NICU-based Interventions To Reduce Maternal Depressive and Anxiety Symptoms: A Meta-analysis

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abstract

CONTEXT: Parents whose infants are being treated in the NICU are at high risk for depression and anxiety, with negative implications for parenting and infant development.

OBJECTIVE: We conducted a systematic review and meta-analysis of NICU-based interventions to reduce maternal depressive or anxiety symptoms.

DATA SOURCES: PubMed, Embase, PsychInfo, Cochrane, and CINAHL were searched for relevant studies. Reference lists from selected studies were reviewed.

STUDY SELECTION: Inclusion criteria included randomized controlled design, a parent-focused intervention delivered in the NICU, valid maternal depressive or anxiety symptom measures at pre- and postintervention, and publication in a peer-reviewed journal in English.

DATA EXTRACTION: Data extraction was conducted independently by 2 coders.

RESULTS: Twelve studies met inclusion criteria for qualitative review; 2 were excluded from quantitative analyses for high risk of bias. Fixed- and random-effects models, with 7 eligible studies assessing depressive symptoms, indicated an effect of −0.16 (95% confidence interval [CI], −0.32 to −0.002; $P < .05$) and, with 8 studies assessing anxiety symptoms, indicated an effect of −0.12 (95% CI, −0.29 to 0.05; $P = .17$). The subset of interventions using cognitive behavioral therapy significantly reduced depressive symptoms (effect, −0.44; 95% CI, −0.77 to −0.11; $P = .01$).

LIMITATIONS: The small number and methodological shortcomings of studies limit conclusions regarding intervention effects.

CONCLUSIONS: Combined intervention effects significantly reduced maternal depressive but not anxiety symptoms. The evidence is strongest for the impact of cognitive behavioral therapy interventions on maternal depressive symptoms.

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Dr Mendelson conceptualized and designed the study, drafted most sections of the initial manuscript, and revised the manuscript; Dr Cluxton-Keller organized and participated in data extraction, selected the risk of bias assessment, conducted analyses, and reviewed and revised the manuscript; Ms Vullo and Dr Tandon participated in data extraction and reviewed and revised the manuscript; Dr Noazin provided guidance and oversight on the analytic strategy and interpretation of findings, conducted analyses to assess publication and other sources of bias, drafted parts of the paper related to statistical analysis, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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An estimated 10% to 12% of the 4 million infants born each year in the United States are admitted to a NICU for medical care.[1,2] Having an infant in the NICU is extremely stressful for most parents because there is often uncertainty regarding the infant's prognosis, the NICU environment is generally unfamiliar and intimidating for parents, and parents are frequently unable to hold and care for their infant in the NICU setting.[3] High rates of depressive and anxiety symptoms have been documented in parents with infants in neonatal care,[3–6] with negative consequences for subsequent parental mental health and child outcomes.[7,8] Interventions to reduce or prevent parental depression and anxiety thus offer potential to improve long-term outcomes for both parents and children.

A number of interventions have been developed to reduce parent depression and anxiety in the NICU. These interventions represent a range of approaches, including educational content[9] and psychotherapeutic strategies, such as cognitive behavioral therapy (CBT).[10] Given that research in this area is relatively recent, it is not yet clear whether these interventions are effective for reducing parent depression and anxiety or whether some approaches are more effective than others. For instance, 1 recent review of research on parent NICU interventions concluded that some interventions appeared promising for reducing maternal stress but did not systematically review evidence for effects on maternal anxiety or depressive symptoms.[11] Another review focused on a range of parent symptom outcomes in literature published from 1990 to 2012 and reported that some interventions had small to moderate effects on reducing maternal symptoms; this systematic review did not include a meta-analysis of intervention effects or effect modifiers due to the small number and heterogeneity of studies reviewed.[12] The only systematic review and meta-analysis of which we are aware reviewed studies conducted between 1990 and 2011 and found positive intervention effects on maternal anxiety and depressive symptoms.[13] This review, however, excluded studies conducted only in the hospital, focusing on interventions with a community component and including samples in which the intervention was initiated any time before the child turned 3 years old, and it did not evaluate whether intervention dose and intensity may moderate impact on depressive and anxiety symptoms.

The continued growth of research in this area warrants an updated summary and synthesis of the literature with a focus on interventions delivered in the NICU setting. This paper reports findings from a systematic review and meta-analysis of randomized controlled studies that evaluated the effects of parent-focused NICU interventions on maternal depressive and anxiety symptoms. This study also contributes to the literature by assessing intervention characteristics that may impact effects, including program content/approach, program duration, and number of program sessions. Maternal depressive and anxiety symptoms were selected as our primary outcomes because few studies included fathers as participants.

METHODS

Study Identification

Five databases were systematically searched through December 5, 2015: PubMed, Embase, PsychInfo, Cochrane, and CINAHL (see Supplemental Table 3 for sample search strategy). The references from articles selected for inclusion were searched for additional studies.

