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Article

Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis

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Objectives: Evidence suggests that childhood maltreatment may negatively affect not only the lifetime risk of depression but also clinically relevant measures of depression, such as course of illness and treatment outcome. The authors conducted the first meta-analysis to examine the relationship between childhood maltreatment and these clinically relevant measures of depression.

Method: The authors conducted searches in MEDLINE, PsycINFO, and Embase for articles examining the association of childhood maltreatment with course of illness (i.e., recurrence or persistence) and with treatment outcome in depression that appeared in the literature before December 31, 2010. Recurrence was defined in terms of number of depressive episodes. Persistence was defined in terms of duration of current depressive episode. Treatment outcome was defined in terms of either a response (a 50% reduction in depression severity rating from baseline) or remission (a decrease in depression severity below a predefined clinical significance level).

Results: A meta-analysis of 16 epidemiological studies (23,544 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (odds ratio=2.27, 95% confidence interval [CI]=1.80–2.87). A meta-analysis of 10 clinical trials (3,098 participants) revealed that childhood maltreatment was associated with lack of response or remission during treatment for depression (odds ratio=1.43, 95% CI=1.11–1.83). Meta-regression analyses suggested that the results were not significantly affected by publication bias, choice of outcome measure, inclusion of prevalence or incidence samples, study quality, age of the sample, or lifetime prevalence of depression.

Conclusions: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression.

(Am J Psychiatry Nanni et al.; AiA:1–11)

Major depression is a common and impairing illness, often exhibiting a recurrent and progressive course. Depression ranks among the most common psychiatric disorders worldwide, with a 12-month prevalence between 10% and 17% and a lifetime prevalence between 17% and 40% (1, 2). Because the lifetime prevalence of depression is at most four times its 12-month prevalence, depressive episodes are not independent events uniformly distributed in the population but rather tend to cluster in the same individuals. Consistent with this evidence, 60% of individuals who have recovered from a depressive episode will have a recurrence within 5 years (3). The rate of recurrence may be even higher in individuals who experience more persistent depressive episodes and in those who have a poor treatment outcome with residual subthreshold symptoms (3, 4). Because of the large health impact and economic burden associated with a poor longitudinal course of depressive illness, it is important to identify factors that predict risk of developing recurrent and persistent depressive episodes and lack of remission or response during treatment for depression.

Childhood maltreatment may predict an unfavorable course of illness and treatment outcome. Compared with individuals who have not been maltreated, those with a history of childhood maltreatment are at greater risk of meeting criteria for a depressive episode at any point in life (5). Maltreated individuals are also at greater risk of enduring cognitive (6) and biological (7) vulnerabilities associated with heightened stress sensitivity (8), which might predispose them to an unfavorable course of illness and treatment outcome. For example, maltreated individuals tend to have elevated inflammation levels (7, 9), which have been associated with recurrent depressive episodes (10) and poor treatment response (11).

To test whether individuals with a history of childhood maltreatment are at elevated risk of an unfavorable depression course and treatment outcome, we performed meta-analyses of epidemiological studies investigating the association between childhood maltreatment and depression recurrence or persistence and of clinical trials investigating the association between childhood maltreatment and outcome of psychological, pharmacological, or

combined treatment. We also explored the effects of various possible sources of artifact or bias on the results of the meta-analyses.

Method

Inclusion Criteria

We identified studies satisfying the following criteria: definition of childhood adversities consistent with childhood maltreatment (physical abuse, sexual abuse, neglect, or family conflict or violence); diagnosis of depressive disorder, ascertained either in population-based or in clinical samples; and evaluation of relevant depression measures (12). Depression recurrence was defined in terms of number of depressive episodes over the period of observation or as risk of a new depressive episode in individuals with prior history of depression. Depression persistence was defined as prolonged duration of uninterrupted illness, including dysthymia, over the period of observation. Treatment outcome was defined as a change in depression scores between the beginning and the end of treatment, either as a continuous measure (i.e., improvement, defined as percentage improvement on a depression rating scale) or as a categorical outcome (i.e., response, defined as a reduction of depression rating scale score by 50% or more; or remission, defined as a decrease of depressive symptoms below a predetermined clinical significance level).

Identification of Studies

We searched MEDLINE, PsycINFO, and Embase databases for articles describing the relationship between childhood maltreatment (search terms: child* maltreatment, child* abuse, child* neglect, early experience) and relevant depression measures (search terms: depress*, mood disorder, MDD, recurrence, persistence, chronic, duration, length, improvement, response, remission, treatment, psychotherapy, CBT, pharmacotherapy, antidepressant, SSRI) using human subjects, written in English, and published by December 31, 2010.

Data Extraction

Two authors independently extracted data from eligible articles. Inconsistencies were resolved in consensus meetings and confirmed with the authors of the primary studies when necessary.

