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Early Life Adversity and Telomere Length: A Meta-Analysis

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Abstract

Early adversity, in the form of abuse, neglect, socioeconomic status, and other adverse experiences, is associated with poor physical and mental health outcomes. To understand the biologic mechanisms underlying these associations, studies have evaluated the relationship between early adversity and telomere length, a marker of cellular senescence. Such results have varied in regards to the size and significance of this relationship. Using meta-analytic techniques, we aimed to clarify the relationship between early adversity and telomere length while exploring factors affecting the association, including adversity type, timing, and study design. A comprehensive search in July 2016 of PubMed/MEDLINE, PsycINFO, and Web of Science identified 2 462 studies. Multiple reviewers appraised studies for inclusion or exclusion using *a priori* criteria; 3.9% met inclusion criteria. Data was extracted into a structured form; the Newcastle-Ottawa Scale assessed study quality, validity and bias. Forty-one studies (N =30 773) met inclusion criteria. Early adversity and telomere length were significantly associated (Cohen's *d* effect size = −0.35; 95% CI, –0.46 to –0.24, $p < 0.0001$). Sensitivity analyses revealed no outlier effects. Adversity type and timing significantly impacted the association with telomere length ($p < .0001$ and $p = .0025$, respectively). Subgroup and meta-regression analyses revealed that medication use, medical or psychiatric conditions, case-control versus longitudinal study design, methodological factors, age and smoking significantly affected the relationship. Comprehensive evaluations of adversity demonstrated more extensive telomere length changes. These results suggest that early adversity may have long-lasting physiological consequences contributing to disease risk and biological aging.

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Keywords

Telomere; meta-analysis; childhood maltreatment; early life stress; adversity; poverty; low socioeconomic status (SES); child abuse

Introduction

Early life adversity is a major public health problem experienced by over 19.4 million children[1, 2]. Children with a history of early adversity are at a greater risk of developing poor physical and mental health outcomes, including diabetes, asthma, depression, anxiety, and post-traumatic stress disorders[3–5]. These conditions are often chronic and severe, exacting costs in excess of $124 billion through suffering, disability, treatment, and loss of productivity over the lifespan[6]. Investigation into the biologic mechanisms by which early adversity increases risk for poor health outcomes provides evidence of accelerated biologic aging through shortened telomere length[7–9].

Telomeres are DNA-protein complexes comprised of tandem TTAGGG repeats ranging from a few to 15 kilobases in length that are essential for maintaining chromosomal and genetic stability[10]. Telomeres shorten with each DNA replication cycle and, as such, telomere length serves as a biomarker of biological aging[11]. When telomeres become critically short, cells may enter senescence or undergo apoptosis[9, 12]. Telomere length is influenced by stress and inflammation[9]. Many chronic illnesses involve prolonged states of stress and/or inflammation, which may contribute associations between telomere length and somatic conditions, including heart disease, diabetes, asthma, obesity, chronic pain, irritable bowel syndrome, and neurodegenerative disorders[11, 13–16]. Proposed mechanisms underlying associations between stress and telomere length include mitochondrial dysfunction and telomerase inactivation due to heightened and prolonged stress signaling[9, 17, 18]. In addition to reflecting biologic stress, telomere attrition often precedes chronic disease development, suggesting that telomere erosion may be a causal link connecting early adversity and later disease[12].

Telomere attrition early in life may be particularly detrimental[19], leading to premature development of stress-related health disorders[9, 12]. Less than a decade ago, preliminary evidence suggested that childhood adversity was associated with telomere shortening[20]. Since then, numerous studies have examined associations between early adversity and telomere length[9, 14]. Shortened telomeres have been linked to adversity at multiple developmental stages[18, 21–23] and after several types of adverse exposures[24–26]. Some investigations suggest a cumulative and dose-dependent negative relationship between early adversity and telomere length[27, 28]. However, numerous studies have not observed shorter telomeres after early adversity[29–43].

Several issues arise when assessing the existing body of knowledge relating telomeres and early adversity. Most studies have modest sample sizes, limiting the ability to draw definitive conclusions. Additionally, variability in study design, methodology, subject characteristics, early adversity type and developmental timing limits the generalizability of available data. This meta-analysis aims to clarify the relationship between early adversity and telomere

length by means of a systematic examination of the literature, comparing subjects with early adversity exposure to those without, and to identify moderators of the association with telomere length. We hypothesized that early adversity would be associated with reduced telomere length, and that this relationship would be modified by study and subject characteristics.

Methods and Materials

Protocol and Registration

A protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42016035239). This study was designed, executed, and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[44] and the Cochrane reporting items for meta-analyses[45]. The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Guidelines[46] were also followed and adapted into PRISMA.

Study Eligibility

Included studies: 1) examined the effects of early adversity in the form of abuse, neglect, socioeconomic status (SES), or other adverse exposures on human subjects occurring prenatally up to age 18; 2) provided adequate description of adversity assessments; and 3) presented sufficient data to calculate effect sizes. Prospective, observational, and retrospective studies were considered. Studies using indirect proxies of early adversity, such as parental education alone, were excluded. When two manuscripts presented results from non-independent datasets, the manuscript with the larger number of subjects was included.

Information Sources and Search Strategy

A comprehensive electronic search in July 2016 identified English language studies indexed in PubMed/Medline, PsycINFO, and Web of Science; no publication date limitations were set. The search was performed by investigators with topic clinical and research experience (M.L., K.K.R.) in consultation with a librarian trained in systematic reviews. Investigators reviewed titles, abstracts, and articles; disagreements were settled by consensus. The search strategy included terms and combinations to identify early adversity and telomeres: “child neglect”, placenta, antenatal, prenatal, trauma, poverty, “child abuse”, “socioeconomic status”, “childhood maltreatment”, “parental loss”, environment, neighborhood, abuse, maltreatment, adversity, “early life stress”, telomerase, telomeres, telomere, telo* (Supplemental Table 1). Primary study and review article references were searched; studies were appraised for inclusion or exclusion using *a priori* criteria as described under study eligibility.

Data Extraction

Data were extracted independently (M.L., L.G., K.K.R.) using a structured form. Extractors were not blinded to study results, authors, or institutions; inter-rater reliability was high (>97%). Conflicts regarding data extraction were resolved by consensus with another reviewer (S.J.R.). Data extraction variables are listed in Table 1. When provided, data fully adjusted for potential covariates were abstracted rather than partially adjusted or unadjusted

values. Study quality was assessed using Cochrane Review[45] and Agency for Healthcare Research and Quality[47] guidelines. The Newcastle-Ottawa Scales (NOS) for cross-sectional, case-control, or cohort designs[48] were used to assess risk of bias for all studies (L.G.); blinded replications of these assessments had good reproducibility (97%; M.L.).

When studies did not report an overall effect but instead included data on various types of adversity exposures in the same group of subjects[31, 33–35, 42, 43, 49], data were converted to standardized mean differences (SMDs) and pooled to allow comparison of a grouped early adversity value in the main meta-analysis[50], unless the adversity grouping was not limited to early life[36]. When studies presented more than one independent dataset by one of the subgroups examined in this study (e.g., adversity type, medical/psychiatric condition), these were treated as separate datasets represented by the first author's last name, publication date, and alpha character[32, 34, 39, 40, 51, 52].