Identification of Eligible Studies

The following inclusion criteria were used to select studies: (1) randomized controlled design, (2) assessment of a psychotherapeutic, behavioral, educational, or complementary and alternative interventions for parents with an infant in the NICU, (3) intervention delivery occurred exclusively or primarily in the NICU, (4) samples were comprised of biological mothers, (5) valid and reliable measures of maternal depressive or anxiety symptoms administered at baseline and postintervention, (6) publication in a peer-reviewed journal, and (7) publication in English. The exclusion criteria included: (1) studies that did not provide new data, (2) dissertations, book chapters, and meeting abstracts, and (3) studies assessing interventions specifically tailored for parents of infants with specialized medical issues, such as cerebral injuries, heart defects, and other life-threatening medical illnesses. Each study identified in our systematic search was screened by examining the title and, if available, the abstract. The articles potentially meeting eligibility criteria were retrieved for review.

Data Extraction and Coding

The primary variables extracted were the baseline and postintervention mean scores of depressive and/or anxiety symptoms and their SDs separately for the intervention and the control arms. By using the Population Intervention Comparison Outcome framework,[14] studies were also coded for participant characteristics (ie, sample size, eligibility criteria, recruitment setting, sampling method, marital/cohabitant status, and income), intervention characteristics (ie, prevention versus treatment, intervention content, session length and frequency, number of sessions, and intervention content),

study design characteristics (ie, type of control group and length of follow-up), and outcome characteristics (ie, key outcomes assessed, measures used, and study results). We rated the study quality using the Grades of Recommendation, Assessment, Development, and Evaluation system.[15–17] Three coders trained by the first author conducted data extraction and coding. Data extraction for each study was conducted independently by 2 coders. The lead author independently reviewed and coded articles for which discrepancies arose, after which the coders and lead author discussed and resolved the issue. Abstracted data were entered in Microsoft Excel spreadsheets created for the study and were checked for accuracy. If data needed for extraction were not reported in an article, we contacted the authors and attempted to obtain the information from them.

Statistical Analysis

Effect Size Calculations

We defined effect size as the standardized mean difference (SMD) between the control and intervention arms with respect to change in mean depressive (or anxiety) symptom score from baseline to follow-up. Thus, for each study, we measured the change in depressive (or anxiety) symptoms by subtracting the mean score at follow-up from the mean score at baseline separately for the intervention and control arms. The SMD between the 2 study arms in these change values constituted the effect size. SMD was calculated as the bias-adjusted difference (Hedge's g) between the 2 study arms after standardization by their pooled SD. The pooled estimate of effect was computed after weighting individual effects by the inverse of their variance. This approach weights each study proportionately to its sample size, giving more influence to larger, more reliable studies.

Sensitivity Analyses

We conducted sensitivity analyses to gauge the impact of studies that were distinct from others (ie, in their assessed risk of bias and in intervention content).

Heterogeneity and Moderator Analyses

In addition to analyzing the entire set of included studies, we also conducted stratified meta-analyses to evaluate the effect of characteristics that could potentially cause confounding. Decisions regarding which variables to select for stratification were made before performing data analysis; however, we were unable to conduct all planned stratified analyses due to the small number of studies that reported adequate data on some variables (eg, socioeconomic status). We used Cochran's Q and I^2 statistics to assess heterogeneity due to differences in intervention characteristics.[18] We also evaluated heterogeneity in stratified analyses. We examined both fixed- and random-effect models and compared the results. Fixed-effect models assume that differences between effect sizes are due to chance only and that all observed effect sizes reflect identical population values plus some measurement error.[19] Random-effect models, in contrast, assume that differences between effect sizes do not purely reflect chance but also an underlying distribution of values. Random-effect models lead to larger confidence intervals (CIs) than fixed-effect models and assign more balanced weights to various studies to reduce the impact of study size on the pooled effect. Random-effect models are more appropriate than fixed-effect models in the presence of significant heterogeneity (ie, when included studies are very different in their settings and methods).

Publication and Other Sources of Bias

We conducted funnel plot analysis to evaluate the possibility of bias. A funnel plot can indicate the possibility of bias not only due to the "file drawer" effect, (ie, publication and selection bias) but also due to factors, such as heterogeneity or overestimation of the pooled effect as a result of undue influence of low-quality studies.[20] A symmetric funnel-shaped graph with a greater spread for smaller studies with larger SEs and less spread for larger studies with smaller SEs would be indicative of lack of bias. We used Stata (Stata Corp, College Station, TX) "metafunnel" and "metabias" commands to produce a funnel plot and statistically test for bias using Begg's test. Data were analyzed by using Stata version 13.

RESULTS

Systematic Literature Search

Our systematic search yielded 1053 records, of which 12 studies were determined to meet study inclusion criteria (Fig 1). Of these 12 studies, 9 assessed changes in depressive symptoms and 9 assessed changes in anxiety symptoms. We excluded 2 of the 12 studies from quantitative analyses due to high risk of bias, as described below.

Sample and Design Characteristics

Table 1 displays sample and study design characteristics. The 12 included studies contained a total of 1044 participants; sample sizes ranged from 19 to 245 participants with a mean of 81 (SD = 64.27). Infant reasons for NICU stay were low birth weight and/or prematurity, with 2 studies including only infants of very low birth weight <1500 g.[21,22] Mean maternal age ranged from 18 to 34 years, with most studies reporting an average maternal age of ~27 to 28 years. Annual household income was characterized as predominantly low in 5 studies[9,21,23–25] and moderate

to high in 6 studies,[10,22,26–29] with 1 study reporting ~50% of mothers to be low income.[30] One study was conducted in Iran[24] and another in Brazil[21]; the remaining studies were conducted in the United States. Four studies included a majority of white participants[9,10,22,26]; maternal race and ethnicity varied across the remaining studies, as shown in Table 1. Of the 9 studies that assessed depressive symptoms, 5[,22,25,27,29] reported the percentage of participants with clinically significant depressive symptoms at baseline. Across these 5 studies, an average of 59% of participants reported clinically significant baseline depressive symptoms. Four[21,22,27,29] of the 8 studies assessing anxiety symptoms reported the percentage of participants with clinically significant anxiety; 43% of participants across these 4 studies reported clinically significant baseline anxiety symptoms.

