REVIEW

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Meta-analysis: Exposure to Early Life Stress and Risk for Depression in Childhood and Adolescence

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Objective: Early life stress (ELS) is associated with increased risk for the development of major depressive disorder (MDD) in adulthood; however, the degree to which ELS is associated with an early onset of MDD (ie, during childhood or adolescence) is not known. In this meta-analysis, we estimated the associations between ELS and the risk for onset of MDD before age 18 years. In addition, we examined the associations between eight specific forms of ELS (ie, sexual abuse, physical abuse, poverty, physical illness/injury, death of a family member, domestic violence, natural disaster, and emotional abuse) and risk for youth-onset MDD.

Method: We conducted a systematic search in scientific databases for studies that assessed both ELS and the presence or absence of MDD before age 18 years. We identified 62 journal articles with a total of 44,066 unique participants. We assessed study quality using the Newcastle−Ottawa Scale. When heterogeneous effect sizes were detected, we tested whether demographic and/or methodological factors moderated the association between ELS and MDD.

Results: Using a random-effects meta-analysis, we found that individuals who experienced ELS were more likely to develop MDD before the age of 18 years than were individuals without a history of ELS (odds ratio = 2.50; 95% confidence interval 2.08, 3.00). Separate meta-analyses revealed a range of associations with MDD: whereas some types of ELS (eg, poverty) were not associated with MDD, other types (eg, emotional abuse) were associated more strongly with MDD than was ELS considered more broadly.

Conclusion: These findings provide important evidence that the adverse effect of ELS on MDD risk manifests early in development, prior to adulthood, and varies by type of ELS.

Key words: depression, stress, abuse, youth

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As many as 25% of adolescents meet criteria for major depressive disorder (MDD),[1] which is associated with long-term adverse consequences, including social and economic hardship, poorer physical health, and increased risk for the recurrence of depressive episodes during adulthood.[2-5] In particular, early-onset MDD is associated with increased risk for substance abuse, bipolar disorder, high-risk sexual behaviors, and suicide.[5] Given the prevalence and substantial costs of depression in childhood and adolescence, there is a pressing need to identify factors that contribute to risk for MDD in youth.

In this context, experiences of early life stress (ELS; eg, exposure to trauma, violence, and forms of maltreatment) have been found to be a significant predictor of MDD in adulthood[6]; in fact, recent meta-analyses indicate that ELS is associated with a twofold increase in risk for MDD in adults.[7-9] Although several individual studies have examined the effects of ELS on the onset of depression in childhood or adolescence, all meta-analyses to date have focused explicitly on MDD in adulthood,[7,8] have included predominantly adult samples,[9,10] or have not examined whether ELS differentially predicts youth-onset versus adult-onset depression.[10] Using meta-analysis to quantify the association between ELS and MDD in childhood and adolescence across studies is critical in understanding the nature of the impact of ELS on the subsequent experience of depression in youths.

There are important differences between MDD in childhood or adolescence and MDD in adulthood with respect to the etiology, clinical presentation, and course of depression that raise the possibility that different risk factors are associated with an earlier onset of the disorder. For example, risk for youth-onset depression is influenced by the biological and physical changes of puberty, developmental differences in neural maturation, increased susceptibility to psychosocial stressors, and reduced availability of cognitive coping strategies.[5,11,12] Moreover, children and adolescents who are depressed are

more likely than adults who are depressed to endorse somatic complaints and to experience behavioral problems.[11,12] Given differences between youth and adults in the etiology, clinical presentation, and course of depression, it is possible that the nature of the relation between ELS and depression also differs as a function of developmental stage. Consistent with this formulation, the only meta-analysis to date that has examined the association between ELS and depression in adolescents found that the association between childhood abuse/neglect and depression was stronger in adolescent than in adult samples.[9] Because the authors focused exclusively on studies that used the Childhood Experience of Care and Abuse (CECA) interview, only four studies with adolescent samples were included in their analyses. Thus, a broad systematic examination is needed to quantify the nature of the association between ELS and child- or adolescent-onset depression.

In the present meta-analysis, we quantify, for the first time, the association between ELS and childhood- or adolescent-onset depression. To conduct a careful assessment of childhood- and adolescent-onset MDD, we included only those studies in which depression was assessed with diagnostic interviews of youths less than 18 years of age. We defined ELS broadly to include any event with characteristics that would be considered stressful during early life, including divorce, hospitalization, and death of a family member, as is consistent with definitions of ELS put forth elsewhere.[13] Moreover, when defining ELS, we included assessments that used either dichotomous (ie, presence versus absence of ELS) or continuous measures of ELS, and that allowed multiple forms of ELS. In addition, given the likelihood that different types of ELS are implicated differentially in risk for depression,[8,9] we conducted subsequent analyses with those studies that assessed a specific type of ELS (ie, sexual abuse, physical abuse, poverty, physical illness/injury, death of a family member, domestic violence, natural disaster, and emotional abuse). These analyses are critical, because although previous meta-analyses have reported that multiple forms of ELS predict depression in adulthood,[8] findings with children and adolescents have been inconsistent.[14] Finally, whenever we found significant heterogeneity in the effect size for each set of analyses, we examined whether effect sizes varied based on theoretically and methodologically relevant moderators.

METHOD

Study Selection

Studies included in this meta-analysis satisfied the following criteria: (1) dichotomous or continuous measurement of ELS; (2) diagnostic assessment of depression using a clinical interview; (3) MDD assessment prior to a mean age of 18 years; and (4) inclusion of a nondepressed control group.