Statistical Analysis

Data were converted into SMDs using the effect size calculator[53] and reported as Cohen's *d*[54]. The SMD is the mean difference in telomere length between the early adversity-exposed and non-exposed groups divided by the pooled standard deviation, resulting in a unitless effect size measure comparable between studies. By convention, effect sizes of 0.2, 0.5, and 0.8 are small, medium and large, respectively[54]. If correlations (r) or odds ratios (OR) were reported, they were converted to Cohen's d using the formulas $d = 2r/(1-r^2)^{1/2}$ or $d = OR(3^{1/2}/\pi)$, respectively[50] .

Analyses were performed using Comprehensive Meta-Analysis Software (V2.2.064 Biostat, Englewood, New Jersey). Heterogeneity was calculated using the I^2 statistic, which provides a measure of the variance attributable to between-study differences[55] (0% = none, 25% = low, 50% = moderate and 75% = high heterogeneity). A random effects model was utilized after initial fixed effects model analyses revealed high inter-study heterogeneity ($I^2 = 74\%$). Confidence intervals (CI; 95%) and p-values ($\alpha = .05$) were calculated. Sensitivity analyses were performed utilizing the "leave-one-out" strategy[56]. Publication bias was assessed with Egger's regression intercept[57]. Duval and Tweedie's trim and fill analysis[58] on both sides of the mean calculated effect size estimates accounting for reporting bias.

Moderator analyses

Meta-regression and subgroup moderator analyses were performed to examine potential sources of inter-study heterogeneity. The Benjamini and Hochberg[59] method was used to control for multiple comparisons, with a false discovery rate (FDR) set to .05. Method of moments random-effects meta-regression[50] was used for the moderators of mean age, percent cigarette users, percent females, NOS score, developmental exposure period, and time since exposure. Developmental stages were defined using the Center for Disease Control (CDC) definitions[60] and neurodevelopmental data[61]; CDC stages were further collapsed to ensure a sufficient number of studies (k) for each grouping while maintaining developmental relevance. Groupings were: early development (prenatal-4 years; $k = 7$), childhood (up to12 years; $k = 10$), and adolescence (up to 18 years; $k = 23$); one study did

not provide assessment age[42]. Time since exposure was defined as mean study population age minus the maximal age at adversity exposure.

Subgroups—For categorical moderators, subgroup analyses were conducted using a continuous random effects model[62]. Subgroups were delineated using the following criteria: *Medical condition* (some or all subjects had a current chronic medical condition; $k = 8$), *psychiatric condition* (some or all subjects had a current[27, 28, 30, 39, 40, 49, 63–65] or current and/or past[36, 43, 52, 66] psychiatric condition; $k = 14$), and *medication use* (some or all subjects were taking medication at the time of telomere measurement tissue collection; $k = 5$). Only studies specifying participant conditions and medication use were included in this subgroup analysis.

Telomere measurement technique—$k = 36$ studies examined the ratio of telomere repeat copy numbers to single-copy gene numbers (T/S ratio) using quantitative real-time polymerase chain reaction (qPCR). Two studies utilized Southern blot[31, 42], one study used terminal restriction fragment (TRF) analysis[67] and one study with two datasets used low-coverage whole-genome sequencing[39]. We compared qPCR to all other telomere measurement techniques.

Source tissue—Telomere measurement source tissues were: leukocyte ($k = 31$; included one study of lymphocytes), buccal cells ($k = 4$), saliva ($k = 4$), and cord blood ($k = 2$).

Study design—Study design was grouped as: case-control ($k = 12$), cross-sectional ($k = 25$), and prospective ($k = 4$).

Early adversity type and comprehensiveness of assessment—We wanted to examine if the comprehensiveness of adversity assessment impacted the relationship between telomeres and early adversity. As such, studies were grouped according to whether they narrowly assessed one or two forms of abuse (emotional, physical, sexual, or verbal abuse; $k = 6$), assessed all forms of abuse and neglect ($k = 8$), or assessed all forms of abuse, neglect, and other forms of adversity ($k = 4$). We also examined assessments of SES ($k = 8$) and maternal depression ($k = 2$). A broad category of other adversity (including child welfare involvement, non-supportive/conflict-driven parenting, institutionalization, family instability, domestic violence, psychosocial stress, bullying, divorce, parental separation, serious illness, or neighborhood disorder; $k = 17$) was created to include assessments of exposures not already categorized. For manuscripts assessing more than one type of adversity and presenting data on telomere length related to that adversity, effect sizes were calculated for each presented data and included in the appropriate subgroup. Supplemental Table 2 contains study descriptions of adversity assessment and resulting categorizations.

Results

After initial search and screening, 95 studies were assessed for eligibility. Thirty-four studies with 41 independent datasets met full inclusion criteria (N = 30 773, Figure 1). The cumulative average age at time of telomere measurement was 31 ± 22 years; 60 ± 25% were

female. Thirty-eight percent of studies assessed other adversities, 18% abuse and neglect, 18% SES, 13% abuse, 9% abuse, neglect, and other adversities, and 4% maternal depression.

The overall association between early life adversity ($k = 41$) and telomere length as Cohen's d was −0.35 (Figure 2; 95% CI, –0.46 to –0.24, $p < .0001$). Sensitivity analyses did not alter the overall Cohen's d, suggesting the results were not driven by a single study. Egger's regression suggested funnel plot asymmetry (Supplemental Figure 1; B = −2.04, 95% CI, −3.22 to −0.87, $t = 3.51$, $p = .001$), suggesting reporting bias and/or heterogeneity between studies[68]. Heterogeneity was detected in the primary meta-analysis ($I^2 = 42\%$); moderator analyses were performed to examine significant sources of this heterogeneity.

Type of early life adversity, developmental timing, and telomere measurement

Moderator analysis by type of early adversity revealed a significant difference between groups ($p < .0001$, Figure 3, panel A). Studies with comprehensive adversity assessments (abuse, neglect and other adversities, $d = −0.711$) had negative effect sizes of greater magnitude than those with narrow adversity assessments (abuse and neglect or narrow focus on abuse; $d = −0.13$ and −0.055, respectively). Meta-regression of Cohen's d versus developmental stage of adversity exposure revealed adversity in earlier developmental periods showed greater telomere shortening ($B = 0.216$, 95% CI, 0.076 to 0.356, $p = .0025$, $R^2 = .18$; Figure 4, panel A). Increased temporal proximity to adversity exposure was also associated with shorter telomere length ($B = 0.011$, 95% CI 0.0045 to 0.0017, $p = .0007$, $R^2 = .10$; Figure 4, panel B).

Medical or psychiatric conditions, medication use, and demographics

Moderator analysis of studies including medical conditions vs. no medical condition and psychiatric conditions vs. no psychiatric condition were significant ($p < .0001$ for both). Studies with no medical or psychiatric conditions had negative effect sizes of greater magnitude than those with medical and psychiatric conditions, respectively (Figure 3 panel B). Similarly, moderator analysis of participant medication use was significant ($p < .0001$), with studies containing no participants on medications showing a negative Cohen's d of greater magnitude (Figure 3 panel B).

Larger negative effects were seen in studies with younger participants ($B = 0.010$, 95%, CI 0.0049 to 0.0153, $p < .0001$, $R^2 = .19$), and with less cigarette users ($B = 0.009$, 95% CI, 0.0005 to 0.0174, $p = .038$, $R^2 = .16$). The relationship between percent female subjects and Cohen's d was not significant ($p = .098$).

Telomere measurement technique

Studies grouped by telomere measurement technique were significantly different ($p < .0001$; Figure 3, panel C), with studies utilizing qPCR showing a significant and larger effect size ($p < .0001$). Studies utilizing other techniques also revealed a significant, negative effect size ($p = .024$).