Six studies included a single postintervention assessment[10,21–23,27,30]; the remaining studies included additional follow-ups, ranging from 2[24] to 6[25] postintervention assessments. The timing of the initial postintervention assessment varied across studies and is difficult to compare because some studies specified conducting postintervention assessments immediately after the intervention, others specified timing as the duration of time from intake, and others specified the duration of time after discharge, and the duration of stay varied by participant.

Participant Recruitment, Retention, and Fidelity of Implementation

Ten of the 12 studies (83.3%) reported refusal rates among eligible women approached for study participation. Refusal rates ranged from 9.9% to 57.8% with a mean rate of 32.8%. Attrition was reported in 11 studies (91.7%). Attrition rates ranged from 5% to 26%, with a mean rate of 14.4%. Eight studies (66.7%) reported assessing some aspect of fidelity of implementation.

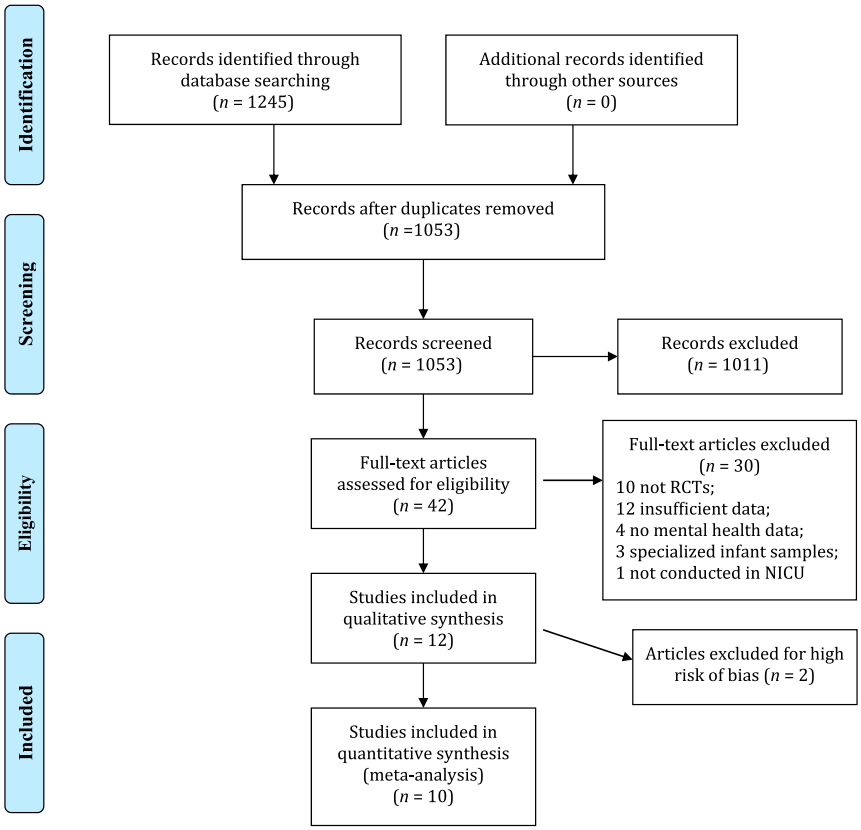

FIGURE 1
Flowchart of study inclusion.

Intervention Characteristics

Three studies assessed CBT interventions,[10,25,27] 4 studies assessed education-based approaches,[9,21,24,26,31] 1 study assessed an intervention to promote anxiety reduction and infant sensitivity training,[22] 1 study assessed a series of mother–infant "calming activities,"[29] 1 study assessed 2 methods involving infant stimulation and touch, kangaroo care, and an auditory–tactile–visual–vestibular intervention,[28] 1 study assessed an interview tool to improve parent–physician communication,[30] and 1 study assessed bright light therapy.[23] Three of the studies on education-based approaches assessed the same intervention, the Creating Opportunities for Parent Empowerment Program (COPE)[9,21,24,26]; all other studies assessed different interventions.

Risk for Bias

As shown in Table 2, 2 studies were evaluated as having high risk for bias,[10,28] 4 studies as having moderate risk for bias,[21,23,25,30] and 5 studies as having low risk for bias.[9,22,24,26,27] We excluded the studies at high risk of bias from quantitative analyses based on recommendations for best practices in meta-analyses.[32]

Overall Measures of Effect

Figures 2 and 3 present forest plots of posttreatment effects sizes, with odds ratios (ORs) and 95% CIs for each study. The pooled effect of interventions to reduce depressive symptoms was –0.16 (95% CI, –0.32 to –0.002; $P = .05$), with the pattern of findings generally in the predicted direction (Fig 2). As shown in Fig 3,

