The Impact of Maternal Depression During Pregnancy on Perinatal Outcomes: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Depression often remains undertreated during pregnancy and there is growing evidence that untoward perinatal outcomes can result. Our systematic review and meta-analysis was conducted to determine whether maternal depression during pregnancy is associated with adverse perinatal and infant outcomes.

Data Sources: MEDLINE, EMBASE, CINAHL, and PsycINFO were searched from their start dates to June 2010. Keywords utilized included *depressive/mood disorder*, *postpartum/postnatal*, *pregnancy/pregnancy trimesters*, *prenatal* or *antenatal*, *infant/neonatal outcomes*, *premature delivery*, *gestational age*, *birth weight*, *NICU*, *preeclampsia*, *breastfeeding*, and *Apgar*.

Study Selection: English language studies reporting on perinatal or child outcomes associated with maternal depression were included, 3,074 abstracts were reviewed, 735 articles retrieved, and 30 studies included.

Data Extraction: Two independent reviewers extracted data and assessed article quality. All studies were included in the primary analyses, and between-group differences for subanalyses are also reported.

Results: Thirty studies were eligible for inclusion. Premature delivery and decrease in breastfeeding initiation were significantly associated with maternal depression (odds ratio [OR] = 1.37; 95% CI, 1.04 to1.81; $P = .024$; and OR = 0.68; 95% CI, 0.61 to 0.76; $P < .0001$, respectively). While birth weight (mean difference = −19.53 g; 95% CI, −64.27 to 25.20; $P = .392$), low birth weight (OR = 1.21; 95% CI, 0.91 to 1.60; $P = .195$), neonatal intensive care unit admissions (OR = 1.43; 95% CI, 0.83 to 2.47; $P = .195$), and preeclampsia (OR = 1.35; 95% CI, 0.95 to 1.92; $P = .089$) did not show significant associations in the main analyses, some subanalyses were significant. Gestational age (mean difference = −0.19 weeks; 95% CI, −0.53 to 0.14; $P = .262$) and Apgar scores at 1 (mean difference = −0.05; 95% CI, −0.28 to 0.17; $P = .638$) and 5 minutes (mean difference = 0.01; 95% CI, −0.08 to 0.11; $P = .782$) did not demonstrate any significant associations with depression. For premature delivery, a convenience sample study design was associated with higher ORs (OR = 2.43; 95% CI, 1.47 to 4.01; $P = .001$).

Conclusions: Maternal depression during pregnancy is associated with increased odds for premature delivery and decreased breastfeeding initiation; however, the effects are modest. More research of higher methodological quality is needed.

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Contrary to previous belief, pregnancy is not protective against a major depressive episode, a condition that can be severe and life threatening.[1] Ten percent of pregnant women meet diagnostic criteria for major depressive disorder,[2] with the prevalence increasing from the first trimester (7.4%) to the second (12.8%) and third (12.0%) trimesters[3]; 18% of women exhibit depressive symptoms antenatally.[4] Not only is the disorder underrecognized, treatment uptake is also poor; women continue to experience symptoms into the postpartum time and 54.2% of women with "postpartum depression" have actually had depression before or during pregnancy.[1] Although pregnancy has been associated with discontinuation of treatment in general,[5] concern about the safety of using antidepressant medication during pregnancy is one reason for low rates of medication use,[4,6,7] and clinicians are advised to weigh the risks of depression with the risks of treatment.[8]

Unfortunately, making an evidence-based decision has been challenging, partially because of limited research into the risks of untreated depression as well as contradictory findings. For example, both significant[9–13] and nonsignificant[14–18] associations have been found in antenatal depression and increased preterm birth, low birth weight, decreased Apgar score, and increased neonatal intensive care unit (NICU) admissions. Many studies are observational and have methodological limitations, such as a lack of standardized assessments or no control of important confounding variables, including antidepressant medication use, making it difficult to draw of conclusions.[19,20] In order to make treatment decisions that weigh risks and benefits, the effect of depression alone should be established. Only 1 meta-analysis[20] has been completed that examined the relationship between antenatal depression exposure and perinatal outcomes. While an association between antenatal depression and preterm delivery and low birth weight was found, this review examined only 3 outcomes.

Our systematic literature review and meta-analysis is part of a larger project that seeks to create an evidence-based reference guide for clinicians to use with their depressed pregnant patients in reaching treatment decisions. We sought to update the meta-analysis by Grote et al[20] and examine other reported outcomes regarding the effects of maternal depression, such as birth weight, gestational age, Apgar scores, NICU admissions, preeclampsia,

Clinical Points

- Maternal depression during pregnancy may be associated with premature delivery.
- Depressed mothers may be less likely to start breastfeeding.
- The effects of maternal depression during pregnancy must be considered when making treatment plans.

and breastfeeding initiation. We also completed subgroup analyses in which we examined the following potentially effect-modifying variables: antidepressant use, study quality, use of diagnostic measures of depression, use of adjusted estimates for confounders, adjustment for smoking, country of origin, socioeconomic status, and use of convenience samples.

DATA SOURCES AND STUDY SELECTION

Details of our methods have been previously described.[21] Independent literature searches were conducted by 2 professional librarians who have expertise in the areas of psychiatry and psychopharmacology. Keywords utilized included *depressive/mood disorder*, *postpartum/postnatal*, *pregnancy/pregnancy trimesters*, *prenatal* or *antenatal*, *infant/neonatal outcomes*, *premature delivery*, *gestational age*, *birth weight*, *NICU*, *preeclampsia*, *breastfeeding*, and *Apgar* (a full list of keywords is provided in supplementary material). Databases (searched from start date to June 30, 2010) included MEDLINE (Ovid); MEDLINE In-Process (Ovid), to access current literature (keyword searching only); PsycINFO (American Psychological Association; Ovid); CINAHL (Nursing; Allied Health); EMBASE (Excerpta Medica, Elsevier; Ovid); and Scopus (Elsevier), to access current literature (keyword searching only). Review and meta-analyses reference lists were searched, but no further sources were found.

Inclusion and Exclusion Criteria

Original prospective studies published in English were eligible. For cases in which a sample was repeated in more than 1 publication, the article that most closely addressed our research question was selected. Studies were identified that compared clinical outcomes in populations that were exposed to depression antenatally compared to those unexposed. Measurement of depression at any antenatal time point was considered, as well as the use of validated or unvalidated depression measures that provided dichotomous or continuous data. For cases in which multiple time points were presented, combined time points were used as per the original data, if possible; when this was not possible, second and third trimester data, adjusted data, or the data reflecting continuous depression were selected. All studies that examined adversity to the child and/or mother in the gestational, delivery, neonatal and/or postpartum/developmental periods were accepted. We excluded studies that pooled antenatal and postpartum depression scores, as well as studies that had adolescent samples. Abstracts, conference proceedings, and unpublished data were also excluded because of the volume of studies potentially eligible.

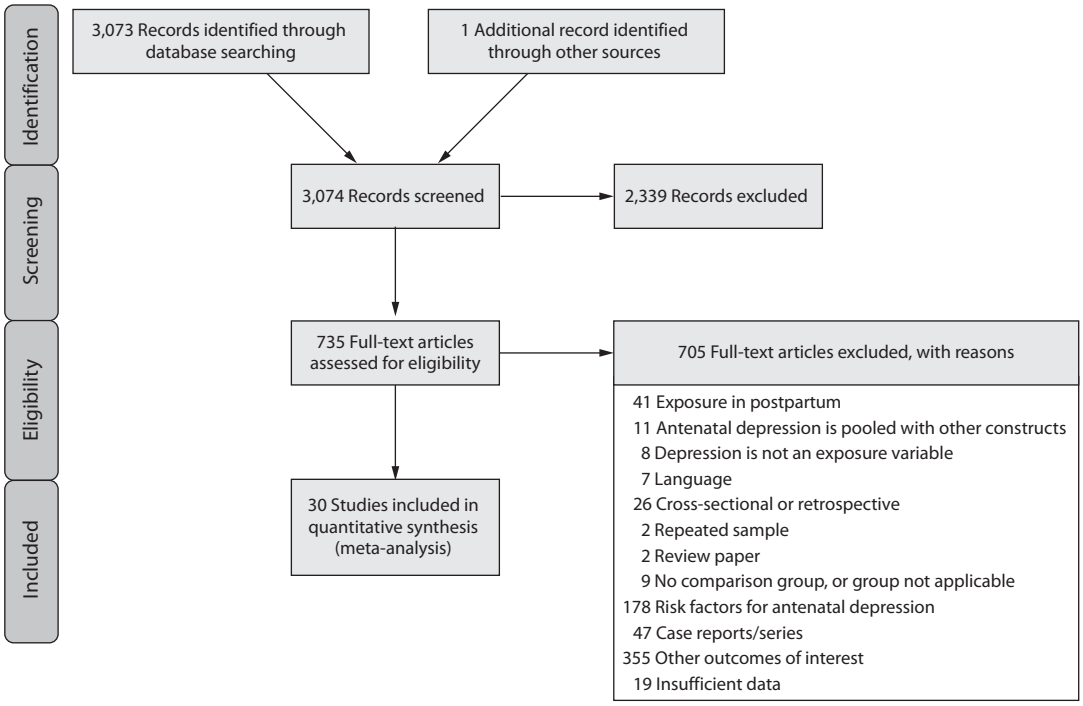
DATA EXTRACTION

Both the data extraction and quality assessment methods have been published previously, as this study was 1 of a large program of research.[21] All articles were screened by their title and abstract by 2 independent research assistants, and those eligible were retrieved. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria[22] were used to create the data extraction forms, which were completed for each eligible study. Extracted data included source, study design, participants (sample, control, demographics, and clinical characteristics), inclusion/exclusion criteria, antidepressants examined, dosage, duration of exposure, primary and secondary outcomes, outcome assessment methods, and loss to follow-up. Requests for raw data were sent to authors for original studies that did not provide all data, and, of the 8 contacted, replies were received from 3 authors. Further data were not provided for the following reasons: confidentiality policy, unable to meet our timeline, and no reply for further explanation of data. As available, adjusted estimates as well as their variances were extracted. Where adjusted estimates were not provided in the published data, we calculated crude odds ratios or mean differences and sample variances. Before calculating the odds ratio for studies that included cells with a 0 count, we added 0.5 to these cells. The research team in conjunction with an advisory committee of key stakeholders composed of representatives from psychiatry, family medicine, obstetrics, neonatology, public health, patient advocacy, and policy identified the outcomes of interest. Outcomes examined included (based on there being at least 3 articles to pool for meta-analysis): premature delivery (< 37 weeks' gestation where defined), birth weight, low birth weight (< 2,500 g where defined), gestational age, Apgar scores at 1 minute and at 5 minutes, NICU admissions, preeclampsia, and breastfeeding initiation, as defined by the authors of the original publication.

Quality Assessment

The quality assessment tool utilized for this program of research has been previously described.[21] The Systematic Assessment of Quality in Observational Research (SAQOR) was based on the Downs and Black[23] checklist and the Newcastle-Ottawa Scale[24] and adapted for this specific area of research. Each article's outcome was assessed by 19 criteria under 5 categories: (1) sample, (2) control group, (3) quality of exposure/outcome measure, (4) follow-up, and (5) distorting influences. The distorting influences category took into account any controls for antidepressant or other psychotropic medications, as well as other confounders (ie, smoking, alcohol, or illicit drug use). Using a modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[25] we assigned a final quality rating based on the SAQOR criteria of high, moderate, low, or very low. For the purposes of this

Figure 1. Identification of Independent Studies for Inclusion in Meta-Analysis (adapted from PRISMA 2009 flow diagram[31])



meta-analysis, high, moderate, and low studies were categorized as "above quality threshold," and the very low were "below quality threshold." For each study, results of the data extraction and quality assessment procedures were compared between raters, and consensus by the principal investigators was used to resolve any differences.

Statistical Analyses

In the few instances where adjusted hazard ratios or relative risks were given, these were considered as estimated odds ratios, since, for the most part, events were rare. We obtained pooled estimates of the odds ratio for binary outcomes or the weighted mean difference for continuous outcomes with the DerSimonian and Laird random-effects model.[26] A fixed-effects pooled estimate was used when there were only 2 eligible studies for an outcome. We visually inspected funnel plots portraying individual study estimates (on the log scale for odds ratios) against their standard error to assess for publication bias. The L estimator of Duval and Tweedie[27] was used to estimate the number of unpublished studies (k). If k was 1 or more, then k studies were imputed by reflection of the k largest effects around the summary estimate. The standard errors of the k "reflected" studies were utilized for the k imputed ones and the summary odds ratio was reestimated in this expanded dataset. There was no evidence for publication bias if k was estimated to be 0. If publication bias was found, then we used Duval and Tweedie's trim-and-fill method[27] to adjust for it and estimate exposure effects. Cochrane *Q* and visual inspection of forest plots were used to assess between-study heterogeneity, which was then quantified by I^2. If *Q* is not significant and I^2 is small, this would suggest that there is a common underlying effect, and variations in estimated study effects are not true study-to-study variation (heterogeneity) but rather due to just random variation. I^2 may be interpreted as the proportion of the total variance due to heterogeneity and may be categorized as a low ($I^2 = 25\%$), moderate ($I^2 = 50\%$), or high ($I^2 = 75\%$) degree of heterogeneity.[28] Sources of heterogeneity were explored through subgroup analyses for all outcomes (regardless of *Q* significance). These subgroup analyses examined within-group effects and between-group differences in pooled effects based on a number of study characteristics chosen a priori: study quality (ie, those above threshold compared with those below); use of a diagnostic measure of depression, convenience sample (ie, not consecutive or random sample), or adjusted estimates; use of antidepressant medication; and sources of heterogeneity as determined by socioeconomic status, smoking, and country. Statistical analyses were completed with the metafor package in R (2.14.2)[29] and similar to our other work.[30]

RESULTS

Of the 3,074 abstracts reviewed, 2,339 were excluded on the basis of title and abstract. In total, 735 articles were retrieved and assessed for eligibility, and 30 articles met the inclusion criteria (Figure 1)[31] and were included in the quantitative analysis (Table 1).[9–18,32–51] Twenty-six of the 30 studies were above our quality threshold, and 4 were below. Of the studies that we could pool, most reported data on more than 1 outcome: 16 reported on premature delivery, 7 on low birth weight, 6 on NICU admissions (including 1 special care nursery), 4 on preeclampsia, 4 on breastfeeding