Statistical Analysis

Extracted data were converted to odds ratio effect sizes (13) reflecting the probability of unfavorable outcomes, with odds ratios above 1 reflecting a greater likelihood of recurrence, persistence, or poor treatment outcome in individuals with a history of childhood maltreatment compared to those without. The meta-analysis of clinical trials examined the difference in outcome between depressed patients with a history of childhood maltreatment and those without in the same active treatment arm. Where only continuous outcomes were reported, the risk of unfavorable outcomes was derived using validated methods (14). Heterogeneity between studies was tested with Cochran's Q test (15). In the presence of a homogeneous distribution, we carried out meta-analyses using fixed-effects models weighting each study by a measure of sampling error, such as the inverse variance. If the dispersion of effect sizes was greater than expected from sampling error alone (i.e., heterogeneity), we carried out meta-analyses using random-effects models, which include both sampling and study-level errors. Fixed- and random-effects meta-analyses were performed using the *meta* and *metan* programs applied in the Stata software package (StataCorp, College Station, Tex.). Additional analyses explored the effects of various possible sources of artifact or bias on the results.

First, we assessed the presence of publication bias visually by funnel plot (16) and formally by its direct statistical analogue, Begg's adjusted-rank correlation test (17), using the *metabias* program applied in Stata. In the presence of significant rank correlation tests, we adopted a nonparametric trim-and-fill method (18) using the *metatrim* program applied in Stata.

Second, we assessed the sensitivity of meta-analysis results to different outcome measures through subgroup analyses.

Third, we assessed the sensitivity of the results to different sampling strategies through subgroup analyses. Studies in clinical (or prevalence) samples and those in population (or incidence) samples could lead to different results because of ascertainment bias (19). The potential ascertainment bias could not have affected the results of clinical trials, which were restricted to clinical samples.

Fourth, we assessed the impact of study quality on the meta-analysis results through meta-regression using the *metareg* program applied in Stata. The quality of epidemiological studies was assessed with the Newcastle-Ottawa Scale (20), which has been recommended by the Cochrane collaboration (21) and has been used in previous studies (22). The quality of clinical trials was assessed by an adapted version of the Jadad scale (23) based on randomization, consideration of dropouts, and blinding. Because the contrast of interest was between individuals with a history of maltreatment and those without in the same active treatment arm, we considered blinding to maltreatment status rather than to treatment allocation.

Fifth, we assessed the presence of age effects through meta-regression analyses. Age effects could have influenced the meta-analysis results in two ways. With regard to the epidemiological studies, it was possible that because maltreated individuals are younger at the onset of depression than individuals without a history of maltreatment (24), they could spend more time at risk of recurrence and show greater depression recurrence and persistence for this reason. It was not possible to extract information on age at illness onset from the studies examined. However, we reasoned that the relative contribution of earlier age at onset to the total time that maltreated individuals spend at risk decays as the age of the sample increases. Therefore, if age at onset explained the association between childhood maltreatment and depression recurrence and persistence, we should have observed a significant negative correlation between mean age of the samples and effect sizes. With regard to the clinical trials, previous research has suggested that individuals at different ages could have a different response to the same antidepressant treatment (25). Therefore, it was possible that the age of the sample could have explained between-study differences in the association between childhood maltreatment and treatment outcomes in depression.

Finally, we assessed the presence of recall bias through meta-regression analyses. Most of the studies we examined were based on retrospective recall of childhood maltreatment. The reliability of retrospective recall of childhood maltreatment may be limited in individuals with a lifetime history of depression (26, 27) because of biases in autobiographical memory (28, 29). Therefore, to the extent that lifetime history of depression was different between the studies, it was possible that recall bias could have explained between-study differences in the association between childhood maltreatment and depression course. Recall bias was not an issue for the meta-analysis of the clinical trials, because all participants were depressed at the time the assessment of maltreatment history was carried out.