TABLE 1 Characteristics of Included Studies

Study	Participants	Experimental Group	Intervention Dose and Modality	Control Group	Outcomes Included in Meta-analysis	Measures	Reported Effect
Bernard et al, 2011[10]	*N* = 39 with BDI-II data Race/ethnicity: 56% W, 20% H, 20% A, 0.04% O Low income: No	CBT	3 45–55 min individual sessions over 2 wk	Standard NICU care	Depressive symptoms	BDI-II	Trend ($P = .06$) toward lower depressive symptoms in experimental group
Carvalho et al, 2009[21]	*N* = 59 Race/ethnicity: South American Low income: Yes	Psychological support[a] + print and video materials on prematurity	Unclear	Psychological support without prematurity materials	Depressive symptoms Anxiety symptoms	BDI STAI-State	No statistically significant difference in depressive symptoms. Significant pre–post decrease in anxiety in experimental but not control group; no significant between-group effects
Clarke-Pounder et al, 2015[30]	*N* = 19 Race/ethnicity: 68% W, 32% AA Low income: 53%	Education-based decision-making tool for the NICU	Unclear	Standard NICU care	Anxiety symptoms	STAI-State	No statistically significant reduction in anxiety for experimental group
Holditch-Davis et al, 2014[28]	*N* = 192 Race/ethnicity: 19.2% W, 68.3% AA, 8.3% H, 4.2% O Low income: 20%	Education-based (1) Auditory–tactile–visual–vestibular; (2) Kangaroo care	At least 15 min per day at least 3 times per week during the hospitalization.	Attention control condition: discussion of preterm infant safety procedures	Depressive symptoms Anxiety symptoms	CES-D STAI-State	No statistically significant differences in maternal depressive symptoms and anxiety among the study groups
Lee et al, 2013[23]	*N* = 30 Race/ethnicity: 73% AA, 13% W, 10% H, 0.03% O Low income: 70%	Bright light therapy	3 wk of 30 min daily light treatment + sleep hygiene booklet	Attention control condition: 3 wk of placebo red light treatment + nutrition information booklet	Depressive symptoms	EPDS	Pattern of greater decrease in depressive symptoms for experimental group (nonsignificant; $d = 0.40$) posttreatment at 3 wk
Melnyk et al, 2001[26]	*N* = 42 Race/ethnicity: 64% W, 26% AA, 5% A, 2% H, 2% O Low income: No	Education-based (COPE)	4-phase program beginning at 2–4 d postbirth through 1 wk after discharge from the NICU.	4-phase audio and print program on NICU services, discharge, and immunizations	Anxiety symptoms[b]	STAI-State	No group differences in anxiety at 3 mo corrected age
Melnyk et al, 2006[9]	*N* = 245 mothers with data for analysis Race/ethnicity: 67% W, 23% AA, 4% H, 3% A, 3% O Low income: No	Education-based (COPE)	See ref 26	See ref 26	Depressive symptoms Anxiety symptoms	BDI-II STAI-Trait STAI-State	Lower depressive symptoms and STAI state anxiety in experimental versus control group mothers at 2 mo corrected age

TABLE 1 Continued

Study	Participants	Experimental Group	Intervention Dose and Modality	Control Group	Outcomes Included in Meta-analysis	Measures	Reported Effect
Mianaei et al, 2014[24]	*N* = 90 Race/ethnicity: Iranian Low income: Yes	Education-based (COPE)	Used 2 phases of the 4-phase program (see ref 26)	Content of each phase of the COPE program was used, and a researcher answered their questions	Anxiety symptoms	STAI-State	Significant decrease in anxiety in experimental group at time 3
Shaw et al, 2013[27]	*N* = 98 Race/Eth: 61% W, 28% H, 11% not reported Low income: 22%	Trauma-focused CBT + "infant redefinition" education adapted from COPE program	6 1-on-1 sessions delivered 45-55 min sessions over 3-4 wk	Attention comparison condition: 45 min session on NICU & prematurity, referral to parent mentor program, and standard NICU care.	Depressive symptoms Anxiety symptoms	BDI-II BAI	Greater reduction in depressive symptoms in experimental than in control group (d = 0.59). No significant differences between groups for anxiety at 1 wk postintervention
Silverstein et al, 2011[25]	*N* = 47 Race/ethnicity: 28% AA, 40% H, 32% not reported Low income: Yes	Problem-solving education based in CBT	4 1-on-1 sessions weekly or biweekly	Standard NICU care	Depressive symptoms	QIDS	Greater reduction in depressive symptoms in the experimental group than in the control group but there were no statistically significant differences between groups 1 mo postintervention
Welch et al, 2016[29]	*N* = 85 Race/ethnicity: 50% W, 21% H, 20% AA, 9% O Low income: 18%	Education-based family nurture intervention	Holding sessions at least 4 times per week; length of each session is unclear	Standard NICU care	Depressive symptoms Anxiety symptoms	CES-D STAI-State	Experimental group showed reductions in depressive symptoms and anxiety but no statistically significant differences between groups at the near-to-term age time point
Zelkowitz et al, 2011[22]	*N* = 98 Race/ethnicity: not reported Low income: not reported	CBT and attachment-based intervention (Cues program)	6, 1-h 1-on-1 sessions (5 in NICU and 1 postdischarge)	Attention control condition: 6 1-on-1 sessions with information on infant care	Depressive symptoms Anxiety symptoms	EPDS STAI-State	No significant group differences 2–4 wk postintervention

A, Asian; AA, African American; BDI-II, Beck Depression Inventory, Second Edition; EPDS, Edinburgh Postnatal Depression Scale; H, Hispanic; O, Other; QIDS, Quick Inventory of Depressive Symptoms; STAI, State Trait Anxiety Inventory; W, white.