Source tissue was a significant moderator of effect size ($p < .0001$; Figure 3, Panel C). Studies using leukocyte, buccal, or saliva cells showed a significant effect size ($p < .0001$,

< .0001, and .029 respectively). Although the cord blood group Cohen's *d* was largest in magnitude, it was not a significant grouping ($p > .05$).

Study design significantly moderated the relationship between early adversity and telomere length ($p < .0001$; Figure 3, panel C). Cross-sectional and case-control studies showed significant Cohen's *d* ($p < .0001$ for both), but the effect size of the small number of prospective studies was not significant ($p > .05$). Risk of bias as determined by NOS score was not significantly associated with Cohen's *d* ($p > .05$). All reported significant overall subgroup and regression analyses survived Benjamini-Hochberg correction for FDR.

Discussion

This meta-analysis supports an association between reduced telomere length and early life adversity. Using Cohen's categorization[54], the overall effect is between small to medium. Moderators can affect the relationship between telomere length and early adversity and reveal variables that have an additive or opposing effect. The Cohen's *d* effect size magnitude was medium to large in some moderator analyses, including type of adversity, comorbidities, and medication use. Trim and fill analysis indicated asymmetry in the funnel plot. Cumulative effects analysis revealed the effect size approached that estimated by trim and fill analysis with the addition of the top six to seven weighted studies (data not shown), suggesting asymmetry due to heterogeneity between studies[68]. Our results help explain the existing literature, which includes mixed findings concerning the relationship between early adversity and telomeres.

The developmental timing of adversity exposure significantly influenced the effect size, with adversity earlier in development showing greater negative effects. This finding suggests that exposure to early adversity may impact a child's developmental trajectory and health. Our finding that the magnitude of the negative association between early adversity and telomere length decreased with increasing years since exposure suggests that telomere shortening might be reversible over time, underscoring the fact that additional life experiences contribute to overall health. In our review of the literature on telomeres and early adversity, there was little data regarding consistency of care providers, nurturing relationships, and other resilience-associated factors[69]. To better understand the impact of all exposures, future studies would benefit from a comprehensive examination of both adversity and resilience factors.

The heterogeneity and magnitude of effect detected between early adversity and telomere length varied by the type of adversity exposure. Studies comprehensively assessing adversity, such as those examining abuse, neglect, and other adversities, revealed a negative Cohen's *d* of greater magnitude than studies narrowly assessing only abuse. The abuse subgrouping was non-significant ($p = .26$), which may reflect undetected effects of neglect and other adversities occurring in both the abuse and comparison groups missed by the narrow assessment. The effect for the maternal depression grouping was large ($d = -1.34$), but included two studies with a total of 300 subjects. These two studies did not assess the influence of maternal depression on child experience; as such this finding warrants further investigation. Studies of SES reached significance ($p = .017$) with a small effect size. Only

one SES study[26] assessed SES as related to emotional stress [66]; future investigations of environmental adversity and stress perception rather than SES alone may provide novel insights.

Mechanisms underlying early adversity and telomere length associations are largely unknown[14, 25]. Telomeres shorten after repeated cellular divisions and cellular stress exposures[70]. It has been speculated that early adversity directly activates or is associated with increased cellular stress and replication, resulting in accelerated telomere shortening[8, 17]. Telomerase activity, a key regulator of telomere length, is decreased with adversity exposure[71]. Telomere repair and lengthening strategies vary depending on the developmental phase of the cell[72]; it is possible these strategies are differentially responsive to adversity and may explain the relationship between developmental stage at adversity and impact on telomere length.

Previous meta-analyses reported a negative relationship between psychiatric disorders and telomere length[73, 74]. In this analysis, the Cohen's *d* for studies including subjects with psychiatric disorders was of smaller magnitude than studies excluding psychiatric disorders. This finding likely reflects inclusion of subjects with psychiatric disorders in both the early stress cases and controls, confounding the ability to detect telomere shortening due to early stress alone. The inter-study heterogeneity was greater for the groups with psychiatric conditions compared to those without (I^2 = 58% versus 0%), further suggesting that the relationship between psychiatric conditions and telomere length may confound the relationship between early adversity and telomeres. The analysis of medical conditions yielded similar results. Grouping studies based on subject medication use also impacted the magnitude of the relationship between early adversity and telomere length. This may reflect the underlying medical or psychiatric comorbidities or a direct effect of medication on telomere length.

Telomere measurement technique, source tissue, and study design all significantly moderated the association between early adversity and telomere length. qPCR showed a slightly larger Cohen's *d* than other techniques combined, although both groupings were significant. As the effect size for studies using qPCR was in the same direction and of similar magnitude to both the overall effect size and other telomere measurement techniques, and given the comparable ease of qPCR compared to some telomere measurement techniques such as Southern blot, these results support the use of qPCR as valid technique. Studies using leukocytes, buccal cells and saliva all had significant relationships between early adversity and telomere shortening, suggesting that early adversity may involve systemic processes affecting multiple somatic tissues. The cord blood grouping was not significant. There were only two studies utilizing this source tissue; the magnitude of the effect was large ($d = -1.07$), but the confidence intervals were wide. These preliminary results suggest that further investigations utilizing cord blood are warranted, as definitive conclusions cannot be drawn without additional data.

Study design affected the relationship between telomere length and early adversity, with cross-sectional and case-control studies showing highly significant effects. Prospective studies did not have a significant effect and there was substantial heterogeneity in this group

(I^2 = 60%). Of the four studies in the prospective group, one examined newborns exposed to perinatal adversity[67], one examined children[22], and two examined adult populations with early adversity and psychiatric disorders[30, 66]. The effect sizes ranged from 0.003 to −1.73. The results of this meta-analysis suggest that differences in developmental timing of adversity exposure and comorbidities likely contributed to the heterogeneity. Further prospective studies are needed to clarify the relationship between early adversity and telomere length over time.

When examining the association between early adversity and telomere length by cigarette use, the Cohen's *d* decreased in magnitude with an increasing percentage of smokers in the study ($p = .038$). Older subject age was also associated with effects that were smaller in magnitude ($p < .0001$). These findings may be influenced by the fact that studies of young children were assumed not to include smokers, and our finding that adversity at an earlier developmental stage was associated with a larger effect on telomere length.

The limitations of this meta analysis include the use of peer-reviewed, trial-level published data to increase confidence in the validity of the data, which is common practice in meta-analyses, but constrains Cohen's *d* effect size calculations to data obtained from published studies. A pooled individual patient analysis approach could prove useful, especially for understanding moderator effects. Our analysis of developmental stage at adversity exposure is limited by the fact that many studies assessed adversity during large developmental timeframes rather than during discrete time periods. Most papers published were from developed nations; as such our ability to detect the long-term sequelae of poverty was limited due to the populations represented in the existing literature.