Table 1. Study Characteristics of 30 Studies Included in the Meta-Analyses on the Impact of Maternal Depression

Article	Quality Threshold	Country	SES	Sample Size	Confounders[a]	Depression Classification	Results	Outcome Definition
Steer et al,[32] 1992[b,c]	A	United States[d]	Lower	389 women depressed in third trimester vs not depressed in third trimester (only total number of adult women provided)	Adjusted for low prepregnancy BMI, parity, ethnicity, inadequate weight gain, smoking, prior history of low birth weight or preterm delivery Excluded: drug or alcohol abuse, histories of chronic disease (nonobstetric), history of psychiatric illness (including known diagnosis or treatment for depression)	BDI score ≥ 21	Preterm delivery: 25% in depressed vs 8.1% in not depressed (AOR = 3.39; 95% CI, 3.24 to 3.56) Low birth weight: 20% in depressed vs 7.6% in not depressed (AOR = 3.97; 95% CI, 3.80 to 4.15)	Preterm delivery: < 37 weeks' completed gestation Low birth weight: < 2,500 g
Hoffman and Hatch,[33] 2000[e]	A	United States	Lower used	Depressed in second and third trimester, n = 35 Not depressed in any trimester, n = 70	Adjusted for gestational age, smoking, obstetric factors, demographic factors Excluded: spontaneous abortion before first interview, second trimester spontaneous abortions, stillbirths, multiple pregnancies	CES-D score ≥ 16	Birth weight: β = −179.7; 95% CI, −358.2 to −1.2	…
Kurki et al,[34] 2000[f]	A	Finland	Mixed	Depressed in early pregnancy, n = 185 Not depressed in early pregnancy, n = 438	Adjusted for smoking, age, alcohol consumption, SES, marital status, bacterial vaginosis Excluded: termination of pregnancy, spontaneous abortion, previous elevated risk for preeclampsia (essential hypertension, gestational diabetes, and twins), second trimester fetal death	13-Item BDI (Finnish modification) score ≥ 3	Preeclampsia: 7.6% in depressed vs 3.2% in not depressed (AOR = 2.5; 95% CI, 1.1 to 5.4)	Preeclampsia: increased blood pressure (more than 140/100 mm Hg) and proteinuria (0.3 g during 24 hours or more) after 20 weeks' gestation.
Chung et al,[35] 2001[b,c,g]	A	China, Hong Kong[d]	Mixed	Depressed, n = 67 Not depressed, n = 575 In first or third trimester	Adjusted for age, gestation, low birth weight, actual birth weight, parity, male fetus, past psychiatric history, medical complications (gestational hypertension, maternal diabetes, antepartum hemorrhage, thyroid disorders, fetal presentation), induced labor, previous cesarean section, labor augmentation, mode of delivery Excluded: did not provide informed consent, leaving Hong Kong within 12 months of delivery, ethnicity other than Chinese. No reported history for alcohol or substance abuse or smoking during pregnancy	BDI score > 14.5	Preterm delivery: third trimester exposure (ARR = 0.23; 95% CI, 0.03 to 1.90; *P* = .15) Low birth weight: third trimester exposure (ARR = 1.60; 95% CI, 0.69 to 3.72; *P* = .27) NICU: 24% in depressed during third trimester vs 19% in not depressed (ARR = 2.18; 95% CI, 1.02 to 4.66; *P* = .03)	…
Orr et al,[36] 2002[b]	A	United States	Lower	Depressed, n = 110 Not depressed, n = 1,286	Adjusted for low prepregnancy BMI, alcohol consumption, drug use, smoking, previous poor pregnancy outcome, bleeding, depressive symptoms Excluded: medically indicated preterm births, preterm births with undetermined etiology, multiple pregnancy, pregnancy loss, relocation from the area, lost medical record	CES-D score > 33	Preterm delivery: 12.7% in depressed vs 8.0% in not depressed (AOR = 1.96; 95% CI, 1.04 to 3.72)	Spontaneous preterm birth: preterm premature rupture of the membranes at < 37 completed gestational weeks or preterm labor

continued

Table 1 (continued). Study Characteristics of 30 Studies Included in the Meta-Analyses on the Impact of Maternal Depression

Article	Quality Threshold	Country	SES	Sample Size	Confounders[a]	Depression Classification	Results	Outcome Definition
Wu et al,[37] 2002[e,h]	A	United States	Mixed	Depressed in third trimester, n = 264 Not depressed in third trimester, n = 1,433	Excluded: women who could not speak English were not offered participation (Assessed confounders for other outcomes)	CES-D score ≥ 16	Gestational age, mean (SD), wk: depressed, 39.3 (2.0) vs not depressed, 39.1 (2.1) (P = .72) Birth weight, mean (SD), g: depressed, 3,385 (590) vs not depressed, 3,308 (578) (P = .91)	…
Dole et al,[16] 2003[b]	A	United States	Mixed	Depressed (high count), n = 464 Not depressed, n = 1,123	Adjusted for SES, smoking, alcohol, bacterial vaginosis but retained only if the association changed by 10% Excluded: inability to speak English, < 16 years old, multiple gestation, no telephone access, delivery planned elsewhere from study site	CES-D score ≥ 25 (high count)	Preterm delivery: depressed (high count) vs not depressed (risk ratio = 1.2; 95% CI, 0.9 to 1.5)	Preterm delivery: < 37 completed weeks' gestation
Andersson et al,[14] 2004[b,c,g]	A	Sweden[d]	Mixed	Depressed in second trimester, n = 164 Not depressed in second trimester, n = 1,261	Adjusted for BMI, age, smoking habits, SES, marital status Excluded: multiples, not a live birth, language difficulties (inability to read/understand questionnaire), missed spontaneous abortion or malformation found at ultrasound examination, incomplete medical records for newborn, informed consent not provided, bipolar disorder	Primary Care Evaluation of Mental Disorders	Preterm delivery: 6.7% depressed vs 5.2% in not depressed (AOR = 1.19; 95% CI, 0.59 to 2.40) Low birth weight: 2.4% in depressed vs 2.2% in not depressed (AOR = 1.19; 95% CI, 0.40 to 3.56) NICU: 10.4% in depressed vs 11.7% in not depressed (AOR = 0.90; 95% CI, 0.51 to 1.58)	Preterm delivery: < 37 weeks' completed gestation Low birth weight: < 2,500 g
Larsson et al,[38] 2004[e,h,i]	A	Sweden	Mixed	Gestational age: Depressed in third trimester, n = 237 Not depressed, n = 250 Birth weight: Depressed in third trimester, n = 186 Not depressed, n = 252 Breastfeeding: Depressed in third trimester, n = 217 Not depressed, n = 255	Excluded inability to understand Swedish (Assessed confounders for other outcomes)	EPDS score > 10	Gestational age, mean (SD), wk: depressed, 39.6 (1.5) vs not depressed, 40.7 (1.3) (P < .001) Birth weight, mean (SD), g: depressed, 3,594 (477) vs not depressed, 3,581 (494) (P = .799) Breastfeeding: 96.8% in depressed vs 96.9% in not depressed (P = .956)	…
Suri et al,[39] 2004[e,g,h,j]	A	United States[d,k]	Mixed	Depressed and no fluoxetine, n = 18 Not depressed and no fluoxetine, n = 16	Adjusted for gestational age (for birth weight) Excluded: multiple gestation, psychotic symptoms present, suicidality, use of alcohol/cigarettes/substances during pregnancy, use of other psychotropic medications, use of medications known to cause adverse affects for the fetus	Structured Clinical Interview for *DSM-IV* (SCID) (CES-D score > 16 considered positive for depressive symptoms following study entry)	Gestational age, mean (SD), wk: depressed and no fluoxetine, 39.6 (1.7) vs not depressed and no fluoxetine, 38.8 (1.8) (95% CI, −2.02 to 0.42) Birth weight, mean (SD), kg: depressed and no fluoxetine, 3.7 (0.43) vs not depressed and no fluoxetine, 3.3 (0.6) (95% CI, −0.76 to −0.04) Apgar 5 min, mean (SD): depressed and no fluoxetine, 8.8 (0.6) vs not depressed and no fluoxetine, 9.0 (0.4) (95% CI, −0.15 to 0.55) NICU admissions: 11% in depressed and no fluoxetine vs 19% in not depressed and no fluoxetine (95% CI, 0% to 32%)	…

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Table 1 (continued). Study Characteristics of 30 Studies Included in the Meta-Analyses on the Impact of Maternal Depression

Article	Quality Threshold	Country	SES	Sample Size	Confounders[a]	Depression Classification	Results	Outcome Definition
Berle et al,[15] 2005[b,c]	A	Norway	Mixed	Depressed, n = 19 Not depressed, n = 661	… (Assessed confounders for other outcomes)	Hospital Anxiety and Depression Rating Scale-Depression score ≥ 8	Preterm delivery: N = 0 in depressed vs N = 16 in not depressed ($P \geq .05$) Low birth weight: 5.3% in depressed vs 2.7% in not depressed (OR = 1.78; 95% CI, 0.23 to 14.0; $P = .584$)	Preterm delivery: gestational length < 37 weeks Low birth weight: < 2,500 g
Dayan et al,[9] 2006[b]	A	France[d]	Mixed	Depressed and antidepressant exposure, n = 93 Not depressed, n = 548	Adjusted for maternal age, gestational age at enrollment, smoking habits in pregnancy, partner violence, hospitalization during second trimester, vaginal and/or cervical infection, vaginal bleeding during third trimester, polyhydramnios, consultation type at enrollment, depression, trait anxiety score, state anxiety score Secondary analysis: excluded psychotropic drug users Excluded: multiple gestation, cervical cerclage, placenta previa, postenrollment cases of preterm births that were medically indicated (eg, abruption placenta, severe maternal hypertension, nonreassuring fetal state, severe intrauterine growth retardation), delivery at another hospital	EPDS score ≥ 14	Preterm delivery: depressed (excluding antidepressant exposed) (AOR = 4.9; 95% CI, 1.6 to 14.9; $P = .006$)	Spontaneous preterm delivery: resulting from either preterm prelabor rupture of membranes or preterm labor or preterm and delivery prior to 37 weeks' completed gestation
Field et al,[11] 2006[b]	B	United States[k]	Mixed	Depressed, n = 275 Not depressed, n = 234	Excluded: illicit drug use (Reported assessment of confounders)	CES-D score ≥ 16 and SCID	Preterm delivery: 9.5% in depressed vs 4.2% in not depressed ($F = 9.78$; $\chi^2 = 5.99$; $P = .01$)	…
Evans et al,[17] 2007[c,e]	A	England	Mixed	Depressed, n = 1,519 Not depressed, n = 9,448	Adjusted for maternal age, smoking, educational level, gestational age, infant gender, parity, alcohol/caffeine use during pregnancy, prepregnancy BMI, history of miscarriage, ethnicity, cesarean section, prior preterm births or low birth weight, chronic disease Excluded: preterm births (< 37 weeks' gestation), multiple births	EPDS score > 12	Birth weight: women scoring > 12 on EPDS at 18 weeks vs not depressed (adjusted mean difference = −1.1; 95% CI, −22.1 to 24.3; $P = .4$) Low birth weight: AOR = 1.38; 95% CI, 0.94 to 2.01	Low birth weight: < 2,500 g

continued

Table 1 (continued). Study Characteristics of 30 Studies Included in the Meta-Analyses on the Impact of Maternal Depression

Article	Quality Threshold	Country	SES	Sample Size	Confounders[a]	Depression Classification	Results	Outcome Definition
Suri et al,[40] 2007[b,e,f,g,h,j,l]	A	United States[d,k]	Mixed	Depressed and no antidepressant or limited exposure, n = 22 Not depressed and no antidepressant exposure, n = 19	Adjusted for maternal age, weight gain in pregnancy, BMI (prepregnancy), parity, infant sex, gestational age at birth, hypertension (including pregnancy induced), preterm birth historical/developing risk factors, preeclampsia Excluded: positive urine drug screen, use of any medication known to affect the fetus adversely, another current Axis I disorder (*DSM-IV*), actively suicidal	SCID	Preterm delivery: 0% in depressed and no antidepressant exposure vs 5.3% in not depressed and no antidepressant exposure Gestational age, mean (SD), wk: depressed and no antidepressant exposure, 39.4 (1.1) vs not depressed and no antidepressant exposure, 39.7 (1.2) (mean values used in our analysis: $t_{39} = 0.61$, NS, Bonferroni corrected) Birth weight, mean (SD), kg: depressed and no antidepressant exposure, 3.39 (0.38) vs not depressed and no antidepressant exposure, 3.36 (0.43) (adjusted difference in weight = 111 g; SD = 130) Preeclampsia: 4.5% in depressed and no antidepressant exposure vs 0% in not depressed and no antidepressant exposure Apgar 1 min, mean (SD): depressed and no antidepressant exposure, 8.2 (0.71) vs not depressed and no antidepressant exposure, 8.0 (1.1) Apgar 5 min, mean (SD): depressed and no antidepressant exposure, 9.0 (0.23) vs not depressed and no antidepressant exposure, 8.9 (0.25) Special care nursery admission: 9% in depressed and no antidepressant exposure vs 0% in not depressed and no antidepressant exposure	Preterm delivery: < 37 wk
Deave et al,[41] 2008[b,i]	A	England	Mixed	Depressed, n = 2,299 Not depressed, n = 8,799	Excluded: multiple births, noncompleters of the antenatal questionnaires at both 18 and 32 weeks of gestation (Assessed confounders for other outcomes)	EPDS score ≥ 14	Preterm delivery: 150/2,299 in depressed vs 462/8,799 in not depressed Breastfeeding: 70.3% in depressed vs 77.9% in not depressed	Breastfeeding: ever breastfed
Vollebregt et al, [42] 2008[f]	A	The Netherlands	Unspecified	Depressed (high), n = 399 Not depressed (low), n = 1,715	Excluded: previous parity, multiples, delivered < 24 weeks (Assessed confounders for other outcomes)	CES-D	Preeclampsia: n = 16 in depressed (high) vs n = 64 in not depressed (low)	Preeclampsia: gestational hypertension and proteinuria ≥ 0.3 g/24 h or dipstick ≥ ++ after 20 weeks of gestation

continued

Table 1 (continued). Study Characteristics of 30 Studies Included in the Meta-Analyses on the Impact of Maternal Depression