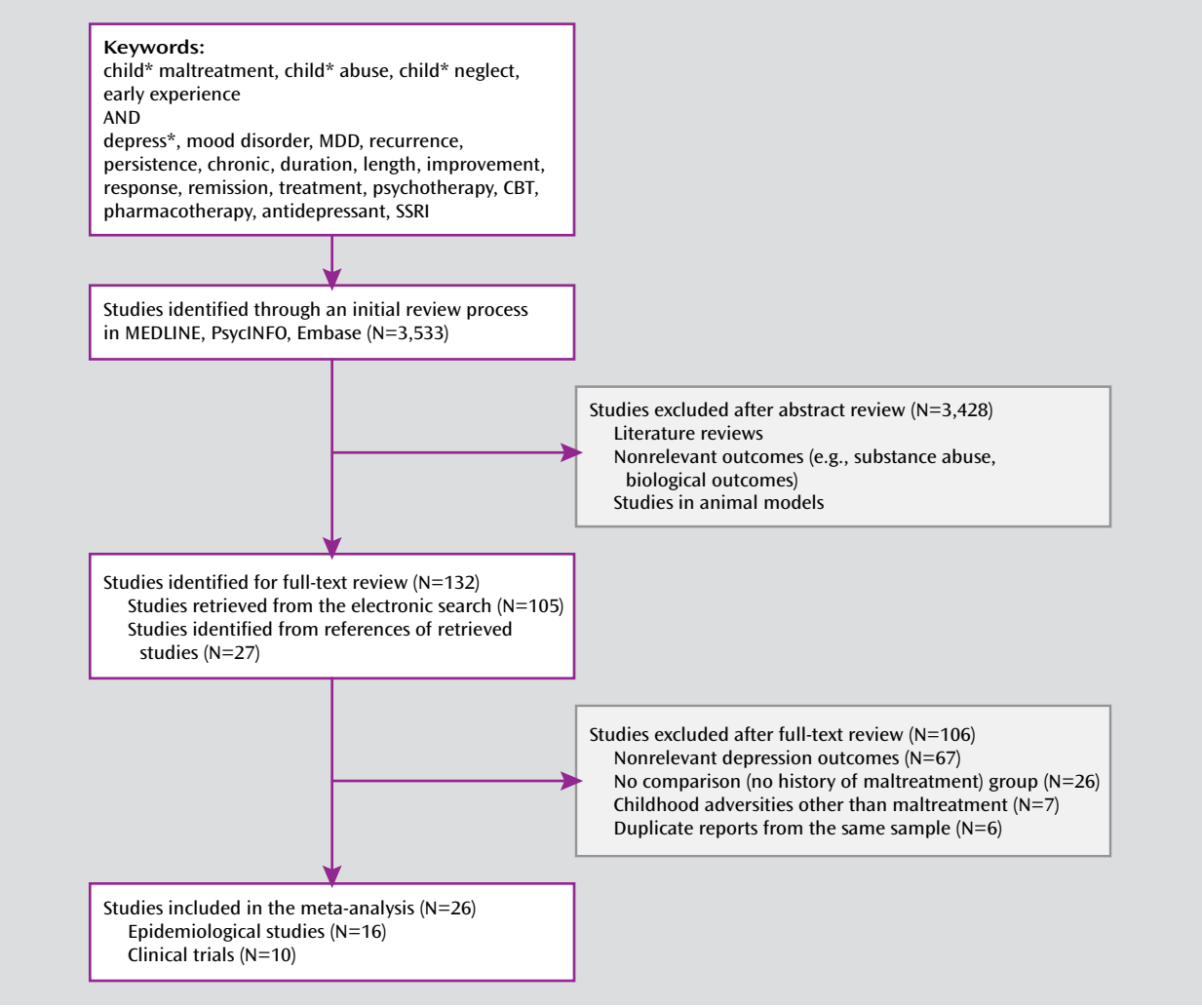
Results

The study selection procedure is summarized in Figure 1.

Epidemiological Studies

The association between childhood maltreatment and poor longitudinal course of depressive disorder (i.e., recur-

FIGURE 1. Study Selection Procedure for a Meta-Analysis of the Association Between Childhood Maltreatment and Course of Illness and Treatment Outcome in Depression



rence or persistence) was tested in 16 studies with a total of 23,544 participants (Table 1) (7, 30–44). We identified significant heterogeneity across studies (Q=46.1, df=15, p<0.001) and therefore performed an analysis using a random-effects model. A meta-analysis of these studies showed that compared to those without a history of childhood maltreatment, maltreated individuals were twice as likely to have an unfavorable longitudinal course of depression (odds ratio=2.27, 95% confidence interval [CI]=1.80–2.87) (Figure 2). We performed additional analyses to explore the effects of possible sources of artifact or bias on these results.

Publication bias. The funnel plot showed asymmetrical distribution of the studies, and results of Begg's adjusted-rank correlation test were significant (p=0.027), suggesting the possibility of publication bias. However, the trim-and-fill procedure achieved a similar combined effect size (odds ratio=1.78, 95% CI=1.38–2.31) to the nonfilled analysis, suggesting that potential publication bias did not significantly affect the results.

Sensitivity analyses. First, we performed sensitivity analyses to examine whether the association between childhood maltreatment and course of illness was comparable across different measures of depression course (Figure 2). The association between childhood maltreatment and depression recurrence was tested in seven studies. We identified significant heterogeneity across studies (Q=15.1, df=6, p=0.020) and therefore performed an analysis using a random-effects model. A meta-analysis of these studies showed that maltreated individuals were twice as likely as those without a history of childhood maltreatment to develop recurrent depressive episodes (odds ratio=2.24, 95% CI=1.62–3.10). The association between childhood maltreatment and depression persistence was tested in nine studies. We identified significant heterogeneity across the studies (Q=30.60, df=8, p<0.001) and therefore performed an analysis using a random-effects model. A meta-analysis of these studies showed that maltreated individuals were twice as likely as those without a history of childhood mal-

TABLE 1. Selected Characteristics of Epidemiological Studies Investigating the Association Between Childhood Maltreatment and Depression Course: Recurrence and Persistence[a]