Telomere shortening may be a mechanism by which early adversity impacts disease risk. This may reflect underlying biological processes triggered by early life adversity, such as dysregulated stress signaling, altered metabolism and mitochondrial dysfunction, and increased inflammation and oxidative stress. Early adversity not only impacts children at an immediate, emotional and physical level[75], but may have long-lasting health sequelae that are biologically-based as well. These results highlight the importance of preventing, recognizing and intervening on multiple forms of adversity including abuse, poverty, and caregiver loss and neglect. Heterogeneity within these results suggests that there are likely factors impacting individual susceptibility to telomere shortening after early life adversity exposure. Prospective studies with rich measures of exposures, medical and psychiatric conditions, and targeted interventions will help determine the causality and reversibility of the observed association between early adversity and telomere length, as well as help identify factors that may determine susceptibility or protection against early life adversity-associated telomere shortening. Additionally, individual-level patient analyses of these moderators may add to our understanding. Research examining the biological mechanisms by which early life adversity is associated with telomere attrition should focus on causal links, developmental stage of exposure, and interventions that may reverse these deleterious effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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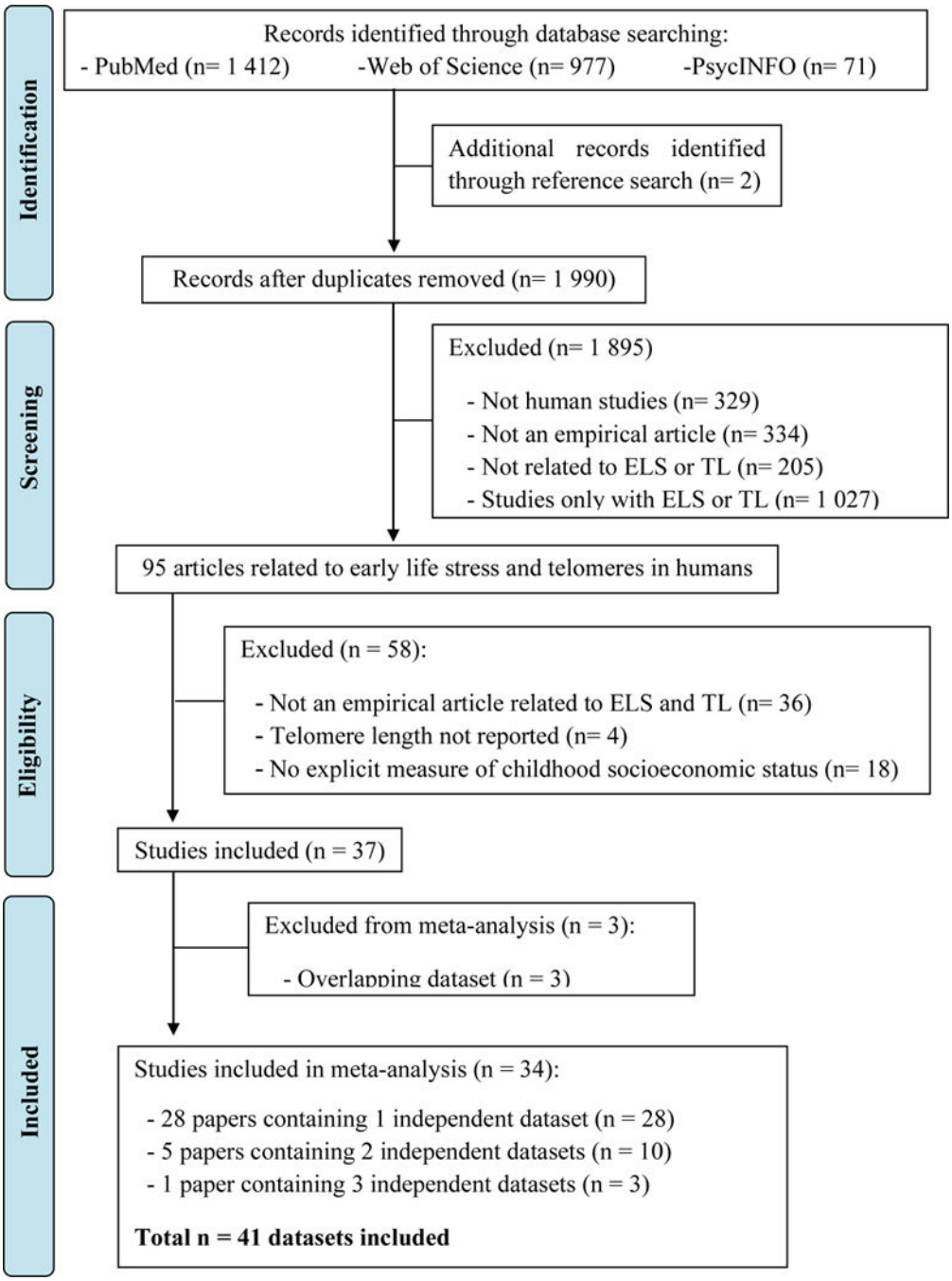

Figure 1. PRISMA flow diagram of included studies

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for identification and inclusion of studies in the meta-analysis.

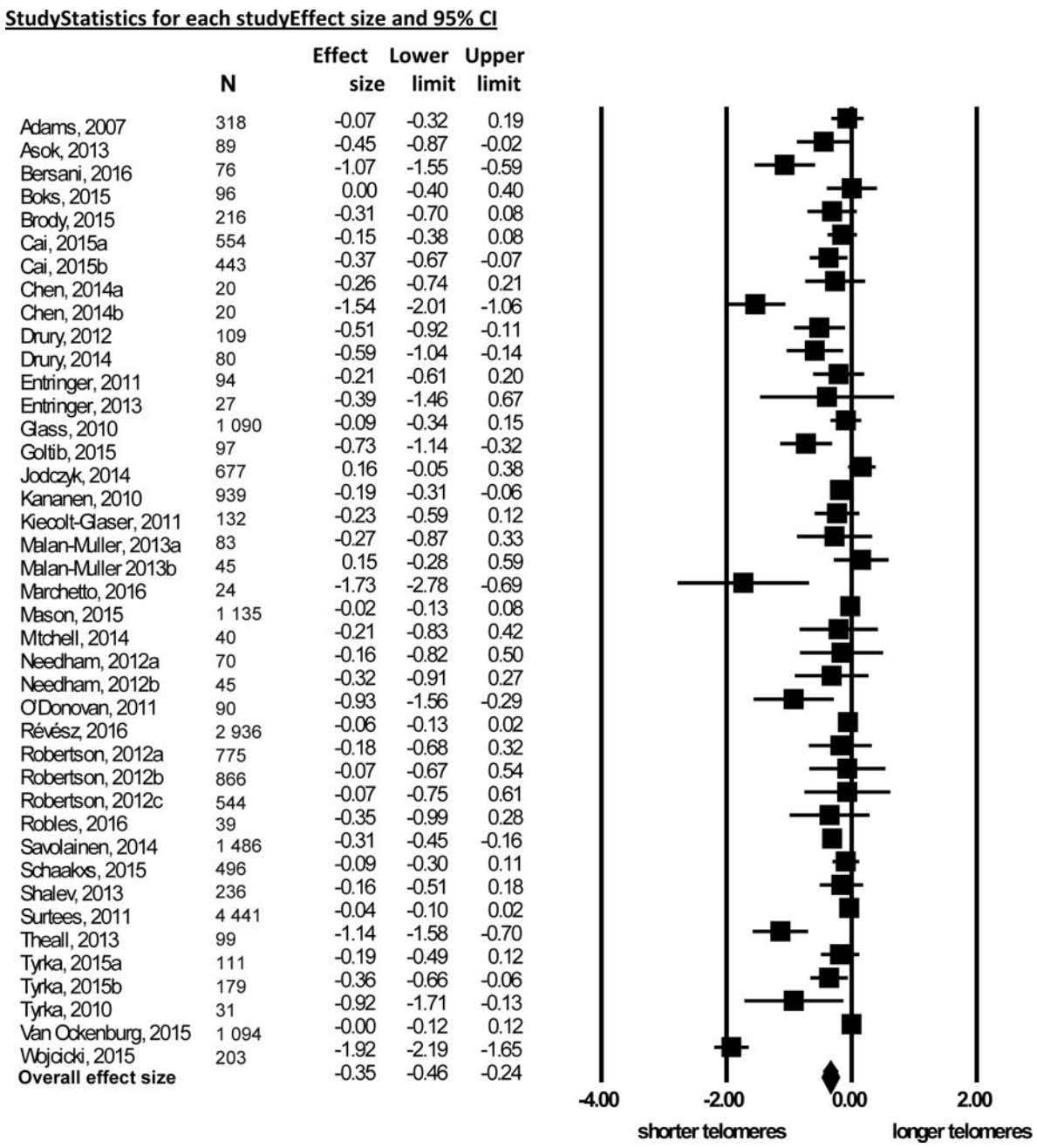

Figure 2. Forest plot of early life adversity and telomere length

Forest plot of effect sizes reported as Cohen's *d* (x-axis) evaluating early life adversity and telomere length using the random effects model. Points represent effect size; lines represent 95% confidence intervals (CI). Diamond indicates overall effect size and 95% CI.