Search Procedure

We used several strategies, outlined in the PRISMA flowchart (Figure 1), to identify the 62 journal articles that were ultimately included in this meta-analysis. First, we conducted computer-based searches using PubMed and PsycINFO for articles published in English from inception to June 2018, using the following keywords (or stems): ("Affective Disorder*" OR "Mood Disorder*" OR depress* OR MDD) AND (child OR childhood OR children OR infant OR adolescent OR adolescence) AND ("early life stress" OR "early adversity" OR maltreatment OR "physical abuse" OR "sexual abuse" OR "emotional abuse" OR "psychological abuse" OR trauma OR neglect). Second, we reviewed the bibliographies for additional studies using forward and backward searching. Third, we sent emails describing our meta-analysis and its inclusion criteria to professional membership LISTSERVs of research organizations including the Society for a Science of Clinical Psychology, the Association for Behavioral and Cognitive Therapies, and Society of Clinical Child and Adolescent Psychology of the American Psychological Association.

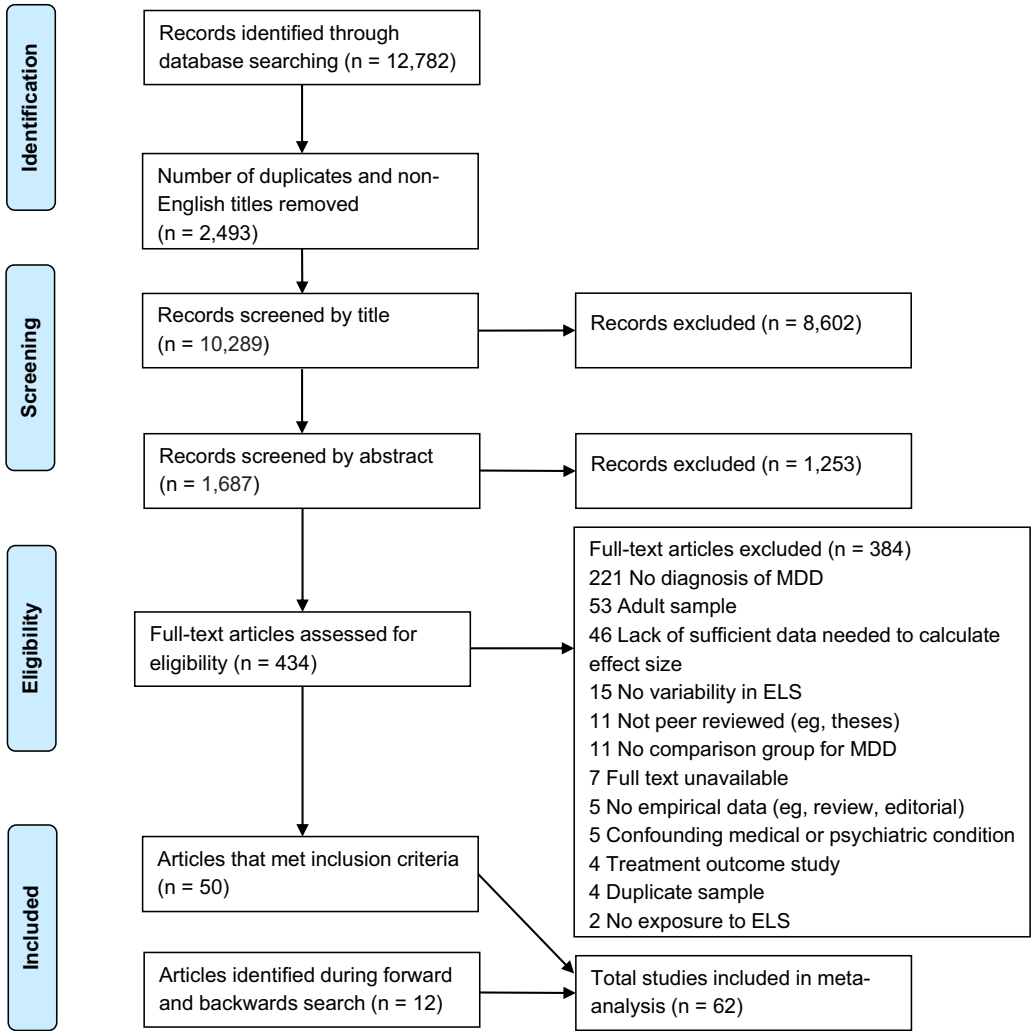
Data Extraction

Two trained raters independently extracted effect sizes and moderator codes. Rater agreement for moderator codes was 95%. When raters provided contradictory judgments, disagreements were discussed, and the lead authors made a final determination.

Moderator Variables

When our analyses yielded heterogeneous effect sizes, we tested whether demographic and methodological factors moderated the association between ELS and MDD. We coded the following demographic characteristics when available: average age of the sample at the time of assessment of depression (in years); average age (in years) at the time of the ELS; sex composition (proportion of participants who identified as female); racial diversity (proportion Caucasian); and continent on which the study was conducted. We also coded the following methodological characteristics: sample size; year published; study design (cross-sectional, longitudinal); sample source (student, clinic-referred, population-based, volunteer/community, other/mixed); diagnostic criteria used to assess depression (eg, *DSM-III, DSM-IV*); presence of MDD only versus MDD and other depressive disorders; type of report used to assess early life stress (interview, questionnaire, record review); time frame for ELS assessment (time-limited; whole life); ELS type (single measure, composite measure); whether ELS interviewers were blinded to MDD diagnosis; whether MDD interviewers were blinded to ELS; and informant for MDD

FIGURE 1 PRISMA Flowchart of Identification of Independent Studies for Inclusion in Meta-analysis



Note: *ELS = early life stress; MDD = major depressive disorder.*

and ELS (child, parent, or both). We also coded study quality using the Newcastle Ottawa Scale,[15] which was recommended for use by the Cochrane Collaboration.[16] We used the original scales to assess case-control and cohort studies, and a modified version[17] to assess cross-sectional studies.

