experienced during childhood predict negative health outcomes in adulthood (Felitti *et al*., 1998; Shonkoff & Garner, 2012; Wegman & Stetler, 2009). There are a number of biological and behavioural pathways that early trauma affects, such as inflammation and changes in health behaviours, and these also interact with telomere length; thus the causal factors linking early trauma and later disease are likely due to a variety of inter-related factors. (Danese & McEwens, 2012). Telomere length appears to be one of the causal factors, as recent mendelian genetic studies of telomere length have shown direct prediction of earlier onset of certain diseases of aging (Codd *et al*., 2013; Zhan *et al*., 2015).

The findings of the present meta-analysis extend findings of previous research on psychological states and telomere length in focusing on the relationship between actual events experienced in childhood and later telomere length. Prior meta-analyses reported significant associations between perceived stress and telomere length (Mathur *et al*., 2016; Schutte & Malouff, 2014). Prior meta-analyses also found significant associations between anxiety levels and telomere length (Malouff & Schutte, in press) and between depression and telomere length (Schutte & Malouff, 2015). Childhood psychosocial stressors predict telomere shortening, and negative psychological states (perceived stress, anxiety, and depression) may operate as mediators linking stressors and telomere shortening. Some studies have found that recent psychosocial stressors in adults are also associated with shorter telomeres (*e.g*., Schaakxs *et al*., 2015). Telomere functioning is dynamic (Blackburn *et al*., 2015) and shortened telomeres may recover as time passes after exposure to a stressor (Verhoeven *et al*., 2015), and thus we predicted that time would moderate effect size. We found a moderation trend consistent with this view. However, remarkably, childhood stressors were still significantly associated with shortened telomeres decades later. It is unknown whether childhood psychosocial stressors are more or less associated with telomere length than stressors experienced by adults, but it is possible that childhood stressors have more impact because childhood is a critical period of development of biological systems (Shonkoff & Garner, 2012) or because of the limited coping ability of children. Studies have found exposure to other environmental factors, such as pesticides, to be associated with telomere length (Hou *et al*., 2013). The present findings add meta-analytic results for early-life psychosocial environmental factors. One interesting meta-ana-

Table 2. Categorical moderator analysis.

Moderator	*k*	*r*	CI 95%			Homogeneity Analysis		
			Lower	Upper	P	Q	df	P
Memory-based retrospective assessment of stressor[1] $Q(1)=1.01$, P=0.32								
No	4	-0.06	-0.1	-0.01	0.02	2.57	3	0.46
Yes	22	-0.09	-0.14	-0.04	<0.001	105.96	21	<0.001
TL cell type[2] $Q(1)=0.04$, P=0.84								
Buccal	6	-0.06	-0.19	0.07	0.39	12.25	5	0.03
Leukocyte	20	-0.07	-0.11	-0.03	<0.001	81.97	19	<0.001
TL assay type, $Q(1)=4.49$, P=0.03								
Southern blot	2	0.01	-0.07	0.08	0.90	0.64	1	0.42
qPCR	25	-0.10	-0.13	-0.05	<0.001	106.77	24	<0.001
Categorical stressor $Q(1)=4.39$, P=0.04								
Yes	11	-0.14	-0.23	-0.06	<0.001	57.19	10	<0.001
No	16	-0.04	-0.08	-0.00	0.04	38.59	15	0.001
Age controlled $Q(2)=4.95$, P=0.08								
All same age	4	-0.02	-0.07	0.03	0.34	0.35	3	0.95
No	6	-0.15	-0.28	-0.02	0.03	21.00	5	<0.001
Yes	17	-0.09	-0.14	-0.03	<0.001	85.81	16	<0.001
Sex controlled $Q(1)=0.32$, P=0.85								
All same sex	6	-0.10	-0.18	-0.01	0.02	30.19	5	<0.001
No	5	-0.11	-0.23	0.02	0.10	11.34	4	0.02
Yes	16	-0.08	-0.13	-0.02	0.01	63.91	15	<0.001
Other variables controlled for $Q(1)=0.89$, P=0.35								
No	15	-0.06	-0.12	-0.01	0.02	44.62	14	<0.001
Yes	12	-0.10	-0.17	-0.04	<0.01	61.35	11	<0.001
Log transformed $Q(1)=3.39$, P=0.07								
Yes	4	-0.04	-0.08	0.00	0.03	4.29	3	0.23
No	23	-0.10	-0.15	-0.05	<0.001	104.67	22	<0.001

[1]Shalev *et al.* (2014) excluded because study used mixed methods. [2]Levandowski *et al.* (2016) excluded because study used "blood."