Moderator	*k* (N)	Cohen's *d*	95% CI	*p*-value	I^2
A					
Maternal depression	2 (300)	-1.34	-2.50 to -0.17	.025	0%
Abuse, neglect and other adversity	4 (212)	-0.71	-1.42 to -0.01	.050	0%
Other adversity	17 (9 780)	-0.30	-0.42 to -0.18	<.0001	28%
Abuse and neglect	8 (3 518)	-0.13	-0.25 to -0.02	.024	28%
SES	8 (9 125)	-0.12	-0.22 to -0.02	.017	0%
Narrow focus on abuse	6 (19 249)	-0.06	-0.15 to 0.04	.259	17%
B					
No medical condition	18 (1 852)	-0.47	-0.70 to -0.24	< .0001	0%
Medical condition	8 (11 747)	-0.11	-0.20 to -0.01	.034	61%
No psychiatric disorder	11 (681)	-0.65	-0.98 to -0.32	< .0001	0%
Psychiatric disorder	14 (23 241)	-0.36	-0.55 to -0.17	< .0001	58%
No medications	11 (754)	-0.61	-0.91 to -0.30	< .0001	7%
Medication use	5 (11 970)	-0.35	-0.66 to -0.04	.028	21%
C					
qPCR	36 (17 857)	-0.35	-0.47 to -0.23	< .0001	40%
Other techniques	5 (12 916)	-0.27	-0.51 to -0.04	.024	47%
Saliva	4 (11 809)	-0.46	-0.87 to -0.46	.029	14%
Buccal cells	4 (514)	-0.40	-0.60 to -0.20	< .0001	0%
Leukocytes	31 (18 399)	-0.31	-0.43 to -0.19	< .0001	47%
Cord blood	2 (51)	-1.07	-2.38to 0.24	.11	0%
Case-control	12 (3 297)	-0.30	-0.43 to -0.17	< .0001	10%
Cross-sectional	25 (24 184)	-0.39	-0.55 to -0.23	< .0001	39%
Prospective	4 (3 292)	-0.20	-0.52to 0.12	.22	60%

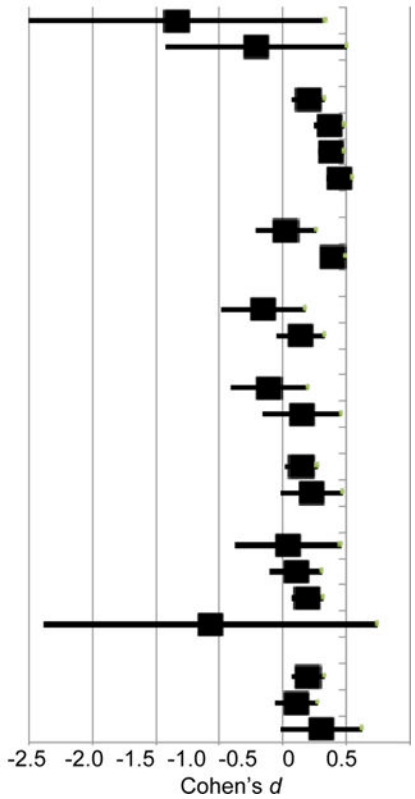

Figure 3. Subgroup moderator analyses

Subgroup analyses. Sub-group analyses were conducted using a continuous random effects model. Black squares represent the Cohen's *d* effect size and lines represent 95% confidence interval (CI). A. Subgroup analysis by type of adversity exposure. B. Subgroup analysis by medical conditions, psychiatric disorders, and medication use. C. Subgroup analysis by study techniques. *k* = number of studies per group, N = total number of subjects from all studies; SES = socioeconomic status; qPCR = quantitative polymerase chain reaction.