Article	Quality Threshold	Country	SES	Sample Size	Confounders[a]	Depression Classification	Results	Outcome Definition
Diego et al,[10] 2009[e,h]	A	United States[d]	Mixed	Depressed, n = 40 Not depressed, n = 40	Marital status, SES, and maternal age used as covariates Excluded: current or previous pregnancy complication (anemia, vaginal bleeding, hypertensive disorder, intrauterine growth restriction), abnormal pregnancy BMI, smoking/alcohol/recreational drug use in pregnancy, antidepressants/other psychotropic medications in pregnancy, HIV/other infectious disease, metabolic/eating disorder, all other psychiatric disorders	SCID	Gestational age, mean (SD), wk: depressed, 38.04 (1.65) vs not depressed, 38.48 (1.17) ($F_{1,74} = 0.97$; $P = .336$; $\eta^2 = 0.01$); mean values used in our analyses Birth weight, mean (SD), g: depressed, 3,105.18 (480.88) vs not depressed, 3,437.22 (436.63) ($F_{1,74} = 6.47$; $P = .013$; $\eta^2 = 0.08$); mean values used in our analyses	…
Fairlie et al,[43] 2009[b,i]	A	United States	Mixed	Depressed, n = 125 Not depressed, n = 1,311	Adjusted for parity, gestational age, maternal age, country of origin, maternal education, household income, prepregnancy BMI, high pregnancy-related anxiety Excluded: multiple gestation, gestational age > 22 completed weeks, inability to answer questions in English, plan to move out of area prior to delivery	EPDS score ≥ 13	Preterm delivery: 5.6% (7/125) in depressed vs 6.5% (85/1,311) in not depressed Initiated breastfeeding: 84% in depressed vs 87% in not depressed (raw data used in our analyses) (Failure to initiate breastfeeding: AOR = 1.03; 95% CI, 0.59 to 1.80)	Preterm birth: < 37 weeks Breastfeeding initiation: subjects initiated breastfeeding by putting their baby to their breast (whether the baby got milk or not) or having fed their baby their breast milk
Gavin et al,[44] 2009[b]	A	United States[d]	Mixed	Depressed and no antidepressant exposure, n = 432 Not depressed and no antidepressant exposure, n = 2,383	Adjusted for age, maternal race, parity, smoking status, Medicaid status, BMI Excluded: history of diabetes, congenital or chromosomal abnormalities, < 15 years old, multiple births, poor English	CES-D score > 24	Preterm delivery: depressed and no antidepressant exposure vs not depressed and no antidepressant exposure (AOR = 0.6; 95% CI, 0.4 to 0.9)	Preterm birth: < 37 weeks
Li et al,[45] 2009[b]	A	United States	Mixed	Depressed high score, n = 172 Not depressed (CES-D < 16), n = 465	Adjusted for maternal age, race/ethnicity, education, gravidity, vitamin use, history of miscarriage, low birth weight, preterm delivery, vomiting, and smoking Excluded: ended pregnancy prior to 20 weeks' gestation (including miscarriage), very early preterm delivery (< 33 weeks)	CES-D score ≥ 22	Preterm delivery: 9.3% in depressed vs 4.1% in not depressed (adjusted hazard ratio = 2.2; 95% CI, 1.1 to 4.7)	Preterm birth: < 37 weeks
Mattes et al,[46] 2009[h]	B	Australia	Mixed	Depressed, n = 18 Not depressed, n = 63	Excluded: history of complicated pregnancies, smokers, other preexisting medical conditions, manifested seafood allergies, > 2 fish meals consumed per week, use of fish oil supplements	BDI score > 10	Gestational age, mean (SD), d: depressed, 275.3 (7.0) vs not depressed, 274 (8.2) ($P = .53$)	…

continued

Table 1 (continued). Study Characteristics of 30 Studies Included in the Meta-Analyses on the Impact of Maternal Depression

Article	Quality Threshold	Country	SES	Sample Size	Confounders[a]	Depression Classification	Results	Outcome Definition
Setse et al,[47] 2009[c,g]	B	United States	Mixed	Depressed, n = 30 Not depressed, n = 170	Excluded: inability to provide written informed consent, > 14 weeks' gestation at recruitment time, HIV/any active cancer diagnosis (Assessed confounders for other outcomes)	CES-D score ≥ 16	Low birth weight: 2 infants in depressed vs 17 in not depressed (P = .4) NICU: 1 infant in depressed vs 4 in not depressed (P = .1)	Low birth weight: < 2,500 g
Warnock et al,[48] 2009[j,l]	A	Canada[d]	Unspecified	Depressed and no antidepressant exposure, n = 10 Not depressed and no antidepressant exposure, n = 10	Excluded: not full-term (birth weight < 2,500 or > 3,200 g and/or < 37 weeks' gestational age), prenatal medication/drug exposure besides SSRIs, central nervous system malformations, delivery complications, congenital heart disease, neurologic impairments, bipolar disorder, illicit drug use, Axis II disorders	Clinical diagnosis	Apgar 1 min, mean (SD): depressed and no antidepressant exposure, 8.40 (0.84) vs not depressed and no antidepressant exposure, 8.50 (0.85) Apgar 5 min, mean (SD): depressed and no antidepressant exposure, 9.00 (0.00) vs not depressed and no antidepressant exposure, 9.10 (0.57)	…
Wisner et al,[49] 2009[b,e,g]	A	United States[d,k]	Mixed	Continuous depression and no SSRI exposure, n = 14 Not depressed and no SSRI exposure, n= 131	Adjusted for maternal age, race, infant gestational age at birth Excluded: multiples, chronic disease, active substance use disorder, or gestational use of certain drugs, bipolar disorder, psychosis	SCID	Preterm delivery: 3 infants in continuous depression and no SSRI exposure vs 8 in not depressed and no SSRI exposure (adjusted rate ratio = 3.71; 95% CI, 0.98 to 14.13) Birth weight, mean (SD), kg: continuous depression and no SSRI exposure, 3.22 (0.6) vs not depressed and no SSRI exposure, 3.53 (0.5) NICU admissions: 21% in continuous depression and no SSRI exposure vs 8% in not depressed and no SSRI exposure	Preterm delivery: < 37 weeks
Ertel et al,[50] 2010[h]	A	United States	Mixed	Depressed, n = 69 Not depressed, n = 769	Excluded: multiple gestation, inability to answer questions in English, > 22 weeks' gestational age at first prenatal visit, plans to move out of area prior to delivery (Assessed confounders for other outcomes)	EPDS score > 13	Gestational age, mean (SD), wk: depressed, 39.51 (1.54) vs not depressed, 39.6 (1.7) (P = .67)	…
Field et al,[51] 2010[b,e]	B	United States	Mixed	Depressed, n = 181 Not depressed, n = 345	Excluded: multiple fetuses, < 18 years old, HIV/AIDS status, medical complications	SCID	Preterm delivery: 6.5% in depressed vs 6.0% in not depressed Birth weight, mean (SD), g: depressed, 3,355.57 (404.14) vs not depressed, 3,352.17 (448.26)	…
Henrichs et al,[13] 2010[e,f,h]	A	The Netherlands	Mixed	Depressed, n = 941 Not depressed, n = 5,372	Adjusted for maternal education, maternal age, height, parity, prepregnancy BMI, prenatal smoking, ethnicity, gestational diabetes, hypertension, preeclampsia, fetal sex, family stress, gestational age, maternal anxious symptoms Excluded: multiple births, fetal death	Depression items from Brief Symptom Inventory Top 15% = depressed group	Gestational age, mean (SD), wk: depressed, 39.8 (1.8) vs not depressed, 39.9 (1.7) (P > .05) Birth weight, mean (SD), g: depressed, 3,347 (552) vs not depressed, 3,431 (554) (P < .001); adjusted difference in birth weight, β = –22.42 (95% CI, –53.05 to 8.21) Preeclampsia: 2.2% in depressed vs 1.8% in not depressed (P > .05)	…

continued

Table 1 (continued). Study Characteristics of 30 Studies Included in the Meta-Analyses on the Impact of Maternal Depression

Article	Quality Threshold	Country	SES	Sample Size	Confounders[a]	Depression Classification	Results	Outcome Definition
Imran and Haider,[12] 2010[b,c]	A	Pakistan[k]	Lower	Depressed in third trimester, n = 73 Not depressed in third trimester, n = 103	Excluded: < 16 or > 50 years old, pregnancy not in third trimester, inability to give consent, acutely unwell (Reported comparison of confounders)	EPDS score > 12	Preterm delivery: n = 18 in depressed vs n = 12 in not depressed (P = .024) Low birth weight: n = 26 in depressed vs n = 43 in not depressed	Low birth weight: < 2,500 g
Lancaster et al,[18] 2010[e,h,i,j,l]	A	United States[k]	Mixed	Depressed, n = 159 Not depressed, n = 685	Excluded: deliveries at < 20 wk, fetal deaths in utero (Compared confounders for other outcomes)	CES-D score ≥ 16	Gestational age, mean (SD), wk: depressed, 38.5 (2.5) vs not depressed, 38.8 (2.4) (P = .16) Birth weight, mean (SD), kg: depressed, 3.3 kg (0.7) vs not depressed, 3.4 (0.6) (P = .27) Breastfeeding: 74.0% in depressed vs 80.4% in not depressed (P = .07) Apgar 1 min, mean (SD): depressed, 7.8 (1.5) vs not depressed, 7.9 (1.5) (P = .65) Apgar 5 min, mean (SD): depressed, 8.8 (0.7) vs not depressed, 8.8 (0.8) (P = .55)	…

[a]Only matching, exclusions, or adjusted data for outcome of interest are listed, and adjustments may not apply to all outcomes. Individual studies may have collected or compared groups on other characteristics or adjusted data on other outcomes not reported.
[b]Included in premature delivery meta-analysis.
[c]Included in low birth weight meta-analysis.
[d]Included in antidepressants excluded/controlled subgroup.
[e]Included in birth weight meta-analysis.
[f]Included in preeclampsia meta-analysis.
[g]Included in NICU admissions meta-analysis.
[h]Included in gestational age meta-analysis.
[i]Included in breastfeeding initiation meta-analysis.
[j]Included in Apgar 5 minute score meta-analysis.
[k]Included in convenience sample subgroup.
[l]Included in Apgar 1 minute score meta-analysis.
Abbreviations: A = above quality threshold, AIDS = acquired immune deficiency syndrome, AOR = adjusted odds ratio, ARR = adjusted relative risk, B = below quality threshold, BDI = Beck Depression Inventory, BMI = body mass index, CES-D = Center for Epidemiologic Studies Depression Scale, EPDS = Edinburgh Postnatal Depression Scale, HIV = human immunodeficiency virus, NICU = neonatal intensive care unit, SES = socioeconomic status, SSRI = selective serotonin reuptake inhibitor.

initiation, 9 on gestational age, 11 on birth weight, 3 on Apgar score at 1 minute, and 4 on Apgar score at 5 minutes.

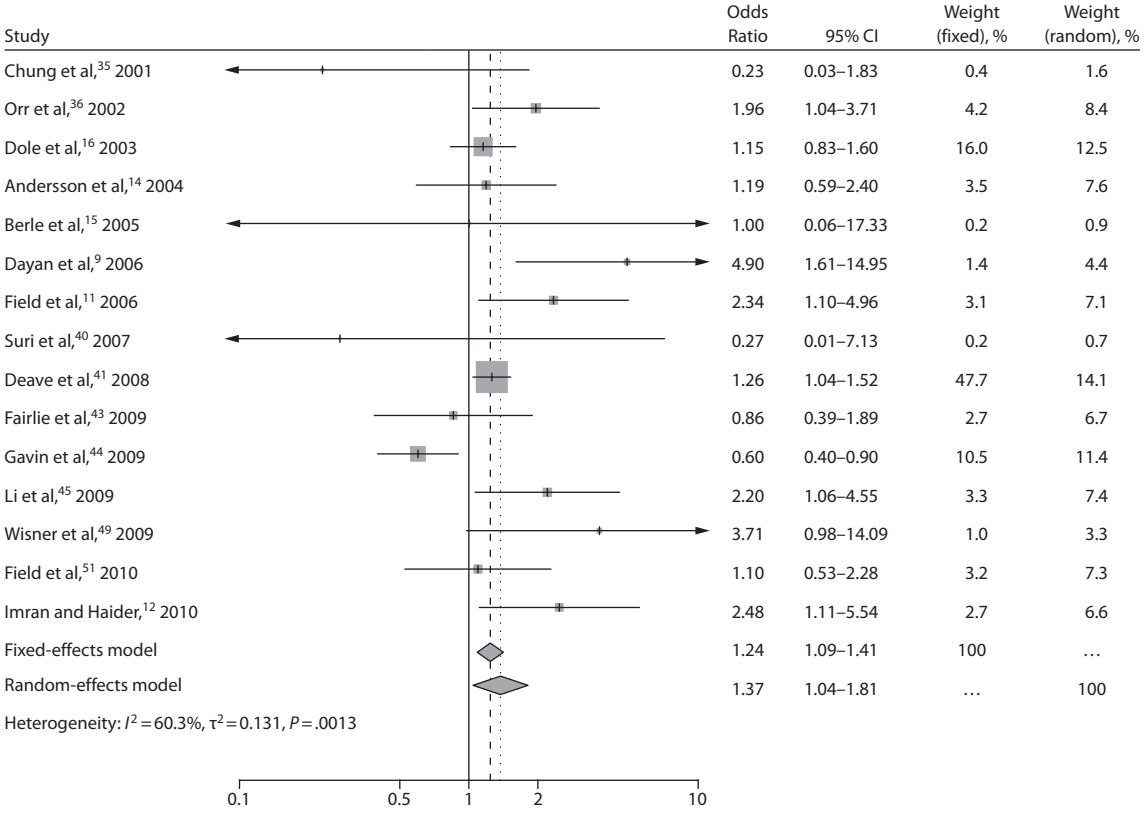
Premature Delivery

Sixteen studies were initially pooled and a borderline significant effect was found for exposure to maternal depression and the odds of premature delivery (odds ratio [OR] = 1.53; 95% CI, 0.997 to 2.34; P = .052). One study by Steer et al[32] was an outlier, and the analysis was repeated with the 15 remaining studies; the pooled OR became significant (OR = 1.37; 95% CI, 1.04 to 1.81; P = .024; Figure 2). Significant heterogeneity was found across studies (Q_{14} = 35.27, P < .0013; Table 2) in the medium range (I^2 = 60.3%). In our subgroup analyses, where we examined significant sources of heterogeneity, only sample type was a significant moderator variable (Q_1 = 5.5, P < .019, I^2 = 16%); the OR between exposure to depression and premature delivery was twice as high in studies using convenience samples as it was in those using nonconvenience samples (Table 2). Although no other variable was a statistically significant effect moderator, there were noteworthy results. Several subanalyses had significant ORs: studies with unadjusted data, those that did not exclude or control for antidepressant medication, and those that did not exclude or control for smoking. The nonsignificant ORs from studies with adjusted data, those that excluded medication, those that did exclude or control for smoking, and studies from other countries had high heterogeneity (Table 2).