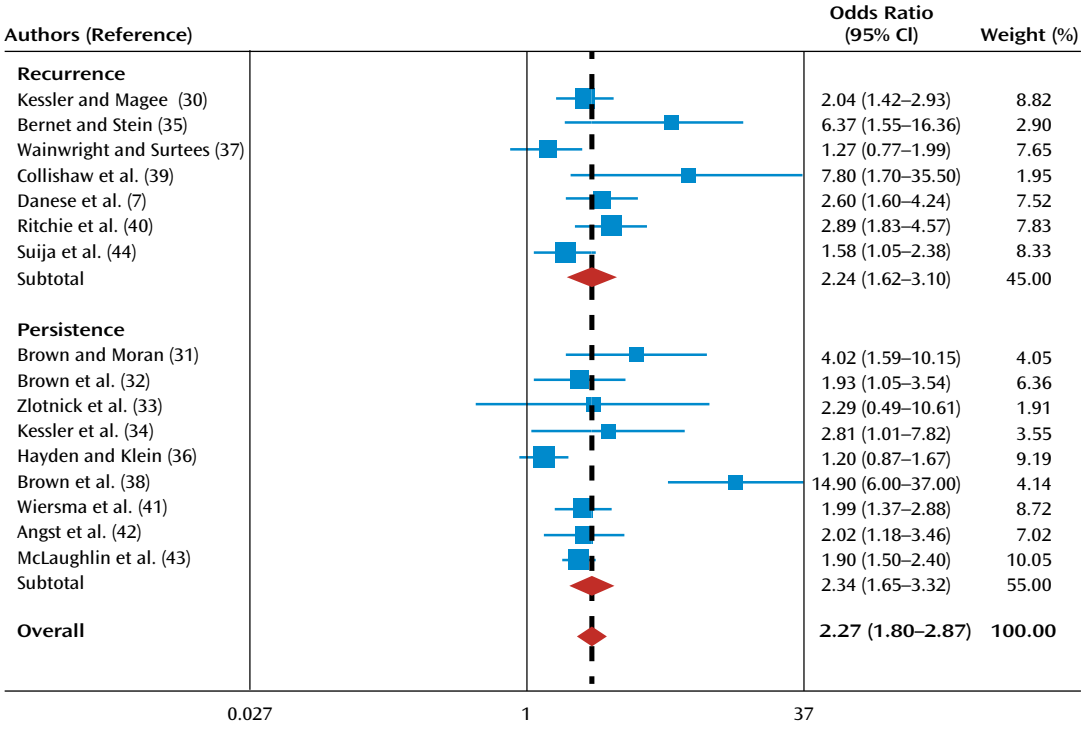
Authors (Reference)	Study N	Mean Age or Range (Years)	% Female	Sample Type	Depression Measure	Maltreatment Measure	Outcome Definition	Length of Observation (Years)	Results
Kessler and Magee (30)	1,024	33	50	Population	DIS, FHRDC	Own questionnaire	Recurrence: new depressive episode(s) in individuals with history of depression	16	Family violence associated with greater recurrence (odds ratio=2.04, 95% CI=1.42–2.93)
Brown and Moran (31)	404	18–50	100	Population	PSE	CECA	Persistence: depressive episode lasting 12 months or more	3	Childhood adversity associated with greater persistence (odds ratio=4.02, 95% CI=1.59–10.15)
Brown et al. (32)	125	18–60	100	Clinical	PSE	CECA	Persistence: nonrecovery from depression over 12 months	2	Childhood adversity associated with greater persistence (odds ratio=1.93, 95% CI=1.05–3.54)
Zlotnick et al. (33)	37		100	Clinical	Semi-structured interview	Own questionnaire	Persistence: non-recovery (HAM-D <7 for 3 consecutive months after hospital discharge)	1	Childhood adversity not associated with persistence (odds ratio=2.29, 95% CI=0.49–10.61)
Kessler et al. (34)	5,877	15–54	50	Population	CIDI	Own questionnaire	Persistence: risk of dysthymia	40	Childhood adversity associated with greater persistence (odds ratio=2.81, p<0.05)
Bernet and Stein (35)	88	42	50	Clinical	SCID	CTQ	Recurrence: number of depressive episodes	25	Childhood trauma associated with greater recurrence (t=4.78, p<0.0005)
Hayden and Klein (36)	86	31.1	75.6	Clinical	SCID, longitudinal interval follow-up evaluation	EHEI	Persistence: nonrecovery from dysthymic disorder (<8 consecutive weeks with minimal or no symptoms)	5	Physical abuse associated with greater persistence (smaller recovery: hazard ratio=0.83, 95% CI=0.60–1.15)
Wainwright and Surtees (37)	3,353	62.3	55.2	Population	Structured self-assessment	Own questionnaire	Recurrence: number of depressive episodes	46	Physical abuse not associated with greater recurrence (relative risk=1.27; 95% CI=0.77–1.99)
Brown et al. (38)	198	34	100	Population	SCAN	CECA	Persistence: depressive episode lasting ≥12 months	17	Childhood adversity associated with greater recurrence (odds ratio=14.9, 95% CI=6.0–37.0)
Collishaw et al. (39)	3,624	44.2	50	Population	SADS-L	CECA	Recurrence: ≥3 lifetime depressive episodes	28	Childhood adversity associated with greater recurrence (odds ratio=7.80, 95% CI=1.7–35.5)
Danese et al. (7)	1,037	32	48	Population	DIS	Prospective observation + retrospective reports	Recurrence: ≥2 lifetime depressive episodes	21	Childhood adversity associated with greater recurrence (odds ratio=2.60, 95% CI=1.60–4.24)
Ritchie et al. (40)	942	72	58	Population	MINI diagnosis or CES-D >16 or current antidepressant treatment	Own questionnaire	Recurrence: ≥2 depressive episodes	4	Childhood adversity associated with greater recurrence (odds ratio=2.89, 95% CI=1.83–4.57)
Wiersma et al. (41)	1,230	40.7	67.3	Clinical	CIDI	CTI	Persistence: depressive episode lasting ≥24 months	4	Physical abuse associated with greater persistence (odds ratio=1.99, 95% CI=1.37–2.88)
Angst et al. (42)	110	27–41	60	Clinical	SPIKE	Own questionnaire	Persistence: depressive symptoms for most days over 2 years or daily for 12 months	13	Childhood adversity associated with greater persistence (p=0.05)
McLaughlin et al. (43)	5,692	36.7	42	Population	CIDI	Own questionnaire	Persistence: time since more recent episode, controlling for age at onset and time since onset	20	Physical abuse associated with greater persistence (odds ratio=1.9, 95% CI=1.5–2.4)
Suija et al. (44)	123	39	85	Clinical	CIDI	CTI	Recurrence: new depressive episode in individuals with history of depression	1	Childhood trauma associated with greater recurrence (odds ratio=1.58, 95% CI=1.05–2.38)