Calculation of Effect Size

All effect sizes were converted to odds ratios (ORs). When raw numbers were not provided by the study authors, we used the effect size values provided in the manuscript. Following recommendation of experts,[18] when any cell that was used to calculate the OR had a value of 0, we inserted 0.5 to all 4 cells to calculate the effect size. An OR of 1 indicated that a diagnosis of depression was equally likely in children with and without exposure to ELS, whereas an OR of >1 or <1 indicated that depression in the ELS group was more or less likely, respectively, to occur relative to the group that was not exposed to ELS. The 95% CI for the OR represents the relative precision of the measurement (wider ranges are less precise). For each study, one OR value was included in the analyses of all forms of ELS measure; if multiple types of ELS were examined, we calculated an average OR. In addition, we calculated separate ORs for eight specific forms of ELS: sexual abuse, physical abuse, poverty, physical illness/injury, death of a family member, domestic violence, natural disaster, and emotional abuse. Thus, the same study could yield as many as nine unique OR values: one for all forms ELS, and one for each of the eight specific forms of ELS. These procedures produced 79 ORs included in analyses from the 62 eligible articles. Of the 62 articles, 57 provided unique samples (5 articles with

overlapping samples were included only in analyses on specific types of ELS). The number of unique studies ranged from 4 for both emotional abuse and natural disaster to 57 for any type of ELS.

Statistical Analysis

Odds ratios were transformed using a logarithmic transformation. We conducted random-effects models, using the DerSimonian and Laird method. Given that our outcome variable was dichotomous, we used the Begg[19] test and visual inspection of the corresponding funnel plots to assess publication bias. To estimate heterogeneity of effect sizes, we used the standard Cochran Q Test, which approximates a χ^2 distribution with k−1 degrees of freedom, where k is the number of effect sizes,[20] and the I^2, which provides the percentage of variability that is due to heterogeneity.[21] When the p value associated with the Q statistic was ≤ 0.05, we conducted leave-one-out sensitivity analyses and random-effects meta-regression analyses using the Knapp−Hartung method to examine individual moderators. If more than one moderator significantly predicted variance in effect size, we examined the moderators jointly as predictors. We used STATA 14 to conduct statistical analyses.

RESULTS

Meta-analysis

ELS (All Forms) and MDD. A total of 57 studies reported on the diagnosis of MDD in childhood or adolescence as a function of ELS (Table 1,[22-83] with additional details presented in Table S1, available online), with a wide range of ORs (Figure 2). The random-effects meta-analysis indicated that individuals who experienced ELS were more likely to develop depression in childhood or adolescence than were children without a history of ELS (OR = 2.50, 95% CI = 2.08, 3.00), an effect that differed significantly from zero ($Z = 9.87$, $p < .001$). There was significant heterogeneity across studies ($Q_{56} = 548.91$, $p < .001$, $I^2 = 90\%$); for this and all other analyses that yielded significant heterogeneity, we conducted leave-one-out sensitivity analyses (see Supplement 1 and Table S2, available online) and moderator analyses (see below).

Specific Types of ELS and MDD. Table 2 presents the results of random-effects meta-analyses for each of the 8 types of ELS examined in relation to a diagnosis of MDD. Forest plots are presented in Figures S1 to S8, available online. The random-effects meta-analyses indicated that individuals who experienced sexual abuse, physical abuse, death of a family member, domestic violence, or emotional abuse were significantly more likely to develop depression by childhood or adolescence than were individuals without a history of exposure. In contrast, individuals who experienced poverty, illness/injury, or a natural disaster were not significantly more likely to develop depression in childhood or adolescence than were those without a history of exposure. Again, we conducted leave-one-out sensitivity analyses (see Supplement 1 and Table S2, available online) and moderator analyses (see below) for each subtype of ELS in which there was significant heterogeneity (as reported in Table 2).

Moderator Analyses

We examined methodological and demographic study-level variables that might explain variation in effect sizes for outcomes with significant heterogeneity. We tested each moderator separately using simple regressions, weighted by the sample size for each study. No variable significantly predicted variance in the effect sizes obtained for the analysis examining all forms of ELS (p values $>.05$).

Moderator analyses within the studies that examined the association between sexual abuse and depression yielded two variables that were significantly associated with observed effect sizes: source of participants and method of assessing ELS. Source of participants was dummy coded based on whether the sample was from a clinical population or from a volunteer community population. Both sets of analyses yielded a statistically significant effect of sample source (clinical sample: coefficient = −0.78, SE = 0.21, $t_{18} = -3.62$, $p = .002$; volunteer sample: coefficient = 1.19, SE = 0.39, $t_{18} = 3.09$, $p = .007$). Studies that were not based on selecting clinical participants (OR = 2.42; 95% CI = 1.74, 3.36; $k = 8$) had a larger estimated effect size than did studies that included clinical participants (OR = 1.08; 95% CI = 0.83, 1.39; $k = 11$); only those studies that did not include clinical participants yielded an effect size that differed significantly from zero ($p < .001$). Furthermore, studies that included volunteer community participants (OR = 4.43; 95% CI = 2.37, 8.28; $k = 3$) had a larger estimated effect size than did studies that did not include volunteer community participants (eg, clinical, population-based, or other) (OR = 1.41; 95% CI = 1.11, 1.79; $k = 16$), although both sources of participants yielded an effect size that differed significantly from zero ($p < .01$). In addition, the method of assessing ELS was significantly associated with the effect sizes reported in the association between sexual abuse and depression. Specifically, sexual abuse assessed via interview was associated with a significantly greater effect size than were other forms of assessment (eg, questionnaire, record review; coefficient = 0.66, standard error [SE] = 0.23, $t_{18} = 2.86$, $p = .011$). Studies that used an interview to assess sexual abuse (OR = 2.14; 95% CI = 1.67, 2.74; $k = 8$) had a larger estimated effect size