Gestational Age

There was no significant association between exposure to maternal depression and gestational age when the 9 studies were pooled (mean difference = −0.19 weeks; 95% CI, −0.53 to 0.14; P = .262; see Supplementary eFigure 1). Heterogeneity was found across studies (Q_8 = 66.69, P < .0001), although none of the moderators appeared to account for the variability (Table 2).

Figure 2. Exposure to Depression in Utero and the Odds Ratio for Premature Delivery: Meta-Analysis Results for All Studies



Birth Weight

There was no significant association between exposure to maternal depression during pregnancy and birth weight when 11 studies were pooled (mean difference = −19.53 g; 95% CI, −64.27 to 25.20; $P = .392$; Supplementary eFigure 2). Heterogeneity was found across studies ($Q_{10} = 31.06$, $P = .001$). Although the moderator analyses were not significant, socioeconomic status accounted for 10% of the variability, approaching significance (Table 2).

Low Birth Weight

There was no significant association found between exposure to maternal depression and the odds of having a low birth weight (< 2,500 g) infant when 7 studies were pooled (OR = 1.46; 95% CI, 0.72 to 2.97; $P = .295$). Steer et al[32] was once again an outlier and excluded; however, pooling the remaining 6 studies did not result in a significant association (OR = 1.21; 95% CI, 0.91 to 1.60; $P = .195$; see Supplementary eFigure 3). Study heterogeneity was not significant nor were moderators. However, the OR for the subanalyses using adjusted data was significant as was the OR for studies that excluded smoking (Table 2).

Preeclampsia

Preeclampsia was not significantly associated with exposure to maternal depression on the basis of the OR of the 4 pooled studies (OR = 1.35; 95% CI, 0.95 to 1.92; $P = .089$; see Supplementary eFigure 4). No significant heterogeneity was found; none of the subanalyses resulted in any between-group differences, but the adjusted data subanalysis (ie, smoking), which was based on 1 study, was significant, with an OR of 2.5 (95% CI, 1.13 to 5.54; $P = .024$) (Table 2).

Breastfeeding Initiation

The pooled OR for the 4 studies analyzing breastfeeding initiation was significant (OR = 0.68; 95% CI, 0.61 to 0.76; $P < .0001$; Figure 3), which indicates that maternal depression was associated with reduced rates of breastfeeding initiation. Heterogeneity was not significant across studies. No significant differences between groups were found in any of the subanalyses performed (Table 2).

Apgar Score at 1 Minute

The pooled mean difference for the 3 studies investigating the association between maternal depression and Apgar scores at 1 minute was not significant (mean difference = −0.05; 95% CI, −0.28 to 0.17; $P = .638$; see Supplementary eFigure 5). Heterogeneity was not significant across studies. There were also no significant differences between groups for any of the subanalyses performed (Table 2).

Apgar Score at 5 Minutes

On the basis of 4 pooled studies, no significant association was found between exposure to maternal depression and

Table 2. Effect of Maternal Depression on Birth Outcomes: Meta-Analyses Results

		Within Group					Effect of Moderator		
				Heterogeneity					
Analysis	No. of Studies	Odds Ratio or Mean Difference (95% CI)[a]	*P* Value	$Q_{(df)}$ Within	*P* Value	I^2 (percentage of variance explained)	$Q_{(df)}$ Between	*P* Value	I^2 (percentage of variance explained)
Premature delivery									
All studies	15	1.37 (1.04 to 1.81)	.024	35.27_{14}	.001	60.3			
Study quality									
Above quality threshold	13	1.34 (0.99 to 1.82)	.057	32.36_{12}	.001	63.0	0.17_1	.679	0.0
Below quality threshold	2	1.59 (0.76 to 3.35)	.219	2.01_1	.157	50.0			
Diagnostic measure of depression									
Diagnostic	5	1.54 (0.95 to 2.50)	.078	5.28_4	.260	24.0	0.27_1	.606	1.0
Not diagnostic	10	1.32 (0.94 to 1.85)	.103	28.87_9	.001	69.0			
Any adjusted data									
Adjusted findings	7	1.53 (0.80 to 2.94)	.198	27.41_6	.0001	78.0	0.29_1	.591	1.0
Unadjusted findings	8	1.27 (1.07 to 1.52)	.007	7.53_7	.376	7.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	6	1.22 (0.52 to 2.86)	.655	19.80_5	.001	75.0	0.09_1	.760	0.0
Antidepressant medication use not excluded/controlled	9	1.39 (1.14 to 1.71)	.001	10.28_8	.246	22.0			
Smoking									
Smoking excluded/adjusted	7	1.32 (0.81 to 2.16)	.263	24.41_6	.0004	75.0	0.08_1	.785	0.0
Smoking not excluded/adjusted	8	1.44 (1.05 to 1.96)	.023	9.46_7	.221	26.0			
SES group									
Low SES group	2	2.15 (1.30 to 3.54)	.003	0.20_1	.652	0.0	3.20_1	.074	9.0
Mixed/unspecified SES group	13	1.27 (0.94 to 1.70)	.119	30.08_{12}	.003	60.0			
Country									
Europe	4	1.53 (0.90 to 2.57)	.113	5.63_3	.131	47.0			
North America	9	1.31 (0.89 to 1.94)	.169	23.33_8	.003	66.0	0.32_2	.853	1.0
Other/unspecified	2	0.92 (0.09 to 9.19)	.945	4.39_1	.036	77.0			
Convenience sample									
Convenience samples	4	2.43 (1.47 to 4.01)	.001	2.12_3	.548	0.0	5.50_1	.019	16.0
No convenience samples	11	1.21 (0.91 to 1.62)	.189	25.75_{10}	.004	61.0			
Gestational age									
All studies	9	-0.19 (−0.53 to 0.14)	.262	66.69_8	<.0001	88.0			
Study quality									
Above quality threshold	8	−0.23 (−0.60 to 0.13)	.209	64.9_7	<.0001	89.0	0.00_1	>.999	0.0
Below quality threshold	1	0.16 (−0.38 to 0.70)[b]	.565						
Diagnostic measure of depression									
Diagnostic	3	−0.15 (−0.74 to 0.45)	.633	3.38_2	.185	41.0	0.04_1	.845	0.0
Not diagnostic	6	−0.22 (−0.62 to 0.19)	.291	63.31_5	<.0001	92.0			
Any adjusted data									
Adjusted findings	0								
Unadjusted findings	9	−0.19 (−0.53 to 0.14)	.262	66.69_8	<.0001	88.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	3	−0.15 (−0.74 to 0.45)	.633	3.38_2	.185	41.0	0.04_1	.845	0.0
Antidepressant medication use not excluded/controlled	6	−0.22 (−0.62 to 0.19)	.291	63.31_5	<.0001	92.0			
Smoking									
Smoking excluded/adjusted	3	0.05 (−0.54 to 0.64)	.876	3.95_2	.138	49.4	0.81_1	.369	1.0
Smoking not excluded/adjusted	6	−0.28 (−0.69 to 0.13)	.175	61.56_5	<.0001	91.9			
SES group									
Low SES group	0								
Mixed/unspecified SES group	9	−0.19 (−0.53 to 0.14)	.262	66.69_8	<.0001	88.0			
Country									
Europe	2	−0.59 (−1.57 to 0.39)	.235	49.4_1	<.0001	98.0	1.0_2	.600	2.0
North America	6	−0.07 (−0.33 to 0.19)	.599	8.6_5	.128	42.0			
Other/unspecified	1	0.16 (−0.38 to 0.70)[b]	.565						
Convenience sample									
Convenience samples	3	−0.14 (−0.63 to 0.35)	.576	3.04_2	.219	34.0	0.08_1	.777	0.0
No convenience samples	6	−0.23 (−0.65 to 0.19)	.277	63.65_5	<.0001	92.0			
Birth weight									
All studies	11	−19.53 (−64.27 to 25.20)	.392	31.06_{10}	.001	67.8			
Study quality									
Above quality threshold	10	−24.49 (−74.97 to 25.99)	.342	30.97_9	.0003	71.0	0.36_1	.547	1.0
Below quality threshold	1	3.40 (−72.12 to 78.92)[b]	.930						
Diagnostic measure of depression									
Diagnostic	5	−39.99 (−247.49 to 167.51)	.706	18.90_4	.001	79.0	0.08_1	.776	0.0
Not diagnostic	6	−9.34 (−46.30 to 27.62)	.620	11.94_5	.036	58.0			

continued

Table 2 (continued). Effect of Maternal Depression on Birth Outcomes: Meta-Analyses Results

		Within Group							
				Heterogeneity			Effect of Moderator		
Analysis	No. of Studies	Odds Ratio or Mean Difference (95% CI)[a]	*P* Value	$Q_{(df)}$ Within	*P* Value	I^2 (percentage of variance explained)	$Q_{(df)}$ Between	*P* Value	I^2 (percentage of variance explained)
Birth weight (continued)									
Any adjusted data									
Adjusted findings	4	−14.69 (−49.10 to 19.72)	.403	5.54_3	.137	46.0	0.14_1	.712	0.0
Unadjusted findings	7	−34.57 (−134.27 to 65.13)	.497	25.34_6	.0003	76.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	4	−45.48 (−373.24 to 282.28)	.786	16.88_3	.001	82.0	0.05_1	.820	0.0
Antidepressant medication use not excluded/controlled	7	−7.32 (−39.31 to 24.66)	.654	12.01_6	.062	50.0			
Smoking									
Smoking excluded/adjusted	5	−43.15 (−109.66 to 23.37)	.204	19.44_4	.001	79.0	0.76_1	.383	2.0
Smoking not excluded/adjusted	6	−0.39 (−69.69 to 68.91)	.991	10.57_5	.061	53.0			
SES group									
Low SES group	1	−179.70 (−358.20 to −1.20)[b]	.049				3.20_1	.072	10.0
Mixed/unspecified SES group	10	−10.85 (−55.06 to 33.37)	.631	27.50_9	.001	67.0			
Country									
Europe	3	−8.02 (−26.15 to 10.11)	.386	1.39_2	.499	0.0	0.55_1	.459	2.0
North America	8	−49.98 (−159.57 to 59.60)	.371	29.66_7	.0001	76.0			
Other/unspecified	0								
Convenience sample									
Convenience samples	4	8.16 (−226.95 to 243.28)	.946	10.85_3	.013	72.0	0.03_1	.859	0.0
No convenience samples	7	−13.54 (−56.00 to 28.93)	.532	19.50_6	.003	69.0			
Low birth weight									
All studies	6	1.21 (0.91 to 1.60)	.195	3.8_5	.579	0.0			
Study quality									
Above quality threshold	5	1.23 (0.92 to 1.65)	.154	3.11_4	.539	0.0	0.68_1	.409	18.0
Below quality threshold	1	0.64 (0.14 to 2.94)[b]	.569						
Diagnostic measure of depression									
Diagnostic	1	1.19 (0.40 to 3.55)[b]	.755				0.0006_1	.980	0.0
Not diagnostic	5	1.21 (0.90 to 1.62)	.209	3.80_4	.434	0.0			
Any adjusted data									
Adjusted findings	3	1.39 (1.00 to 1.94)	.049	0.19_2	.911	0.0	2.80_1	.096	73.0
Unadjusted findings	3	0.81 (0.46 to 1.40)	.444	0.83_2	.659	0.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	2	1.43 (0.74 to 2.79)	.291	0.18_1	.674	0.0	0.38_1	.539	10.0
Antidepressant medication use not excluded/controlled	4	1.13 (0.79 to 1.62)	.507	3.31_3	.347	9.0			
Smoking									
Smoking excluded/adjusted	3	1.39 (1.00 to 1.94)	.049	0.19_2	.911	0.0	2.80_1	.096	73.0
Smoking not excluded/adjusted	3	0.81 (0.46 to 1.40)	.444	0.83_2	.659	0.0			
SES group									
Low SES group	1	0.77 (0.42 to 1.43)[b]	.412				2.50_1	.112	67.0
Mixed/unspecified SES group	5	1.36 (0.99 to 1.87)	.060	1.27_4	.867	0.0			
Country									
Europe	3	1.37 (0.96 to 1.96)	.079	0.19_2	.910	0.0			
North America	1	0.64 (0.14 to 2.94)[b]	.569				1.20_2	.537	33.0
Other/unspecified	2	1.05 (0.52 to 2.12)	.896	1.87_1	.172	46.0			
Convenience sample									
Convenience samples	1	0.77 (0.42 to 1.43)[b]	.412				2.50_1	.112	67.0
No convenience samples	5	1.36 (0.99 to 1.87)	.060	1.27_4	.867	0.0			
Preeclampsia									
All studies	4	1.35 (0.95 to 1.92)	.089	3.22_3	.358	7.0			
Study quality									
Above quality threshold	4	1.35 (0.95 to 1.92)	.089	3.22_3	.358	7.0			
Below quality threshold	0								
Diagnostic measure of depression									
Diagnostic	1	2.72 (0.10 to 70.80)[b]	.547				0.17_1	.683	5.0
Not diagnostic	3	1.37 (0.90 to 2.09)	.139	3.04_2	.219	34.0			
Any adjusted data									
Adjusted findings	1	2.50 (1.13 to 5.54)[b]	.024				2.80_1	.093	88.0
Unadjusted findings	3	1.18 (0.82 to 1.69)	.364	0.40_2	.820	0.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	1	2.72 (0.10 to 70.80)[b]	.547				0.17_1	.683	5.0
Antidepressant medication use not excluded/controlled	3	1.37 (0.90 to 2.09)	.139	3.04_2	.219	34.0			

continued

Table 2 (continued). Effect of Maternal Depression on Birth Outcomes: Meta-Analyses Results