[a] The psychological support intervention included a group intervention. It is unclear what the length or frequency of group meetings was or whether individual psychotherapy was also provided.

[b] The Profile of Mood States scale was used to measure depressive symptoms, which could not be standardized due to the type of questions. As a result, only anxiety data were included in the meta-analysis.

TABLE 2 Risk for Bias for Included Studies

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
Bernard et al, 2011[10]	?	?	+	__	+	+
Carvalho et al, 2009[21]	?	+	+	+	+	+
Clarke-Pounder et al, 2015[30]	?	?	+	+	+	+
Holditch-Davis et al, 2014[28]	+	+	+	__	+	__
Lee et al, 2013[23]	?	+	+	+	+	+
Melnyk et al, 2001[26]	+	+	+	+	+	+
Melnyk et al, 2006[9]	+	+	+	+	+	+
Mianaei et al, 2014[24]	+	+	+	+	+	+
Shaw et al, 2013[27]	+	+	+	+	+	+
Silverstein et al, 2011[25]	+	+	+	?	?	+
Welch et al, 2016[29]	+	?	+	?	+	+
Zelkowitz et al, 2011[22]	+	+	+	+	+	+

Assessment of study quality. Low risk of bias: first 3 domains scored +, no major concerns with last 3 domains; moderate risk of bias: 1 to 2 domains scored ? or not done; high risk of bias: >2 domains scored ? or not done or a single domain that seriously weakened confidence in the study results. +, low risk of bias; ?, unclear risk of bias; __, high risk of bias.

the pooled effect of interventions to reduce anxiety symptoms was −0.12 (95% CI, −0.29 to 0.05; P = .17). Analysis of the studies based on Cochran's Q and the I^2 statistic did not suggest significant heterogeneity for the analysis of all studies for depressive symptom interventions. For the analysis of all studies of anxiety interventions, we used a random effect model to address the heterogeneity suggested by the data (I^2 = 17.6%).

Sensitivity Analyses

We also reestimated the pooled effect of interventions to reduce anxiety symptoms after removing the study by Clarke-Pounder and colleagues,[30] which was the only study to report an iatrogenic intervention effect and assessed an intervention approach (physician communication intervention) that was quite different from those tested in the other studies. Without this study, the pooled effect of interventions to reduce anxiety symptoms was −0.14 (95% CI, −0.29 to 0.12; P = .07)

Moderator Analyses

We conducted stratified subgroup analyses to explore possible moderating effects of intervention approach (CBT, educational approaches, and maternal–infant responsiveness training), intervention duration (>3 weeks versus <3 weeks), and session length (<4 sessions versus >4 sessions). We excluded from these analyses studies that involved distinct intervention approaches that did not fit the 3 identified categories, as well as studies that did not report program duration or session length. CBT interventions were associated with significant improvement in depressive symptoms (effect = −0.44; 95% CI, −0.77 to −0.11; P = .01), whereas combination and

Studies (N = 7)	Comparison Group (n) M (SD)	Intervention Group (n) M (SD)	Weight (%)	SMD IV, Fixed, 95% CI
Carvalho et al, 2009[21]	23 8.2 (7.1)	36 10.1 (9.7)	8.96	0.05 (-0.48 to 0.57)
Lee et al, 2013[23]	14 5.6 (4.5)	16 7.2 (5.1)	4.72	-0.28 (-1.00 to 0.44)
Melnyk et al, 2006[9]	98 7.2 (5.1)	126 5.6 (5.1)	35.18	-0.09 (-0.36 to 0.17)
Shaw et al, 2013[27]	41 13.5 (7.8)	57 10.5 (7.4)	14.80	-0.48 (-0.89 to -0.08)
Silverstein et al, 2011[25]	25 7.9 (4.7)	22 6.1 (4.2)	7.36	-0.34 (-0.92 to 0.23)
Welch et al, 2015[29]	41 9.6 (6.1)	43 7.6 (6.5)	13.33	-0.21 (-0.64 to 0.22)
Zelkowitz et al, 2011[22]	50 5.0 (4.6)	48 5.2 (4.9)	15.64	0.04 (-0.36 to 0.44)
Total (95% CI)				-0.16 (-0.32 to -0.00)

Heterogeneity: X^2 = 4.84 (df = 6), P = .56; I^2 = 0.0%
Test for overall effect: Z = 1.99, P = .05

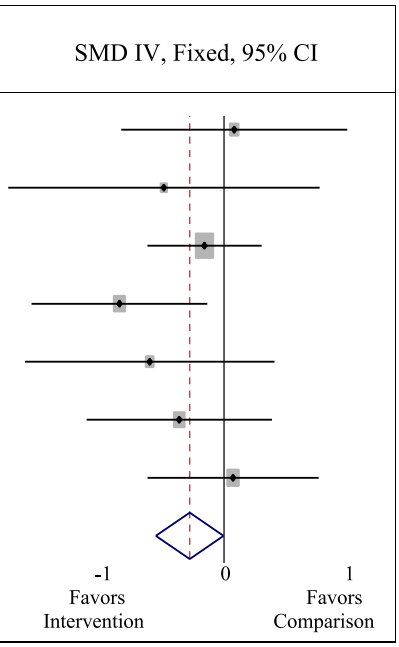

FIGURE 2
Forest plot and effect sizes for studies assessing depressive symptoms. SDs were calculated using Review Manager Version 5.3 Software.[33] M, mean; IV, inverse variance.