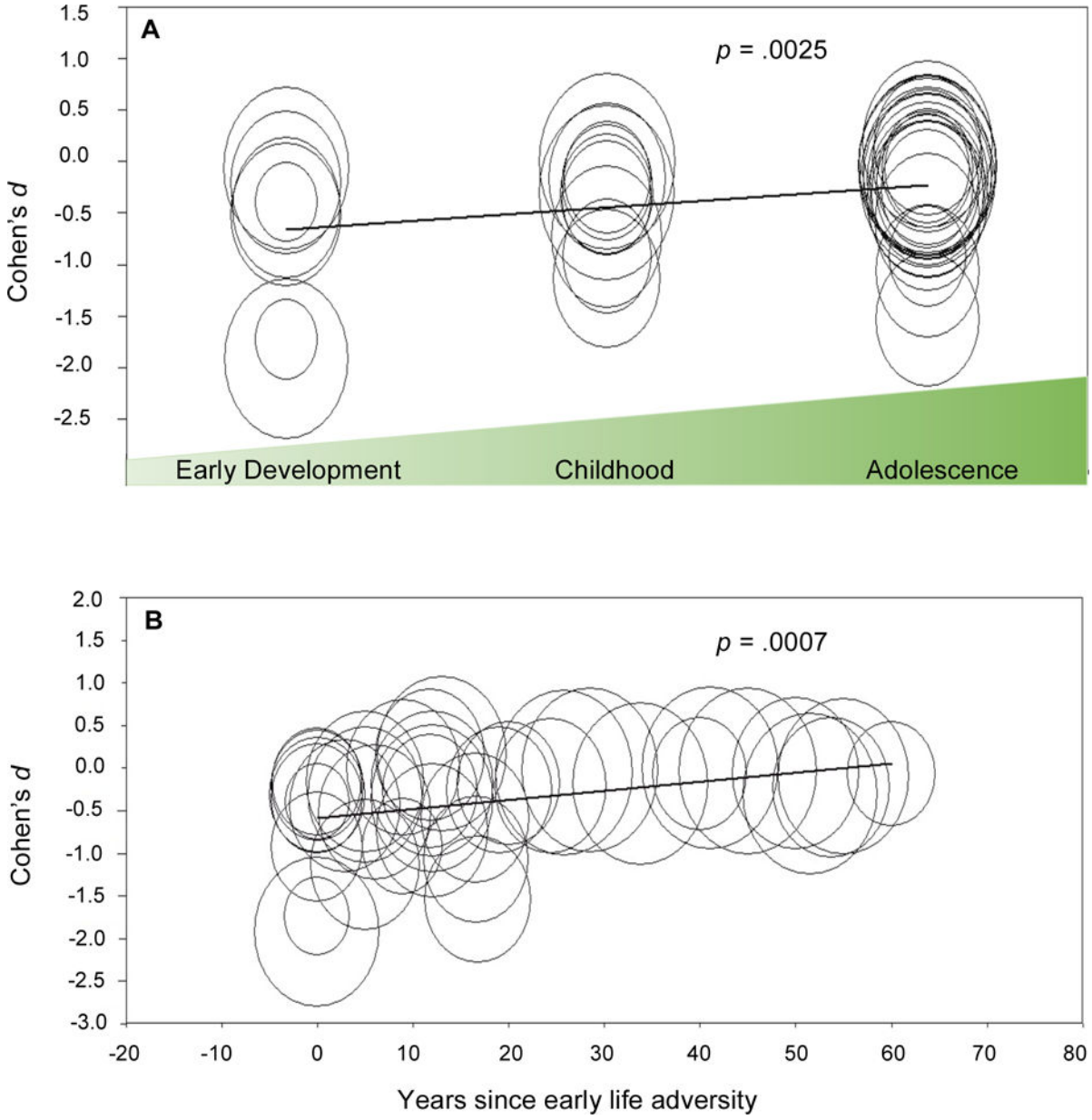

Figure 4. Meta-regression analyses

Meta-regression of early life adversity timing and telomere length. Each circle represents a study with size proportional to that study's weight in the analysis. A. Developmental stage at age of adversity exposure versus Cohen's *d*. Studies were grouped according to the reported age of adversity assessment. $k = 7$ studies assessed adversity during early development (prenatal-4 years), $k = 10$ during childhood (up to 12 years), and $k = 23$ during adolescence (up to 18 years). No studies are represented in more than one category. B. Years since adversity exposure versus Cohen's *d*. X-axis values represent mean study population age minus the oldest age of reported adversity exposure.

Table 1

Characteristics of Included studies

Study characteristics				Participant characteristics						Early adversity exposure			Telomere measurement			
Author, year	**Study design/ Sample**	**NOS**	**Study *N* (exposed)**	**Age (SD)**	**Female**	**Medical condition**	**Psychiatric condition**	**Smoke**	**Medication use**	**Type**	**Timing**	**Assessment Method**	**Adversity and TL Association**	**TL Measurement**	**Tissue**	**Covariates**
Adams, 2007	Cross-sectional/Newcastle Thousand Families Study	6/10	318 (239[1])	50 (NR)	62.2%	NR	NR	NR	NR	SES	Birth	Registrar General's social class	B=85.35, 95% CI −49.95 to 230.60, p>0.05	qPCR	Leukocyte	Pack years smoking, mean rank of dietary antioxidants, BMI, units of alcohol per week and paternal age at birth
Asok, 2013	Case-control/Low and High risk for maltreatment	7/9	89 (51)	4.9 (0.5)	44.9%	NR	NR	–	NR	Other adversity	< 2 years old	Involvement in Child Welfare System	$F(1,83)$=4.37, p<0.05	qPCR	Buccal cells	Income, birth weight, gender, and minority status
Bersani, 2016	Cross-sectional/Combat-exposed male veterans	7/10	76 (−)	34.6 (9.1)	0%	6.5% mild asthma or allergies, 2.6% diabetes II, 2.6% stable angina, 11.8% clinical hypertension and 1.3% prostate cancer	46% PTSD and 22.3% PTSD and MDD	14.4%	2.6% statins, 6.5% NSAID, 17.1% antidepressants, 1.3% antibiotics, 1.3% hormone-drugs for prostate cancer and 1.3% analgesic	Abuse, neglect, and other adversity	< 18 years old	ETI	β=− 0.470, 95% CI −0.164 to −0.054, p<0.001	PCR	Leukocyte	Age, BMI, ethnicity and antidepressant use
Boks, 2015	Prospective cohort/Dutch military before and after deployed to Afghanistan	6/9	96 (−)	27 (9.2)	0%	NR	69.7% with high combat trauma exposure and PTSD symptoms	19.7%	4.1% antibiotics, 3.1% antihistamines and 1.1% benzodiazepine	Abuse, neglect, and other adversity	< 18 years old	ETI	B=0.16, p=0.95	qPCR	Leukocyte	Baseline DNA methylation determined by Illumina 450K chip, time interval between assessment, baseline telomere length
Brody, 2015	Cross-sectional/Adults in the Making (AIM) program	7/10	216 (−)	22 (1.1)	59.1%	NR	NR	NR	NR	Other adversity	< 17 years old	IAI, DQS, CSS and FSI	-Non-supportive parenting B=−0.074, SE=0.024, p<.01	qPCR	Lymphocyte	SES, life stress, and the use of alcohol and cigarettes at age 17, and blood pressure and BMI at age 22
Cai, 2015 (a)(b)	Cross-sectional/Converge Study (Genital SA(a) or Intercourse SA(b) vs. No SA)	5/10	11 670	NR	100%	NR	45.7% depression	NR	41.6% antidepressant	Narrowly defined abuse	< 16 years old	Semi-structured interview	-Genital SA t=−1.27, p=0.20 Characteristics of included studies -Intercourse SA t=−2.45, p=0.01	Low-coverage whole-genome Sequencing qPCR	Saliva	Genome wide variation in single nucleotide polymorphisms
Chen, 2014(a)	Cross-sectional/MDD patients	6/10	20	37 (10.8)	65%	none	100% MDD	30%	none	Abuse, neglect, and other adversity	< 18 years old	ACE scale	r=−.13, p>.10	PCR	Leukocyte	Age and gender
Chen, 2014(b)	Cross-sectional/Healthy controls	6/10	20	34.8 (9.6)	67%	none	none	~22%	none	Abuse, neglect, and other adversity	< 18 years old	ACE scale	r=−.61, p<.05	PCR	Leukocyte	Age and gender
Drury, 2012	Cross-sectional/Bucharest Early Intervention Project	8/10	109 (109)	6 to 10	43.1%	NR	NR	NR	NR	Other adversity	≤ 22 months of age	Records	-Percent time institutionalized up to 22 months B=−0.07027, SE=0.03092, p<0.05	PCR	Buccal cells	Institutionalized versus foster care, ethnicity, age at telomere collection, low birth weight