		Within Group							
				Heterogeneity			Effect of Moderator		
Analysis	No. of Studies	Odds Ratio or Mean Difference (95% CI)[a]	*P* Value	$Q_{(df)}$ Within	*P* Value	I^2 (percentage of variance explained)	$Q_{(df)}$ Between	*P* Value	I^2 (percentage of variance explained)
Preeclampsia (continued)									
Smoking									
Smoking excluded/adjusted	1	2.50 (1.13 to 5.54)[b]	.024				2.80_1	.093	88.0
Smoking not excluded/adjusted	3	1.18 (0.82 to 1.69)	.364	0.40_2	.820	0.0			
SES group									
Low SES group	0								
Mixed/unspecified SES group	4	1.35 (0.95 to 1.92)	.089	3.22_3	.358	7.0			
Country									
Europe	3	1.37 (0.90 to 2.09)	.139	3.04_2	.219	34.0			
North America	1	2.72 (0.10 to 70.80)[b]	.547				0.17_1	.683	5.0
Other/unspecified	0								
Convenience sample									
Convenience samples	1	2.72 (0.10 to 70.80)[b]	.547				0.17_1	.683	5.0
No convenience samples	3	1.37 (0.90 to 2.09)	.139	3.04_2	.219	34.0			
Breastfeeding initiation									
All studies	4	0.68 (0.61 to 0.76)	<.0001	0.94_3	.815	0.0			
Study quality									
Above quality threshold	4	0.68 (0.61 to 0.76)	<.0001	0.94_3	.815	0.0			
Below quality threshold	0								
Diagnostic measure of depression									
Diagnostic	0								
Not diagnostic	4	0.68 (0.61 to 0.76)	<.0001	0.94_3	.815	0.0			
Any adjusted data									
Adjusted findings	0								
Unadjusted findings	4	0.68 (0.61 to 0.76)	<.0001	0.94_3	.815	0.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	0								
Antidepressant medication use not excluded/controlled	4	0.68 (0.61 to 0.76)	<.0001	0.94_3	.815	0.0			
Smoking									
Smoking excluded/adjusted	0								
Smoking not excluded/adjusted	4	0.68 (0.61 to 0.76)	<.0001	0.94_3	.815	0.0			
SES group									
Low SES group	0								
Mixed/Unspecified SES group	4	0.68 (0.61 to 0.76)	<.0001	0.94_3	.815	0.0			
Country									
Europe	2	0.67 (0.60 to 0.75)	<.0001	0.49_1	.484	0.0	0.26_1	0.613	27.0
North America	2	0.73 (0.54 to 1.01)	.055	0.20_1	.656	0.0			
Other/unspecified	0								
Convenience sample									
Convenience samples	1	0.69 (0.46 to 1.04)[b]	.076				0.01_1	0.923	1.0
No convenience samples	3	0.68 (0.61 to 0.76)	<.0001	0.93_2	.627	0.0			
APGAR at 1 minute									
All studies	3	−0.05 (−0.28 to 0.17)	.638	0.88_2	.644	0.0			
Study quality									
Above quality threshold	3	−0.05 (−0.28 to 0.17)	.638	0.88_2	.644	0.0			
Below quality threshold	0								
Diagnostic measure of depression									
Diagnostic	2	0.09 (−0.37 to 0.54)	.709	0.39_1	.531	0.0	0.49_1	.485	55.0
Not diagnostic	1	−0.10 (−0.36 to 0.16)[b]	.450						
Any adjusted data									
Adjusted findings	0								
Unadjusted findings	3	−0.05 (−0.28 to 0.17)	.638	0.88_2	.644	0.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	2	0.09 (−0.37 to 0.54)	.709	0.39_1	.531	0.0	0.49_1	.485	55.0
Antidepressant medication use not excluded/controlled	1	−0.10 (−0.36 to 0.16)[b]	.450						
Smoking									
Smoking excluded/adjusted	0								
Smoking not excluded/adjusted	3	−0.05 (−0.28 to 0.17)	.638	0.88_2	.644	0.0			
SES group									
Low SES group	0								
Mixed/unspecified SES group	3	−0.05 (−0.28 to 0.17)	.638	0.88_2	.644	0.0			

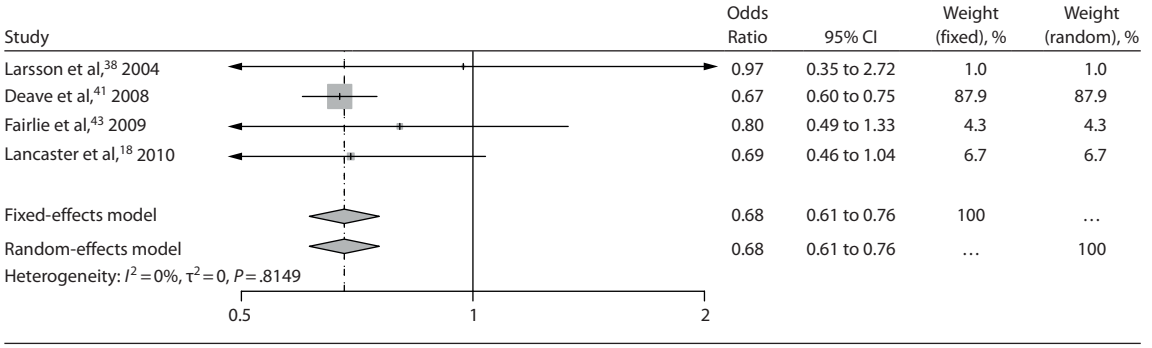
continued

Table 2 (continued). Effect of Maternal Depression on Birth Outcomes: Meta-Analyses Results

		Within Group							
				Heterogeneity			Effect of Moderator		
Analysis	No. of Studies	Odds Ratio or Mean Difference (95% CI)[a]	*P* Value	$Q_{(df)}$ Within	*P* Value	I^2 (percentage of variance explained)	$Q_{(df)}$ Between	*P* Value	I^2 (percentage of variance explained)
Apgar at 1 minute (continued)									
Country									
Europe	0								
North America	3	−0.05 (−0.28 to 0.17)	.638	0.88_2	.644	0.0			
Other/unspecified	0								
Convenience sample									
Convenience samples	2	−0.05 (−0.29 to 0.19)	.682	0.86_1	.353	0.0	0.02_1	.899	2.0
No convenience samples	1	−0.10 (−0.84 to 0.64)[b]	.791						
Apgar at 5 minutes									
All studies	4	0.01 (−0.08 to 0.11)	.782	3.27_3	.352	8.3			
Study quality									
Above quality threshold	4	0.01 (−0.08 to 0.11)	.782	3.27_3	.352	8.3			
Below quality threshold	0								
Diagnostic measure of depression									
Diagnostic	3	−0.01 (−0.20 to 0.18)	.906	3.14_2	.208	36.0	0.01_1	.922	0.0
Not diagnostic	1	0.00 (−0.12 to 0.12)[b]	>.999						
Any adjusted data									
Adjusted findings	0								
Unadjusted findings	4	0.01 (−0.08 to 0.11)	.782	3.27_3	.352	8.3			
Antidepressant medication									
Antidepressant medication use excluded/controlled	3	−0.01 (−0.20 to 0.18)	.906	3.14_2	.208	36.0	0.01_1	.922	0.0
Antidepressant medication use not excluded/controlled	1	0.00 (−0.12 to 0.12)[b]	>.999						
Smoking									
Smoking excluded/adjusted	1	−0.20 (−0.54 to 0.14)[b]	.248				1.70_1	.196	51.0
Smoking not excluded/adjusted	3	0.03 (−0.06 to 0.12)	.497	1.60_2	.449	0.0			
SES group									
Low SES group	0								
Mixed/unspecified SES group	4	0.01 (−0.08 to 0.11)	.782	3.27_3	.352	8.3			
Country									
Europe	0								
North America	4	0.01 (−0.08 to 0.11)	.782	3.27_3	.352	8.3			
Other/unspecified	0								
Convenience sample									
Convenience samples	3	0.02 (−0.10 to 0.14)	.759	2.83_2	.243	29.0	0.39_1	.533	12.0
No convenience samples	1	−0.10 (−0.45 to 0.25)[b]	.579						
NICU admission									
All studies	6	1.43 (0.83 to 2.47)	.195	6.46_5	.264	22.6			
Study quality									
Above quality threshold	5	1.48 (0.78 to 2.81)	.235	6.46_4	.167	38.0	0.001_1	.979	0.0
Below quality threshold	1	1.43 (0.15 to 13.26)[b]	.752						
Diagnostic measure of depression									
Diagnostic	4	1.23 (0.56 to 2.70)	.601	4.07_3	.254	26.0	0.94_1	.332	15.0
Not diagnostic	2	2.09 (1.02 to 4.28)	.045	0.12_1	.726	0.0			
Any adjusted data									
Adjusted findings	2	1.35 (0.57 to 3.20)	.497	3.35_1	.067	70.0	0.22_1	.637	3.0
Unadjusted findings	4	1.84 (0.70 to 4.87)	.216	2.57_3	.463	0.0			
Antidepressant medication									
Antidepressant medication use excluded/controlled	5	1.48 (0.78 to 2.81)	.235	6.46_4	.167	38.0	0.001_1	.979	0.0
Antidepressant medication use not excluded/controlled	1	1.43 (0.15 to 13.26)[b]	.752						
Smoking									
Smoking excluded/adjusted	3	1.20 (0.58 to 2.49)	.621	4.01_2	.134	50.0	1.50_1	.218	23.0
Smoking not excluded/adjusted	3	2.79 (0.91 to 8.55)	.073	0.51_2	.776	0.0			
SES group									
Low SES group	0								
Mixed/unspecified SES group	6	1.43 (0.83 to 2.47)	.195	6.46_5	.264	22.6			
Country									
Europe	1	0.90 (0.51 to 1.58)[b]	.715				3.90_2	.143	60.0
North America	4	1.84 (0.70 to 4.87)	.216	2.57_3	.463	0.0			
Other/unspecified	1	2.18 (1.02 to 4.66)[b]	.044						
Convenience sample									
Convenience samples	3	1.90 (0.54 to 6.72)	.320	2.51_2	.285	20.0	0.24_1	.626	4.0
No convenience samples	3	1.33 (0.68 to 2.60)	.402	3.37_2	.186	41.0			

[a]Pooled effect size estimated by using random-effects model. [b]Pooled effect size estimated by using fixed-effects model.
Abbreviations: NICU = neonatal intensive care unit, SES = socioeconomic status.

Figure 3. Exposure to Depression in Utero and the Odds Ratio for Breastfeeding Initiation: Meta-Analysis Results for All Studies



Apgar score at 5 minutes (mean difference = 0.01; 95% CI, −0.08 to 0.11; $P = .782$; see Supplementary eFigure 6). Heterogeneity was not significant across studies and none of the subanalyses performed resulted (Table 2) in significance.

Neonatal Intensive Care Unit Admissions

No significant associations were found between exposure to maternal depression and the odds of NICU admissions (OR = 1.43; 95% CI, 0.83 to 2.47; $P = .195$; see Supplementary eFigure 7) in the main analysis, which pooled 6 studies. Heterogeneity was not significant, nor were the moderator analyses. However, the subanalyses based on the use of nondiagnostic measures of depression were significant as was the analysis based on studies using "other or unspecified" countries, but this analysis was based on only 1 study (Table 2).

Publication Bias

We did not find evidence for the presence of publication bias for the majority of outcomes, except breastfeeding initiation, Apgar at 5 minutes, birth weight, and NICU admissions. We used Duval and Tweedie's trim-and-fill procedure[27] to assess for publication bias and found there was only minor impact on the estimates. The adjusted OR for breastfeeding initiation was 0.67 (95% CI, 0.61 to 0.74; $P < .0001$) following the trim-and-fill procedure. The adjusted mean difference following trim and fill was 0.04 (95% CI, −0.06 to 0.15; $P = .399$) for Apgar at 5 minutes and was −7.35 (95% CI, −56.29 to 41.60; $P = .769$) for birth weight. The NICU adjusted OR was 1.21 (95% CI, 0.71 to 2.08; $P = .482$).

DISCUSSION

This study reports on a systematic review and meta-analysis examining the effect of maternal depression antenatally on perinatal outcomes. It is the first, as far as we are aware, to report on diverse perinatal outcomes, including premature delivery, gestational age, birth weight, low birth weight, preeclampsia, breastfeeding initiation, Apgar scores at 1 and 5 minutes, and NICU admissions. Of the various outcomes, few significant associations were found, which is reassuring given how common depression is. Our most consistent findings were the associations of maternal depression with premature delivery and the lower likelihood of breastfeeding initiation.

Premature delivery was associated with maternal depression during pregnancy in our main analysis and many of our subanalyses. As there was a moderate amount of study heterogeneity, we found that the moderator of sample type accounted for 16% of the variance overall and that convenience samples pooled to an OR of over 2. Subgroup analyses for studies that did not adjust for significant confounders, such as smoking or antidepressant medication use, and for studies that were based on low socioeconomic status samples had significant pooled ORs, yet the moderator analyses were not significant and thus did not account for significant variability. Interestingly, it was typically the methodologically inferior groupings that had significant pooled ORs (ie, unadjusted data, convenience samples, and medication not controlled for). Moreover, regardless of significance, the pooled ORs for the preterm outcome analyses were largely of the same magnitude and were generally below 2, which suggest the effects are modest, albeit statistically significant.[52] The ORs for premature delivery pooled from convenience samples and low socioeconomic status mothers were above 2 but potentially confounded. Convenience samples that were included consisted primarily of women attending specialty hospital clinics, and thus these women may have had other reasons for a higher likelihood of premature delivery.

Breastfeeding was also less likely to be initiated when mothers were depressed during pregnancy. Once again, however, the ORs were not striking and only 4 studies were included in the analysis, although this association does appear plausible. Breastfeeding can be challenging to establish, and for women who are experiencing depressive symptoms that limit their abilities to stay focused, it is not surprising that they may be less likely to engage. Interestingly, however, we cannot exclude that the mothers were less likely to breastfeed because they were taking antidepressant medication, as none of the studies provided any data or eligible data that we could pool on breastfeeding that adjusted for antidepressant medication exposure.

Low birth weight was found to be associated with maternal depression in the subanalysis using adjusted data, but this finding was based on 3 studies. Other significant subanalyses were also found, but they were based on no more than 3 studies and the effects were of a low magnitude. Additional research is warranted to further understand if there is a

relationship between maternal depression during pregnancy and the outcomes that did have significant subanalyses.