TABLE 1 Characteristics of Studies Included in the Meta-analysis

Study authors, year, reference	Sample size	Age, y (mean)	% Female participants	% White	Sample source	ELS type(s)
Adams et al. (2013)[22,a]	3,424	14.50	49%	71%	National Survey of Adolescents—Replication, USA	Violence exposure
Adams *et al.* (2014)[23]	1,541	14.50	51%	71%	"Tornado-affected communities," Alabama and Missouri	Physical assault, physical abuse, witnessed violence, and serious accidents
Ahmadkhaniha *et al.* (2007)[24]	87	10.98	36%	0%	Street children, Tehran, Iran	Sexual abuse
Barzilay *et al.* (2018)[25]	9,308	14.21	52%	56%	Community sample, USA	Experienced natural disaster, accident, witnessed/experienced violence, and sexual abuse
Bielas *et al.* (2016)[26]	130	16.84	0%	NS	Juvenile detention center, Switzerland	Adverse childhood experiences, low SES
Brown *et al.* (1999)[27]	639	17.99	48%	NS	Random sample, New York state	Physical abuse, sexual abuse, or neglect
Busso *et al.* (2017)[28]	51	16.96	61%	27%	School and community-based sources, USA	Physical and sexual abuse
Carey *et al.* (2008)[29]	94	14.25	63%	NS	Trauma clinic, South Africa	Sexual abuse
Clark *et al.* (2003)[30]	342	16.22	60%	74%	Clinical and community sources, USA	Physical and sexual abuse
Cohen *et al.* (1996)[31]	105	14.70	70%	NS	Psychiatric inpatient program, USA	Physical and sexual abuse
Copeland *et al.* (2007)[32]	1,420	16.00[c]	44%	69%	Random sample, North Carolina	PTSD criterion A traumatic event
Crombach *et al.* (2014)[33]	112	15.93	0%	0%	Boys living on the streets or in families in Burundi	Life on the street experience
Cruz-Fuentes *et al.* (2014)[34]	516	14.43	47%	NS	Mexican Adolescent Mental Health Survey	Abuse, neglect, life-threatening childhood physical illness, and other family stressors[e]
Daviss *et al.* (2009)[35]	104	13.78	37%	80%	Mental health clinic and from community, USA	Sexual abuse, physical abuse or threat, family violence or threat, and non-victimization event
Eksi *et al.* (2007)[36]	160	14.43	64%	0%	Schools near epicenter of earthquake, Turkey	Earthquake-related, and post-earthquake traumatic experiences
Flisher *et al.* (1997)[37]	665	13.10	52%	9%	Community sample, San Juan or New York state	Physical abuse
Giaconia *et al.* (1995)[38]	384	17.90	49%	99%	Public school system, USA	Traumatic events (military combat, rape, physical assault, disaster, seeing someone hurt/killed, etc)
Gilman *et al.* (2003)[39]	1,089	13.99	47%	73%	Offspring from the National Collaborative Perinatal Project, Providence, RI	Low SES, family disruption, and residential instability

(continued)

TABLE 1 Continued

Study authors, year, reference	Sample size	Age, y (mean)	% Female participants	% White	Sample source	ELS type(s)
Glod and Teicher (1996)[40]	34	8.91	35%	NS	Inpatient or outpatient psychiatric clinic, USA	Physical and sexual abuse
Green *et al.* (1999)[41]	31	15.10	100%	55%	Clinic-referral, USA	Physical and sexual abuse
Greger *et al.* (2015)[42]	335	16.85	59%	NS	Residential child welfare institutions, Norway	Witnessing violence, victim of violence, sexual abuse
Hanson *et al.* (2008)[43,a]	3,906	14.49	49%	72%	National Survey of Adolescents, USA	Sexual abuse, physical abuse, and witnessing violence
Harkness *et al.* (2006)[44]	103	15.46	65%	98%	Community mental health agencies and local high schools, Ontario, Canada	Childhood abuse and neglect
Hazel *et al.* (2008)[45]	705	15.00[c]	51%	NS	Community sample, Brisbane, Australia	Multiple family stressors,[f] and child chronic illness
Horesh *et al.* (2003)[46]	40	17.12	55%	0%	Psychiatric clinic, Israel Psychiatric clinic, Gothenburg, Sweden	Deaths, losses, and sexual abuse
Ivarsson *et al.* (2016)[47]	50	15.90	56%	93%	OCD clinic patients in Gothenburg, Sweden	Attachment-related trauma, peer cruelty, interpersonal violence, loss of parent or other
Jaffee *et al.* (2002)[48]	998	15.00[c]	48%	NS	Dunedin Multidisciplinary Health and Development Study, New Zealand	Multiple family stressors,[g] and unwanted sexual contact
Jenness *et al.* (2017)[49]	10,142	15.19	49%	66%	National Comorbidity Survey Replication—Adolescent Supplement; US	Physical injury
Kaplan *et al.* (1998)[50]	198	15.00[d]	50%	100%	New York State Department of Social Services, New York	Physical abuse
Kaufman (1991)[51]	56	9.58	52%	66%	Department of Children and Youth Services, Waterbury, CT	Physical, emotional, and sexual abuse; neglect
Kaufman *et al.* (2004)[52]	101	10.00	54%	21%	Larger study of childhood trauma, Connecticut	Physical, emotional, and sexual abuse, neglect, exposure to domestic violence
Kazdin *et al.* (1985)[53]	79	10.40	32%	72%	Psychiatric inpatient facility, Pittsburg, PA	Physical abuse
Kiliç *et al.* (2017)[54]	121	15.18	49%	NS	Psychiatric outpatient unit, Turkey	Emotional, physical and sexual abuse; neglect
Kilpatrick *et al.* (2003)[55]	3,907	14.5[d]	49%	72%	National Survey of Adolescents, USA	Physical assault, sexual assault, or witnessed violence
Klasen *et al.* (2015)[56]	309	14.44	49%	0%	Boarding school for former child soldiers, Uganda	Stressors related to war[h]
Kolko *et al.* (1988)[57]	103	9.90	27%	72%	Child psychiatric unit, USA	Sexual and physical abuse
Kuyken *et al.* (2006)[58]	50	15.92	82%	NS	Clinical, school, and community sources, UK	Trauma history, any sexual assault, childhood sexual abuse