Drury, 2014	Case-control/Low vs. High Family Instability	6/9	80 (46)	10.2 (2.9)	49%	NR	NR	NR	NR	Other adversity	< 15 years old	Questions extracted from the Preschool Age Psychiatric Assessment	Control: M 1.9, SD 0.5 Case: M 1.7, SD 0.3 t=2.51, p=.01	PCR	Buccal cell	Child gender, age, maternal and paternal age at conception, race, and maternal education
Entringer, 2011	Case-control/Prenatal stress vs. Non-stress	8/9	94 (45)	24.4 (0.7)	77.6%	none	none	none	none	Other adversity	Gestational period up to Birth	Semi-structured interview	B=−0.090, 95% CI = −0.179 to −0.001, p<0.05	PCR	Leukocyte	Age, BMI, sex, birth weight, and early-life and concurrent stress level
Entringer, 2013	Cross-sectional/Mother-newborn dyads	7/10	27 dyads (−)	0	52%	–	–	–	–	Other adversity	≤ 9.2 weeks of gestation	Pregnancy-specific stress scale	B=−0.099, 95% CI −0.197 to −0.002, p=0.04	PCR	Cord blood	Gestational age at birth, weight, sex, antepartum obstetric complications
Glass, 2010	Case-control/Twins UK cohort with Abuse vs. no Abuse	5/9	1 090 (PA n=20; SA n=34)	NR	NR	NR	NR	NR	NR	Narrowly defined abuse	NR	Two single questionnaire items assessed PA and two items assessed SA	-Physical Abuse Case: M 7.04, SD 0.58 Control: M 6.97, SD 0.67 p=0.61 -Sexual Abuse Case: M 6.86, SD 0.53 Control: M 7.05, SD 0.66 p=0.10	Southern blot	Leukocyte	Age, sex, BMI and smoking
Gotlib, 2015	Case-control/daughters of mothers with MDD vs. Mothers with no psychiatric disorders	6/9	97 (50)	11.9 (1.5)	100%	none	none	NR	NR	Maternal depression	≤ 14 years old	SCID with mother	Case: M 1.524, SD 0.265 Control: M 1.754, SD 0.361 t(95)=3.582, p=0.001	PCR	Leukocyte	none
Jodczyk, 2014	Cross-sectional/Christchurch Health and Development Study	6/9	677 (SA n=83, PA n=112)	28–30	NR	none	42.9% MDD, 33.7% Anxiety disorders and 28.7% Suicidal ideation/attempt	31.4%	NR	Narrowly defined abuse	≤ 16 years old	PBI, CTS and interview	-SA[2] Case: M 1.24, SD 0.39 Control: M 1.17, SD 0.37 -PA[2] Case: M 1.22, SD 0.51 Control: M 1.17, SD 0.33	PCR	Leukocyte	Sex, ethnic origin and family SES at birth
Kananen, 2010	Cross-sectional/Health 2000 National cohort in Finland	5/10	939 (552)	49.8 (1.2)	63%	NR	32.9% anxiety; 28% of the cases have comorbid MDD and 22% a comorbid alcohol use disorder	NR	NR	Other adversity; SES	< 16 years old	Interview	-Number of childhood adversities β= − 0.091, SE=0.32, p= 0.005 -Parental unemployment β=−0.157, p=0.008	PCR	Leukocyte	Age and sex
Kiecolt-Glaser, 2011	Cross-sectional/community sample; caregiver vs. noncaregiver	7/10	132 (42 Abuse and 74 Adversity)	69.7 (10.1)	72%	none	NR	3.8%	Excluded patients using statins, systemic steroids, orantibiotics	Other adversity; Abuse and neglect	≤ 16 years old	CTQ and semi-structured interview	-Other adversity t(73)=1.95, p=0.05 -Abuse and neglect t(74)=0.67, p=0.50	Southern blot	Leukocyte	Age, sex, BMI, exercise, sleep, alcohol use, caregiving status
Malan-Müller, 2013 (a)(b)	Case-control/ACE vs. No ACE (without(a) or with(b) HIV-positive)	6/9	128 (66)	29.8	100%	64.84% HIV-positive	NR	NR	16% antiretroviral treatment	Abuse and neglect	< 18 years old	CTQ	HIV(−) Control: M 1.02, SD 0.38 HIV(−) Case: M 0.92, SD 0.35 HIV(+) Control: M 0.59, SD 0.19 HIV(+) Case: M 0.62, SD 0.2	PCR	Leukocyte	none
Marchet-to, 2016	Prospective cohort/Mother-newborn dyads	7/9	24 dyads (6)	0	NR	–	–	–	–	Other adversity	≤ third trimester of gestation	Holmes & Rahe Stress Scale	Case: M 6.98, SD 0.89 Control: M 8.74, SD 1.05 t=−3.99, p=0.003	TRF	Cord blood	Maternal age, gestational age at birth, and birth weight no different between groups
Mason, 2015	Cross-sectional/Nurses Health Study II (NHSII)	8/10	1 135 (PA −660; SA - 467)	45.5 (4)	100%	86% type 2 diabetes or cardiovascular disease	NR	NR	NR	Narrowly defined abuse	≤ 17 years old	Revised Conflict Tactics Scale (PA) and interview (SA)	-Sexual abuse Control: M −0.744, SD 0.3 Case:	PCR	Leukocyte	Age at blood draw, paternal age at participant's birth, race, participant's parental SES,