Grote and colleagues' meta-analysis[20] also found that women with antenatal depression were at increased risk for preterm birth; however, their results were also not striking, with overall relative risks that were below 2 and were found to vary depending on whether or not categorical measures of depression were used as well as socioeconomic status in some subanalyses. The risk of low birth weight was significantly associated with depression during pregnancy but was larger in developing countries. Our results concur with Grote and colleagues' overall preterm birth analysis, [20] though we found the use of convenience samples to inflate the magnitude of the ORs. The pooled OR for our low socioeconomic status subgroup was significant, while the mixed/unspecified socioeconomic status subgroup was not. However, high heterogeneity was found among the studies using Huedo-Medina and colleagues' cutoffs,[28] with I^2 of 25% representing low heterogeneity, 50% medium, and 75% high. The overall moderator analysis with socioeconomic status did approach significance ($P = .07$). Our birth weight analysis did not demonstrate a significant association with maternal depression during pregnancy. Although our birth weight subanalysis approached significance for socioeconomic status as a source of heterogeneity, there was only 1 study in the low socioeconomic status group. Our low birth weight subanalyses for studies that used adjusted data and for those that excluded smoking were significant; the mixed or unspecified socioeconomic status grouping approached significance, which concurs with the Grote et al analysis.[20] Differences from the Grote et al analyses[20] can be explained by the inclusion of different studies. For example, we included 6 additional studies[11,12,35,41,43,51] in our preterm analysis that Grote et al[20] did not, while Grote et al[20] included 14 studies overall that we did not. The 14 articles we excluded were for the following reasons: they did not report data on a comparison group,[53–55] had a cross-sectional design,[54] had an unclear measure of depression,[56–58] were not published in English (though we did include an article[9] that was a future publication and utilized the same cohort of women),[59] or did not present data in a suitable form.[60–66] Moreover, our analyses replicated and extended Grote et al,[20] as we included 7 additional outcomes.

Preterm birth, although poorly understood, is not a benign birth outcome, but rather a recognized public health concern. Premature infants are at increased risk for death and morbidity, especially neurodevelopmental disabilities.[67–69] Although substantial advances have been made in obstetrical care, these advances do not appear to have had a significant impact on the rates of preterm birth, with rates in Canada rising from 7.0% in 1995 to 8.2% in 2004.[68] The impact on the health care system is also substantial. Preterm infants incur higher costs compared to term infants, with average in-hospital costs for a singleton preterm (< 37 weeks) infant of $9,233 as compared to $1,050 for full-term infants, and the costs rise with decreasing gestational age.[69] As a result, even the modest increase in preterm birth seen to be associated with maternal depression during pregnancy in this study can have a substantial impact, as the North American preterm birth rate is approximately 13%.[70] Similarly, a recent review[71] concluded that breastfeeding is associated with reduced risk for a variety of pediatric diseases, including acute otitis media, gastroenteritis, lower respiratory tract infections that become severe, atopic dermatitis, asthma in childhood, types 1 and 2 diabetes and obesity, leukemia during childhood, and, lastly, sudden infant death syndrome. Infants born to mothers who experience antenatal depression may be at increased risk for these diseases, as these mothers are less likely to initiate breastfeeding. However, insisting a woman breastfeed if she is having difficulty or experiencing anxiety or depression should be weighed with the adverse psychological effects this may incur, such as increased symptomatology and guilt.[72,73]

Preeclampsia as an outcome was not significant overall, but the pooled OR did approach significance. The adjusted data subanalysis was significant, albeit it was based on 1 study. This outcome has implications for both the mother and baby and can be an obstetrical emergency as well as life threatening. As a result, clinicians must be made aware of this potential association, despite the fact that future research will need to further assess this potential outcome. Maternal depression during pregnancy in this analysis was found to be associated with some adverse perinatal outcomes, and, although more research is needed of superior methodological quality, the risks of untreated depression on both mother and baby must be taken into consideration when making treatment decisions.

Strengths and Limitations

The primary strength of our work is our concurrent investigation of a number of outcomes and possible moderator variables. Having a broader understanding of many outcomes aside, assessing for the effects of potential confounders has the potential to advance the field, given our concerns that the known methodological limitations may have an untoward impact on our conclusions. An additional strength of this work is our application of a rigorous quality assessment procedure in the evaluation of the identified studies. Because of a limited number of studies that fell below the quality threshold, we reported results on all studies. The quality of studies was not a significant source of heterogeneity for any of the outcomes; however, most studies were above the quality threshold, with only 1 or 2 studies falling below the threshold for any given analysis.

The primary limitations of our work follow from the weaknesses of the original articles included in our meta-analysis. For example, our analysis indicates that the association between preterm birth and maternal depression was stronger among studies drawing from convenience samples, suggesting that study design may well influence the likelihood of observing a significant effect of a given outcome. Convenience samples were those that did not appear to have been derived from consecutive or random sampling. Moreover, heterogeneity in the main analyses was found for preterm birth, gestational age, and birth weight.

We conducted subgroup analyses for the remainder of the outcomes for consistency, as they were planned a priori. We did expect to find heterogeneity among the other outcomes, given the limitations of many of the studies and that some of the moderator variables are known to affect birth outcomes, but, regardless, their pooled ORs were not significant. This may be a question of not having had enough power. Alternatively, the settings from which the populations were drawn varied from a tertiary care academic institution of mostly high-risk obstetrical women[18] to a tertiary hospital in Pakistan in which mainly failed or complicated deliveries are seen[12] to studies from countries such as Sweden in which antenatal care rates and public hospital delivery rates are almost 100%.[14,38] These differences in study populations can not only affect generalizability of the results but also account for the heterogeneity seen. Most of the studies were based on small sample sizes; for example, in the preterm analysis, 6 of the studies were based on fewer than 100 patients in the depressed group and, of these, 3 had fewer than 25 women. Moreover, several of the subanalyses were based on fewer than 3 studies, limiting any conclusions. Although we did find evidence of publication bias for 4 outcomes, the effect did not appear to significantly affect the outcomes.

Clinical research, which is often observational in nature, suffers from inherent issues of feasibility and practicality—namely, with regards to identifying a large enough sample with sufficient data on both exposure to untreated antenatal depression and pregnancy outcomes. However, there are a few simple means of improving study design when investigating the impact of maternal depression during pregnancy. In order to improve the quality of the assessment of exposure in future research, it is critical to have a diagnostic measure of depression along with a rating measure (either clinician rated or self-report) in order to assess the impact of depression severity. Although our meta-analysis did not find that results differed on the basis of whether diagnostic measures were used, Grote et al[20] did find this. For our preterm outcome, only 5 articles utilized a structured interview to classify subjects with a major depressive episode versus those that did not meet criteria, and only 1 article combined it with a depression inventory to ensure a minimum level of depression severity for classification of the depressed group at study entry. Even though half the number of studies used diagnostic measures compared to those that did not, the pooled OR was higher (1.54 versus 1.32) albeit not statistically significant but approached it ($P = .078$). As the studies utilizing rating scales as opposed to diagnostic measures of depression were used to classify the depressed group, it is unclear how many of those women in the 10 pooled studies that did not use diagnostic measures actually had a clinical diagnosis of a major depressive episode, as rating scales measure the probability of the disorder. Furthermore, the studies that used the rating scales also did not use the same cutoff scores. For example, while 13 is the recommended cutoff for the EPDS when used with an antenatal population, Larsson et al[38] used > 10 in order to not miss any women with "minor depression," while other studies utilized a cutoff of 13 or 14.[9,12,17,41,43,50] The 3 studies that measured depression with the 21-item BDI each utilized a different cutoff score (≥ 10 to include "mild to moderate depression,"[46] > 14.5 for "elevated"/"high-level" of depressive symptomatology,[35] and ≥ 21 to include just "presumptive clinical depression"[32]). Studies utilizing the CES-D[16,18,33,36,37,42,44,45,47] similarly employed a range of cutoff scores from 16 to 33. These differences lead to a further mixture in the analyses of the level of depression severity. Adverse neonatal outcomes may be related to the more severe end of the depression severity spectrum, although this association remains to be determined.

Similarly, standard definitions of outcomes should also be used. For example, preterm birth was found to be defined in numerous ways across studies, which posed challenges when trying to pool the data. The implications or causes of preterm birth may differ for births at < 37 weeks, which is what was used in this meta-analysis where defined, versus those < 35 weeks. In the 4 studies[18,38,41,43] included in our breastfeeding analysis, breastfeeding measures or definitions were not stated or clearly delineated in most cases. One study[38] reported "yes/no" breastfeeding, with no definition or measurement noted; another[41] reported "ever breastfed," with no definition or measurement explained; another[18] outlined that electronic medical records were examined to determine "breast" versus "bottle-feeding status"; and still another[43] defined "breastfeeding initiation" by obtaining postdelivery interviews that asked mothers whether they had put their baby to their breast or had fed their baby their breast milk. Without standard definitions of outcome, we simply cannot be confident that we are pooling equivalent data and, thus, less confident in their being affected by maternal depression.

It is essential to measure and control for potential confounders that have been associated with adverse pregnancy outcomes in order to isolate the impact of the mood disorder itself. For example, although 7 studies in the preterm analysis controlled for or excluded smoking, 12 did not control for or exclude alcohol use. Smoking and alcohol use during pregnancy already have been associated with adverse outcomes, including spontaneous preterm delivery and fetal growth restriction.[74,75] Further, both smoking and comorbid alcohol use have been associated with depression.[76,77] Any study on maternal depression, therefore, should address the effects of these potential confounders in order to examine the independent effect of depression. To address the highly debated issue of antidepressant use during pregnancy, researchers must control for exposure to psychotropic medication, and antidepressants in particular. These medications also have been implicated in adverse outcomes, and it is essential to be able to understand both their independent as well as their potentially synergistic effects. In our preterm birth analysis, for example, 6 studies did not appear to have antidepressant contamination. The subanalysis of studies that excluded antidepressant medications was not found to be statistically significant in our work, suggesting an effect for medication; however, the magnitude of the OR was similar to the pooled OR for studies that did not exclude antidepressant medication. Large-scale, prospective studies that control for various

confounding variables are needed to further examine the effects of maternal depression on perinatal outcomes so that clinical recommendations can be made with increased confidence.

Implications

This study was part of a larger investigation that sought to develop a reference guide to inform evidenced-based decisions when deciding on antidepressant treatment during pregnancy. Although more methodologically rigorous research is needed and depression did not appear to affect all perinatal outcomes, the effects of depression were not without consequence and should be given consideration. It is important to note that the controversy surrounding treatment of depression during pregnancy often ignores the effects of depression. Although we did study multiple perinatal outcomes, we did not exhaust them. For example, depression can significantly impact quality of life, not only for the mother but also for her family. Suicide can be a consequence of depression, and clinicians must always assess their patients for it as well as weigh heavily its potential when making treatment decisions. Nonpharmacologic treatment options for depression do exist, but research on their effectiveness during pregnancy is lacking. Clearly there is a need for additional research in the antenatal period.

Drug names: fluoxetine (Prozac and others).

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Potential conflicts of interest: In the last 5 years, **Dr Grigoriadis** has received honoraria as a consultant and a member of an advisory committee or for lectures from Wyeth Pharmaceuticals, GlaxoSmithKline, Pfizer, Servier, Eli Lilly Canada and Lundbeck; and has received research grant support from the Canadian Institutes of Health Research (CIHR), Ontario Ministry of Health, Ontario Mental Health Foundation, and CR Younger Foundation. **Dr Steiner** has been a consultant to AstraZeneca, Azevan, Servier, Bayer Canada, and Lundbeck; has received grant/research support from CIHR, Pfizer, Eli Lilly, and Lundbeck; and has received honoraria from the Society for Women's Health Research and AstraZeneca. **Drs Tomlinson**, **Dennis**, **Koren**, **Mousmanis**, **Cheung**, **Martinovic**, and **Ross** and **Mss VonderPorten**, **Mamisashvili**, and **Radford** have no financial disclosures to report.

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Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: The Impact of Maternal Depression During Pregnancy on Perinatal Outcomes: A Systematic Review and Meta-Analysis

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List of Supplementary Material for the article

1. **Keywords** Keywords
2. **eFigure 1** Exposure to depression in utero and the difference in gestational age (weeks): meta-analysis results for all studies
3. **eFigure 2** Exposure to depression in utero and the difference in birth weight (grams): meta-analysis results for all studies
4. **eFigure 3** Exposure to depression in utero and the odds ratio for low birth weight (<2500 grams): meta-analysis results for all studies
5. **eFigure 4** Exposure to depression in utero and the odds ratio for preeclampsia: metaanalysis results for all studies
6. **eFigure 5** Exposure to depression in utero and the difference in APGAR scores at 1 minute: meta-analysis results for all studies
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8. **eFigure 7** Exposure to depression in utero and the odds ratio for Neonatal Intensive Care Unit (NICU) admissions: meta-analysis results for all studies