[a] CECA=Childhood Experience of Care and Abuse; CES-D=Center of Epidemiological Studies Depression Scale; CIDI=Composite International Diagnostic Interview; CTI=Childhood Trauma Interview; CTQ=Childhood Trauma Questionnaire; DIS=Diagnostic Interview Schedule; EHEI=Early Home Environment Interview; FHRDC=Family History Research Diagnostic Criteria; HAM-D=Hamilton Depression Rating Scale; MINI=Mini-International Neuropsychiatric Interview; PSE=Present State Examination; SADS-L=Schedule for Affective Disorders and Schizophrenia–Lifetime; SCAN=Schedule of Clinical Assessment in Neuropsychiatry; SCID=Structured Clinical Interview for DSM-IV; SPIKE=Structured Psychopathological Interview and Rating of the Social Consequences of Psychic Disturbances for Epidemiology.

treatment to develop persistent depressive episodes (odds ratio=2.34, 95% CI=1.65–3.32).

Second, we performed sensitivity analyses to examine whether the association between childhood maltreatment and course of illness was comparable across clinical and population samples. The association between childhood maltreatment and depression course was tested in seven clinical (prevalence) samples. Heterogeneity approached

FIGURE 2. Meta-Analysis of Epidemiological Studies Investigating the Association Between Childhood Maltreatment and Depression Course (Random Effects)[a]



[a] The red diamonds show the combined effect sizes for studies concerned with depression recurrence and depression persistence as well as the overall effect size of the meta-analysis (top to bottom).

significance across studies (Q=10.69, df=6, p=0.098), so we performed an analysis using a random-effects model. A meta-analysis of the studies with clinical samples showed that maltreated individuals were nearly twice as likely as those without a history of childhood maltreatment to develop recurrent or persistant depressive episodes (odds ratio=1.78, 95% CI=1.36–2.34). The association between childhood maltreatment and depression course was tested in nine population (incidence) samples. We identified significant heterogeneity across the studies (Q=30.12, df=8, p<0.001) and therefore performed an analysis using a random-effects model. A meta-analysis of the studies with population samples showed that maltreated individuals were more than twice as likely as those without a history of childhood maltreatment to develop recurrent or persistent depressive episodes (odds ratio=2.75, 95% CI=1.94–3.91).

Bias owing to study quality. Meta-regression analysis showed that between-study differences in quality ratings based on the Newcastle-Ottawa Scale did not explain the between-study variability in the association of childhood maltreatment with depression course (p=0.611), suggesting that bias due to study quality was unlikely. (The study quality assessment is reported in the data supplement that accompanies the online edition of this article.)

Effect of age at illness onset. This analysis was based on proxy measures of mean age of the samples. We extracted data on mean age from 15 studies. We did not observe the negative correlation between age of the samples and effect sizes that was expected in the presence of an age-at-onset effect (r=–0.075, 95% CI=–0.541 to 0.392). In addition, meta-regression analysis showed that between-study differences in age of the sample did not explain the between-study variability in the association of childhood maltreatment with depression course (p=0.819), suggesting that confounding by age at onset was unlikely.

Recall bias. This analysis was based on proxy measures of lifetime history of depression. We extracted data on lifetime prevalence of depression from 14 studies. Meta-regression analysis showed that between-study differences in lifetime prevalence of depression did not explain the between-study variability in the association of childhood maltreatment with depression course (p=0.878), suggesting that recall bias was unlikely.