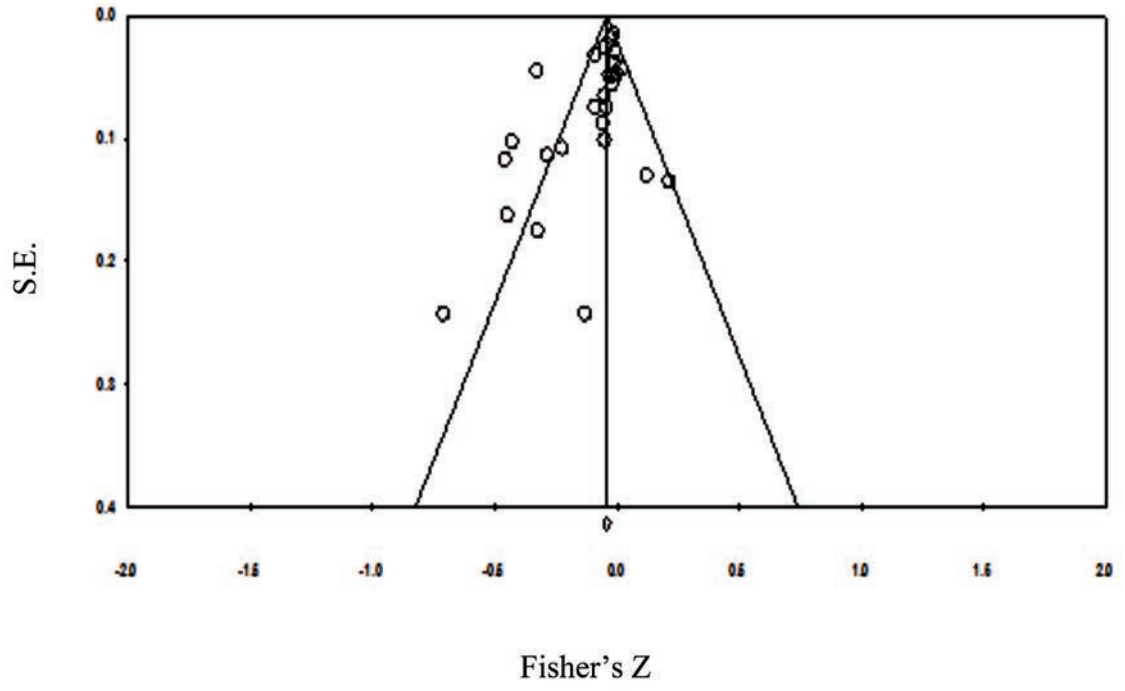

Figure 3. Funnel plot of standard error by effect size (Fisher's Z).

lytic moderator finding involved the significantly greater effect size for comparison of extreme groups on level of childhood stressors than for correlational studies with various levels of stressors. Similarly, a meta-analysis of the association between anxiety level and telomere length found that analyses of extreme groups showed much greater effect sizes than correlational studies, although the difference was not significant (Malouff & Schutte, 2016). It could be that only extreme levels of childhood psychosocial stressors have long-term effects on telomere length.

Studies that used qPCR assays had significantly higher effect sizes than Southern blot studies. Because only two studies in the meta-analysis used Southern blot, that finding may be a statistical fluke.

The moderator results are best viewed as suggestive. First, with only 27 samples included, the moderator analyses had limited power to identify significant differences. Second, moderator analyses are always quasi-experimental – no one randomly assigned some studies to use one method and other studies to use another. Third, the statistical significance of some moderators in this meta-analysis varies with how conservative one wants to be regarding using one-tailed tests and controlling for alpha inflation

Future research on child psychosocial stressors and telomere length might systematically compare different types of psychosocial stressors and examine the role of possible mediators and moderators, including potential buffers such as social support. In addition, it will be important to examine in more depth the characteristics of the stressors and symptoms of distress. This type of research will help identify both predictors of vulnerability and resilience to the lifelong effects of severe childhood stressors.

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