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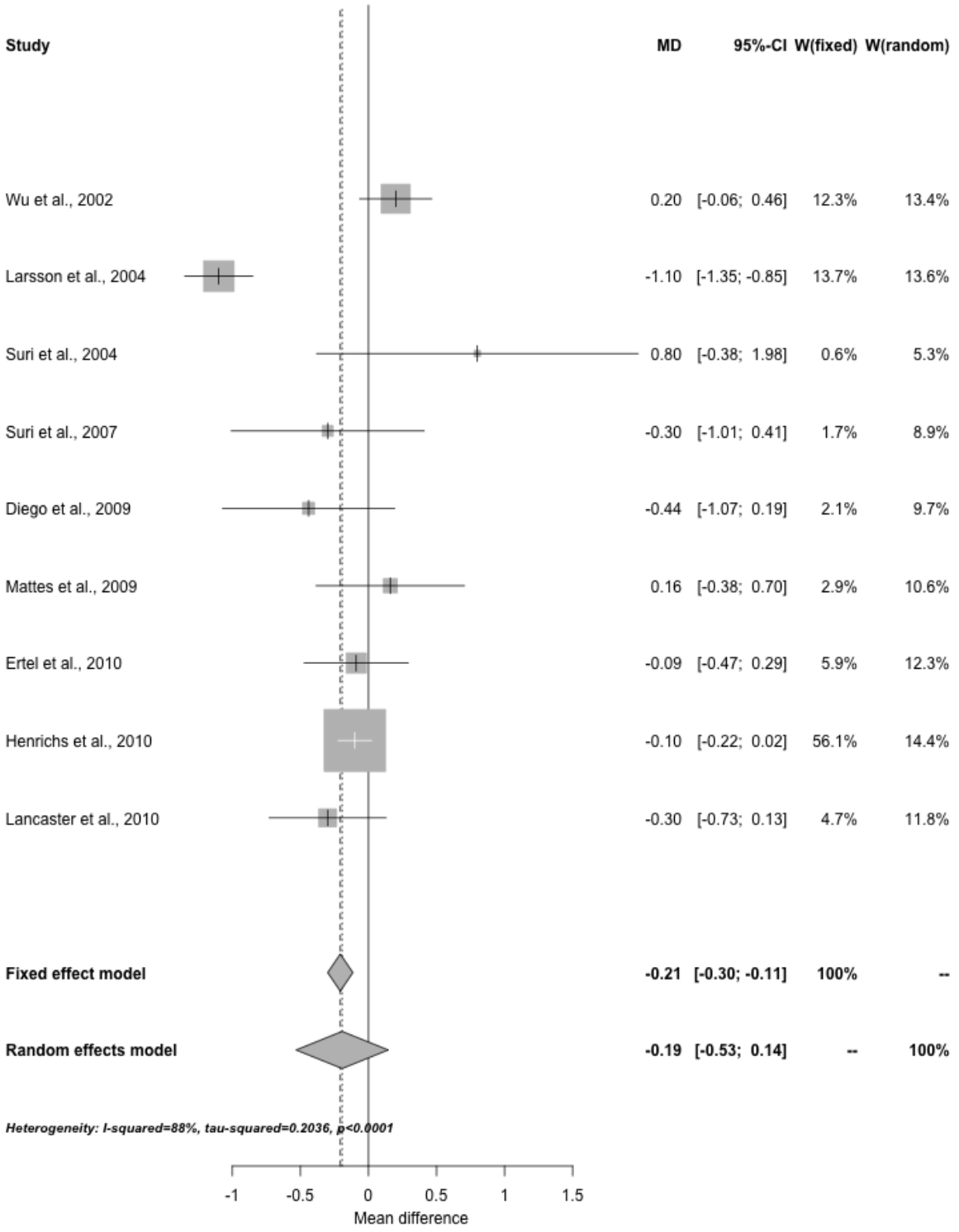
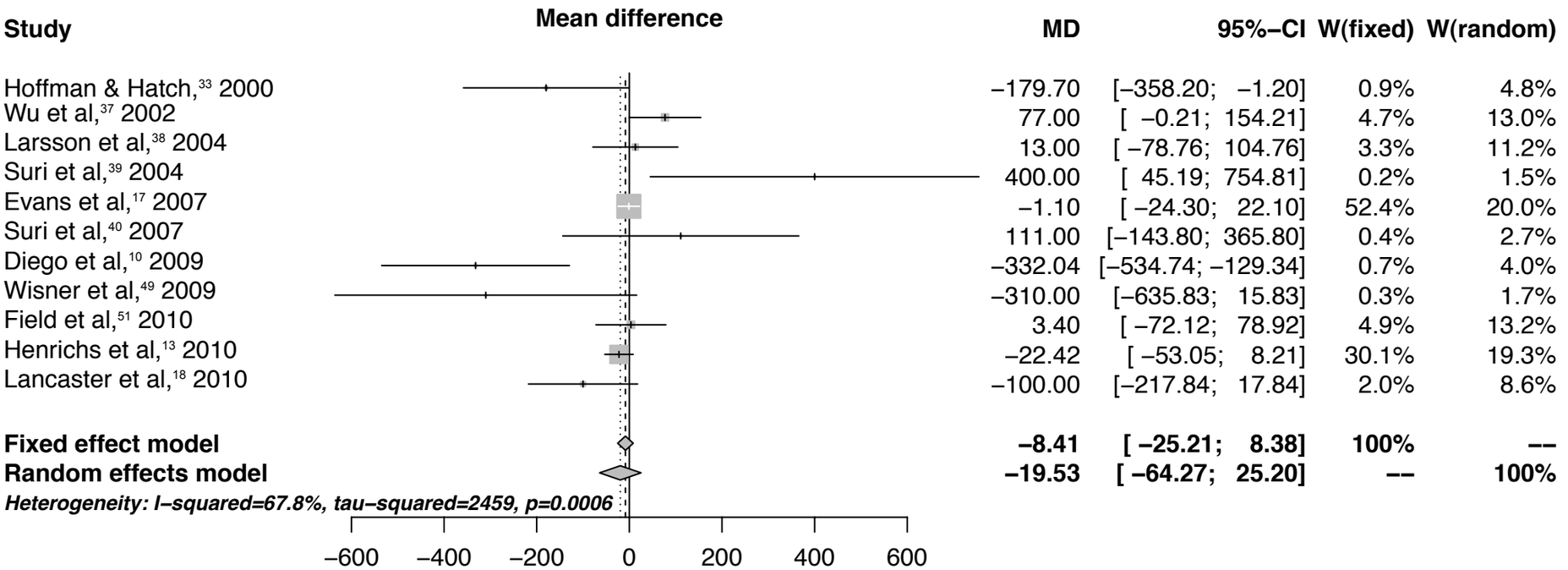
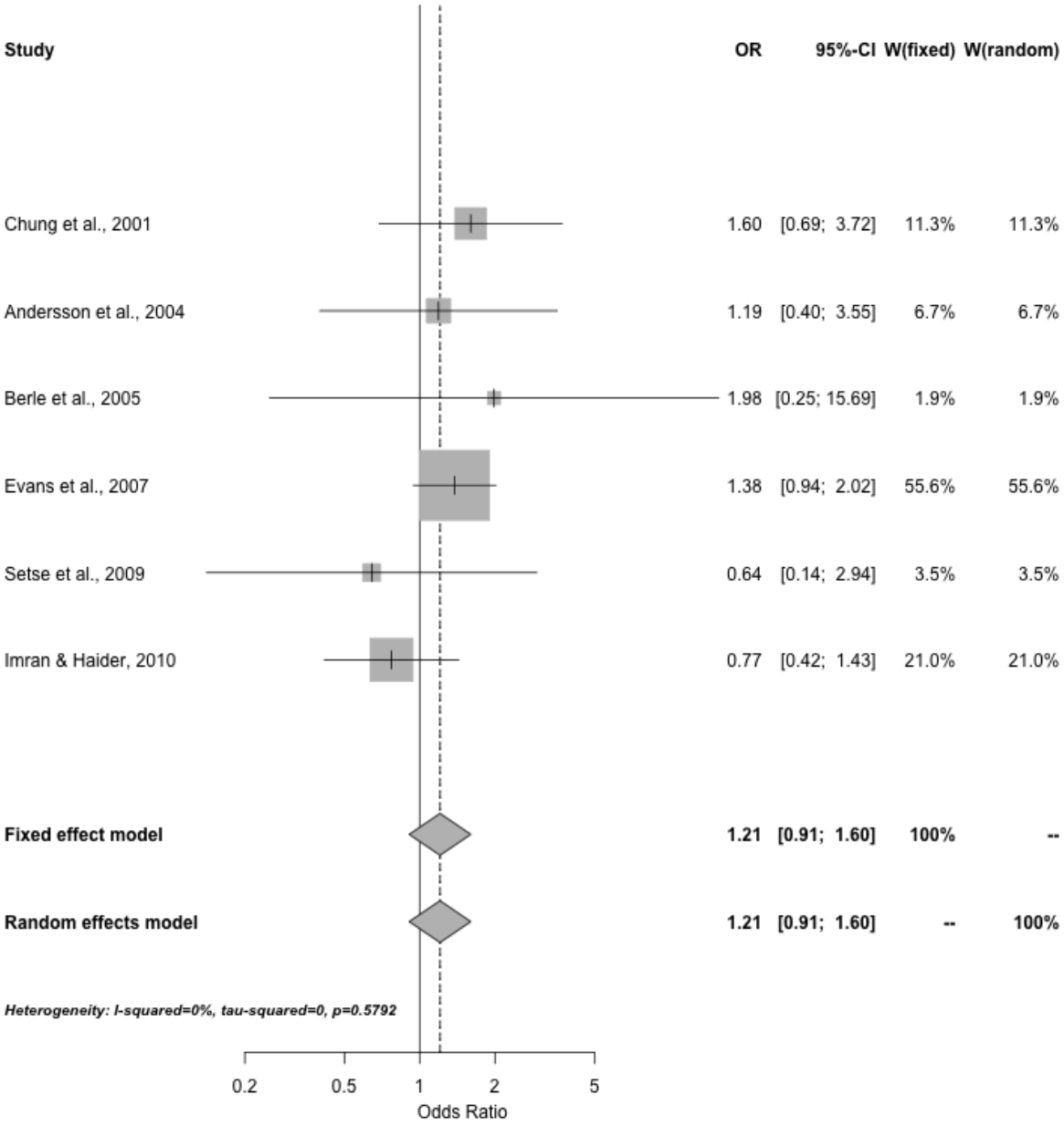


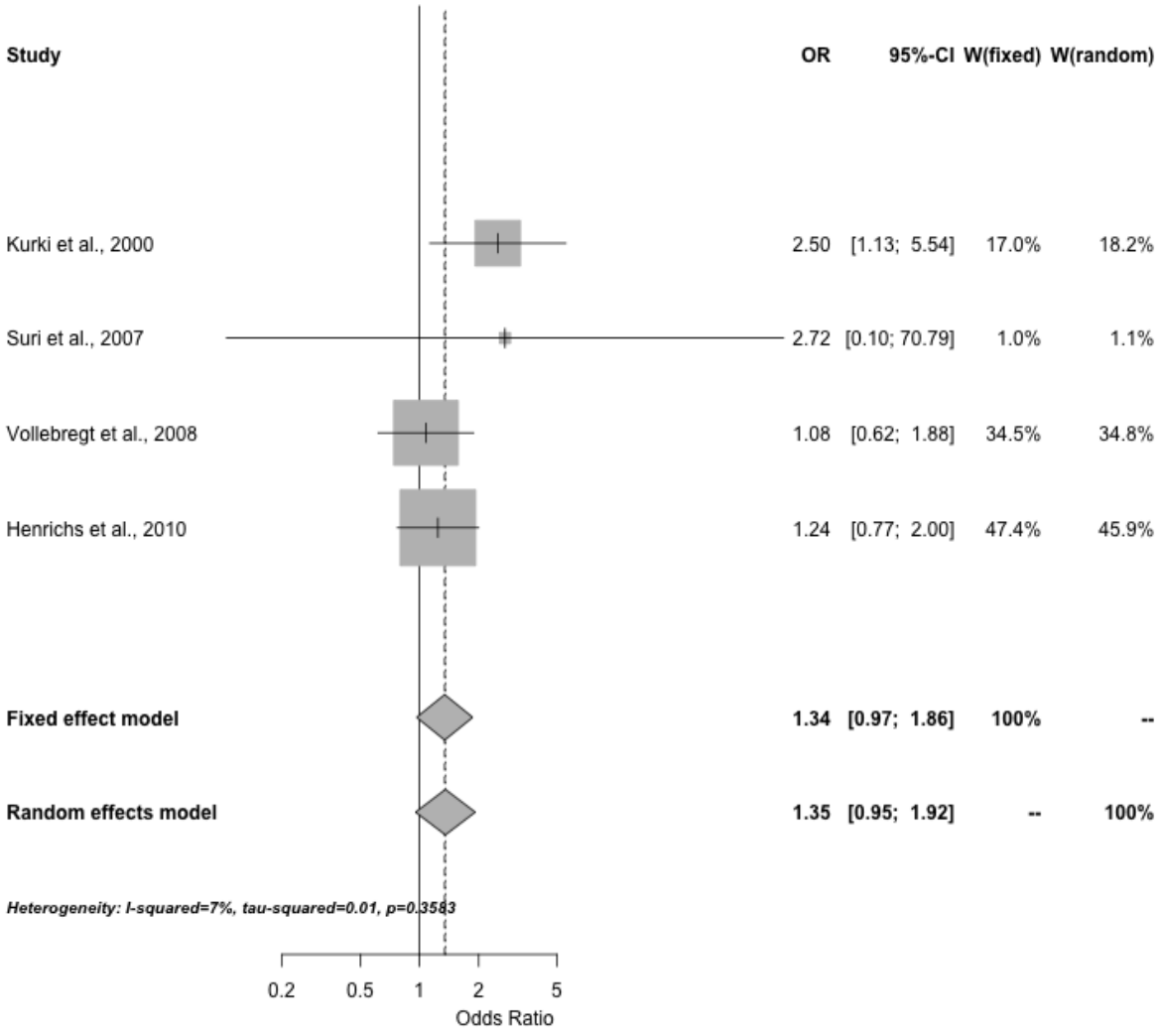
Supplementary eFigure 1. Exposure to depression in utero and the difference in gestational age (weeks): meta-analysis results for all studies. Abbreviations: see Figure 2.