Studies ($N = 8$)	Comparison Group (n) M (SD)	Intervention Group (n) M (SD)	Weight (%)	SMD IV, Random, 95% CI
Carvalho et al, 2009[21]	23 45.2 (12.0)	36 41.8 (15.2)	9.08	-0.12 (-0.65 to 0.40)
Clarke-Pounder et al, 2015[30]	10 45.3 (7.1)	9 46.3 (5.0)	3.20	0.59 (-0.33 to 1.51)
Melnyk et al, 2001[26]	22 30.5 (11.2)	20 29.2 (8.4)	6.96	0.26 (-0.35 to 0.87)
Melnyk et al, 2006[9]	98 30.8 (7.9)	127 28.7 (8.0)	26.10	-0.09 (-0.35 to 0.18)
Mianaei et al, 2014[24]	45 52.8 (11.1)	45 38.3 (15.6)	13.12	-0.56 (-0.98 to -0.14)
Shaw et al, 2013[27]	41 12.4 (7.9)	57 11.3 (9.6)	14.15	-0.19 (-0.59 to 0.21)
Welch et al, 2015[29]	41 33.9 (8.6)	44 30.7 (9.4)	12.88	-0.16 (-0.59 to 0.27)
Zelkowitz et al, 2011[22]	50 28.8 (13.8)	48 28.4 (13.5)	14.50	-0.01 (-0.40 to 0.39)
Total (95% CI)				-0.12 (-0.29 to 0.05)

Heterogeneity: $X^2 = 8.49$ (df = 7), $P = .29$; $I^2 = 17.6\%$
Test for overall effect: $Z = 1.37$, $P = .17$

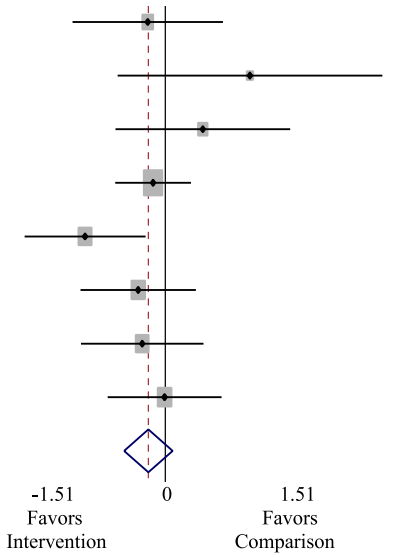

FIGURE 3
Forest plot and effect sizes for studies assessing anxiety symptoms. SDs were calculated using Review Manager Version 5.3 Software.[33]

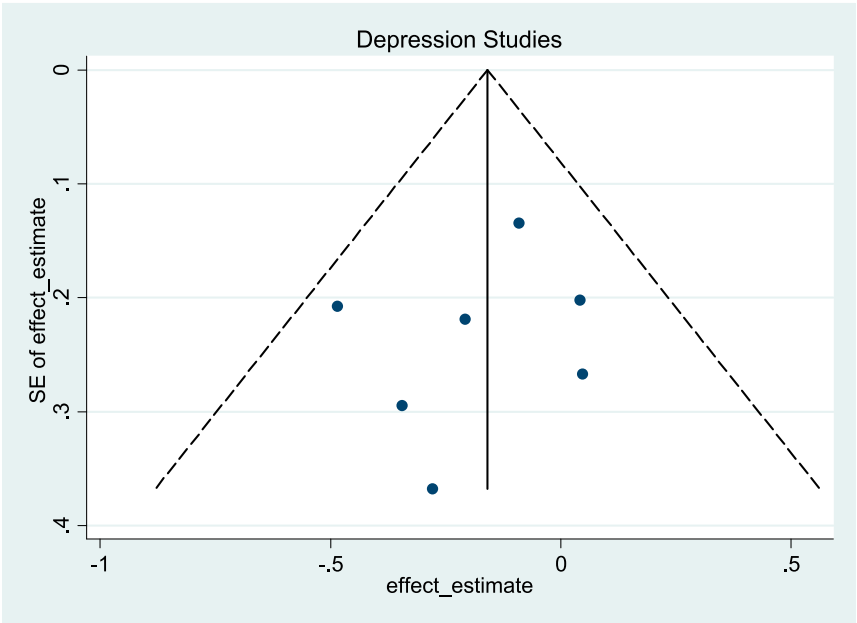

FIGURE 4
Funnel plot to assess publication bias in studies assessing depressive symptoms.

education-based approaches were not. The intervention approach did not moderate changes in anxiety symptoms. Interventions of longer duration were associated with a marginally significant improvement in depressive symptoms (effect = −0.23; 95% CI, −0.47 to 0.004, $P = .054$), whereas those of shorter duration were not. Shorter versus longer duration were not differentially associated with improvements in anxiety symptoms. Shorter versus longer session lengths were not differentially associated with improvements in depressive or anxiety symptoms.