(continued)

TABLE 1 Continued

Study authors, year, reference	Sample size	Age, y (mean)	% Female participants	% White	Sample source	ELS type(s)
López *et al.* (2017)[59]	3,614	14.67	50%	65%	National Survey of Adolescents—Replication, USA	Polyvictimization (physical/sexual assault, physical/sexual abuse, domestic/community violence)
Luby *et al.* (2014)[60,b]	246	10.91	48%	57%	Primary care and daycare sites, St. Louis, MO	Traumatic life events
Mac Giollabhui *et al.* (2018)[61]	173	12.5	56%	NS	Community sample, USA	Negative life events
McLeer *et al.* (1994)[62]	49	9.66	51%	NS	Psychiatric outpatient clinic, Pennsylvania	Sexual abuse
Miskovic *et al.* (2010)[63]	62	14.29	100%	NS	Child protection agencies and community, Ontario, Canada	Emotional, physical and sexual abuse, neglect
Morais *et al.* (2018)[64]	498	15.93	0%	57%	Residential sex offender treatment facility, USA	Sexual abuse
Moss *et al.* (1995)[65]	73	10.98	0%	95%	Fathers of participants enrolled in Center for Education and Drug Abuse Research, Pittsburgh, PA	Father has current substance use disorder diagnosis
Münzer *et al.* (2016)[66]	178	11.51	45%	NS	Health care and child welfare institutions, Germany	Maltreatment, sexual victimization, and witnessing and/or indirect victimization
Okello *et al.* (2007)[67]	153	15.39	37%	0%	Children with and without war-abduction histories, Uganda	War abduction
Olsson (1999)[68]	150	16.50[d]	77%	NS	High-schools, Uppsala, Sweden	Multiple family stressors[i]
Pantle and Oegema (1990)[69]	111	15.60	100%	NS	Crisis/assessment unit of hospital, Grand Rapids, MI	Sexual abuse
Patton *et al.* (2003)[70]	300	14.50	53%	NS	Population based cohort study, Victoria, Australia	Negative life events
Pelcovitz *et al.* (2000)[71,a]	185	15.16	52%	100%	New York State Department of Social Services, New York	Interparental violence exposure
Phillips *et al.* (2005)[72]	630	14.9	49%	88%	Population based cohort study, Queensland, Australia	Multiple family stressors[j]
Rizzo *et al.* (2010)[73]	155	15.00	76%	81%	Psychiatric inpatient unit, southern New England, USA	Dating violence victimization
Shanahan *et al.* (2011)[74,a]	1,004	12.5[c]	44%	NS	Random sample, North Carolina	Poverty, stressful life events, parental psychopathology, maltreatment, and family dysfunction
Spindola *et al.* (2017)[75]	81	9.56	47%	NS	Community and school-based, Brazil	Physical abuse, neglect, emotional maltreatment, and sexual abuse
Stoddard *et al.* (1989)[76]	60	13.30	57%	87%	Hospital burn unit, Boston, MA	Burn victim
Tang *et al.* (2017)[77]	435	14.00	58%	0%	Schools in Baoxing County, China	Pre-existing exposure to previous earthquake, or losing family member in current earthquake

(continued)

TABLE 1 Continued

Study authors, year, reference	Sample size	Age, y (mean)	% Female participants	% White	Sample source	ELS type(s)
Vila *et al.* (1999)[78]	44	7.75[d]	48%	50%	Classrooms with and without hostage-taking history in the same school, Paris, France	Hostage experience
Wahab *et al.* (2013)[79]	51	15.06	100%	NS	Suspected Child Abuse and Neglect (SCAN) clinic of a hospital, Kuala Lumpur	Sexual abuse
Weeramanthri *et al.* (2003)[80]	46	10.30	100%	NS	London Child Sexual Abuse Psychotherapy Outcome Study, UK	Sexual abuse
Williamson *et al.* (1995)[81]	74	15.43	50%	54%	Depression clinic at the New York State psychiatric clinic, New York	Negative dependent life events
Wilson *et al.* (2014)[82]	1,698	16.99	54%	98%	Minnesota Twin Family Study, Minnesota	Physical abuse/assault and sexual abuse/assault
Zwierzynska *et al.* (2013)[83]	1,706	13.00[c]	52%	97%	Longitudinal birth cohort study, UK	Peer victimization

Note: Studies in italics represent studies that were included in various subgroup analyses but were not included in the analysis of all forms of ELS due to duplicate samples. ELS = early life stress; NS = not specified; OCT = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; SES = socioeconomic status.

[a]*Studies that were included in various subgroup analyses but were not included in the analysis of all forms of ELS due to duplicate samples.*

[b]*Authors provided raw values*

[c]*Age at last assessment.*

[d]*Median of range provided.*

[e]*Family dysfunction; parental maladjustment; parental death; parental divorce/economic adversity.*

[f]*Maternal axis I diagnosis prior to age 5 years, financial hardship, parental discord, maternal stressful life events, and mothers' separation from partners.*

[g]*Mother's internalizing symptoms, mother's rejecting behavior, parents' criminal conviction history, parental disagreement about discipline, number of residence changes, number of parent figure changes, SES, parental loss.*

[h]*Recruited by force, exposure to shooting, beaten by rebels, without food for >2 days, threatened with death by rebels, witnessed killing, exposure to air raid, exposure to bomb explosion, witnessed a massacre, without drinking water for >2 days, witnessed physical injury, suffered severe physical injuries, raped by rebels, looted or burned houses, abducted other children, injured someone, directly involved in fighting, killed someone, punished/tortured other children.*