Clinical Trials

The association between childhood maltreatment and the outcome of treatment with psychological therapy, antidepressant medication, or combined treatment was tested in 10 studies (15 active treatment arms) with a total of 3,098 participants (Table 2) (45–54). We identified significant heterogeneity across studies (Q=24.77, df=14, p=0.037) and therefore performed an analysis using a random-effects model. A meta-analysis of these stud-

TABLE 2. Selected Characteristics of Clinical Trials Investigating the Association Between Childhood Maltreatment and Treatment Outcome of Depression: Improvement, Response, and Remission[a]

Authors (Reference)	Study N	Mean Age (Years)	% Female	Depression Measure	Maltreatment Measure	Treatment Description	Length of Treatment (Weeks)	Outcome Definition	Results
Sakado et al. (45)	60	43	50	SCID	PBI	Tricyclic antidepressant	16	Remission: HAM-D-17 <8	Low paternal care associated with lack of remission (odds ratio=1.9, 95% CI=1.7–2.2)
Nemeroff et al. (46)	681	43	65.3	SCID	CTS	CBASP, nefazodone, combination	12	Improvement: HAM-D-24 score reduction	Childhood abuse associated with poor outcome within the pharmacological treatment arm and good outcome within the psychotherapy treatment arm (trauma-by-treatment interaction F=3.13, df=1, 495, p=0.045)
Barbe et al. (47)	107	15.8	75.7	K-SADS; BDI ≥ 13	CBQ	CBT, SBFT, NST	12–16	Remission: free from major depressive disorder diagnosis for ≥2 months	Family conflict associated with lack of remission (relative risk=0.95, 95% CI=0.91–0.998)
Enns and Cox (48)	171	41.8	64.3	Unstructured interview	DMQ, PBI	Various antidepressants and psychological treatments	52	Response: 50% decrease in BDI score Remission: BDI <10	Sexual abuse associated with lack of response (χ^2=4.32, p=0.038) and lack of remission (χ^2=4.38, p=0.036); low parental care or overprotection were unrelated to outcome (p=0.58)
Asarnow et al. (49)	287	15.9	69.8	CDRS-R ≥40; CGI ≥4; resistance to SSRIs	CBQ, clinical interview	Medication switch alone (SSRI or venlafaxine), medication switch plus CBT	12	Response: CDRS-R score reduction ≥50%	Childhood abuse associated with lack of response to CBT but not to pharmacotherapy or combination (abuse-by-treatment interaction β=0.15, p<0.001)
Johnstone et al. (50)	195	32	57	Not specified	PBI, own questionnaire	Fluoxetine, nortriptyline	6	Improvement: MADRS score percentage reduction	Maternal overprotection was associated with less improvement (odds ratio=0.93, 95% CI=0.89–0.97). Parental care and childhood abuse were unrelated to outcome
Klein et al. (51)	808	43.6	55	SCID, HAM-D-17 ≥20	MOPS, CTQ	Texas Medication Algorithm	12	Remission: HAM-D-17 <8	Childhood abuse associated with lack of remission (odds ratio=0.52, p<0.01)
Shirk et al. (52)	50	15.9	68	C-DISC-IV	LEQ	CBT	12	Remission: free from major depressive disorder diagnosis at the end of treatment Improvement: BDI score reduction	Childhood trauma associated with lack of remission (ρ=−0.31 to −0.35, p<0.05)
Lewis et al. (53)	427	14.6	54	K-SADS-PL, CDRS-R >45	PTSD section of K-SADS-PL	Fluoxetine, CBT, combination, placebo	12	Improvement: reduction in CDRS-R score	Childhood trauma associated with poor response to CBT but not with response to fluoxetine or combination treatment (trauma-by-treatment-by-time interaction F=2.02, p<0.05)
Miniati et al. (54)	312	39	73	SCID	Clinical interview	Medication (citalopram or escitalopram), IPT, combination	12	Time to remission (Remission: HAM-D-17 <8)	Childhood abuse associated with longer time to remission across treatments (hazard ratio=1.68, 95% CI=1.09-2.59)