Publication Bias

The funnel plot of depression studies (Fig 4) does not suggest a notable lack of symmetry. The study by Lee and colleagues[23] was somewhat unique in its moderate effect size and large SE, which likely reflect its distinct intervention approach. To assess potential bias resulting from this study, we conducted a sensitivity analysis and did not observe a notable impact by excluding the study.

The funnel plot of anxiety interventions (Fig 5) demonstrates a wide range of effect sizes with moderate SEs for most trials. The wide range of effect sizes explains the heterogeneity we observed among these trials; the relatively large study by Welch and colleagues[29] with a moderate SE had the most extreme positive intervention effect. On the

opposite extreme were 2 studies that did not support intervention effectiveness.[26,30] To assess potential bias toward null in our meta-analysis pooled effect size, we conducted a sensitivity study by removing the trial by Clarke-Pounder and colleagues[30] because this study was the most extreme in both its effect size and SE and, as noted above, differed from the other studies with respect to its intervention content and approach. Exclusion of this study moved the meta-analysis effect size away from null somewhat but not significantly.

We also evaluated publication bias statistically via Begg's test, which indicated no significant publication bias among the depressive or anxiety symptom studies. Such tests, however, have relatively low power when few studies are included in the analysis.[32]

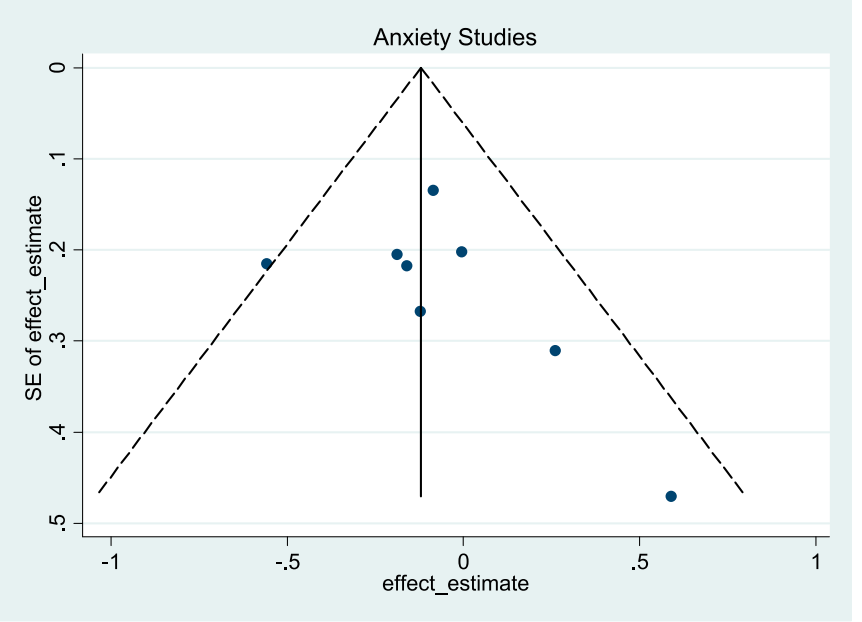

FIGURE 5
Funnel plot to assess publication bias in studies assessing anxiety symptoms.

DISCUSSION

This systematic review and meta-analysis identified and evaluated randomized controlled studies of interventions designed to reduce depressive and anxiety symptoms among mothers with infants in the NICU. Our primary analysis of studies that assessed maternal depressive symptoms as an outcome indicated a significant intervention impact on reduction of maternal depressive symptoms by postintervention ($P < .05$). In subgroup analyses, CBT studies were associated with significant improvements in maternal depressive symptoms, whereas educational approaches and interventions focused on improving maternal–infant responsiveness were not and interventions of longer duration were marginally significant with respect to improving maternal depressive symptoms ($P = .05$). Our primary analysis of studies that assessed maternal anxiety symptoms as an outcome did not indicate a statistically significant intervention effect on reduction of anxiety symptoms. Subgroup analyses indicated that variations in intervention modality, intervention duration, and session length were not differentially associated with reductions in anxiety.

This study adds to previous literature reviewing the effects of interventions on the mental health of NICU parents by providing an updated, rigorous, and more focused critique of these interventions. Unlike several earlier studies with broader inclusion criteria,[13,34,35] we evaluated randomized trials of interventions delivered in the NICU setting in which maternal depressive and anxiety symptoms were assessed as outcomes. The only previous meta-analysis in this area,[13] which reported significant intervention benefits for maternal anxiety and depressive symptoms, required inclusion of a community intervention component, whereas the current meta-analysis evaluated interventions delivered fully or primarily in the NICU setting. NICU-based interventions may offer potential advantages with respect to cost and feasibility,[34] as well as facilitating early involvement before difficulties become more pronounced.[36]

With respect to maternal depressive symptoms, 5 of 7 interventions produced depressive symptom scores that were at least slightly lower for the intervention as compared with the control group (ie, located to the left of 0 in Fig 2). In 1 of the 2 studies that did not fit this pattern,[21] a psychological support group with the addition of educational materials was compared with a psychological support group alone. Both groups improved in depressive and anxiety symptoms, and there were no significant between-group differences, most likely because individuals in both study conditions were receiving the psychological support group. The other study that did not report intervention benefits[22] compared a skills-based intervention (the Cues program) with an attention control condition (the Care program) and found that both groups improved; scores in the intervention versus control group showed a pattern in the predicted direction

for anxiety, the primary outcome, whereas the groups did not show a pattern of differences for depressive symptoms, a secondary outcome.