[i]*Alcohol abuse in parent; serious conflicts/quarreling; divorce; serious illness in a family member; death of parent or sibling; serious economic problems; familial fights involving adults; family member physically injured; scared of being hurt in the family; police involvement in the family; violent death of a family member.*

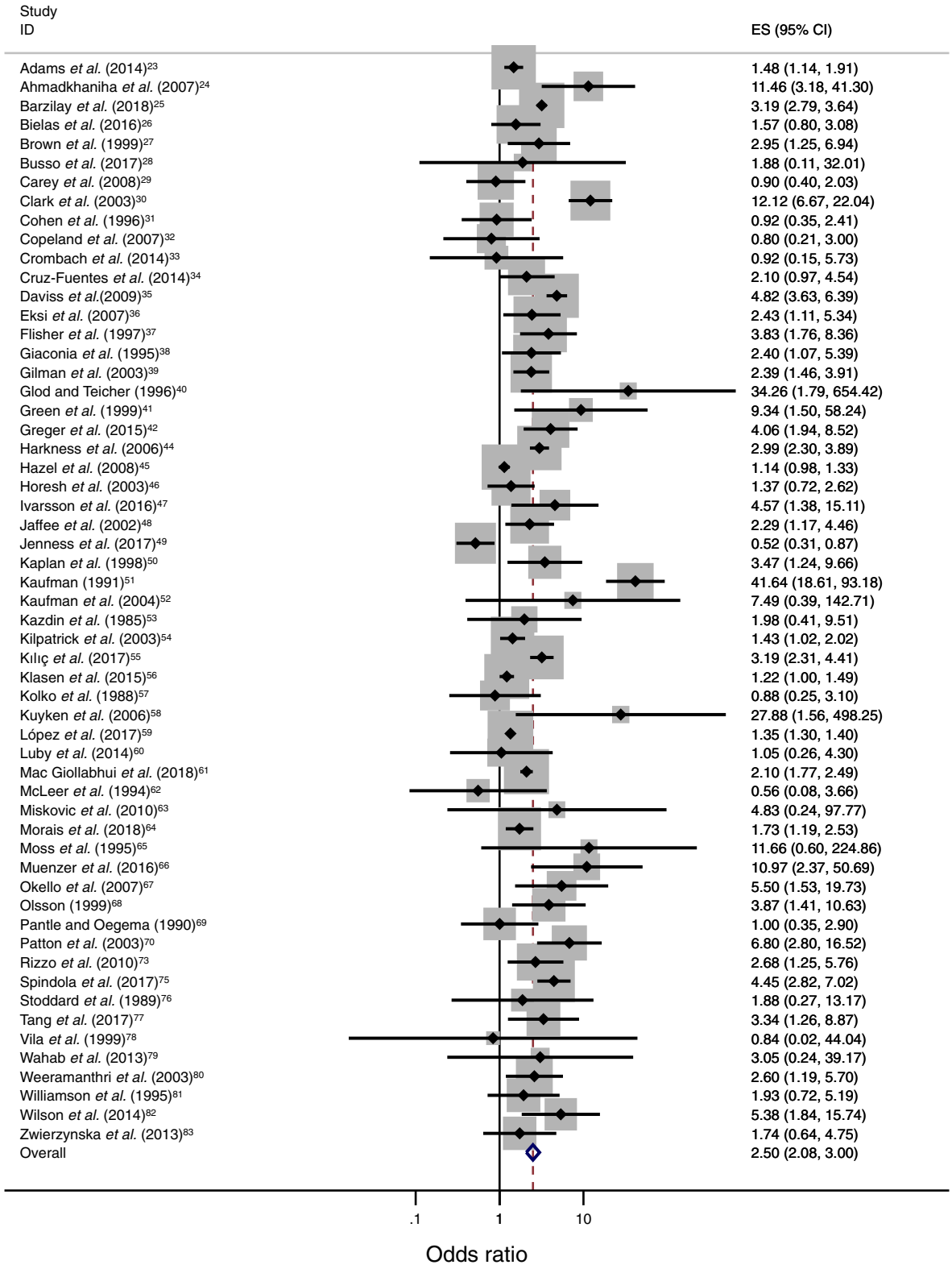
[j]*Mother's relationship with partner, economic hardship, early childhood health problems, parental deviance, and maternal stressful life events.*

than did studies that used other methods to assess sexual abuse (OR = 1.18; 95% CI = 0.80, 1.75; $k = 11$); only those studies that assessed sexual abuse via interview yielded an effect size that differed significantly from zero ($p < .001$). When both source of participants and method of assessing ELS were considered in the same model, only source of participants remained a significant predictor of heterogeneity in effect sizes for the association between sexual abuse and youth-onset MDD.

For studies that examined the association between poverty and depression, the time period of the poverty assessment was associated with the size of the estimated effect (time-limited [versus whole life]: coefficient = −0.97, SE = 0.32, $t_5 = -2.97$, $p = .041$). Studies that used a limited time frame for assessing poverty (OR = 0.81; 95% CI = 0.64, 1.01; $k = 4$) had a smaller estimated effect size than did studies that included participants' whole life (OR = 2.08; 95% CI = 0.92, 4.70; $k = 2$), although neither group yielded an effect size that differed significantly from zero.