Study characteristics																
				Participant characteristics						Early adversity exposure			Telomere measurement			
Author, year	Study design/ Sample	NOS	Study *N* (exposed)	Age (SD)	Female	Medical condition	Psychiatric condition	Smoke	Medication use	Type	Timing	Assessment Method	Adversity and TL Association	TL Measurement	Tissue	Covariates
													M −0.749, SD 0.3			
Mason, 2015 (cont.)													-Physical abuse Control: M −0.736, SD 0.3 Mild Case: M −0.752, SD 0.4 Moderate Case: M −0.773, SD 0.3 Severe Case: M −0.722, SD 0.4			childhood somatogram score, parental history of depression and medical issues
Mitchell, 2014	Case-control/Harsh vs. Nurturing environment	6/9	40 (20)	9	0%	NR	NR	NR	NR	Abuse, neglect, and other adversity	≤ 9 years old	Social disadvantage by survey Conflict Tactics Scale for physical and emotional abuse, CHDI for maternal depression	Control: M 10.3, SD 2.5 Case: 9.6, SD 4.1	PCR	Saliva	None
Need-ham, 2012 (a)(b)	Cross-sectional/AMERICO study: high(a) and low income(b)	5/10	70 (14 <$40,000; 45 $40–$60,000)	9.9 (1.5)	52%	none	none	NR	NR	SES	≤ 10 years old	SES Questionnaire	-Comparison with family income ≥$70,000 $40,000–$69,000 per year	PCR	Leukocyte	Sex, age and race/ethnicity
Need-ham, 2012 (a)(b) (cont.)													OLS=−0.33, 95% CI −0.68 to 0.03, p=0.07 −<$40,000 per year OLS=−0.38, 95% CI −0.82 to 0.06, p=0.09			
O'Donovan, 2011	Cross-sectional/ACE vs. No ACE (with or without PTSD)	7/10	90 (18)	30.55 (7.4)	51.1%	none	47.7% PTSD	20.4%	none	Abuse and neglect	≤ 14 years old	Life Stressor Checklist	r=−0.42., p=0.003	PCR	Leukocyte	Age
Révész, 2016	Prospective/Netherlands Study of Depression and Anxiety (NESDA)	6/9	2 936 (−)	41, 47	66%	~ 33.3% one or more somatic diseases	7.4% current or remitted diagnosis of a depressive and/or anxiety disorder	38.7%	NR	Abuse and neglect; SES[3]	< 16 years old	Childhood Trauma Interview (CTI) and interview	Childhood trauma determinants of 6-year TL attrition β=−23.81, SE=7.74, p=0.002 Neighborhood quality/SES[5] B = −173.80, 95% CI: −298.80,− 49.01 p = 0.006)	PCR	Leukocyte	Age and sex
Robertson, 2012 (a)	Cohort/The West of Scotland Twenty-07 Study- 1970s	7/9	775 (−)	35	53.3%	NR	NR	NR	NR	SES	≤ 15 years old	Interview	-Parental class "V" B=−0.772, SE=0.363, p=0.034 - Household financial difficulties B=−1.021, SE=0.817 p=0.212	PCR	Leukocyte	Gender and assay variation
Robertson, 2012 (b)	Cohort/The West of Scotland Twenty-07 Study- 1950s	7/9	866 (−)	55	54.2%	NR	NR	NR	NR	SES	≤ 15 years old	Interview	-Parental class "V" B=−0.153, SE=0.326, p=0.640 - Household financial difficulties B=−0.837, SE=1.057, p=0.429	PCR	Leukocyte	Gender and assay variation
Robertson, 2012 (c)	Cohort/The West of Scotland Twenty-07 Study- 1930s	7/9	544 (−)	75	56.8%	NR	NR	NR	NR	SES	≤ 15 years old	Interview	-Parental class "V" B=−0.286, SE=0.393, p=0.467 - Household financial difficulties B=−0.113, SE=0.490, p=0.818	PCR	Leukocyte	Gender and assay variation
Robles, 2016	Cross-sectional/Children reporting warmth or conflict in the parent-child dyad	6/10	39 (−)	11 (1.5)	59.3%	NR	NR	NR	NR	Other adversity	≤ 11 years old	Youth Everyday Social Interaction, Mood measure and Child Home Data Questionnaire (marital interactions)	Parent–child conflict B=−0.33, 95% CI −0.86, 0.19, p>0.05 Marital conflict B=−1.51, 95% CI−2.49 to −0.53, p<.001	PCR	Leukocyte	none
Savolainen, 2014	Case-control/ACE vs. No ACE from Helsinki Birth Cohort Study	6/9	1 486 (Separated, n=215; EA, EN or PA, n=953)	61.5 (2.9)	68.2%	4.2% coronary heart disease, 2.6% stroke and 15.2% type 2 diabetes	5,7% has been hospitalized for psychiatric disorder	23.1%	NR	Other adversity; Abuse and neglect	< 10	Finnish National Archives' register for parental separation, retrospective question of trauma and TEC for lifespan experiences	-Non-separated vs. Separated *B*=−0.108, 95% CI −0.255 to 0.039, p=0.414 -Abuse and neglect *B*=−0.033 CI=−0.0179, 0. 110 (p=0.696)	PCR	Leukocyte	Age, sex, DNA concentration, smoking, alcohol use, BMI, physical activity, any hospitalized mental disorders, medical issues, education, father's occupation status in childhood, mother's age at delivery.
Schaakxs, 2015	Cross-sectional/Netherlands Study of Depression in Older Persons (NESDO)	7/10	496 (336)	70.6 (7.4)	65.1%	Chronic diseases, 1.45 (1.17) median	74.1% depressive disorder	NR	NR	Other adversity; Abuse and neglect	< 16 years old	CTI and interview	- Childhood other adversity B=−79.88, SE=38.18, p=0.04 -Abuse and neglect B= −2.73, SE=8.01, p= 0.73	PCR	Leukocyte	Age, sex, and chronic diseases
Shalev, 2013	Prospective/EnvironmentRisk Longitudinal Twin Study	7/9	236 (108)	5y then 10y	49%	NR	NR	NR	NR	Other adversity; Narrowly defined abuse	≤ 10 years old	CTS for WV, interview for bullying and PA	-Other adversity B=−0.052, SE=0.021, p=0.015 -Physical abuse B= − 0.084 (SE=0.035, p= 0.018)	PCR	Buccal cells	Baseline TL at 5 years age, sex, socioeconomic deprivation and BMI at age 10
Surtees, 2011	Cross-sectional/EPIC-Norfolk study	8/10	4 441 (2 235)	62 (−)	100%	9.8% diabetes or myocardial infarction or stroke	19.2% MDD and 4.3% GAD	40.6%	NR	Other adversity	< 17 years old	HLEQ	B=0.013, 95% CI 0.002 to 0.024, p=0.015 (positive B=shorter telomeres)	PCR	Leukocyte	Age, physical health score, social class, obesity, smoking, self-reported health, disease
Theall, 2013	Cross-sectional/Recruited through urban schools in New Orleans	6/10	99 (36)	4–14	52.9%	–	–	NR		SES	≤ 14 years old	U.S. Census for economic deprivation, interview for neighborhood disorder	-Neighbor-hoods with high perceived disorder β=−0.478, SD=0.184, p<0.05 -Percent below poverty line β=−0.010, SD=0.004, p<0.05	PCR	Saliva	Age, sex, household socioeconomic position, and years living in the neighborhood
Tyrka, 2015(a)	Case-control/ACE vs. No ACE (with lifetime psychiatric disorder)	8/9	111 (72)	33.4 (11.4)	66%	none	11.7% MDD, 22.5% depressive, 2.7% PTSD and 11.7% anxiety	13.5%	none	Other adversity; Abuse and neglect	< 18 years old	CTQ and interview	-Combined Case: M 5642.7, SD 4138.2 Control: M 7181.00, SD 4362.80 -Other adversity Case: M 6482.9, SD 3932.3 Control: M 7181.00, SD 4362.80 -Abuse and neglect Case: M 6034.1, SD 3784.0 Control: M 7181.0, SD 4362.8	PCR	Leukocyte	Age, gender, education, BMI, and childhood socioeconomic adversity
Tyrka, 2015(b)	Case-control/ACE vs. No ACE (Healthy sample)	8/9	179 (66)	29.5 (9.9)	57.5%	none	none	7.8%	none	Other adversity	< 18 years old	CTQ and interview	Case: M 6432.9, SD 3372.7 Control: M 7181.00, SD 4362.8	PCR	Leukocyte	Age, gender, education, BMI, and childhood SES
Tyrka, 2010	Case-control/ACE vs. No ACE	8/9	31 (10)	26.9 (10.1)	70.9%	none	none	9.6%	none	Abuse and neglect	< 18 years old	CTQ	Case: M 0.70, SD 0.24 Control: M 1.02, SD 0.52 t(29) = 2.4, p=0.03	PCR	Leukocyte	Age, sex, smoking, OCP, BMI, race, SES, education,stress
Van Ockenburg, 2015	Cross-sectional/Prevention of REnal and Vascular ENd stage Disease (PREVEND)	9/10	1 094 (430)	53.1 (11.4)	53.7%	19.1% chronic disease	NR	23.9%	NR	Other adversity	< 12 years old	LTE	*B*=−0.001, SE=0.012, p=0.936	PCR	Leukocyte	Age, sex, BMI, chronic diseases, frequency of sports, smoking, level of education
Wojcicki, 2015	Cross-sectional Recruited prenatally at two hospitals in San Francisco	8/10	203 (65)	4 and 5	NR	NR	Child behavior: 3.1% attention, 3.5% anxiety, 4.6% affective, 5.1% Developmental, 5.0% Oppositional defiant	–	NR	Maternal depression	≤ 3	Center for Epidemiologic Studies Depression Scale, Edinburgh Postpartum Depression Scale or major depressive episode/dysthymia per the MINI	β= = 363.99, p=0.01	PCR	Leukocyte	Maternal TL, paternal age, child anxiety at 5 years and oppositional defiant behavior at 3, 4 or 5 years

Note: BMI, body mass index. ETI, Early Trauma Inventory; MDD, Major depressive disorder; PCR, polymerase chain reaction; TRF, Telomere Restriction Fragment assay; PBI, Parental Bonding Instrument. SCID, Structured Clinical Interview for DSM-IV; CTQ, Childhood Trauma Questionnaire; WV, witnessing domestic violence; SL, separation and loss; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; IAI, Ineffective arguing inventory; DQS, Discussion quality scale; CSS, Carver support scale; FSI, Family support inventory; ACE, Adverse Childhood Experiences. CTS, Conflict Tactics Scale; TEC, Traumatic Experiences Checklist; TL, Telomere length; HLEQ, Health and Life Experiences Questionnaire; M, mean; SD, standard deviation; SES, socio-economic status; LTE, List of Threatening Events; OCP; oral contraceptive pill use.

1=based on percentages reported in Adams J et al, J Epidemiol Community Health 2004. Dec;58(12):1028–9;

2=values obtained from systematic review reporting means and standard deviation;

3=values obtained from Park M et al, PLoS One 2015. 10(6):e0128460, which utilizes the same dataset.