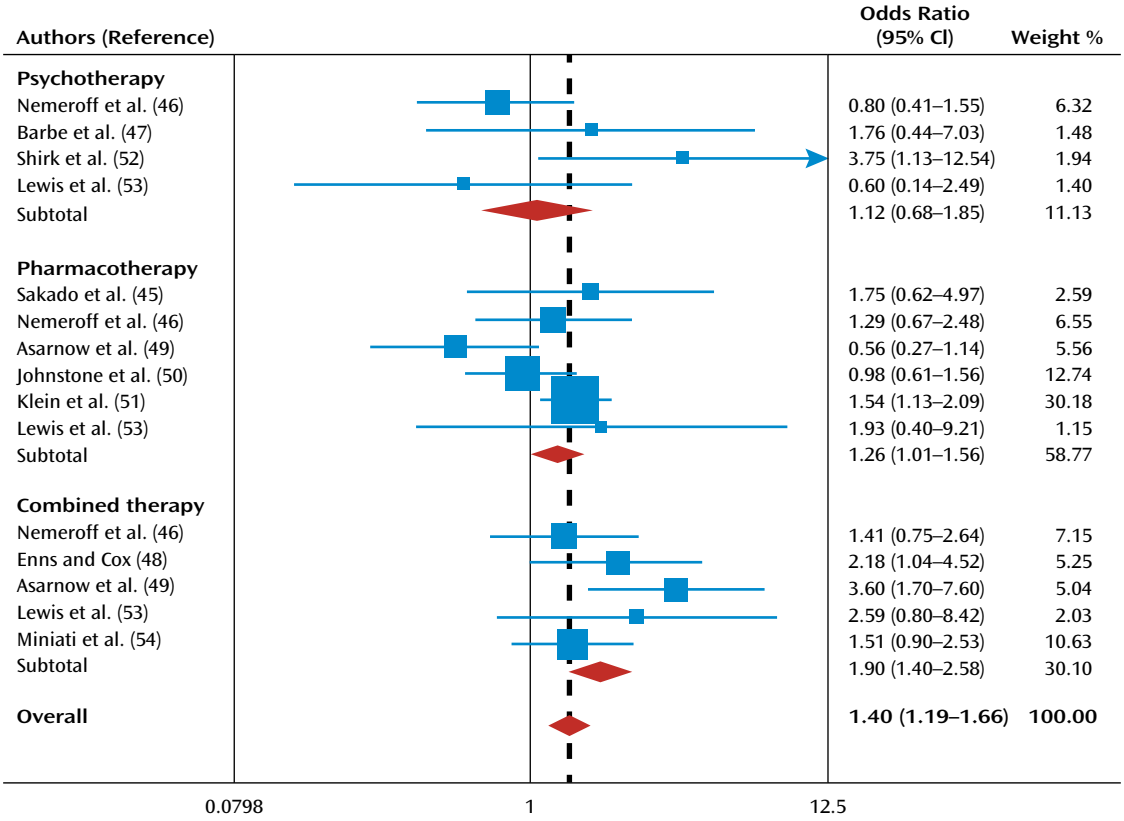
[a] BDI=Beck Depression Inventory; CBASP=Cognitive Behavioral Analysis System of Psychotherapy; CBQ=Conflict Behavior Questionnaire; CBT=cognitive-behavioral therapy; C-DISC-IV=Computerized Diagnostic Interview Schedule for Children; CDRS-R=Children's Depression Rating Scale—Revised; CGI=Clinical Global Impressions scale; CTQ=Childhood Trauma Questionnaire; CTS=Childhood Trauma Scale; DMQ=Developmental Milestones Questionnaire; HAM-D=Hamilton Depression Rating Scale; IPT=interpersonal psychotherapy; K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; LEQ=Life Events Questionnaire; MADRS=Montgomery-Åsberg Depression Rating Scale; MOPS=Measure of Parental Style; NST=nondirective supportive therapy; PBI=Parental Bonding Instrument; SBFT=systemic behavioral family therapy; SCID=Structured Clinical Interview for DSM-IV; SSRI=selective serotonin reuptake inhibitor.

ies revealed that maltreated individuals were more likely than those without a history of childhood maltreatment to show poor treatment outcome (odds ratio=1.43, 95% CI=1.11–1.83) (Figure 3). We performed additional analyses to explore the effect of possible sources of artifact or bias on these results.

Publication bias. The funnel plot showed symmetrical distribution of the studies and Begg's adjusted rank correlation test was nonsignificant (p=0.553), suggesting that publication bias was unlikely.

Sensitivity analyses. We performed sensitivity analyses to examine whether the association between childhood maltreatment and treatment outcome was comparable across different treatment modalities (Figure 3). The association between childhood maltreatment and the outcome of psychotherapy was tested in four studies. We did not

FIGURE 3. Meta-Analysis of Clinical Trials Investigating the Association Between Childhood Maltreatment and Treatment Outcome of Depression (Fixed Effects)[a]



[a] Based on the evidence of homogeneous distributions of effect sizes within treatment groups, we present here the results of fixed-effects model meta-analyses for different treatment groups. The overall effect size across treatment groups was estimated with a random-effects model meta-analysis with the following study weights: Nemeroff (psychotherapy): 7.88; Barbe: 2.78; Shirk: 3.49; Lewis (psychotherapy): 2.65; Sakado: 4.36; Nemeroff (pharmacotherapy): 8.03; Asarnow (pharmacotherapy): 7.32; Johnstone: 10.96; Klein: 14.09; Lewis (pharmacotherapy): 2.25; Nemeroff (combined therapy): 8.42; Enns: 7.07; Asarnow (combined therapy): 6.90; Lewis (combined therapy): 3.61; Miniati: 10.18. The red diamonds show the combined effect sizes for studies concerned with psychotherapy, pharmacotherapy, and combined therapy, as well as the overall effect size of the meta-analysis (top to bottom).

identify significant heterogeneity across studies (Q=6.03, df=3, p=0.110) and therefore performed an analysis using a fixed-effects model. A meta-analysis of these studies revealed that compared to those without a history of childhood maltreatment, maltreated individuals showed a nonsignificantly higher risk for poor outcome of psychotherapy (odds ratio=1.12, 95% CI=0.68–1.85). The association between childhood maltreatment and the outcome of pharmacological treatment was tested in six studies. We did not identify significant heterogeneity across studies (Q=8.41, df=5, p=0.135) and therefore performed an analysis using a fixed-effects model. A meta-analysis of these studies revealed that maltreated individuals showed a poorer outcome of pharmacological treatment compared to those without a history of childhood maltreatment (odds ratio=1.26, 95% CI=1.01–1.56). The association between childhood maltreatment and the outcome of combined treatment (psychotherapy and antidepressant medications) was tested in five studies. We did not identify significant heterogeneity across studies (Q=4.84, df=4, p=0.304) and therefore performed an analysis using a fixed-effects model. A meta-analysis of these studies revealed that maltreated individuals showed poorer outcome of combined treatment compared to those without a history of childhood maltreatment (odds ratio=1.90, 95% CI=1.40–2.58).