Sample size was significantly associated with the size of the effect between physical illness/injury and MDD (coefficient = −0.0001, SE = 0.00004, $t_6 = -2.90$, $p = .034$). One study (Jenness[49]), which had a sample size (n = 10,142) substantially larger than the other studies (average sample size of n = 254), appeared to be driving this effect; with this study removed, the effects sizes were no longer

FIGURE 2 Estimated Odds Ratio for the Association Between All Forms of Early Life Stress and Diagnosis of Major Depressive Disorder in Childhood or Adolescence



Note: *Estimates of 1 indicate no differences, whereas an effect size of >1 indicates a greater likelihood of developing depression in childhood or adolescence following exposure to early life stress. The size of the box around each estimate reflects the relative weight of the study; the black line represents the confidence interval of that study estimate.*

TABLE 2 Results From Random-Effects Meta-analyses for Each Type of Early Life Stress (ELS) Examined in Relation to a Diagnosis of MDD

ELS Type	*k*	OR (95% CI)	*Z*	*Q*	I^2	Moderators
Sexual abuse	19	1.62 (1.26, 2.06)	3.83***	53.22***	66%	Sample source; ELS assessment
Physical abuse	13	2.13 (1.61, 2.81)	5.33***	21.59*	44%	None
Poverty	9	1.22 (0.69, 2.21)	0.67	768.89***	99%	ELS time frame
Illness/injury	7	1.40 (0.76, 2.56)	1.08	21.93***	73%	Sample size; MDD only vs. depressive disorders
Illness/injury (without Jenness *et al.*[49])	6	1.76 (1.14, 2.71)	2.57**	6.79	26%	N/A
Death	7	2.96 (2.00, 4.39)	5.39***	9.34	36%	N/A
Domestic violence	6	2.34 (1.71, 3.19)	5.35***	12.45*	60%	None
Natural disaster	4	1.62 (0.66, 3.97)	1.05	16.59***	82%	None
Emotional abuse	4	2.97 (1.51, 5.82)	3.16**	37.53***	92%	None

Note: k = *number of studies; OR = odds ratio; MDD = major depressive disorder; N/A = not applicable given there was no significant heterogeneity.* *p < .05; **p < .01; ***p < .001.

heterogeneous, and there was a significant association between physical illness/injury and MDD (Table 2). Furthermore, studies that assessed only MDD differed significantly from studies that assessed MDD and other depressive disorders (coefficient = −1.15, SE = 0.40, t_6 = 2.90, p = .034). Studies that assessed MDD and other depressive disorders (OR = 0.78; 95% CI = 0.46, 1.30; k = 4) had smaller effects than did studies that assessed only MDD (OR = 2.27; 95% CI = 1.50, 3.44; k = 3); finally, only those studies that assessed only MDD yielded an effect size that differed significantly from zero (p < .001).

None of the examined moderators predicted significant variance in the association between other types of ELS (ie, physical abuse, domestic violence, natural disaster, or emotional abuse) and depression in childhood or adolescence.

Publication Bias

A visual inspection of the funnel plots (see Figures S9−S17, available online) did not suggest publication bias, with the possible exception of the analysis on all forms of ELS. The Begg publication bias test yielded no significant publication bias for any outcomes (p values >.10; see Table S2, available online).

DISCUSSION

In this article, we report the results of a meta-analysis conducted to examine the association between ELS and youth-onset MDD (ie, during childhood or adolescence). Following a comprehensive search, we identified 62 journal articles that met our inclusion criteria, consisting of a total of 44,066 unique individuals. We found that individuals who had been exposed to ELS were 2.5 times more likely to meet diagnostic criteria for depression in childhood or adolescence than were individuals who had not been exposed to ELS. We also examined the effects of eight different types of ELS. Sexual abuse, physical abuse, death of a family member, domestic violence, and emotional abuse were associated with significantly higher risk for MDD before the age of 18 years. In contrast, poverty, illness/injury, and a natural disaster were not significantly associated with youth-onset MDD. It is important to note that despite carefully examining the potential for study quality to influence the size of the association between ELS and MDD, we found no evidence that study quality moderated the size of the obtained effects.

Overall, the effect of ELS on child- and adolescent-onset depression found in this meta-analysis (OR = 2.50) was commensurate with the strength of the effect found in meta-analyses examining depression in adulthood. For example, Nelson *et al.*[84] found that any type of maltreatment was associated with depression in adulthood (OR = 2.66). Similarly, Li *et al.*[7] found that childhood maltreatment prospectively predicted adult depression (OR = 2.03). Although Infurna *et al.*[12] found a stronger association between ELS and adolescent depression in their analysis of 4 studies that used the CECA interview (OR = 4.01), ELS considered more broadly appears to be a comparable risk factor for depression in youth and adults.

Although not tested statistically, examination of the estimated effect sizes and CIs clearly indicates that different forms of ELS varied in the strength of their association with depression in childhood or adolescence. A medium effect (OR = 2.96) was found for the association between death of a family member and early-onset depression. This finding is consistent with theoretical models of depression that posit

a tight coupling between exposure to interpersonal loss and onset of depression.[85] We also found a medium-size effect between emotional abuse and depression (OR = 2.97) that is similar in strength to results from meta-analyses in adults (OR = 2.78).[8] Interestingly, meta-analyses in adults have yielded a stronger association between sexual abuse and depression (OR = 2.42) than between physical abuse and depression (OR = 1.98),[8] whereas we found the opposite pattern of results. It is possible that, in youths, sexual abuse manifests in other ways. For example, childhood sexual abuse may increase risk not only for depression, but also for posttraumatic stress disorder (PTSD), suicide, poor academic performance, and sexual promiscuity. This possibility is consistent with multifaceted models of sexual abuse[86] and with other meta-analytic findings.[87] It is also possible that youth are at highest risk for depression when they are exposed to types of ELS that affect the caregiving environment. Whereas the majority of perpetrators of physical abuse are intrafamilial, the majority of perpetrators of sexual abuse are extrafamilial[86,88]; thus, physical abuse may affect the perceived security of the home environment more directly than does sexual abuse. Interestingly, perceived security of the caregiving environment may also underlie the strong association found between exposure to domestic violence and depression. Although exposure to domestic violence is a marker of increased exposure to other forms of adversity[89] and contributes independently to the prediction of psychopathology,[90] this form of early adversity is often overlooked. Our results contribute to the growing understanding of the pernicious effects of exposure to violence on children's mental health, and highlight that exposure to violence is an important area for future research.