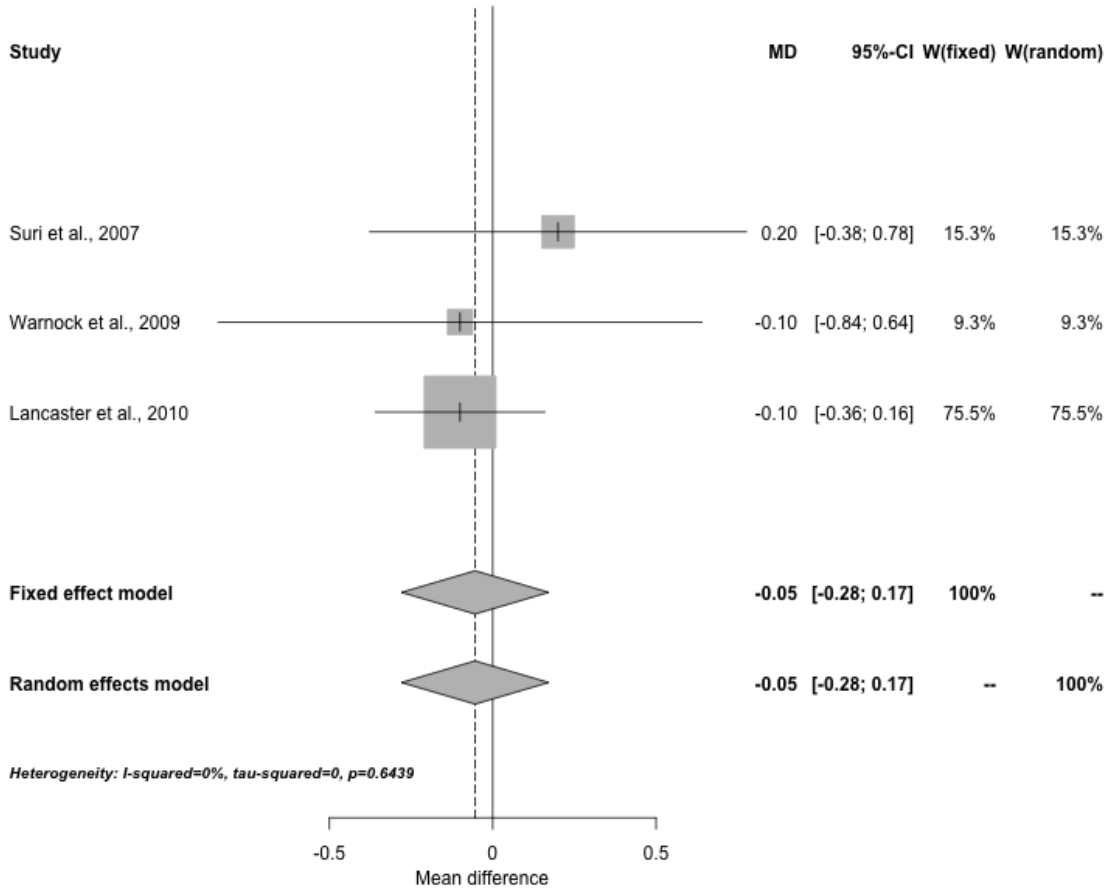
Supplementary eFigure 2. Exposure to depression in utero and the difference in birth weight (grams): meta-analysis results for all studies. Abbreviations: see Figure 2.



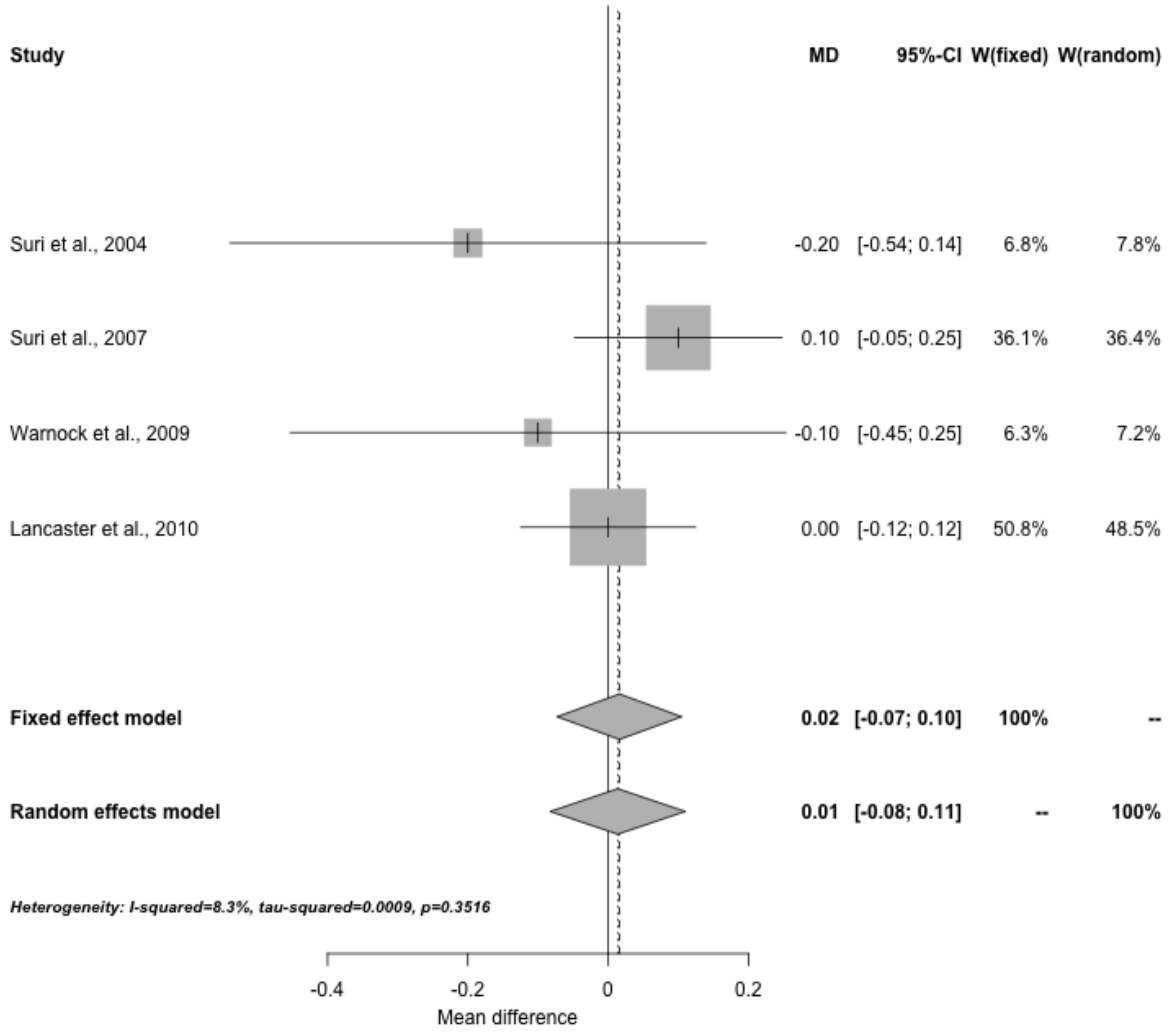
Supplementary eFigure 3. Exposure to depression in utero and the odds ratio for low birth weight (<2500 grams): meta-analysis results for all studies. Abbreviations: see Figure 2.



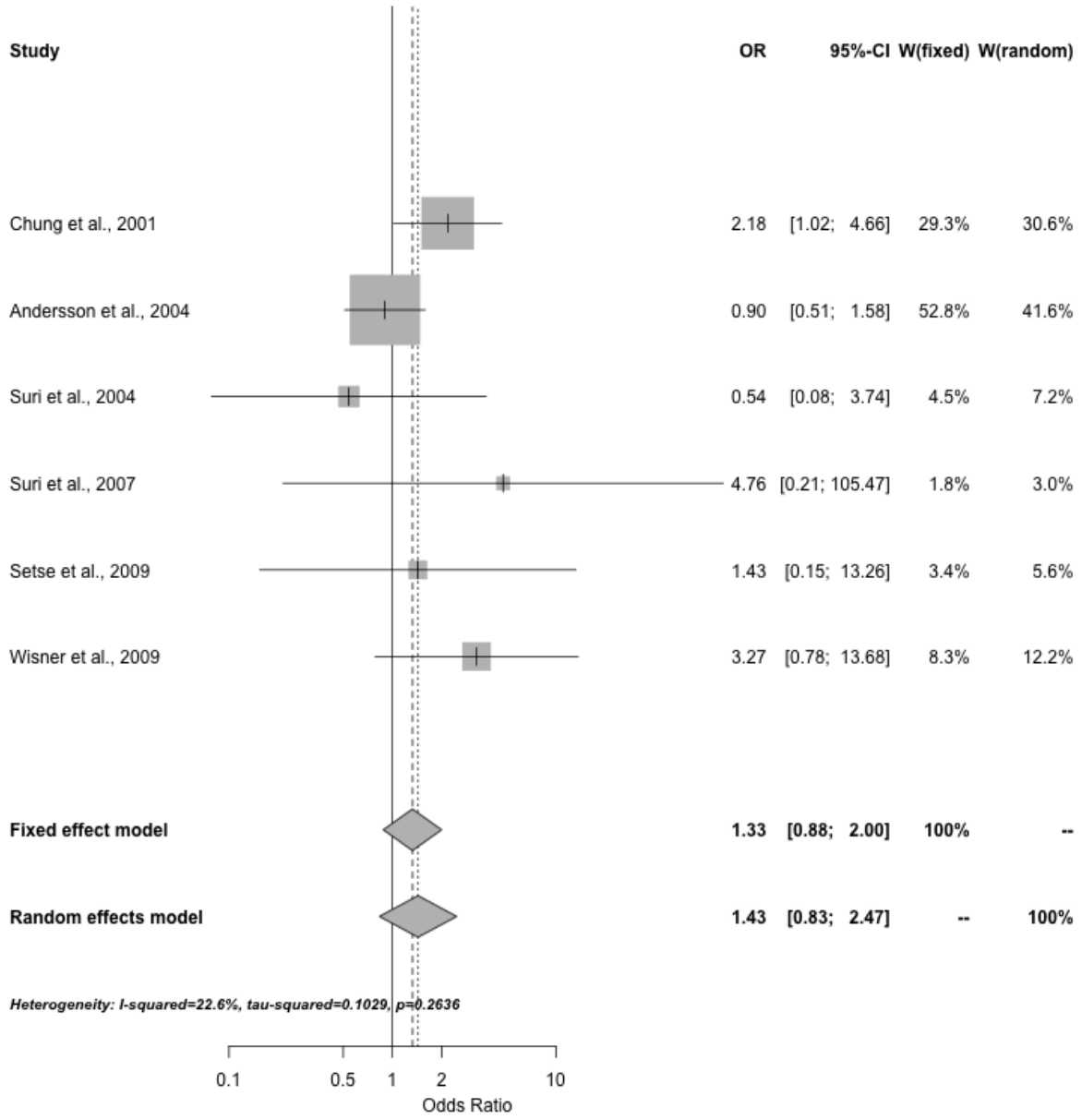
Supplementary eFigure 4. Exposure to depression in utero and the odds ratio for preeclampsia: meta-analysis results for all studies. Abbreviations: see Figure 2.



Supplementary eFigure 5. Exposure to depression in utero and the difference in APGAR scores at 1 minute: meta-analysis results for all studies. Abbreviations: see Figure 2.



Supplementary eFigure 6. Exposure to depression in utero and the difference in APGAR scores at 5 minutes: meta-analysis results for all studies. Abbreviations: see Figure 2.



Supplementary eFigure 7. Exposure to depression in utero and the odds ratio for Neonatal Intensive Care Unit (NICU) admissions: meta-analysis results for all studies. Abbreviations: see Figure 2.

Keywords

- **Antenatal Antidepressant** (search words: Major Depression; Depression; depressive disorder, mood disorder, dysthymic disorder, pregnancy, trimester, pregnancy unplanned/unwanted, prenatal care, pregnant women; antenatal/pregnant/prenatal/perinatal/puerperal; Neonatal withdrawal, neonatal abstinence syndrome, poor adaptation syndrome, neonatal adaptation, prenatal exposure/delayed effects, substance withdrawal symptoms, spontaneous abortion, miscarriage, fetus, fetal, neonatal, newborn, infant, infant outcome; maternal outcome, suicide, maternal suicide; premature birth, premature delivery, neurocognitive outcome or development, neurological outcome or development, infant development/child development, abnormalities, drug induced; attachment/mother/maternal, maternal behaviour; prenatal exposure, first trimester pregnancy/second trimester pregnancy/third trimester pregnancy/pregnancy complication; Tricyclic Antidepressant Drugs/Antidepressant Drugs/SSRIs/Monoamine Oxidase Inhibitors/Pregnancy*)
- **Antenatal Non Drug** (search words: Psychotherapy/ Brief Psychotherapy/Interpersonal Psychotherapy; Support Groups; Counseling; Interpersonal Therapy or Interpersonal Psychotherapy; Supportive Therapy or Narrative Therapy; Cognitive Therapy or Cognitive Behavioral Therapy; Psychoeducational or Psychodynamic; Psychosocial Intervention or Psychological Intervention; Psychosocial care, psychosocial rehabilitation, primary prevention, social support, prevention, therapy; Motivational Interview; emotion-focused counseling, non-directive counseling; Major Depression/Depression; Pregnancy/Prenatal or Antenatal)
- **Antenatal Risk Factors for Depression** (search words: Major Depression; depressive disorders, dysthymic disorders, Depression; Pregnancy; unwanted/unplanned pregnancy, adolescent pregnancy, Prenatal or antenatal; Risk Assessment/ Risk Management/ At Risk Populations/ Risk Factors; Protective Factors; psychosocial support, social support)
- **Postnatal Antidepressant** (search words: depressive disorder/mood disorder, dysthymic disorder; postpartum/postnatal; Major Depression; Depression; Tricyclic Antidepressant Drugs/Antidepressant Drugs/SSRIs/Monoamine Oxidase Inhibitors)
- **Lactation / Breastfeeding**: Postpartum Depression, Antidepressants, etc. (search words: Breast milk, Breast Feeding/ Lactation/ Lactating, weaning; Depression, puerperal depression, postpartum depression, dysthymic disorders, depressive disorders; breast milk and antidepressants, Antidepressant Drugs/Antidepressants*)
- **Postnatal Non Drug** (search words: Postpartum, postnatal; pregnancy, Psychotherapy/ Brief Psychotherapy/Interpersonal Psychotherapy; Support Groups; Counseling; Interpersonal Therapy or Interpersonal Psychotherapy; Supportive Therapy or Narrative Therapy; Cognitive Therapy or Cognitive Behavioral Therapy; Psychoeducational or Psychodynamic; Psychosocial Intervention or Psychological Intervention; psychological rehabilitation, social support, psychoeducational support, Motivational Interview; non-directive counseling, emotion-focused counseling, cognitive rehabilitation, psychotherapeutic techniques, Major Depression/Depression; Postnatal)
- **Risk Factors for Postpartum Depression** (search words: Postpartum/postnatal, postpartum period, prevention/control, therapy, psychosocial care, social support, psychosocial rehabilitation, psychosocial intervention; risk assessment/risk management, at risk populations, risk factors, primary mental health prevention, protective factors, unwanted/unplanned pregnancy, pregnancy; depressive disorders, dysthymic disorders; Postpartum Depression/ Risk Assessment/At Risk Populations/Risk Factors/Risk Management; Protective Factors; child development, attachment behaviour, infant/child behaviour, maternal behaviour, untreated depression, neurocognitive development, mother-child relations, infant care, neurological/neurocognitive development).