Bias owing to study quality. Meta-regression analysis showed that between-study differences in quality ratings based on the adapted Jadad scale did not explain the between-study variability in the association of childhood maltreatment with treatment outcome (p=0.383), suggesting that bias due to study quality was unlikely. (The study quality assessment is reported in the online data supplement.)

Age effect. Meta-regression analysis showed that between-study differences in mean age of the sample did not explain the between-study variability in the association between childhood maltreatment and poor response to antidepressant treatment (p=0.644). Furthermore, a meta-regression analysis showed that classification into pediatric (<18 years) compared with adult samples did not explain the variability in the association between childhood maltreatment and poor response to antidepressant treatment (p=0.498).

Discussion

This meta-analysis addressed the possible developmental origins of heterogeneity in clinically relevant measures of depression such as course of illness and treatment outcome. The epidemiological studies suggested that maltreated individuals were twice as likely as those without a history of childhood maltreatment to develop both recurrent and persistent depressive episodes. Findings from clinical trials were consistent with the epidemiological observations. Compared with depressed individuals without a history of childhood maltreatment, depressed and maltreated individuals appeared to benefit less from treatment (and particularly from combined treatment), thereby incurring greater risk of recurrent and persistent depressive episodes (4).

Limitations

These results should be evaluated in the context of several potential limitations. First, selective publication of studies reporting significant associations between childhood maltreatment and clinically relevant depression measures may influence results. We identified evidence of publication bias in epidemiological studies, but the trim-and-fill procedure suggested that publication bias was unlikely to significantly change the meta-analysis results. In contrast, both graphical and statistical methods suggested that the presence of significant publication bias was unlikely in clinical trials. Second, the results could also be limited to particular outcome measures. However, subgroup analyses appeared to be insensitive to the outcome measures examined. Third, results from epidemiological studies could be limited to clinical or population samples. However, subgroup analyses appeared to be overall insensitive to the sample type examined. Fourth, study quality could have influenced the results. However, differences in study quality could not explain between-study heterogeneity in the association between childhood maltreatment and depression course or treatment outcome. Fifth, the earlier age at onset for depression in maltreated individuals could influence epidemiological study results, leading to spurious findings of greater depression recurrence in maltreated individuals compared with individuals with no history of maltreatment by increasing the amount of time that maltreated individuals spent at risk. However, we could not observe the negative correlation between effect sizes and mean age of the samples that was expected in the presence of age-at-onset effect. In addition, the differences in mean age could not explain between-study heterogeneity in the association between childhood maltreatment and depression course. Sixth, results from epidemiological studies could also be influenced by recall bias owing to between-study differences in lifetime history of depression. However, differences in lifetime history of depression could not explain between-study heterogeneity in the association between childhood maltreatment and depression course. Finally, the available data did not enable us to examine the relative contribution of different maltreatment subtypes or the effect of other potential confounders.

Implications

Despite the potential limitations, the study results have important implications in several areas.

Future research. Childhood maltreatment may be conceptualized as a developmental risk factor triggering a chain of risks (55) such as subsequent depressive episodes that might progressively potentiate the vulnerability to poor course of illness (56, 57). In order to understand the origins of this chain of risks, studies should explore the cognitive and biological correlates of maltreatment in childhood before the accumulation of multiple depressive episodes (58). Furthermore, it will be important to characterize the gene-environment interplay underlying the effects of childhood maltreatment on depression outcomes (59–61). Childhood maltreatment may be conceptualized as an environmental risk factor for poor depression course and a moderator of treatment outcome (62), complementing the emerging genetic markers of vulnerability to recurrent depression (63) and poor treatment response (64, 65).

Clinical care. Information about a history of childhood maltreatment helps identify individuals who are at high risk of developing a recurrent and persistent subtype of depression and those who will respond poorly to treatment. Because of the lack of placebo-controlled studies, we were unable to test whether depressed and maltreated individuals benefit more or less from treatment (versus placebo) than depressed individuals who were not maltreated. In contrast, we observed that depressed and maltreated individuals have a poorer outcome compared with depressed individuals who were not maltreated (i.e., a poor prognosis) within treatment groups. Clinicians may consider that the routine inquiry about childhood maltreatment is not harmful (66) and could add important prognostic information to their assessment. Clinicians may also consider more intensive and alternative treatment options for depressed individuals with a history of childhood maltreatment. The meta-analytical evidence that maltreated and depressed individuals have a poor response to combined treatment with structured psychological therapy and antidepressant medications indicates that simply combining these two common options is not sufficient. It will be important to explore the response of maltreated and depressed individuals to new treatments targeting the biological vulnerabilities described in this subgroup (7, 60), including elevated inflammation levels (67, 68).

Public health. Interventions aimed at reducing childhood maltreatment could help prevent the large health and economic burden linked to poor depression course. Childhood years are thought to be a sensitive developmental window for the maturation of emotion regulation (69).

Therefore, in the same way that childhood educational interventions have greater returns in human capital formation than interventions at later ages (70), early preventive and therapeutic interventions may be more effective (and cost-effective) in preventing a poor longitudinal course of depression than interventions at later ages, when harmful developmental trajectories have already been established.

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