It is noteworthy that exposure to poverty was not significantly associated with youth-onset MDD. While researchers examining the effects of poverty on child and adolescent well-being have documented the adverse effects of poverty on children's health, intellectual development, and later achievements,[91] findings linking poverty and emotional difficulties have been inconsistent.[92] Mirroring this inconsistency, we found significant heterogeneity across studies examining the association between poverty and depression in childhood or adolescence. Studies that used a limited time frame for assessing poverty had a smaller estimated effect size than did studies that assessed poverty across participants' whole life, although it is notable that neither group had an effect size that differed significantly from zero. Potential differences related to the timing of poverty is consistent with research documenting that exposure to poverty across one's entire life is more harmful than is exposure to poverty during acute periods[93]; unfortunately, the design of meta-analyses does not allow us to compare the specific effects of poverty during different states of development (ie, sensitive periods) with the duration of exposure (eg, chronicity). We also found that exposure to a natural disaster was not significantly associated with youth-onset depression. The association between exposure to a natural disaster and depression might be significant only for individuals who already had vulnerabilities prior to the disaster, such as genetic risk or elevations in pre-exposure levels of psychopathology.[94] Alternatively, exposure to a natural disaster may have other psychological manifestations, such as PTSD.[95]

Although our initial analysis yielded a nonsignificant association between physical illness/injury and childhood- or adolescent-onset depression, this lack of association was driven primarily by one study.[83] When this study was removed, there was a significant association between physical illness/injury and depression before the age of 18 years. Given the co-occurrence of different types of ELS,[6,96] the relation between physical illness/injury and depression might be explained by the fact that physical illness/injury can occur in the context of other types of ELS (eg, physical abuse, natural disasters, or poor health conditions). The co-occurrence of multiple types of ELS presents a challenge to the field, and elucidating the unique contribution of each type of ELS remains an important goal for future research.

We also found that method of assessing sexual abuse and sample source moderated the association between sexual abuse and onset of MDD in childhood or adolescence. Sexual abuse assessed via interview was associated with a significantly greater effect size than was sexual abuse assessed via another method (eg, questionnaire, record review); furthermore, only those studies that assessed sexual abuse via interview yielded an effect size that differed significantly from zero. Interview assessments of stress offer advantages over questionnaires and record reviews, both of which have significant limitations; indeed, our finding highlights the importance of using interview-based assessments of stress.[97] We also found that type of participant sample moderated the relation between childhood sexual abuse and depression in childhood or adolescence: only studies that did not include clinical participants yielded an effect size that differed significantly from zero. Other meta-analyses have also found sample source to be a significant moderator of the impact of ELS on depression[9]; however, findings in adult samples have typically been in the opposite direction, with stronger associations between childhood maltreatment and depression in clinical or high-risk samples than in population-based samples. The different pattern that we found in youths may be influenced by the types of families who engage in treatment and, therefore, are classified as clinic referred. Higher-functioning families may be more likely to receive treatment following sexual abuse;

consequently, the adverse effects of exposure to sexual abuse in clinic populations may be buffered by receiving intervention services and/or by having a caregiver who seeks support. This possible moderation should be examined more explicitly and systematically in future research.

We should note three limitations of this meta-analysis. First, we recognize that children who experience one type of ELS are more likely to experience other forms of adversity,[96] but the data did not allow us to address cumulative effects of ELS. Second, most studies included in this meta-analysis were cross-sectional; it is possible, therefore, that ELS was assessed while the participants were depressed. Although we think that it is likely that ELS preceded and played a causal role in depression, we are unable to make strong causal claims concerning the role of ELS in the onset of depression or to determine whether recall bias contributed to the findings reported here. Although some researchers have examined the prospective association between ELS and depression in adulthood,[7] few investigators have explored the prospective association between ELS and childhood- or adolescent-onset depression. Nevertheless, documenting the magnitude of the association between ELS and youth-onset MDD provides important information for public health consumption and prioritization of prevention efforts. Third, because of the small number of studies available for some analyses, the number of studies included in several moderator analyses was limited, which affects the generalizability of our results.

In conclusion, this is the first meta-analysis to examine the association between broadly defined ELS and childhood- or adolescent-onset depression. Although the effect of all forms of ELS on youth-onset depression was similar in strength to findings from meta-analyses of depression in adults,[7,8] there are also important differences that underscore the need to consider developmental factors in understanding the nature of the relation between ELS and depression, including differences in the relative strength of the association between different types of ELS and depression.

We believe that there are several critical next steps in this area of research. First, the current meta-analysis focused on ELS and youth-onset MDD specifically; it is important to note, however, that the effects of ELS may manifest in other ways. For example, ELS has been found to be associated with other internalizing disorders, particularly anxiety disorders; given the high comorbidity of anxiety disorders and MDD, this will be an important avenue for future research.[98] Second, we must gain a better understanding of the mechanisms through which exposure to ELS increases individuals' risk for depression. Recent research has linked dysregulated biological responses to stress to both ELS and depression,[99] and conclusions from a systematic review indicate that interpersonal relationships, cognitive vulnerabilities, and behavioral difficulties may be modifiable predictors of depression following maltreatment[10]; thus, focusing on these factors is a promising avenue for future research. Fourth, the present findings indicate that the interval between adversity and psychopathology can be short, and that efforts to intervene and prevent MDD should occur early in life. Focusing on delivering interventions to those who have experienced ELS during childhood and adolescence, and on identifying targets for the reduction of ELS exposure, must be priorities for clinical scientists seeking to reduce risk for MDD.

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