For anxiety, 6 out of 8 interventions produced anxiety scores that were at least slightly lower for the intervention as compared with the control group (ie, located to the left of 0 in Fig 3). One of the 2 studies that did not fit this pattern reported findings suggesting lower maternal anxiety for intervention versus control mothers at some time points during intervention delivery, but not at the postintervention assessment point we used in our analysis.[26] The other study that did not fit this pattern was the study by Clarke-Pounder and colleagues[30] discussed above, which was unique both in testing a physician communication intervention approach and in identifying iatrogenic intervention effects. Reestimating our analyses without this study moved the meta-analysis effect size away from null somewhat but not significantly. Interventions focused directly on parents, rather than physicians, may yield greater benefits for parent mental health.

Our stratified analyses suggested that a subset of interventions, those using CBT approaches and/or delivered over a greater number of weeks, may have benefits for reducing depressive symptoms. Because the 2 studies categorized as CBT in approach[25,27] were 2 of the 4 studies categorized as longer in duration, it is somewhat difficult to determine whether the marginally significant finding of greater benefit from longer interventions was in fact driven by the inclusion of CBT approaches rather than intervention length.

Of note, the education-based COPE program reduced both maternal anxiety and depressive symptoms when infants were 2 months old (age corrected for prematurity) in a well-designed randomized controlled trial that included an active control condition and the largest sample size of all studies in this review (n = 245). The COPE program also produced other benefits, including reduced NICU and hospital length of stay in comparison with the control condition, a finding with important financial implications. COPE appears promising with respect to feasibility of delivery (ie, informational reading material and CD) and merits additional study.

Data reported in the studies in this review highlight challenges with participant recruitment in the NICU setting. The fact that close to one-third of eligible NICU mothers, on average, refused to participate underlines the difficulty of engaging this population in interventions, possibly due to parents' emotional and practical immersion in the medical treatment of their infants and reluctance to make additional commitments. The high refusal rates also raise questions about the extent to which parents participating in the studies reviewed were representative of the total NICU parent population. It is possible that parents who refused participation were functioning well and did not feel the need for additional support or that they were functioning more poorly and did not feel capable of engaging in additional activities. Qualitative interviews with NICU parents and providers may provide additional insight into what sorts of intervention strategies are most feasible and appealing to NICU parents to increase the potential uptake of parent-focused NICU programs. Brief interventions or intervention modalities that can be used flexibly (eg, audio- or Internet-based) may have advantages in terms of engaging and retaining participants; however, additional research must determine whether brief or less intensive interventions have sufficiently robust effects.

Not surprisingly, attrition was also a problem in many of the studies reviewed. Reasons for attrition included infant deaths, infant discharges or transfers, and participant drop-outs. Reasons, however, were not consistently reported; additional information about attrition would help inform refinements to intervention strategies that maximize parents' ability to maintain involvement in interventions. Use of technology-based intervention strategies, or augmentation of traditional interventions with technological components, merit exploration as a way of reducing attrition in future studies, because these strategies may support longer-term intervention involvement. For instance, text messages or e-mails could be used to prompt skills use, or audio or visual materials could be provided for parents to use on their own time. These sorts of flexible delivery systems may reduce the burden on parents of attending in-person sessions or groups, thus enhancing feasibility and acceptability.

Research in the area of maternal NICU interventions would benefit from larger-scale randomized controlled trials or multisite trials adequately powered to detect effects on maternal depression and anxiety symptoms, inclusion of active control groups, and longer-term follow-ups. Inclusion of structured diagnostic interviews for depression and anxiety would also be useful for better understanding maternal mental health outcomes. Although there are many barriers to enrolling fathers in NICU-based intervention trials (eg, single-parent families, limited availability of working fathers), it is important that future work explore ways to engage fathers in these efforts. In addition, although a range of intervention approaches have been piloted, some potentially promising strategies have not yet been evaluated. For instance,

mindfulness-based strategies are increasingly recognized as effective in the reduction of depression and anxiety and the promotion of stress management techniques[37,38] and may prove useful for parents in the NICU context.

Limitations of this review include the small number of studies meeting inclusion criteria, which reduced our power to detect treatment effects. At this relatively early stage in research on NICU-based parent interventions, studies were predominantly pilot randomized trials rather than large-scale efficacy trials; as a result, sample sizes were relatively small, few studies used attention control groups, and only 42% of studies were judged to have low risk for bias.

CONCLUSIONS

This systematic review and meta-analysis suggest potential intervention benefits for maternal depressive symptoms, particularly for the subset of interventions using CBT approaches. Combined intervention effects did not show a statistically significant effect on maternal anxiety symptoms. Due to the small number of studies meeting inclusion criteria, however, we believe it is more accurate to interpret this finding as a lack of evidence of effect rather than evidence of no effect. Future methodologically rigorous studies can help advance emerging research on NICU-based interventions to promote parent mental health.

ABBREVIATIONS

CBT: cognitive behavioral therapy
CI: confidence interval
COPE: Creating Opportunities for Parent Empowerment Program
OR: odds ratio
SMD: standardized mean difference

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